Understanding blood pressure dynamics in the South African population: a latent variables approach to the analysis and comparison of data from multiple surveys

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This thesis is presented in fulfilment of the requirements for the degree of Doctor of Philosophy in the School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town. The work on which this thesis is based is original research and has not, in whole or in part, been submitted for another degree at this or any other university. The contents of this thesis are entirely the work of the candidate, or in case of any incorporated multi-authored published paper, constitutes work for which the candidate was the lead author.

To my mom Oliva
my sister Silvia
my brother-in-law Massimo
my nephews Gloria, Rachele, Teresa and Alberto.

Always there for me,
even when I wasn't.

Abstract

Background

The 2015 edition of the Global Burden of Diseases Study identified elevated systolic blood pressure — defined as systolic blood pressure greater than the minimum risk category of 110–115 $mmHg$ — as the largest single contributor to the global burden of disease, responsible for 211.8 million disability adjusted life years lost, up 8.8% in the last decade.

Middle-income countries are currently bearing the highest share of this burden, and, because of the rapid demographic transition towards larger and older populations, the burden is bound to increase rapidly in the coming years, unless age-specific values of blood pressure are substantially reduced to compensate for the unfavourable demographic changes.

Achieving this more favourable blood pressure distribution in populations undergoing rapid changes in their socioeconomic structure requires knowledge of the mechanisms underlying temporal variations of blood pressure and the relationships of such variations with socioeconomic variables. However, evidence on these mechanisms and reliable information on the temporal trends of blood pressure themselves are scant outside high-income countries.

Given the large gain in health that would result in low- and middle-income countries if an optimal blood pressure were to be achieved in large sectors of the population, there is little doubt that temporal trends in the distribution of blood pressure in these populations and their possible determinants are an open and important area for investigation.

Objectives

Objectives of the study were:

1. To assess the level of quality and comparability of blood pressure data collected in a series of large-scale surveys carried out between 1998 and 2015 in South Africa, a middle-

income country undergoing rapid demographic and epidemiological transition;

2. To explore the possibility of applying a series of latent variables techniques to improve the comparability of data from the different sources and to minimise the effect of measurement and representation error on the estimation of cross-sectional relationships and temporal trends;
3. To estimate changes in the distribution of blood pressure and derived quantities — such as prevalence of uncontrolled hypertension — in the South African adult population between 1998 and 2015, taking into account between-surveys differences and measurement and representation error that could lead to artefactual conclusions;
4. To estimate the extent to which the estimated changes in the blood pressure distribution during the study period could be explained by concurrent changes in the distribution of a series of biological, behavioural and socioeconomic risk factors.

Methods

A series of techniques within the general framework of structural equation modelling were applied to jointly analyse the data and estimate the temporal trends and relationships of interest.

Latent variables were used to represent the unobserved true systolic and diastolic blood pressure in the South African population, and their distribution at different points in time was estimated based on the relationships with the multiple readings available for the sampled individuals, taking into account the presence of measurement error.

Possible drivers of the observed changes in the distribution were analysed by observing the changes in the temporal trends subsequent to statistical adjustment for different combinations of biological, behavioural and socioeconomic risk factors.

Specific estimation and modelling techniques were applied to deal efficiently with missing data and different number of replicated readings across the various surveys, to take into account the complex sampling designs, and to improve the coherence between sets of sampling weights inconsistently calibrated.

Results

The average systolic and diastolic blood pressure of South African adult women has progressively decreased since 2003-2004, reversing the previous rising trend. Among men, the reversal

happened only for the systolic blood pressure, while the average diastolic blood pressure continued rising, although at a lower pace than previously. In both genders, this pattern resulted in a reduction of the prevalence of uncontrolled hypertension between 2003-2004 and 2014-2015, by 8 percentage points among women and by 4.5 percentage points among men.

This consistent and rapid decrease cannot be explained by changes in the age structure of the population, smoking and alcohol consumption habits, distribution of body mass index or urbanization.

The diffusion of antihypertensive treatment and, among women, cohort effects and rapidly increasing educational level partly explain the recent trend, but a substantial part of the observed decrease remains unexplained by the factors available in our analyses.

Large seasonal variations in both systolic and diastolic blood pressure are present in the South African population, and their magnitude is greater among population strata with low socioeconomic status.

From a methodological point of view, there were two further results of this study. First, estimates of blood pressure and related quantities from the eight nationally representative population surveys carried out in South Africa between 1998 and 2015 are not directly comparable, because of methodological differences and overall data quality. Second, structural equation modelling (and, within this general framework, multiple group modelling, normal-censored regression, mixture analysis with skew-normal distributions and the use of additional parameters and phantom variables) represent a viable and advantageous alternative to current methods of comparative analysis of blood pressure data.

Conclusions

Encouraging signs regarding the future development of the burden of diseases related to elevated blood pressure in the South African population emerge from this study. Age-specific prevalence of uncontrolled hypertension seems to be decreasing, especially among women, and this decrease is accompanied by declining mortality for cardiovascular disease, particularly for stroke, recorded in burden of mortality studies.

The reasons of this decrease are largely unexplained and warrant further investigation. However, among the possible drivers analysed in this study, increased accessibility and efficacy of antihypertensive treatment are likely to be playing a role in the observed decrease in blood pressure. The growing obesity epidemic, on the contrary, is likely to be limiting the achievable benefits. Both of these factors can be targeted to maintain and improve the current decline in population values of blood pressure and prevalence of uncontrolled hypertension. The

large seasonal variations of blood pressure and their unequal distribution across socioeconomic strata also suggest that interventions to reduce exposure to low temperatures might have public health benefit.

From the point of view of the epidemiological investigation, the results of this study suggest that the current methods for the analysis of survey data on blood pressure and the measurement protocols for future data collections should be improved to increase between-surveys comparability and gather more reliable information on temporal changes in BP and gain better understanding of their drivers. Specifically, analytical methods should take explicitly into account known sources of measurement and representation error to reduce their biasing effects, especially when inter-survey comparisons are involved. Protocols for future studies should routinely include collection of auxiliary information and/or explicit validation of devices and procedures in the specific population.

Acknowledgements

First, I would like to thank my supervisor, *Prof. Rodney Ehrlich*, to whom I will be indebted forever for encouraging me to start this study; for his constant attention and support; for the punctual, thorough and timely comments to my drafts; for his attention to details and quality; for helping me not to get lost in analytical minutiæ and always looking at the epidemiological meaning and public health implications of my results.

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Abbreviations

aBIC	sample size-adjusted Bayesian Information Criterion
ABPM	ambulatory blood pressure monitoring
AIC	Akaike Information Criterion
ATE	average treatment effect on the population
ATT	average treatment effect on the treated
BIC	Bayesian Information Criterion
BMI	body mass index
BP	blood pressure
CFI	Comparative Fit Index
CSM	Continuing Sample Member
CTUM	correlated traits uncorrelated methods
CVD	cardiovascular disease
DAG	directed acyclic graph
DALY	disability adjusted life year
DBP	diastolic blood pressure
DG	directed graph
DPS	digit preference score
EA	census enumeration area
EDP	end digit preference
FA	factor analysis
FIML	full information maximum likelihood
GHS	General Household Survey

HTN	hypertension
i.i.d.	independently and identically distributed
IRT	item response theory
LCA	latent class
LMIC	low- and middle-income country
MAP	mean arterial pressure
MAR	missing at random
MCAR	missing completely at random
MGM	multiple group model
ML	maximum likelihood
MLR	robust maximum likelihood
MM	mixture model
NAHNES	United States National Health and Nutrition Examination Survey
NCI	Noncentrality Index
NIDS	National Income Dynamics Study
NMAR	missing not at random
NPSEM	non parametric structural equation model
NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
PP	pulse pressure
pseudo-ML	pseudo maximum likelihood
PSU	primary sampling unit
RAM	reticular action model
RCT	randomised controlled trial
RHR	resting heart rate
RMSEA	Root Mean Square Error of Approximation
SADHS	South Africa Demographic and Health Survey
SAGE	Study on Global Ageing and Adult Health
SANHNES	South Africa National Health and Nutrition Examination Survey
SBP	systolic blood pressure
sd	standard deviation

SEM	structural equation modelling
SES	socioeconomic status
SRMS	Standardized Root Means Residual
sSA	sub-Saharan Africa
THUSA	Transition and Health during Urbanisation of South Africans
TSE	total survey error
TSM	Temporary Sample Member
US	United States of America
WCE	white coat effect
WHO	World Health Organization

Chapter 1

Introduction

Elevated blood pressure (BP) is an important cause of mortality and morbidity worldwide. Strong epidemiological and experimental evidence supports the existence of a causal relationship between BP and the risk of developing a host of pathological conditions. Coronary heart disease, stroke, cardiac failure, peripheral arterial disease, renal failure, retinopathy and visual impairment are among the conditions most directly linked to BP elevations. These relationships have been observed in men and women of all ages, racial/ethnic groups, and countries, independently of other risk factors.[1, 2]

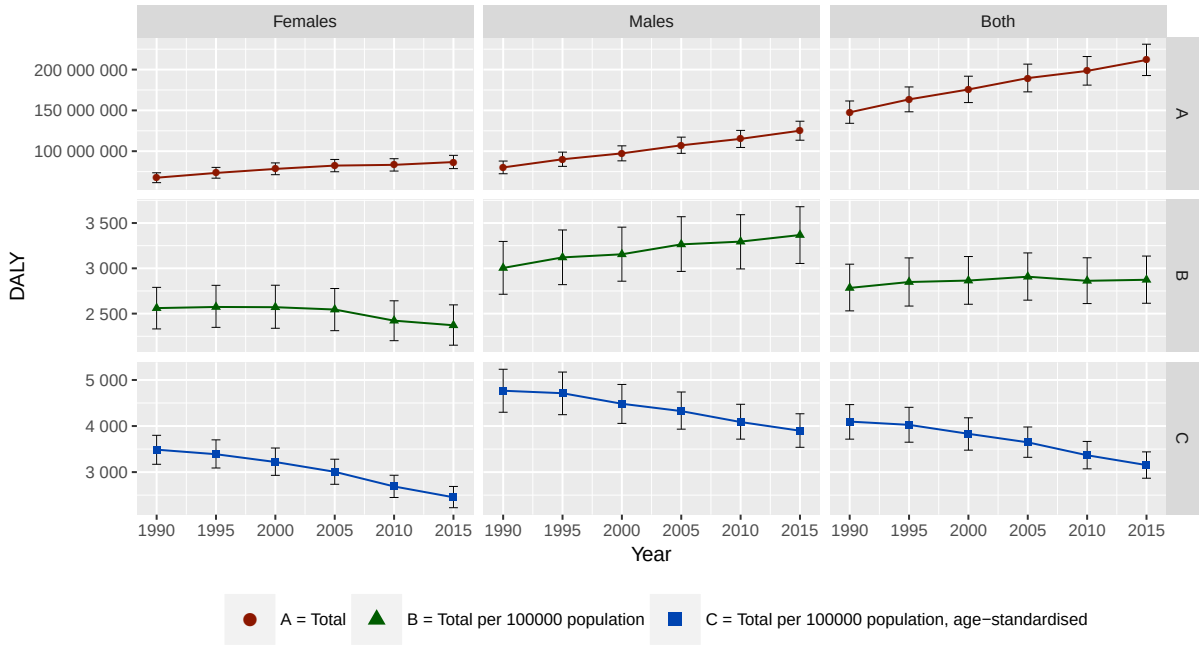
Systolic blood pressure — i.e. the maximum value reached during the cardiac cycle — is generally, even though not unanimously, acknowledged as the BP metric more strongly associated with increased risk of disease and death. However, for many conditions other metrics — including diastolic BP, mean arterial pressure and pulse pressure as defined in the next chapter — have been shown to be independent predictors of risk.[1]

The association between BP and development of disease is often expressed as increased risk among people with sustained BP readings above some threshold[1] (*hypertensive* individuals) compared with those whose usual BP is below this level (*normotensive* individuals). However, plenty of evidence shows that the relationship is characterised by a strong dose-response pattern, with a continuous increase of the risk across all levels of blood pressure, starting from values as low as 115/75 $mmHg$ (systolic/diastolic).[1, 3, 4]

The global burden of disease attributable to elevated BP is large and growing. The 2015 edition of the Global Burden of Diseases, Injuries, and Risk Factors Study identified elevated systolic BP — defined as systolic BP greater than the minimum risk category of 110–115 $mmHg$ — as the largest single contributor to the global burden of disease, responsible for 211.8 million disability adjusted life years (DALYs) lost (95% CI: 192.7 ; 231.1), up 8.8% since 2005 and 13.3% since 1990.[5]

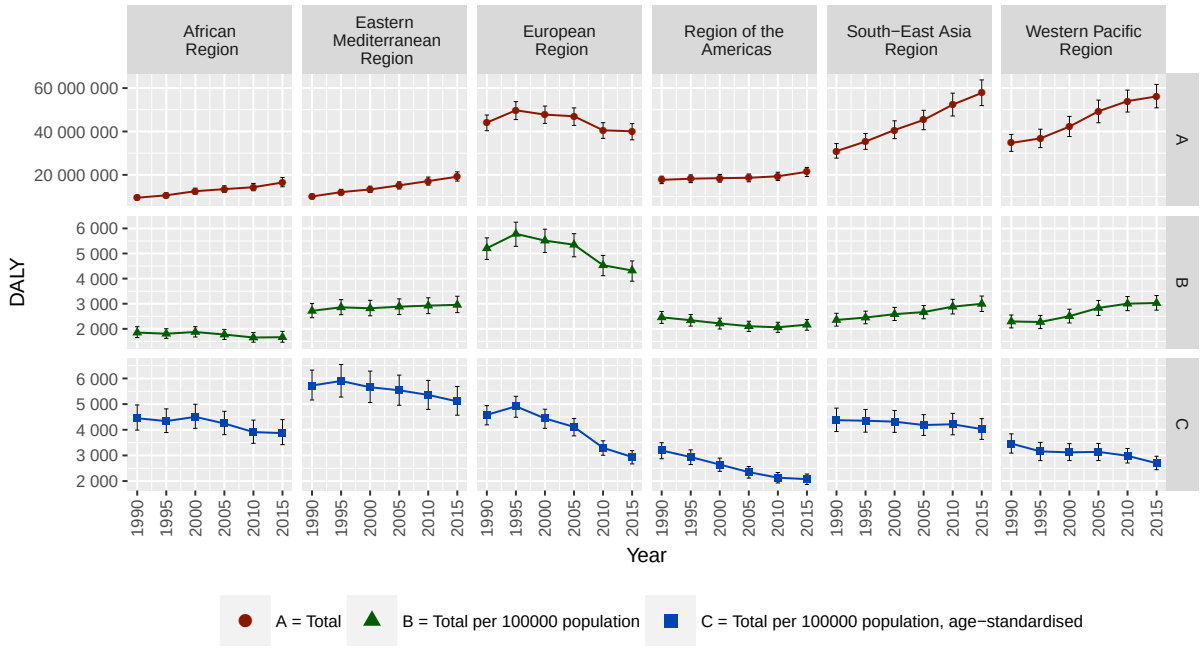
As shown in Figures 1.1 and 1.2, the overall increase in the total number of DALYs lost because of elevated BP is mainly for demographic reasons, i.e. to the increase and ageing[2] of the population in the rapidly developing countries of the Asian and Western Pacific regions. Excluding the demographic driver, the burden of disease for elevated BP has consistently *declined* in the last 25 years, especially among women. Although at different rates, the decline has been observed in all World Health Organization (WHO) macro-regions, as indicated by the downward trends in age-adjusted DALYs per 100 000 population in Figure 1.2. In all areas except the European region, however, this decline in age-adjusted rates has been more than offset by changes in the age structure and by the growing size of the populations. As a consequence the absolute burden of disease has grown everywhere except in Europe.

Figure 1.1: Number of DALYs lost due to elevated systolic blood pressure. Total, per 100 000 population and per 100 000 population age-adjusted. Estimates and 95% confidence intervals.



DALY = Disability-adjusted life year.
Data from: Global Burden of Disease Study 2015 [6]. See Forouzanfar et al. [5] for details and assumptions underlying the estimation procedure.

Figure 1.2: Number of DALYs lost due to elevated systolic blood pressure, per WHO region. Total, per 100 000 population and per 100 000 population age-adjusted. Estimates and 95% confidence intervals.

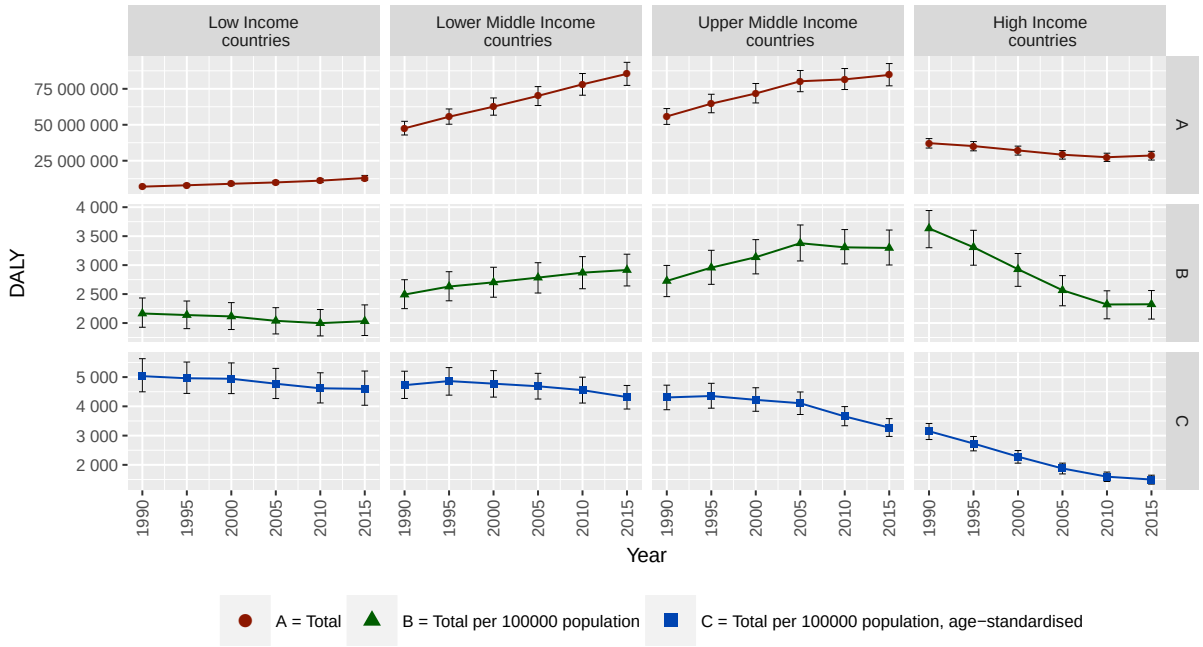


DALY = Disability-adjusted life year.
Data from: Global Burden of Disease Study 2015 [6]. See [7] for the list of countries in each WHO region.

As for many other diseases and risk factors, the distribution of the burden due to elevated BP is far from equal across populations at different stages of socio-economic development. Figure 1.3 shows that age-adjusted DALYs per 100 000 population are clearly an inverse function of the gross national income per capita, and are decreasing at a much slower pace in low- and middle-income countries (LMICs) compared to high-income countries. The pace in LMICs is well below the one needed to counterbalance the fast growth of the population and, especially in middle-income countries, the rapid changes in the age structure towards higher proportions of older subjects. The results is the dramatic increase in the absolute *and* relative (per unit population) burden of disease that middle-income countries are experiencing.

The relationships between the burden of diseases due to elevated systolic BP and stage of development has been studied in detail by Forouzanfar et al. [5]. Using data form the Global Burden of Disease Study, the authors analysed the coevolution between 1990 and 2015 of the excess risk due to elevated systolic BP — measured by the *summary exposure value* (SEV), an indicator of the excess risk in the population compared to a reference where nobody has a systolic BP greater than the chosen 'zero risk' condition of 110-115 $mmHg$ — and the stage

Figure 1.3: Number of DALYs lost due to elevated systolic blood pressure, per World Bank Income level classification. Total, per 100 000 population and per 100 000 population age-adjusted. Estimates and 95% confidence intervals.



DALY = Disability-adjusted life year.
Data from: Global Burden of Disease Study 2015 [6]. See [8] for the list of countries in each income group.

of development measured by the *socio-demographic index* (SDI), a summary index which integrates information on income per capita, average educational attainment over the age of 15 years, and total fertility rate.[3] Their results suggests a reverse-U shaped relationship between socio-economic development and burden of disease due to elevated systolic BP. The excess risk that a population experiences — which is measured in *relative* terms by the SEV, taking into account the changing age structure but *not* the absolute growth of the population — seems to decrease with the development in its initial phases, then it shows a rapid increase in the middle of the process, to decline substantially only in advanced phases of socio-economic development.[5, p. 1700]

The literature findings briefly described above show that middle-income countries are currently bearing, by far, the highest burden associated with elevated BP, both in absolute number of DALYs lost and per unit population.

Moreover, because of the rapid demographic transition towards larger and older populations they are experiencing, the burden is bound to a rapid increase in the next years, unless age-

specific values of BP are substantially reduced in order to compensate for the unfavourable demographic changes. Achieving this reduction requires, in turn, knowledge of the mechanisms underlying temporal trends of BP and their biological, behavioural and socioeconomic drivers.

In the last decades a large body of research has addressed this subject in high-income countries. Cross-sectional studies have consistently found unequal distributions of BP across population strata defined by education, income and other socioeconomic variables — both at individual and contextual level — and identified biological and behavioural factors clearly associated with BP and risk of hypertension with likely causal relationships, chiefly body weight/shape, dietary habits and salt intake, alcohol and tobacco use, physical activity, and stress.[2, 9–11].

A series of studies have also directly addressed the longitudinal dimension of the problem, and, in particular, sought to explain the reasons of the consistent and rapid decrease in BP experienced in the United States of America (US) and Europe despite the increasingly unfavourable distribution of most of the bio-behavioural risk factors above, especially the rapidly increasing prevalence of overweight and obesity. The evidence is far from conclusive, but possible explanations have been found in the increased levels of awareness, the improved guidelines for BP management in hypertensive individuals and treatment protocols, the reduction of salt consumption, and the increased intake of drugs for reasons other than hypertension with antihypertensive side effects.[2, 12–17]

Direct evidence regarding risk factors responsible of the changing distribution of BP is, however, lacking in LMICs, and a growing literature shows that the application of findings from studies conducted in Europe and the US to these contexts is not warranted.[18, 19]

In general, reliable information on the temporal trends of BP themselves is scant in LMICs. Most of the literature relates to small-scale studies in special populations or to cross-sectional analyses, while direct epidemiological data on temporal trends — and, a fortiori, about their possible drivers — is sparse. A recent important meta-analysis by Danaei et al. [17] — who reviewed 143 studies referring to 199 countries and 5.4 million participants over a period of 25 years — has shed light on the evolution of the BP distribution in LMICs, and has produced more reliable estimates[4] of temporal trends of systolic BP than previous, smaller studies. However, (1) the review analysed trends only in the average systolic BP, which is not the only parameter of interest when it comes to the effect of BP on the risk of developing cardiovascular and other diseases, (2) considered only studies conducted before 2010, (3) did not analyse relationships of BP with risk factors.

Given the large potential gain in health that would result in LMICs if an optimal blood pressure distribution were to be achieved in larger sectors of the population, there is little doubt that temporal trends in the distribution of BP in these populations and their possible determinants

remain an open and important area for investigation.

However, recovering reliable estimates of temporal trends in the distribution of BP and/or prevalence of hypertension in a population — and, a fortiori, analysing their possible determinants — is an extremely error-prone operation. The large short-term biological variability of BP and its extreme sensitivity to the measurement conditions, together with the more general problems of sample representativeness affecting all large-scale population surveys, (see Chapter 2) makes the direct comparison between BP estimates recovered from different surveys often unwarranted.

The problem is particularly evident when the comparison involves estimates from *independent* surveys, which is often the case in LMICs and especially in sub-Saharan Africa.[20] In these cases, in fact, large differences in sampling design and realization, measurement devices and protocols, data collection and management are the rule rather than the exception, and this opens the door for the presence of artifactual differences between estimates that, if not taken properly into account, can severely hinder the possibility of inferring trends and their determinants.

When comparisons involve data collected with comparable sampling designs and measurement protocols (such as in repeated cross-sectional surveys of the same population, or truly longitudinal studies where the same individuals are repeatedly surveyed at different time points) the risk of incorporate in the trend estimates artifactual differences is usually reduced. However, even in these cases, the compatibility problems cannot be ruled out both because (2) the actual measurement conditions (e.g. room temperature, season and time of the day of data collection) might greatly affect the results beyond the similarity of protocols and devices, and because (2) the representativeness of the actual sample might still differ over time, despite similar sampling designs[5].

1.1 Rationale, aims and objectives

A series of surveys have collected demographic, anthropometric and bio-behavioural data at different time points spanning 1998 and 2015 on large samples representative of the general population of South Africa, a middle-income country undergoing rapid and complex demographic and epidemiological transition.[21]

The rationale for the study presented in this thesis was to take advantage of these data — relatively little analysed from this point of view, and, from my knowledge, never jointly — to improve the understanding of temporal trends of the distribution of BP and their possible drivers in the South African population and, by extension, to contribute to the understanding of the evolution of the burden of disease due to elevated BP in LMICs.

This *substantive* aim, with evident public health implications, was accompanied by a *methodological* counterpart, consisting of the exploration of the potential and limits of latent variable techniques — widely applied in other fields of scientific investigation, bur relatively underutilised in epidemiology — as a means of minimising the effect of measurement error and jointly analysing survey data from independent sources, overcoming problems arising from differences in methods of data collection and measurement.

Focusing only on the subset of data referring to individuals 15 years or older at the time of data collection ('*adults*'), specific objectives of the study were:

1. To assess the level of quality and comparability of the data on systolic and diastolic blood pressure and related quantities in the different datasets, using both (1) published information on sampling, data management and data collection procedures and (2) statistical analyses of the plausibility and quality of the recorded values;
2. To explore the possibility of applying a series of latent variables techniques within the general framework of structural equation modelling to improve the comparability of data from different sources and to minimize the effect of measurement and representation error on the estimation of cross-sectional relationships and temporal trends;
3. To estimate changes in the distribution of BP and derived quantities (such as prevalence of uncontrolled hypertension) in the South African adult population between 1998 and 2015, taking into account between-survey differences and measurement and representation error that could lead to artefactual conclusions;
4. To estimate the extent to which the estimated changes in the BP distribution during the study period could be explained by concurrent changes in the distribution of a series of biological, behavioural and socioeconomic risk factors.

1.2 Logical structure of the thesis

The logical structure of the study presented in this thesis is shown in Figure 1.4. It consists of three correlated steps — each of them informed by the results of the previous one — which link the logical inputs (i.e aims and objective, previous literature findings and multiple sets of survey data on BP and correlated quantities in the South African adult population) with the study results.

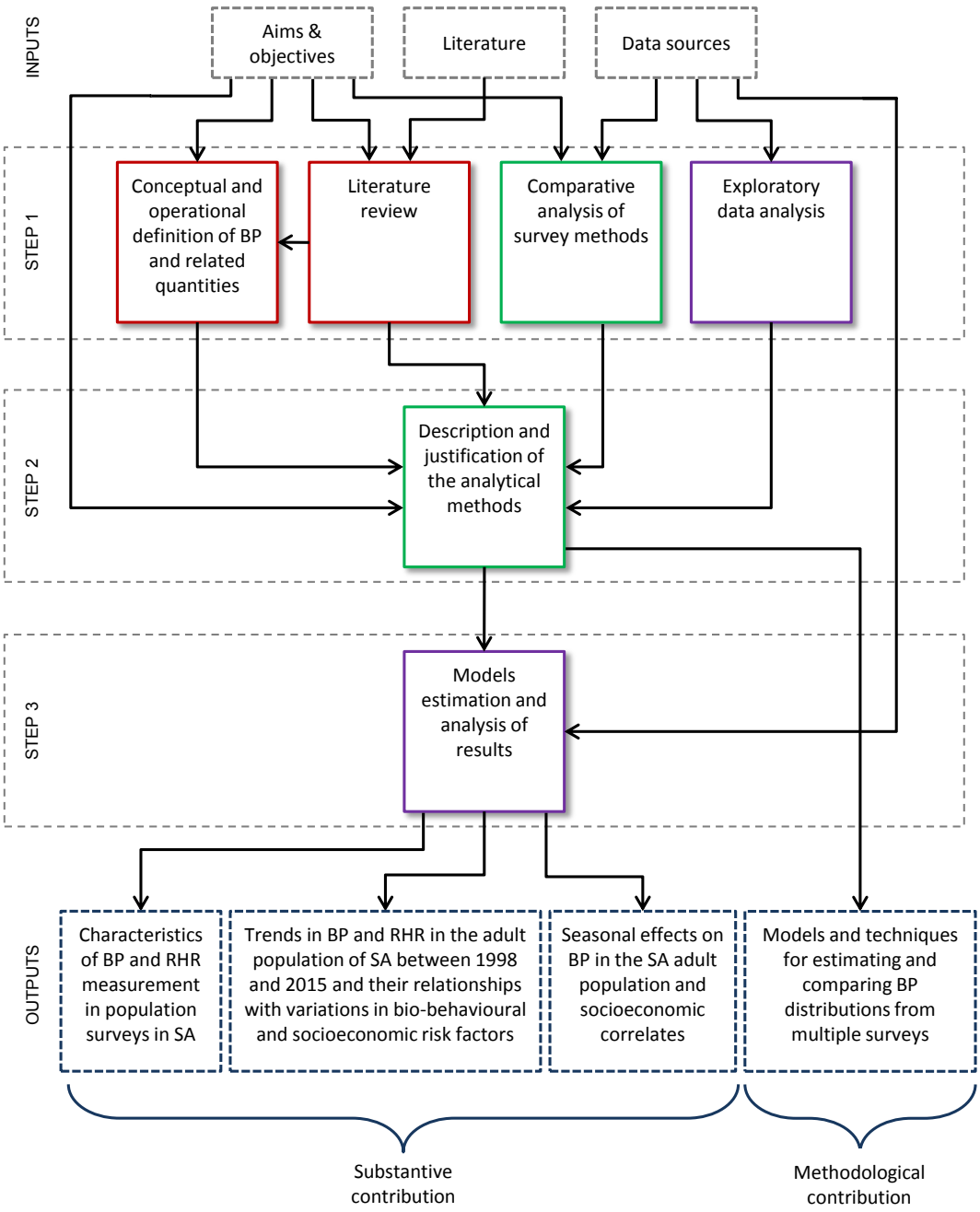
The first logical step includes a review of the literature (1) on conceptual and methodological aspects of the estimation of population values of BP and related quantities in large scale surveys, (2) on long term trends in BP and prevalence of hypertension in sub-Saharan Africa and in South Africa, and (3) on the relationships of BP with bio-behavioural and socioeconomic variables. The results on this review inform the conceptualization and the operational definition of BP and hypertension for the purpose of this study. In this same preliminary phase, the information accompanying the input datasets (i.e. the description of the sampling design and its realization, and details on BP measurement methods and devices) and the data are analysed to identify quality problems, possible sources of measurement and representation error and methodological differences that may introduce bias in the estimation of time trends.

The second step of the study consists in the description and justification of the analytical methods used for the joint analysis of the source data and it is informed — other than by the study objectives — by the results of a literature review on sources of error in survey estimation of BP and relationships with risk factors, and by the characteristics of the datasets. It includes (1) a general presentation of the latent variable approach and the reasons supporting its choice for the objectives of this study, (2) within that approach, a description of the specific models and statistical techniques used to represent and estimate 'true' values of BP and resting heart rate from survey data, to recover trends adjusted for inter-survey methodological differences and to explore possible drivers. The models and techniques in point 2 — which integrate statistical and substantive information — represent the methodological contribution of this thesis, and include applications of latent variable methods to address common problems in survey research on BP, namely:

- Low precision of the estimates due to extreme short-term variability of individual readings of BP;
- Large seasonal variability of BP that may reduce comparability of estimates carried out in surveys with different seasonal distribution of data collection;
- Bias in comparison of BP estimates between surveys when measurements are carried out with different numbers of repetitions;

- Estimation of treatment effects and counterfactual distributions of BP that would have been observed in the population in absence of antihypertensive medication.

Figure 1.4: Logical structure of the present study.



BP = Blood pressure; RHR = Resting heart rate; SA = South Africa;

Finally, step 3 includes the estimation of the parameters of the models defined in the previ-

ous step and the interpretation of the results to produce the substantive contribution of this thesis to the knowledge of distribution and temporal trends of BP in the South African adult population. The output of this phase consists of (1) a description of the characteristics of the measurements of BP and resting heart rate in a set of large population surveys carried out in South Africa between 1998 and 2015, (2) estimates of the population trends on BP and resting heart rate during the same period and of the extent to which these trends are explained by variations in a set of bio-behavioural and socioeconomic risk factors and, (3) estimates of the magnitude of the seasonal variations of BP and their socioeconomic correlates.

The results of the logical steps described above are presented in the next six chapters, distributed as follows:

Chapter 2: Background and literature review

Includes the review of the literature and the conceptual and operational definitions of BP and derived quantities.

Chapter 3: Methods

Includes the description of the sources of data, the procedures of data management and cleaning, the analytical methods and the models.

Chapter 4: Exploratory data analysis

Presents the results of the exploratory data analysis, including an evaluation of the quality of BP according to a series of indices.

Chapter 5: Measurement of blood pressure: analytical issues and inter-survey comparisons

Presents the results of the analysis that support the adequacy of the proposed measurement model to represent the available BP and heart rate data, and the model's invariance between surveys.

The estimated model coefficients are used to recover indices of validity and relative bias of individual and composites measures of BP and resting heart rate. The chapter presents simulation results showing the advantages — in efficiency and reduced bias — of the proposed approach in comparison to more common methods for the estimation of differences in mean BP between populations.

Chapter 6: Trends in blood pressure in the South African adult population

Presents the estimated trends in systolic and diastolic BP, resting heart rate, prevalence of uncontrolled hypertension and number of subjects affected in the South African adult population between 1998 and 2015. Explores the relationship between these trends and

temporal changes in the distribution of a series of biological, behavioural and socioeconomic risk factors, and discusses the extent to which the latter can explain the former.

Chapter 7: Season, blood pressure and socioeconomic status

Presents the results of a sub-study which takes advantage of the longitudinal nature of one of the data sources to estimate and compare seasonal effects on BP across socioeconomic strata of the South African population, and discusses the clinical, epidemiological and public health implications of the findings.

Chapter 8: Discussion

The previous chapters are followed by a concluding discussion chapter where, after a brief summary of the results, strengths and limitations of the study are discussed and the epidemiological and public health implications of the findings are interpreted in the light of the current literature.

Notes

[1]Current cut-offs are 140 $mmHg$ for systolic BP and 90 $mmHg$ for diastolic BP.[2]

[2]For the established direct relationship between BP and age.[3]

[3]The exact definition of the two indicators and the assumption underlying their estimation are detailed in [5]. For the purpose of our discussion, it is sufficient to highlight that both the SEV and the SDI are *relative* indicators bound to vary from 0 (no excess risk or the lowest observed development status) and 1 (maximum observed excess risk or development status).

[4]Within the scope of validity of the modelling assumption the authors used to overcome lack of data for some areas and incongruencies between data sources.

[5]That is, the actual samples represent different populations. In case of repeated cross-sectional surveys the incompatibility often originates from uncertainties in the calculation and calibration of sampling weights used to take into account missing data and individual non-response. In longitudinal studies a major source of error is usually the loss to follow-up, and the uncertainty associated with the methods used to adjust the estimates to take into account the possible biasing effect of this phenomenon.

Chapter 2

Background and literature review

The main aim of this study is estimating with adequate accuracy trends in blood pressure and prevalence of uncontrolled hypertension in the South African adult population and identifying their possible socioeconomic and behavioural drivers.

As detailed in Chapter 1, the proposed method is based on the joint analysis of data from a series of large scale national surveys. The analysis involves the preliminary assessment of quality and comparability of the data, the estimation of the changes of the distribution of BP over time with adjustment for measurement and representation error, and the study of the possible drivers of these changes.

This literature review aims at providing background information to support the methodological and analytical choices underlying each of the steps above. In my conception, this aim requires collecting and summarising three different types of information and this chapter is therefore organised in three separated, albeit interconnected, parts.

1. **Estimation of blood pressure distributions and hypertension prevalence in population surveys**

   This first part provides a general overview of the logical and practical process of estimating population values of blood pressure and related quantities in large scale surveys. The rationale of this review is to present and justify the general framework within which the study has been conducted; to establish an unambiguous set of definitions for the various concepts that recur in it; and to provide guidance for the identification of artefactual differences between estimates from different surveys.

   The presentation starts with an overview of the concepts of blood pressure and hypertension and then provides a set of operational definitions that will be used in the remainder of this thesis (Sections 2.1.1 and 2.1.2).

Section 2.1.3 formalises the concept of error in population surveys and its components according to the *total survey error* framework.

Finally, Section 2.1.4, which constitutes the majority of this first part, reviews and categorises the various sources of errors that can affect population estimates of blood pressure, i.e. in epidemiological studies involving 'field' measurements in large samples, outside controlled laboratory/clinical environments. It also provides an overview of the magnitude of the error that might be introduced by any of them.

2. **Trends in blood pressure and hypertension prevalence in South Africa**

   This second part reviews and attempts a summary of the findings of the relatively scant literature regarding long term trends in blood pressure and prevalence of hypertension in sub-Saharan Africa and, in more detail, in South Africa. Its rationale is to provide a basis to compare the results of this study with those of others, and to highlight shortcomings and inconsistencies in the available evidence.

3. **Blood pressure, socioeconomic variables and biobehavioural risk factors**

   This last part reviews the literature on the association of BP with a series of biological, behavioural and socioeconomic risk factors.

   Its rationale is to provide evidence to guide the model building phase of this study; namely, to identify variables that — because of their association with BP and their variable distribution in the population over time — are potentially able to explain its variations and can be meaningfully included into the models as explanatory variables when analysing potential drivers of the observed BP trends.

   The section focuses particularly, but not exclusively, on the relationships observed in LMICs and in South Africa.

2.1 Estimation of blood pressure distributions and hypertension prevalence in population surveys

2.1.1 Blood pressure

Blood pressure is *conceptually* defined as

> *the pressure exerted by the blood against the walls of the arteries, maintained by the contraction of the left ventricle, the resistance of the arterioles and capillaries, the elasticity of the arterial walls, and by the viscosity and volume of the blood.*
>
> *The American Heritage Medical Dictionary* [22]

Blood pressure is usually measured in millimetres of mercury ($mmHg$). One $mmHg$ represents the extra pressure exerted at the base of a column of mercury 1 millimetre high, when the temperature is $0°C$ and the acceleration due to gravity is 9.80665 m/s^2 (*standard gravity*).[23] In international units

$$1\ mmHg \approx 133.32\ Pa$$

The apparently simple conceptual definition does not translate into an equally simple *operational* definition, that is, into an unambiguous procedure to identify a numerical value (or a set of numerical values) to characterise the blood pressure of an individual in a clinically and epidemiologically meaningful way.

Blood pressure, in fact, fluctuates continuously according to the cardiac cycle, differs in different parts of the arterial system, and shows large physiological variability in response to a multiplicity of stimuli. This extreme spatial and temporal variability results in a number of operational definitions of blood pressure, varying according to *where* (within the arterial system), *when* (in reference to the cardiac cycle), and in *which conditions* (posture and psychophysiological status of the subject, for example) the pressure is measured.

These definitions are anything but equivalent and some of them result in values with show negligible association with other health outcomes both at the individual and population level, and are, therefore, of little interest to the clinician and the epidemiologist.

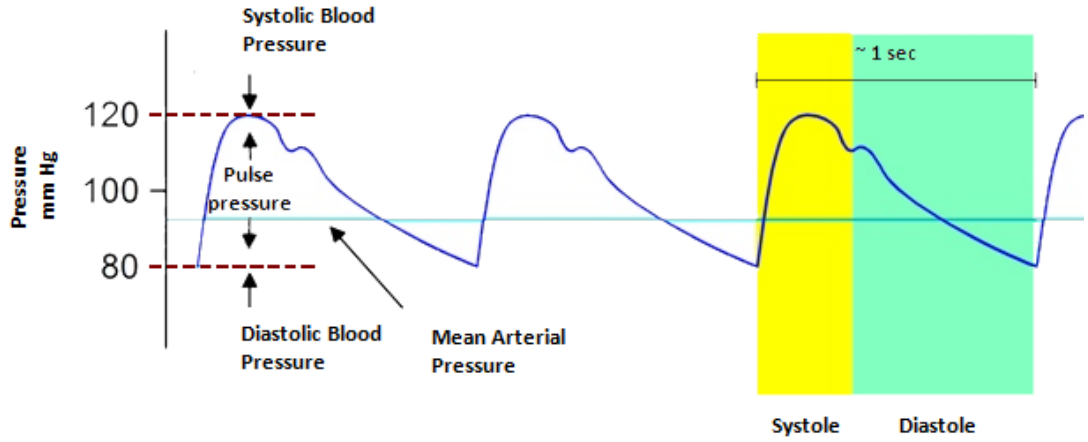
2.1.1.1 *Blood pressure and cardiac cycle*

The cardiac cycle refers to a complete heartbeat from its generation to the beginning of the next beat, and includes two main stages: *systole*, which is the period when the ventricles are contracting, forcing blood into the pulmonary artery and into the aorta, and the *diastole*, i.e.

the period of time between ventricular contractions when the heart muscle is relaxed and the ventricles are filling. The frequency of the cardiac cycle (indicated as *heart rate* and usually expressed as beats per minute, bpm) varies depending on the subject's physical and emotional state.[24] The heart rate in condition of relaxation — the *resting heart rate (RHR)* — in healthy adults varies generally between 60 bpm and 80 bpm, but can be as low as 40 bpm for highly conditioned athletes.[25]

Throughout the cardiac cycle, blood pressure at the exit of the ventricles varies according to the different phases, as shown in the simplified diagram of Figure 2.1.

Figure 2.1: Typical variations of blood pressure in the aorta during a cardiac cycle.



Adapted from The Physiology Web [26]

The maximum value reached by blood pressure near the end of the cardiac cycle is called *systolic blood pressure (SBP)*, and its minimum value, reached near the beginning of the cardiac cycle when the ventricles fill with blood is indicated as *diastolic blood pressure (DBP)*. Their difference is called *pulse pressure (PP)*.

The average value of the pressure during a cardiac cycle is indicated as *mean arterial pressure (MAP)*. Because the configuration of the arterial pressure waveform curve is complex and asymmetrical, the MAP does not correspond to the arithmetic mean of systolic and diastolic blood pressure. For clinical and epidemiological purposes it is often calculated by means of empirical formulæ. The most widespread is the one originating from the work of Gauer [27], which states that the MAP is well approximated by the sum of DBP and one-third of the PP:

$$MAP \approx DBP + \frac{1}{3}PP$$

However, more recent formulæ are available, which seem to produce better approximations of the true MAP, especially in subjects with accelerated heart rate and/or elevated PP.[28, 29]

2.1.1.2 *Blood pressure in the arterial system*

The values of the blood pressure during the cardiac cycle differ substantially in the different parts of the arterial system, and we can distinguish a *central blood pressure* (measured at the exit of the left ventricle, in the aorta), and a *peripheral blood pressure* (measured in one of the large elastic arteries).

The direct measurement of the central blood pressure is an invasive procedure requiring aortic catheterization, and it is rarely performed in clinical practice and, a fortiori, never in epidemiological studies. Therefore, the term 'blood pressure' without further specifications is generally referred to the peripheral blood pressure, and the same convention is followed in this thesis.

The standard point of measurement for the peripheral blood pressure is at the level of the brachial artery as shown in Figure 2.2, which is chosen for its ease of access compared to other large arteries.

The typical variability of blood pressure in different parts of the vascular system is represented in Figure 2.3 for an average healthy individual. The mean arterial pressure decreases monotonically with the distance from the heart, as a consequence of the loss of energy due to the vascular resistance, while both SBP and DBP — largely affected by the elasticity of the different parts of the vascular system — reach their extremes (maximum for the former and minimum for the latter) in the large elastic arteries departing from the aorta.[31]

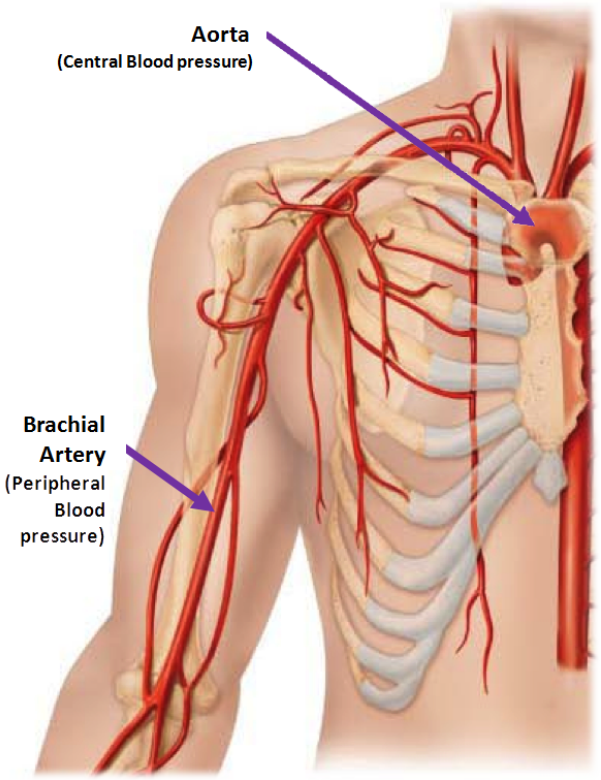
The difference in the mean arterial pressure between the aorta and the elastic arteries is in most cases limited to 1 or 2 $mmHg$ while both systolic and diastolic blood pressure vary to a greater extent. The degree to which peripheral and central SBP/DBP differ depends largely on the stiffness of the arteries, and tends to increase with age.[33, 34]

2.1.1.3 *Short-term physiological variability*

Even neglecting the variability due to the cardiac cycle (using summary measures such as the pair SBP/DBP) and fixing where in the vascular system these values must refer (e.g. at the level of the brachial artery, as per common practice), short-term measures of blood pressure are still subject to large variability.

SBP and DBP vary largely and rapidly according to a multiplicity of external factors, including recent intake of food or other substances (such as caffeine and nicotine), filling level of the urinary bladder, body and arm position, time of the day, emotional state, recent physical

Figure 2.2: Standard measurement point for blood pressure in clinical practice.

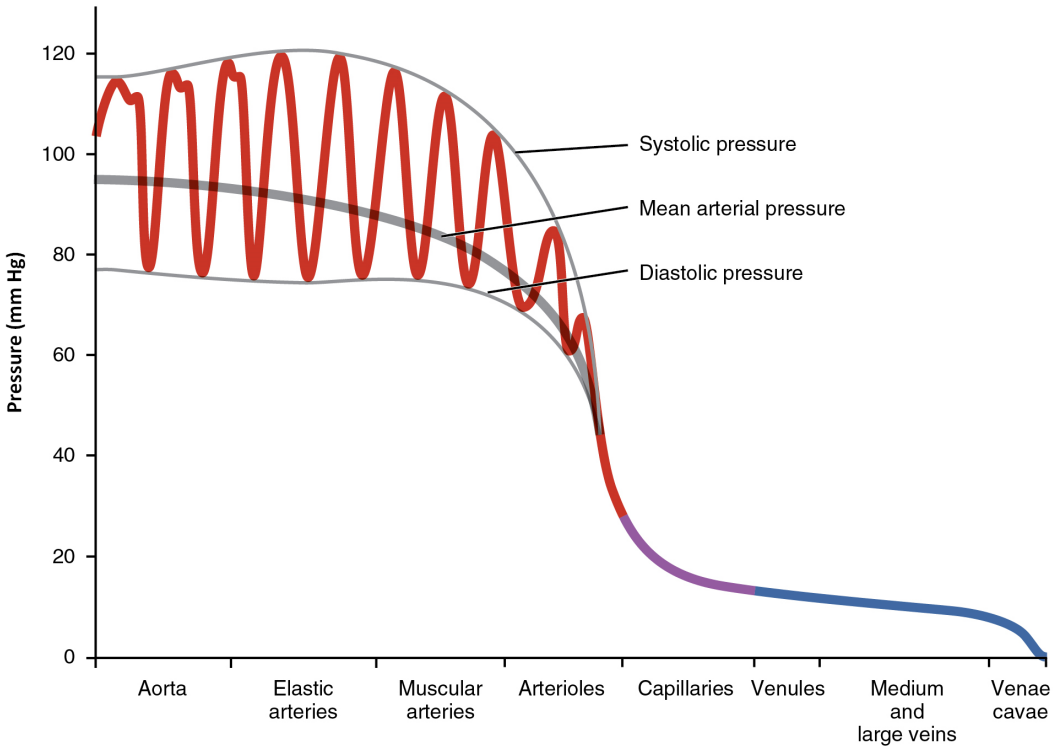


Adapted from Taylor J [30]

activity, and environmental conditions such as room temperature and level of noise.[35–45]

As an example, Table 2.1 shows the results of a study by Clark et al. [46] on 461 untreated hypertensive patients. In the study, the patients' systolic and diastolic blood pressure was recorded, using a portable automatic device every 15 minutes during the day and every 30 minutes during the night for 24 hours. The patients recorded in a diary what they were doing at the moment of each measurement, selecting from a list of 15 activities. The results in the table clearly indicate that both SBP and DBP are heavily dependent on the patient's activity at the moment of measurement. Average changes in blood pressure relative to the blood pressure in status of relaxation were as high as $+20/-10\,mmHg$ for SBP and $+15/-8\,mmHg$ for DBP. These variations accounted for approximately 40% of the observed inter-individual variability.

Figure 2.3: Typical variations of blood pressure in a healthy individual during the cardiac cycle in different parts of the vascular system.



Adapted from OpenStax CNX [32]

2.1.1.4 *The 'components' of the blood pressure*

The large physiological variability of blood pressure translates into the widely accepted conceptualization of the blood pressure of an individual at a given point in time (*casual blood pressure*) as the summation of two components:

- an 'underlying', slow-varying component which represents the 'true' blood pressure of clinical and epidemiological interest;
- a 'nuisance' component, rapidly varying in response to 'accidental' factors (such as changes in body position, food intake and emotional stimuli), with little, if any, prognostic value for cardiovascular events.

This decomposition was first described in 1922 by Addis [47], who, observing the fallacy of diagnoses based on single blood pressure measurements, introduced the concept of *basal blood pressure*, representing the patient's blood pressure when short-term physiological variations in

Table 2.1: Average changes in blood pressure associated with commonly occurring activities, relative to blood pressure while relaxing.

Activity	Systolic Blood Pressure $[mmHg]$	Diastolic Blood pressure $[mmHg]$
Meetings	+20.2	+15.0
Work	+16.0	+13.0
Transportation	+14.0	+9.2
Walking	+12.0	+5.5
Dressing	+11.5	+9.5
Chores	+10.7	+6.7
Telephone	+9.5	+7.2
Eating	+8.8	+9.6
Talking	+6.7	+6.7
Desk work	+5.9	+5.3
Reading	+1.9	+2.2
Business at home	+1.6	+3.2
Television	+0.5	+1.1
Relaxing	*0.0*	*0.0*
Sleeping	-10.0	-7.6

Adapted from Clark et al. [46]

response external factors have been eliminated. Addis operationalised the basal blood pressure as the pressure measured in the "*early morning before the subject had risen from bed*"[47, p. 539].

The idea was further elaborated by Adamson [48], Starr et al. [49], Macgregor and Loh [50], and formalised in a series of articles by Smirk and colleagues [51–54], who maintained that casual blood pressure measurements were

> *...made up of two parts, namely, the relatively stable basal blood pressure and a variable supplemental pressure. The supplemental pressure is the part of the casual blood pressure that is elevated as the result of the patient's physical, mental, and emotional activity, chiefly the latter.*
>
> "Casual and basal blood pressures IV. Their relationship to the supplemental pressure with a note on statistical implications" [54, p. 176]

In the following years (mostly in the 1940s and 1950s), a series of studies, reviewed by Pickering [55] provided "*quite impressive evidence that the basal pressure is both more stable and a*

better predictor of risk than the casual pressure"[55, p. 422]. Notwithstanding these interesting results, the concept of basal blood pressure lost gradually appeal, plausibly because of the "*sheer impracticability of measuring the basal pressure*"[55, p. 422] with the means available at that time, limited to the manual measurement using a mercury sphygmomanometer, with the unavoidable presence of an observer.

For example, based of the recommendations by the 1938 Joint report of the Cardiac Society of Great Britain and Ireland and the American Heart Association[56], measurements of basal blood pressure required hospitalization and a

> *... preparation similar to that used for basal metabolism. It [basal blood pressure] should be determined 10 to 12 hours after the last meal of the previous night and after resting for half an hour in a warmed room.*
>
> "Standardization of methods of measuring the arterial blood pressure: A joint report of the committees appointed by the Cardiac Society of Great Britain and Ireland and the American Heart Association" [56, p. 267]

Shortly after these recommendations, Alam and Smirk suggested that accurate measurements of basal blood pressure could be performed avoiding hospitalization and long fasting periods, provided an appropriate procedure of 'emotional desensibilisation' (to the presence of the observer and to the process of sphygmomanometry) was adopted.[57] However, the procedure remained laborious and time-consuming, as illustrated by the following quote from the methods section of their 1943 article:

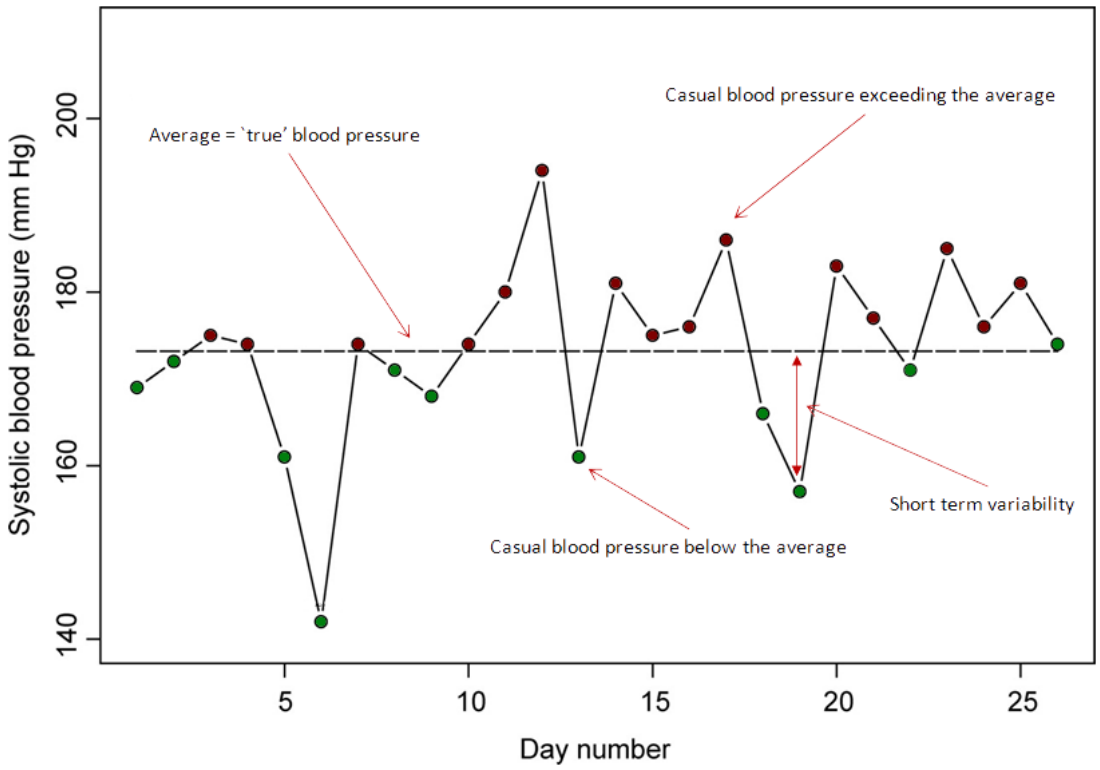
> *The blood pressure was measured on the left arm with the subject sitting in a quiet, warm room. All subjects were instructed to find a comfortable posture, and then to remain still and with the mind blank throughout the half-hour or longer period during which the measurements were made. No conversation was allowed. The observer avoided unnecessary movement, and as a rule no third person entered the room during this time. To allay apprehension the subjects were informed that the investigation would be confined to the repeated measurement of blood pressure. Most subjects became somnolent but in general did not sleep.*
> *The blood pressure was measured as frequently as possible during the first three minutes after adopting the sitting posture. Blood pressure readings were then taken every few minutes throughout the half-hour period of rest, in order to habituate the subject to the procedure of blood pressure measurement. Without habituation of the subject by the continuous presence of the observer and by repeated measurements, the blood pressure falls are less than those we report. Towards the end of the half-hour period the measurements of the blood pressure were made at intervals of about one minute.*

"Casual and basal blood pressures I. In British and Egyptian men" [51, p. 152]

Because of this time-consuming procedure, the measurement of the basal blood pressure became never common neither in clinical nor in epidemiological practice[1].

The role of 'true' blood pressure of interest has been progressively assumed by its average level over prolonged periods of time, while Smirk's 'supplemental pressure' has become a nuisance component simply defined as the deviation of the casual blood pressure from its mean (Figure 2.4)[2].[34, 58]

Figure 2.4: Repeated casual systolic blood pressure readings in a hypertensive patient.



Adapted from Tennant et al. [59]

This decomposition of blood pressure is the most widely accepted today, and an impressive literature has shown that long-term averages of blood pressure (over periods on days or months) are directly and strongly associated with cardiovascular risk, while the nuisance components are not.[2, 60–63]

Current clinical guidelines for diagnosis and treatment of hypertension[3] also assume the above conceptualisation, and prescribe that clinical decisions should be based on repeated measure-

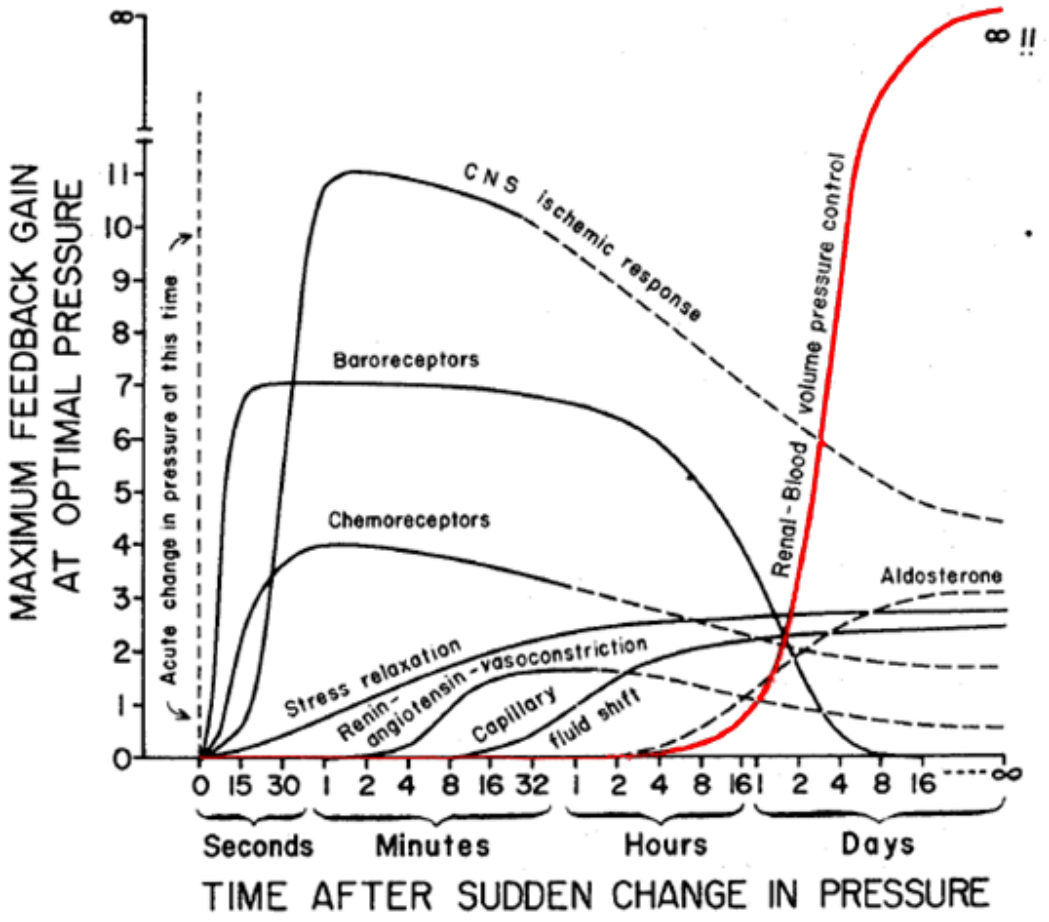
ments performed on separate occasions within a period spreading across months, rather than on casual measurements.

This is not to say that the short- and medium-term[4] variability of blood pressure in response to external stimuli is totally lacking clinical interest but rather to acknowledge that the evidence supporting the prognostic value of long-term averages is overwhelming, compared to the evidence (though growing) for the relevance of measures of variability[5].

Beyond its epidemiological and clinical relevance, the existence of a relatively stable underlying pressure conceptually distinct from the highly variable 'nuisance' pressure is also coherent with the classical circulatory model developed in the 1970s by Guyton [64][6], which attributes the short- and long-term control of blood pressure to two substantially different physiological mechanisms. Short-term control is mainly based on nervous activation followed by a plurality of other slower adaptation mechanisms, while long-term control is substantially due to the control of the volume of the blood fluids exerted by the kidneys. The response time of these different regulatory mechanisms, illustrated in Figure 2.5, are in line with the different rates of change of the 'true' and 'nuisance' blood pressure, the former measured in seconds/minutes and the latter (in red in the figure) in days or months.

According to the considerations above, if not otherwise specified in this thesis we assume that the 'true' value of blood pressure of epidemiological interest — simply BP, characterised by the pair SBP/DBP — is the long term average (weeks to months) of the peripheral blood pressure measured at the level of the brachial artery.

Figure 2.5: Guyton's model of the short-term and long-term regulation of blood pressure.



Adapted from Guyton [65]

2.1.2 Hypertension

Hypertension (HTN), also known as *high blood pressure* or *arterial hypertension*, is a chronic condition characterised by "*abnormally high arterial blood pressure*"[66].

The medical literature sometimes distinguishes between *essential hypertension* (or *primary hypertension*) and *secondary hypertension*. The most common type of hypertension is the former, characterized by the absence of identifiable cause and, usually, by gradual development over years. Secondary hypertension is, as the name suggests, a 'by-product' of an identifiable underlying pathological condition. Many pathological conditions can lead to secondary hypertension, including, for example kidney and thyroid abnormalities, congenital birth defect in blood vessels and some types of tumors.[67]

The concept of 'abnormally high' is generally operationalised by means of a set of thresholds for both systolic and diastolic blood pressure: individuals below the thresholds for both measurements are considered having a 'normal' blood pressure and do not need treatment (*normotensive* individuals), while individuals above the thresholds are considered for treatment. Individuals with SBP above the the threshold but normal DBP are said to have *isolated systolic hypertension*, while the complementary condition is called *isolated diastolic hypertension*.

As pointed out by Pickering [55], the whole idea of using thresholds to characterise hypertensive status and need of treatment has neither clinical nor epidemiological strong foundations:

> *The acceptance of such thresholds implicitly assumes two axioms, both of which in reality rest on very shaky ground.*
> *The first is that the threshold level identifies the point at which risk increases markedly, even though it is well recognized that the relationship between BP and risk is a continuously graded one.*
> *The second is that we can characterize an individual patient's BP level with sufficient precision to be able to distinguish whether it is just above or below the threshold level — again, a highly questionable assumption.*
>
> "What Is the True Blood Pressure? Smirk Revisited" [55, p. 421]

Pickering's opinion is widely shared, and the contemporary clinical guidelines are progressively moving away from the use of blood pressure thresholds to determine the need of treatment, towards a more comprehensive evaluation of the total cardiovascular risk, of which the value of the blood pressure (considered more and more as a continuous rather than a categorical variable) is only an element.[68, p. 3-4]

However, in an epidemiological and public health perspective — which is the perspective of this thesis — the classification of individuals into different categories according to blood pressure thresholds may make more sense. This is not because considering population rather than individual values makes the graded relationship between blood pressure and cardiovascular risk less continuous, but because:

1. in the last decades and until now, eligibility for treatment has been based almost exclusively on BP thresholds. Therefore the proportion of subjects in the different BP categories is a meaningful indicator in many analyses, for example those regarding health system burden and performance;

2. the prevalence of hypertension calculated according to thresholds is widely reported in epidemiological studies, much more frequently than the parameters which charac-

terise the underlying distribution of BP (such as means, ranges or variances). As a consequence, epidemiological analyses of trends and determinants can hardly ignore this indicator, without losing the ability to compare the results with those of other studies.

For these reasons, this thesis considers the estimation of the prevalence of hypertensive subjects in a population based on thresholds as one of its objectives, albeit secondary to the estimation of the actual distribution of SBP and DBP.

If not otherwise specified, the classification will be based on the widely adopted criteria set by the "Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure"[2] which classifies individuals according to the cut-offs shown in Table 2.2

Table 2.2: Classification of blood pressure for adults.

Classification	Systolic Blood Pressure $[mmHg]$		Diastolic Blood Pressure $[mmHg]$
Normal	<120	**and**	<80
Prehypertension	120-139	**or**	80-89
Stage I Hypertension	140-159	**or**	90-99
Stage II Hypertension	$\geq$160	**or**	$\geq$100

From Chobanian et al. [2, p. 1211]

In common, albeit not exclusive, epidemiological practice this definition is referred more properly as *uncontrolled hypertension*, while the term *hypertension* refers to a broader definition that includes pharmacological treatment status. That is, individuals are classified as hypertensive if their BP is above the thresholds indicated in Table 2.2 *and/or* if they are taking antihypertensive drugs.

The classification in Table 2.2 is based on "*the average of 2 or more properly measured, seated BP readings on each of 2 or more office visits*"[2, p. 1211]. The specification that the thresholds refer to *office* visits, i.e to measurements taken in clinical environments, is needed. In fact, for the reasons cited in Section 2.1.1 and reviewed in detail in the next Section 2.1.4.1, values of blood pressure determined with other methodologies are systematically different from those calculated as the average of repeated readings across multiple office visits (*office* or *clinic* blood pressure).

Measurements carried out outside a clinical environment (out-of-office BP measurements) at

present take two forms: *home blood pressure monitoring* and *ambulatory blood pressure monitoring (ABPM)*. Both modalities have been available for more than four decades, but only in recent years have started being commonly applied in clinical practice.[69]

ABPM monitors are portable devices able to take automatic BP readings at preset intervals (typically every 15–30 minutes) throughout the day and night and to reconstruct a 24-hours profile of the subject BP. Home BP monitoring consists of the self-measurement of BP by means of simple devices that can be easily managed by the subjects without external observers. Modern devices are completely automated and often capable of memorising multiple readings for successive analysis.

Home and ambulatory monitoring are increasingly used in clinical practice because of the substantial and growing evidence that both measures are better predictors of cardiovascular risk than measurements taken in clinical settings. Moreover, due to the inherent variability of BP, estimates of the underlying BP level made in the office by averaging a necessarily limited number of readings show generally poor reliability. On the contrary, both home monitoring and 24-hour ABPM calculate averages based on large number of measurements, thus producing more reproducible estimates.[69] The value of out-of-office measurements for epidemiological investigations has also been long acknowledged.[70]

There is general consensus that office, home and ambulatory BP differ systematically. Numerous studies have shown that, on average, ambulatory BP is lower than office BP, and this translates into lower thresholds for the classification of individuals in the different hypertension categories. A consensus papers from the American Society of Hypertension suggests that the upper limits of 'normal' ambulatory BP in low risk populations is 130/80 $mmHg$ for 24-hour average BP, 135/85 $mmHg$ for awake BP and 120/75 $mmHg$ for sleep BP.[69] The almost always lower values of the mean ambulatory BP compared to the office BP is due to effects of sleep (because BP is usually lower during sleep and contributes to lowering the value of the average 24-hour ambulatory BP) and the elimination of the common phenomenon of *white coat effect* (i.e. the emotion-related elevation of BP in presence of external observers)[7].[71]

Home BP (as the average of multiple measurements taken at different time of the day) is also nearly always lower than the office BP due to the absence of the white coat effect. Compared with 24-hour ambulatory BP, home BP is generally higher, because the former includes measurements during sleep. Conversely, home BP is usually lower than daytime ambulatory BP because the former only includes measurements in condition of relaxation, compared with the more varied range of activities included in the latter. The literature is less consistent regarding the magnitude of these differences and on their relevance regarding the classification of individuals in hypertension categories.[71] Proposed upper thresholds for normal home BP vary between 125/75 $mmHg$ to 130/80 $mmHg$.[72, 73] The recommendations of the American Society of Hypertension suggests that home BP values $\leq$ 125/75 $mmHg$ should be considered

adequate without further investigation; patients with home BP between 125/75 $mmHg$ and 135/85 $mmHg$ should be sent for ABPM, and subjects with home BP $\geq$ 135/85 $mmHg$ should be classified as hypertensive and considered for treatment without need of ABPM.[69]

2.1.3 Population estimates of blood pressures

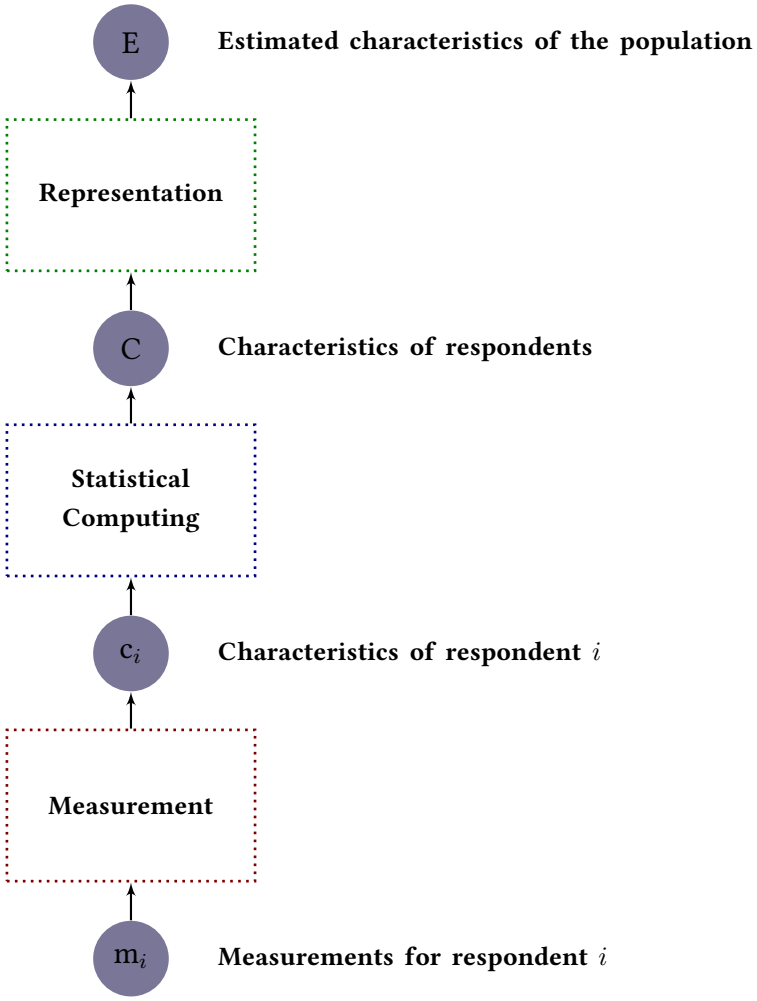
Blood pressure is commonly measured in epidemiological studies of cardiovascular disease (CVD), and the recorded values used for the estimation of population means and marginal distributions, prevalence of the various stages of hypertension, and relationships with other variables of interest.

Survey estimates, even from studies carried out with great attention to quality, are affected by error, and, in the case of surveys involving measurements of blood pressure, the potential magnitude of this error has been of concern for many years.[74–76]

A general representation of the process of survey estimation of blood pressure related quantities[8] according to the total survey error (TSE) framework described by Groves and colleagues is shown in figure 2.6.[77–79]

In the figure, the overall process is represented as the result of two different and conceptually distinct inferential processes[9]. The first process (*measurement*) links the 'imperfect' data on blood pressure recorded for a single participant to a survey to his or her 'true' blood pressure which is not directly observable, while the second inferential process (*representation*) links the true individual values of blood pressure with the population parameters of interest. The two inferential processes are connected by a deterministic procedure (*statistical computing* in the figure), which consists in the calculation of an appropriate summary measure of the values recorded for each individual in the sample (*statistic*).

Figure 2.6: Logical steps in the inferential process of survey estimation.



Adapted from Groves et al. [78]

2.1.3.1 *Measurement*

Figure 2.7 details the logical steps in the measurement process which consists in the estimation of the *unobserved* true blood pressure from a set of one or more *recorded readings*, each of them is an imperfect measure of the patient's casual blood pressure.

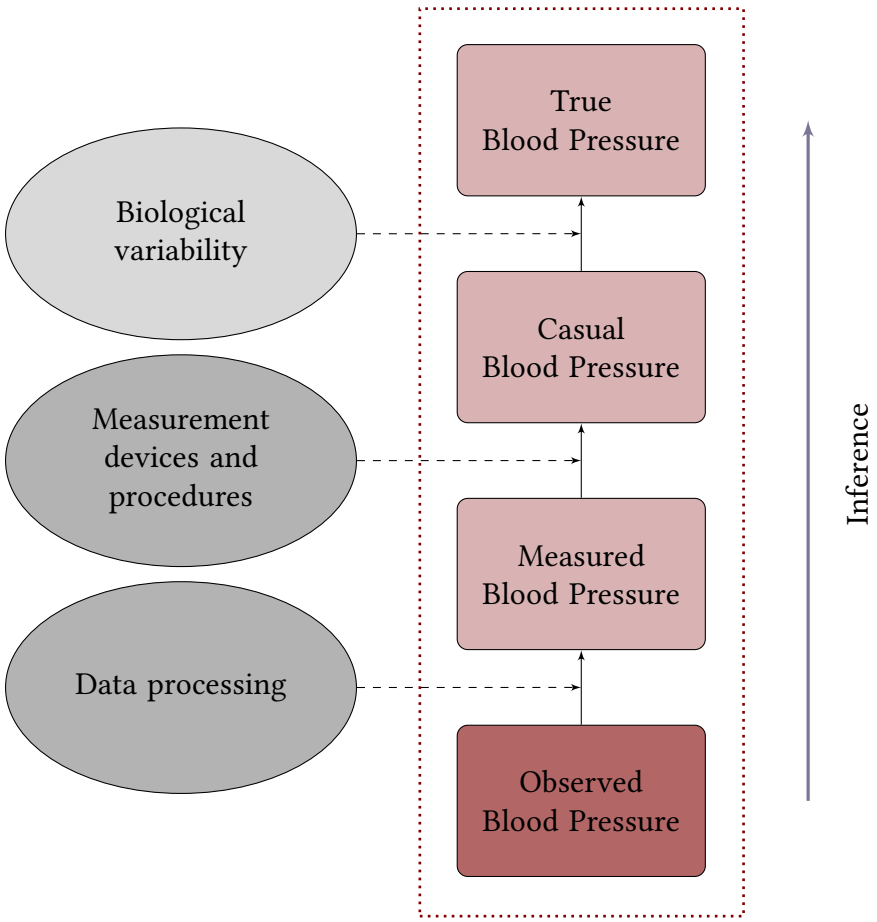
In this conceptualization, we distinguish four different type of blood pressure values:

- BP and *Casual* BP, which are respectively the 'true' individual blood pressure and its value at a specific point in time, as defined in section 2.1.1.
- *Measured* BP, which is the value of BP observed as a result of a measurement procedure.

It is often indicated as a BP *reading*.

- *Recorded* BP, which is the value of BP that is actually recorded.

Figure 2.7: Measurement process and sources of error.



In general, recorded BP differs from observed BP which in turn differs from casual BP and true BP. These discrepancies, collectively indicated as *measurement error* are due to different phenomena.

- The difference between true pressure and casual BP is due to *biological variability*, i.e. to the existence of the 'nuisance component' discussed in section 2.1.1.
- The difference between casual BP and measured BP is due to a multiplicity of reasons which relate to the incorrect conceptualisation and/or application of the *measurement procedures*, and to the use of inaccurate or unreliable *measurement instruments*;

- The difference between measured and recorded BP is due to the *editing procedures* applied to the actual readings from the measurement instruments. These procedures can be *formal* (such as data cleaning procedures applied to the 'raw' datasets resulting from the fieldwork to exclude or impute implausible values) or *informal* (such as the rounding of the readings from measurement instruments to the nearest even number, because of the well know preference of human observers for numbers that end with some digits rather than others). Both translate into differences between the values recorded and used for subsequent analyses and those actually measured.

Biological variability, errors due to measurement procedures/instruments and processing errors, all belong to the category of *measurement errors*, in the sense that they make the recorded blood pressure different from the true blood pressure which we are interested in quantifying. It is, however, important to highlight that, while differences between recorded, observed and casual blood pressure are due to methodological errors (potentially removable with more accurate procedures and instruments and better training of observers), the difference between casual and true blood pressure represents a real biological difference that we can estimate and sometimes adjust for, but never eliminate.

2.1.3.2 *Representation*

Moving from measurement of individual BP to epidemiological investigation, when the goal is the estimation of BP means or other parameters at population level, other types of errors must be taken into account.

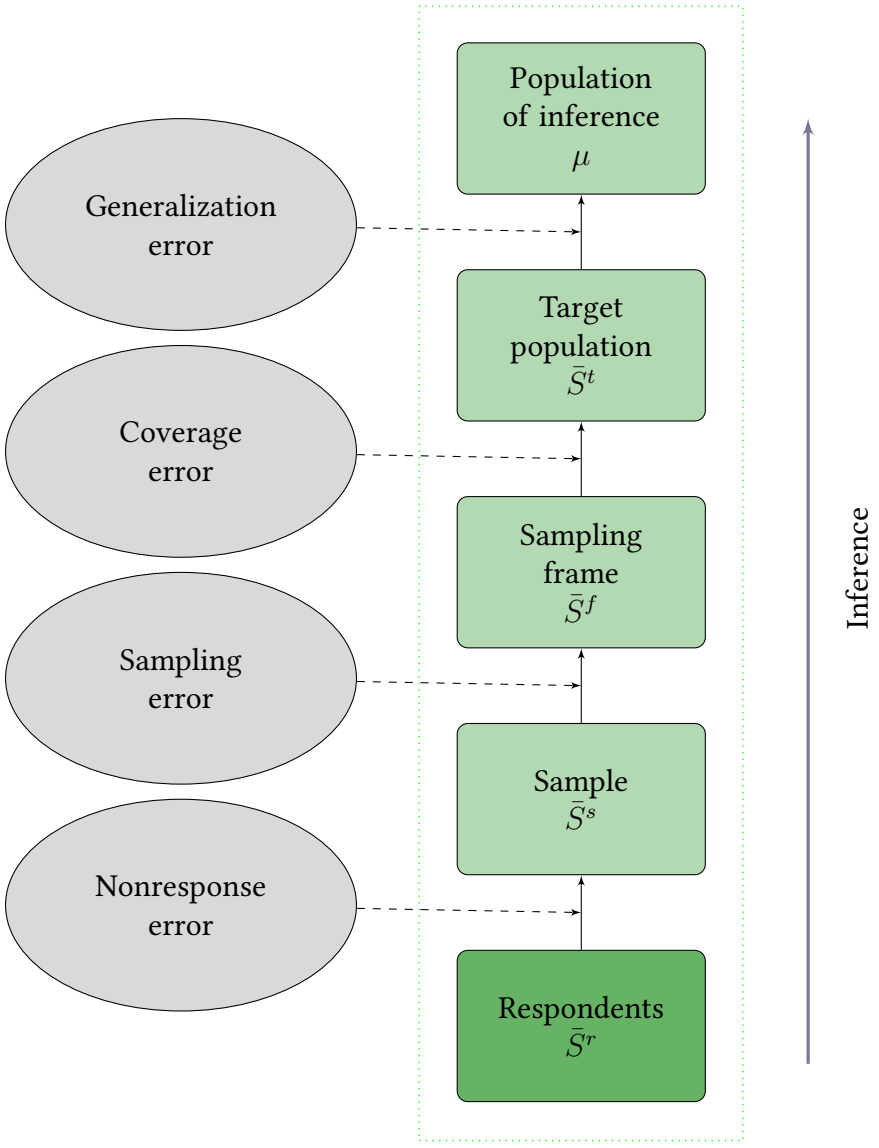
These errors (collectively indicated as *representation error*[77, 78]) are common to all situations where population values of some variables of interest are estimated examining a sample of members of the population, rather than the whole population.

Figure 2.8 shows the logical steps in the representation process that link the value of some statistics summarising the characteristics of a subset of subjects from a larger population (*respondents* or *participants*), to the value of the unobserved population parameter of interest.

In the practical realization of a population survey, the actual respondents are selected from a population of interest (the *population of inference*, to which the researchers aim to generalise their results) though a set of intermediate steps.

The first step entails the definition of the *target population*, i.e. the population that is actually studied. The target and the inferential populations are in general different, and the differences are usually due to logistic/practical reasons. For example, in the South Africa's National Income Dynamics Study (NIDS),[80] the population of inference is the South African population, while the target population formally excludes part of it, and is precisely defined as

Figure 2.8: Representation process and sources of error.



> "*...private households and residents in workers' hostels, convents and monasteries. The frame excludes other collective living quarters such as students' hostels, old age homes, hospitals, prisons and military barracks*" [80, p. 10]

The next step in the process is the identification of the *sampling frame*, that is the totality of members of the target population that have a probability >0 of being selected into the survey sample. In simple cases, the sampling frame consists in a list that includes all subjects in the target population, but in large scale surveys this is generally impossible and other methods are

used. For example, in the NIDS, the sampling frame was defined in geographical terms, as a list of small areas subdividing the whole South African territory, and households and individuals were then selected within each area.[80]

From the sampling frame, a *sample* is then selected, which is the subset of individuals from which the measurements of interest (BP in our example) are sought.

Finally, in almost all surveys, the attempt to measure the variables of interest in all the individuals in the sample does not achieve full success. Those for whom the measurements are successfully taken are called *respondents* and are a subset of the whole sample.

The *representation error* — i.e. the total error associated with the estimation of the average BP in the population from a set of BP values measured in the respondents — consists of different elements, conceptualised as the difference of BP estimates within each of the populations and sub-populations defined above. Specifically:

- The difference between the average BP measured among respondents ($\bar{S}^r$) and the average BP among the totality of the sample ($\bar{S}^s$) is indicated as *nonresponse error*. Nonresponse error originates from systematic differences (in the variables of interest) between sampled individuals and respondents.

- The difference between $\bar{S}^s$ and the average BP for all the individuals in the sampling frame ($\bar{S}^f$) is indicated as *sampling error*.

  All statistical estimation procedures are based on the assumption that the sample is randomly selected from the sampling frame, i.e. that all individuals of the sampling frame have a probability >0 and *known* of being selected. Sampling error is the consequence of the ubiquitous violation of this assumption.

- The difference between $\bar{S}^f$ and the average BP for all the individuals in the target population ($\bar{S}^t$) is indicated as *coverage error*.

  The coverage error is the consequence of incomplete or otherwise incorrect sampling frames. For example, if the sampling frame excludes some subjects belonging the target population, these subjects will have a probability 0 of being selected in the sample, which will be no longer representative of the *whole* population.

- The difference between $\bar{S}^t$ and μ is the *generalization error*, i.e. an error that originates from the fact that the target population does not correspond to the population of inference, so that the values calculated in the former cannot be applied to the latter.

2.1.3.3 *Data analysis*

A final source of error in survey estimates (*inferential error*) originates from the estimation procedure itself, i.e. from incorrect assumptions regarding the statistical properties of the variables and/or other modelling assumptions.

For example, error can arise from incorrectly assuming a normal distribution for blood pressure values in the population, while the 'true' distribution is skewed (which is often the case in real populations), or from adopting unsubstantiated assumptions about the relationships between the variables of interest.

2.1.4 Sources of error in population estimates of blood pressure

2.1.4.1 *Biological variability*

2.1.4.1.1 Food intake

Ingestion of food is associated with acute fall in systolic and diastolic blood pressure and increase of heart rate and cardiac output[10].[81–86]

Postprandial reductions in BP are much more common in older than younger people, with a prevalence as high as 36% among those residing in care homes and as 67% in the older hospitalised population.[87]

The magnitude of reduction is modest and of short duration (less than 30 minutes) in younger subjects, but larger on long lasting in older ages.[81, 88–90] A study in a sample of 20 hypertensive patients aged 31 to 66 years found an inverse correlation between drop in blood pressure and age, with a statistically significant correlation coefficient $r = -0.37$.[82] The increase in heart rate, conversely, has been documented both among young and healthy elder subjects, and magnitudes of 5/6 bpm are common.[85, 86]

The magnitude of the drop in BP observed in different studies varies according to the characteristics of the sample and the experimental conditions, including, non surprisingly, type and quantity of food.[82, 91] A recent systematic review analysed 14 randomised controlled studies on the effect of pharmacological treatment on postprandial change in BP, including 365 subjects aged 41 to 89 years.[87] Among healthy subjects belonging to the control groups, the studies reported postprandial SBP drops between 7 $mmHg$ and 17 $mmHg$, and DBP drops between 5 $mmHg$ and 9 $mmHg$. The observed decreases were as high as 42/14 $mmHg$ (respectively for SBP and DBP) among subjects diagnosed with *autonomic failure*[11]. Studies on younger subjects have usually estimated average postprandial decreases that were smaller (2/3

$mmHg$) and non-statistically significant.[83, 85, 88]

In the elderly, reductions exceeding 20 $mmHg$ (*postprandial hypotension*) and lasting for more than one hour after eating are a relatively common phenomenon[92, 93], and may result in syncope, falls, dizziness, weakness, angina pectoris, and symptomatic or asymptomatic cerebral damage.[92, 94, 95] Some evidence also indicates that the drop varies during the day, with a magnitude significantly lower in the evening.[93]

The physiological mechanisms underlying the postprandial drop in BP (and the concomitant increase in RHR and cardiac output) is complex and involves the interplay of various phenomena. Evidence exists of the central role played by the dilation of the visceral organs and consequent increase of the volume of the circulatory system. In young healthy subjects the drop in pressure due to the increased volume is rapidly compensated by the increase in the cardiac output and the reduction of the volume of the peripheral circulatory system (*peripheral vasoconstriction*), thus explaining the scarce relevance of the phenomenon. The large drops observed in the elderly reflects the lower functionality of this homeostatic mechanisms, because of (1) the reduced activity of the sympathetic nervous system responsible for control of blood pressure stability; (2) the impairment of the baroreflex and peripheral vasoconstriction functions; (3) insulin-induced vasodilation, and release of vasodilatory gastrointestinal peptides.[87, 92, 94, 96]

2.1.4.1.2 Other substances intake

A variety of substances commonly consumed are able to cause acute changes in blood pressure levels. Among these, caffeine, alcohol, nicotine and some over-the-counter medications deserve special consideration because of their widespread use and the consequent potential of affecting population estimates.

Caffeine

Caffeine exerts a variety of stimulatory effects on the central nervous system, and it is probably the most widely used psychoactive substance. Caffeine is frequently ingested in food (e.g. chocolate, energy bars) and it is used as an adjuvant in many prescription and over-the-counter drugs (e.g. analgesics, cough syrup and slimming tablets), but global consumption is overwhelmingly attributable to three beverages: coffee, tea, and caffeinated soft drinks. A 150 ml cup of coffee contains between 60 and 120 mg of caffeine, a 150 ml cup of tea between 20 and 60 mg. A typical 330 ml 'cola' can contain between 30 and 45 mg caffeine, but the content of a single serving of some type of so-called *energy-drinks* can be as high as 400 mg.[97–99]

Caffeine intake has been consistently associated with short-term increase of both SBP and DBP.[100, 101] The magnitude of the observed increase varies across studies, with a clear dose-

response relationship. A series of controlled studies reporting on the increase in blood pressure after ingestion of a single dose of caffeine (200 to 250 mg, equivalent to two to three cups of coffee) both in normotensive and in hypertensive or borderline hypertensive subjects have been reviewed by Nurminen et al. [101]. The results are summarised in Table 2.3 (normotensive subjects) and Table 2.4 (hypertensive/borderline subjects).

Table 2.3: Controlled studies on the effects of acute administration of coffee or caffeine on systolic and diastolic blood pressure in **normotensive subjects**.

Reference	Subjects		Dose	BP Change	
	n	Age $[years]$		Systolic $[mmHg]$	Diastolic $[mmHg]$
Astrup et al (1990)	6	20-32	100 mg caffeine	+2	+3
			200 mg caffeine	+2	0
			400 mg caffeine	+6	+6
Bender et al (1997)	12	21-26	5 mg/kg caffeine	+9	+4
Casiglia et al (1992)	15	24-30	2 cups of coffee	+3	+4
			200 mg caffeine	+6	+7
France & Ditto (1992)	48	16-36	250 mg caffeine	+3	+6
Haigh et al (1993)	8	67-82	250 mg caffeine	+12	+7
Lane & Williams (1987)	30	19-28	250 mg caffeine	+7	+4
Lane et al (1990)	25	18-36	3.5 mg/kg caffeine	+8	+8
Lovallo et al (1989)	34	21-35	3.3 mg/kg caffeine	+6/+7	+4/+8
Lovallo et al (1991)	39	27 ± 1	3.3 mg/kg caffeine	+7/+8	+5/+7
Lovallo et al (1996b)	24	20-39	3.3 mg/kg caffeine	+6	+4
Nussberger et al (1990)	8	24-28	250 mg caffeine	+12	+13
Passmore et al (1987)	8	21-38	90 mg caffeine	+5	+8
			180 mg caffeine	+7	+7
			360 mg caffeine	+11	+8
Pincomb et al (1988)	44	20-36	3.3 mg/kg caffeine	+4	+5
Pincomb et al (1991)	34	20-35	3.3 mg/kg caffeine	+6/+10	+4/+11
Ray et al (1986)	9	nr	4 mg/kg caffeine	+8	+11
Robertson et al (1978)	9	21-30	250 mg caffeine	+14	+10
Smits et al (1983)	12	17-38	2 cups of coffee	+5	+11
Smits et al (1985)	8	21-25	300 ml coffee	+4/5	+8/9
Smits et al (1986a)	10	19-37	2 cups of coffee	+5	+11
Sung et al (1994)	12	30-45	3.3 mg/kg caffeine	+9	+8

n = Sample size; nr = Not reported in the original study
Data and references from Nurminen et al. [101]

The estimated acute effects of caffeine varied between 3 and 14 $mmHg$ for SBP and between 4 and 13 $mmHg$ for DBP among normotensives, and were slightly larger among hypertensive

Table 2.4: Controlled studies on the effects of acute administration of coffee or caffeine on systolic and diastolic blood pressure in **hypertensive/borderline subjects**.

Reference	Subjects		Dose	BP Change	
	n	Age $[years]$		SBP $[mmHg]$	DBP $[mmHg]$
Freestone & Ramsay (1982)	16	nr	500 ml coffee $\approx$ 200 mg caffeine	+10	+7
Goldstein & Shapiro (1987)	18	37-60	200 mg caffeine	+8	+6
Lovallo et al (1996b)	24	20-39	3.3 mg/kg caffeine	+11	+8
Smits et al (1986a)	10	18-56	2 cups of coffee	+13	+11
Sung et al (1994)	18	30-45	3.3 mg/kg caffeine	+12	+11

n = Sample size; nr = Not reported in the original study
Data and references from Nurminen et al. [101]

or borderline subjects. The hypothesis that BP changes in response to caffeine intake are more pronounced in hypertensive or hypertension-prone subjects than in normotensive subjects is also supported by other studies.[102–104]

The increase in blood pressure generally starts within 30 minutes from consumption and can last for several hours (typically one to two, but longer durations have been observed) and is evident at all ages, with some studies suggesting larger increases in older subjects than in the young ones. Generally, studies have found no racial or sex differences in these patterns.[37, 97, 100, 101]

The average effect of acute caffeine intake on BP is stronger in persons who do not normally consume it than in habitual users, and the magnitude of the response seems to be inversely related to the plasma caffeine concentration at the time of administration.[101] This 'habituation' effect might explain while, contrary to the established evidence reviewed above on the existence of *acute* effect of caffeine intake on BP, the literature is inconclusive regarding the possibility that *regular* caffeine intake over long periods of time increases the incidence of hypertension[12].[100]

Finally, the effects of caffeine intake on RHR are much less consistent across studies, individuals and doses. The consumption of moderate doses generally results in no changes or slight decreases in RHR, both in habitual and non-habitual coffee drinkers. However, higher doses (beyond those associates with typical consumption patterns of caffeinated drinks) produce increases in RHR, and can lead to tachycardia and may even induce arrhythmias in predisposed

subjects.[105–108]

Alcohol

Short term effects of alcohol intake on BP are much less consistent, with some studies that have reported an increase of BP, others that have found no change, and some that have reported a decrease.[109–112] These large discrepancies are only partly explained by between-studies differences in the amount and type of alcohol product ingested, timing of administration and individual characteristics, including genetic makeup and level of habitual alcohol consumption.[109, 110, 113, 114]

Overall the bulk of evidence from experimental studies seems to indicate that, in normotensive subjects with moderate or absent habitual consumption of alcohol, the acute administration of small doses of alcohol is most frequently associated with moderate increases in heart rate, cardiac output and BP, with SBP more affected than DBP. The effects start minutes after the consumption of alcohol and can last for several hours. They are less evident among subjects with habitual alcohol use (two to five drinks/day) and are sometimes reversed among hypertensive subjects.[114]

However, the magnitude of the effects reported in the literature varies widely. A few examples of this variability are the results of the studies by Ireland et al. [112] on 14 young university students (+7/+5 $mmHg$, respectively for SBP and DBP); the study by Potter et al. [111] on a similar sample of 22 subjects (+4/+7 $mmHg$); and the relatively atypical results by Minami et al. [109] who studied a sample of healthy Japanese males using ambulatory devices for 24 hour monitoring on blood pressure and found a *decrease* by -7.2/-7.7 $mmHg$ in the subgroup characterised by a genetically determined reduced activity of the aldehyde dehydrogenase enzyme[13].

With large doses of alcohol, the observed effects are generally opposed, with large reductions of both BP and RHR. Very large alcohol doses, sufficient to produce nervous system respiratory depression, almost invariably produce hypotension, bradycardia, and, sometimes asystole (probably via direct nervous reflexes and myocardial effect).[114, 115]

Beyond the acute effect reviewed above, a related phenomenon that can affect the reliability of BP measurements is the short-term increase in BP associated with alcohol withdrawal in habitual drinkers. The phenomenon has been proposed as a partial explanation of the observed association between heavy chronic alcohol consumption and hypertension (the '*withdrawal hypothesis*').[114] Even though the actual relevance of the withdrawal hypothesis in explaining long-term effect of chronic alcohol use on hypertension is controversial, nevertheless the phenomenon itself is a further source of short-term variability of BP measurements. The magnitude of the withdrawal effect can be large, and values as high as +22/+13 $mmHg$ for DBP/DBP and +13 bpm for RHR have been observed among heavy drinkers of both sexes

in the first day after drinking cessation.[116]

The assumption underlying the possible relevance of the withdrawal hypothesis as a source of error in surveys is that some heavier drinkers refrain to drink in anticipation of medical examination, including those associated with surveys, in order to be more socially presentable. This introduces an artefactual increase in the measurement of the casual BP, because their BP at the moment of the measurement is higher that their usual baseline one, due to the withdrawal state.

Nicotine

The nicotine contained in all tobacco products (cigarettes, cigars, smokeless tobacco) and also in electronic cigarettes, and gums and patches used to help quitting smoking, has a proven effect on heart rate and blood pressure. Administration of nicotine (regardless the route) has the consistent effect of increasing RHR and BP. The typical magnitude of the effect varies between 10 an 15 bpm for RHR and between 5 and 10 $mmHg$ for blood pressure, but increases above 40 bpm and 40/20 $mmHg$ (SBP/DBP) have been observed.[117–120]

The onset of the effect is rapid and the peak response is reached in minutes after the administration. The duration and the time course of the increase in RHR and BP are more variable depending on the route of administration. After the cessation of the administration, the values of blood pressure and heart rate decline more rapidly when nicotine is consumed by smoking and more slowly when nicotine is consumed by chewing or snuffing tobacco of by chewing nicotine gums. Pre-administration levels of heart rate and blood pressure are reached usually after 30 to 60 minutes from smoking cessation, but recovery time after oral assumption can extend for more than two hours.[37, 118]

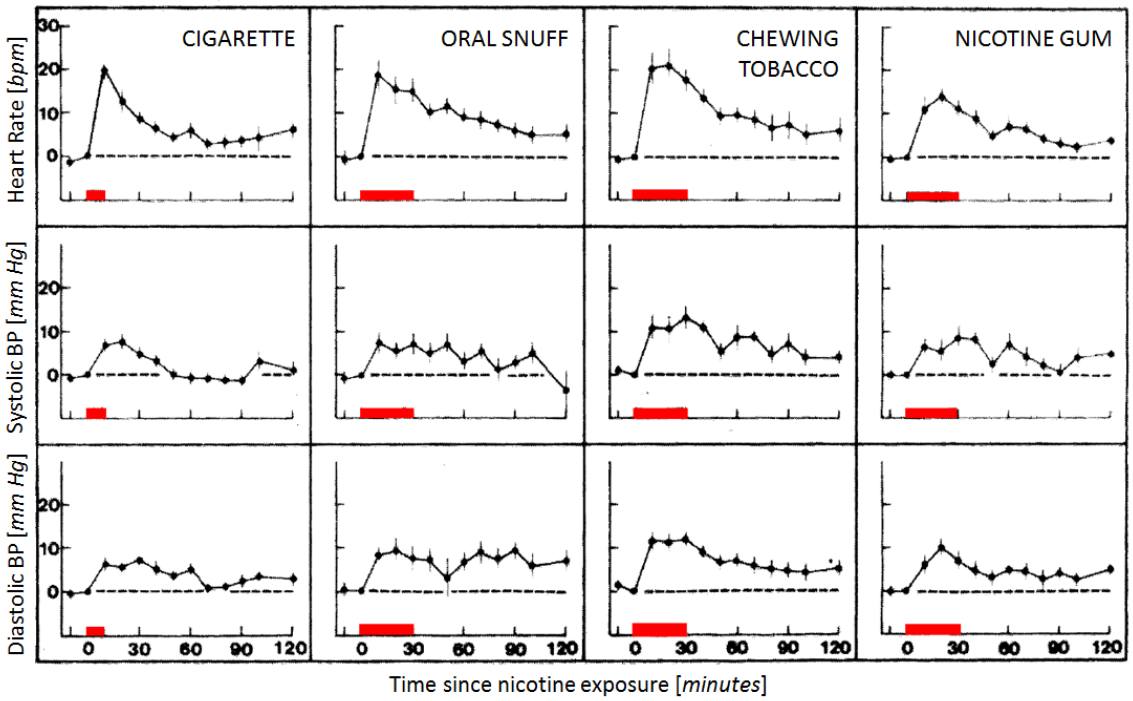
Figure 2.9, adapted from the experimental work by Benowitz et al. [118], show the typical time course of the variation of RHR and BP following acute administration of nicotine by different routes.

Over-the-counter medications

A variety of therapeutic agents available in many countries (including South Africa) without need of medical prescription can induce transient changes in BP.[121] Some of these substances are of widespread use, and, for this reason, more likely to influence the results of large-scale epidemiological investigations. Among these, decongestants and analgesics have a primary role.

Decongestant are frequently consumed to counter the symptoms of common cold. The substances of this large family (pseudoephedrine, phenylephrine and oxymetazoline are some of the most frequently found in over-the-counter medications) relieve nasal stuffiness by narrowing blood vessels and reducing swelling in the nose. This narrowing can affect other blood

Figure 2.9: Average changes in heart rate and blood pressure of 10 healthy male smokers following acute administration of nicotine products.



Red bars above time axis indicate period of nicotine exposure.
Figure adapted from Benowitz et al. [118]

vessels as well, which can increase blood pressure.

A 2005 study by Salerno et al. [122] systematically reviewed the literature reporting results of randomized controlled trials of oral pseudoephedrine treatment in adults vs. placebo. The 24 studies included in the review analysed a mix of short- and medium-term treatments (the mean duration of treatment was 4.6 days). The pooled effect size was a slight elevation of both BP and RHR. The average increase was 0.99 $mmHg$ for SBP, 2.83 bpm for RHR and a non-significant 0.63 $mmHg$ for DBP. The results were heterogeneous, and average elevations as high as 15 $mmHg$, 10 $mmHg$ and 7 bpm (respectively for SBP, DBP and RHR) were reported in some cases. Among the 1108 subjects involved in the reviewed studies, a few extreme cases were also reported: +20 $mmHg$ in the mean arterial pressure in two patients; elevation of BP above the hypertensive cutoffs in 41 hypertensive patients previously controlled; tachycardia in 1 patient. The effects tended to be higher among patients with controlled hypertension, and among men. A direct dose-response relationship was also present.

Of interest, considering our focus here is on acute rather than chronic effects,[14] is the fact

that the review found that immediate-release preparations (compared with long-release formulations) and shorter duration of use were associated with greater increases in BP. Taken together, these results support the hypothesis that irregular, symptom-based administration of decongestants in patient without chronic use (i.e. the typical consumption pattern of over-the-counter formulations used for common cold) might significantly add to short-term variability of blood pressure measured in population surveys.

Other compounds used as decongestants (and also as appetite suppressant) can produce much larger elevations of blood pressure. Phenylpropanolamine, for example has been associated with increases of more than 35 $mmHg$ of both SBP and DBP sixty minutes after consumption.[123] Because of the growing evidence of increased cardiovascular risk among habitual consumers of products containing phenylpropanolamine, in the past decade the substance has been banned in many countries, but it is still available in South Africa under the official pharmacological classification of 'Respiratory System' and 'Decongestants in combination with an analgesics', as a co-ingredient in some over-the-counter medications for cold[15].

The most commonly used over-the-counter analgesics (including the ubiquitous aspirin and ibuprofen) belong to the vast class of nonsteroidal anti-inflammatory drugs (NSAIDs). Another substance of widespread use is paracetamol, which is not generally considered in the same class because of its scarce anti-inflammatory effect (but similar analgesic properties).

Most, if not all NSAIDs in doses adequate to reduce inflammation and pain increase blood pressure in both normotensive and hypertensive individuals.[121] The average effect varies considerably across substances, doses and patients characteristics. A series of meta-analyses carried out in the years 1990s and reviewed by Johnson [124] reported an average increase in MAP of 5 $mmHg$. An exception seems to be represented by aspirin, the short-term effects of which on BP are controversial, and which has been linked by some recent studies with a *decrease*, rather than increase of blood pressure in chronic low-dose use.[125–127]

Paracetamol has been traditionally considered a safer alternative to NSAIDs and inconsistently associated with increase in blood pressure. This evidence has been recently questioned and it use has been associated with increased SBP and risk of hypertension. The evidence is, however, largely inconclusive.[121, 128, 129]

Herbal preparations and 'natural' remedies

The analysis of the possible acute effect on blood pressure by the wide variety of herbal preparations and 'natural' remedies used for treatment of common ailments is well beyond the scope of this review.

However, it is worth noticing that the list of herbs and substances that can cause acute changes in blood pressure, if assumed in the period immediately preceding the measurement, is long,

thus justifying the good clinical practice of inquiring from the patient about all intakes of food/beverages and supporting the uncommon survey practice of recording the same information.

A non exhaustive review of common natural preparations that have been associated with acute (and/or long-term) effect on blood pressure is presented in the studies by Valli and Giardina [130] and Tabassum and Ahmad [131].

2.1.4.1.3 Physical activity

Physical activity causes rapid and significant increases in BP and heart rate. The increases can be considerable, depending on individual characteristics (including age and physical fitness) as well as on intensity and type of exercise.[37]

Short-term responses of healthy subjects of various age groups to treadmill exercises have been studied by Wolthuis et al. [132]. Coherently with other results in the literature, they found that RHR and SBP tended to increase consistently with time and workload (with median increases at maximum effort compared to resting condition above 100 bpm and 60 $mmHg$, respectively[16]), while DBP stayed almost constant or fell slightly with increasing effort.

After exercise, SBP and DBP usually drop substantially, below pre-exercise values (*post-exercise hypotension*). Maximal drops by 18 to 20 $mmHg$ and 7 to 9 $mmHg$, respectively for SBP and DBP, have been observed in normotensive and hypertensive middle-aged and older subjects, with the largest absolute and relative blood pressure reductions seen in hypertensives. The post-exercise decrease in blood pressure can persist for much longer than one hour, and durations of 12–16 hours have been observed.[133, 134]

2.1.4.1.4 Talking

The association between the act of talking and a rapid and significant elevation in BP has been long observed, both in normotensive and hypertensive subjects of all ages.[135–139]

These increases occur rapidly (within 30 sec) after the initiation of talking and subjects with higher baseline BP tend to show greater increases than those with lower baseline pressure. In some hypertensive individuals, increases in BP greater than 40% of the baseline values have been observed.[138]

The increases occur regardless of the content of the communication. However, various studies have found a relationship between the magnitude of the effect and the emotional content of the speech and the level of demands placed on cognitive functioning. For example, a study by Tardy and Allen [140] on 156 healthy students aged 18-35 years reported a lower increase

when mild self-disclosure was involved compared to neutral speeches, and when subjects were asked to talk freely compared to when they were required to prepare their speech beforehand. The effect has also been shown to positively interact with the white coat effect, i.e. the increase in BP related to talking is more evident when the social status of the experimenter is higher (or perceived as such).[138]

Gender and racial ascription differences have also been observed, which is not unexpected given the numerous studies which have reported racial differences in cardiovascular reactivity.[141–143] Study results are consistent regarding sex difference, with men showing greater increases in blood pressure, and women show greater increases in heart rate and cardiac output.[144, 145] The literature on race differences on cardiovascular reactivity to speech (mostly comparing African Americans to Whites) shows less consistent results regarding the overall dynamics of the phenomenon, but generally suggests smaller increases in both BP and RHR among African Americans than among Whites.[140, 146, 147]

The magnitude of the increase in BP and RHR reported in the studies cited above in summarised in 2.5. The average effect of talking is an increase between 2 an 11 bpm for RHR, between 5 and 25 $mmHg$ for SBP and between 4 and 12 $mmHg$ for DBP.

Table 2.5: Average magnitude of the changes in blood pressure and heart rate associated with talking found in studies in various populations.

	Sample		Subsample			Change		
Reference	n	Age [$years$]	Sex	Race	HTN	SBP [$mmHg$]	DBP [$mmHg$]	RHR [bpm]
Saab et al. [146]	24	25-44	M	AA	NT	+15	+10	+5
			M	AW	NT	+25	+12	+11
Gillin et al. [147]	85	35.6†	M	AA	MS	+9.4	+7.3	+3.7
			M	AW	MS	+13.1	+10.8	+4.6
			F	AA	MS	+5.4	+4.4	+2.3
			F	AW	MS	+13.3	+12.2	+4.2
Tardy and Allen [140]	156	18-35	M	AA	NT	+16.3	+9.3	+7.0
			M	AW	MS	+15.2	+12.4	+6.6
			F	AA	MS	+12.1	+8.0	+7.8
			F	AW	MS	+17.0	+10.4	+10.4

n = Sample size; HTN = Hypertension status (NT = Normotensive; HT = Hypertensive; MS = mixed sample); M = Male; F = Female; AA = African American; AW = American White.
† = Mean age. Range not reported.

2.1.4.1.5 Body position

The position of the body affects BP and it is generally acknowledged that both SBP and DBP tend to decrease from the supine to the sitting and standing position.[34, 148] The actual magnitude of the difference is controversial in the literature, and is largely affected by other factors. Among these, the most important is the relative level of the arm compared to the level of the heart.

The results of some studies reporting data on the influence on body and arm position on blood pressure readings, reviewed by Netea et al. [149], are summarised in Table 2.6.

Table 2.6: Average differences in systolic and diastolic blood pressure readings obtained with subjects in different positions.

Reference	n	Body (arm) position A	Body (arm) position B	Difference†	
				SBP $[mmHg]$	DBP $[mmHg]$
Terént and Breig-Asberg [150]	401	Sitting (chair support)	Supine (on bed)	-	+5/+10
Netea et al. [151]	245	Sitting (chair support)	Supine (on bed)	-	+5/+10
Netea et al. [152]	57	Sitting (chair support)	Sitting (at heart level)	+10	+11
Terént and Breig-Asberg [150]	401	Supine (at heart level)	Sitting (at heart level)	+8	-
Ljungvall et al. [153]	74	Supine (on bed)	Supine (at heart level)	+5	+5
Netea et al. [154]	142	Standing (vertical)	Standing (at heart level)	+10	+10

n = Sample size; - = No difference.
† = Difference between average BP in position A and average BP in position B.
Data from Netea et al. [149]

Differences between measurements in the sitting and supine positions[17] averaged 8 $mmHg$ for SBP and were not significant for DBP when the position of the arm was carefully adjusted so that the cuff was at the level of the heart in both position, as in the study by Terént and Breig-Asberg [150]. In more usual conditions when the arm is kept on the chair support in the sitting position and lies on the bed in the supine position, differences tend to increase and be evident both for SBP and DBP. This is an expected result, because of the changes in the hydrostatic load associated with the difference in levels, which can be easily calculated, given the blood density[18]. Considering the average density of the whole blood to be $\approx$ 1060 kg/m^3[155], every cm of difference between the level of the arm and the level of the heart corresponds to a difference in pressure of $\approx$ 0.78 $mmHg$, which is consistent with the observed

differences due to changes in the arm position.

Other postural factors that have shown to significantly affect BP are the position of the subjects' legs in the sitting position, and the presence/absence of arm and back support.

Various studies have consistently reported that crossing legs produces an increase in both SBP and DBP compared to the values measured with feet flat on the floor. Most of the studies in literature have analysed samples exclusively (or predominantly) composed of hypertensive patients and found increases between 6 and 10 $mmHg$ for SBP and between 3 and 8 $mmHg$ for DBP.[156–160]. Studies that analysed samples of healthy subjects found much smaller magnitudes, with increases between 2.3 and 2.7 $mmHg$ for SBP and no change for DBP.[156, 158]

All clinical guidelines recommend that the arm where the cuff is positioned must be (other than positioned at the correct level, for the reasons exposed above) supported. In absence of support, the muscle contraction needed to self-support the arm tends to increase both BP and RHR. Increases by 1.9/6.5 $mmHg$ for BP and 4.1 bpm for RHR have been observed by Silverberg et al. [161] in a sample of 20 healthy subjects aged 15 to 60 year. A more recent study by Familoni and Olunuga [162] in a older sample on 2123 hypertensive subjects and 120 matched normotensive controls found an average increase by 4.87/4.81 $mmHg$ among the hypertensives and 7.61/2.83 $mmHg$ among the normotensives due to absence of arm support. The differences were additive to those due to arm position and sitting/standing posture.

Differences in DBP (but not in SBP) have also been observed between measurements taken with the subject sitting in a chair with back support compared to a stool, with the latter associated with average +6.5 $mmHg$ difference.[163]

2.1.4.1.6 Bladder status

When a normal bladder is distended beyond approximately 300 ml, the consequent sympathetic nervous system stimulation may cause a substantial increase in BP.[2, 37]

The effect seems to appear rapidly and only when the bladder is almost full, while there is no evidence that significant variation in blood pressure occur during the normal distension of the bladder before the desire to urinate appears. Average increases by 27/22 $mmHg$ have been observed in healthy subjects, with extreme values of up to 50/40 $mmHg$ reached when the bladder was uncomfortably distended with urgent need of urinating. In healthy patients blood pressure falls rapidly to pre-stimulation values when the bladder is emptied.[164] The acute increase can be much higher in subjects with high spinal cord injuries and autonomic disfunction.[2]

2.1.4.1.7 Room temperature

Differences in room temperature during measurement have been consistently shown to affect significantly BP readings, leading clinical guidelines to recommend comfortable temperature in the examining rooms.[34, 148]

Blood pressure responses to acute exposure to cold are well described in literature, and average increases greater than 13/7 $mmHg$ are documented when a subject's hand is immersed in cold water (4 °C) as part of the *cold pressor test* used to identify hyperreactive subjects who might have an increased risk of hypertension.[165, 166]

Barnett et al. [167] jointly analysed data on SBP collected in 25 populations during the World Health Organization MONICA Project[168]. The pooled results indicated average decreases by 0.31 $mmHg$ for each increase of the examination room temperature by 1 °C, reasonably similar across populations (95% Bayesian predictive interval: 0.19 to 0.44 $mmHg$). The estimates were adjusted for outdoor temperature and seasonal effects.

Average decreases with increase in temperature by 0.68 $mmHg/°C$ in DBP have been found by Heller et al. [169] in their secondary analysis of the data collected during the United Kingdom Heart Disease Prevention Project. Even higher drops (up to 15 $mmHg$ for an increase in room temperature from 12 $mmHg/°C$ to 24 $mmHg/°C$) have been reported by Kay [170] in his review on factors affecting the accuracy of BP measurement in family practices.

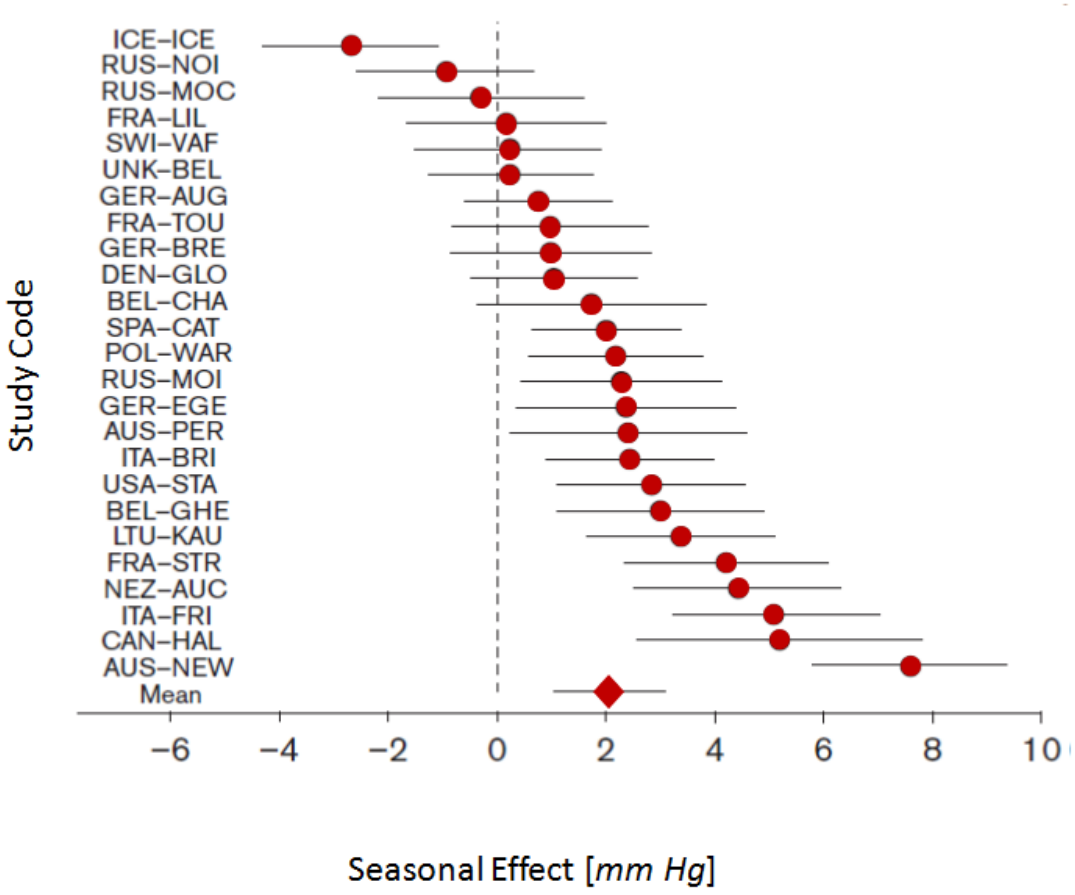
2.1.4.1.8 Seasonal effect

Winter peaks and summer troughs in BP values have been consistently observed in a large number of studies[19], in clinical[171–174], general[175–177] and special populations such as children[178] and pregnant women[179, 180].

The size or amplitude of the seasonal effect (measured as the difference between the winter peak and summer trough of the population averaged annual cycle) varies across populations and studies. A joint analysis of the SBP data collected in 25 populations during the World Health Organization MONICA Project, found a pooled effect of 2.01 $mmHg$ (95% Bayesian posterior interval: 1.05 to 3.08 $mmHg$). The magnitude of the effect varied largely across countries (Figure 2.10) with lower values recorded in cold countries and a statistically significant linear association with increasing latitude (Figure 2.11).[167]

Average seasonal effects for both SBP and DBP have been calculated in a recent meta-analysis of data from 24 adult population surveys in 15 countries.[181] The results confirm the existence of a clear seasonal pattern in blood pressure, with higher values consistently recorded in winter and lower values in summer. In the northern hemisphere, the magnitude of the pooled effect

Figure 2.10: Population specific seasonal effects on systolic blood pressure in the MONICA project.



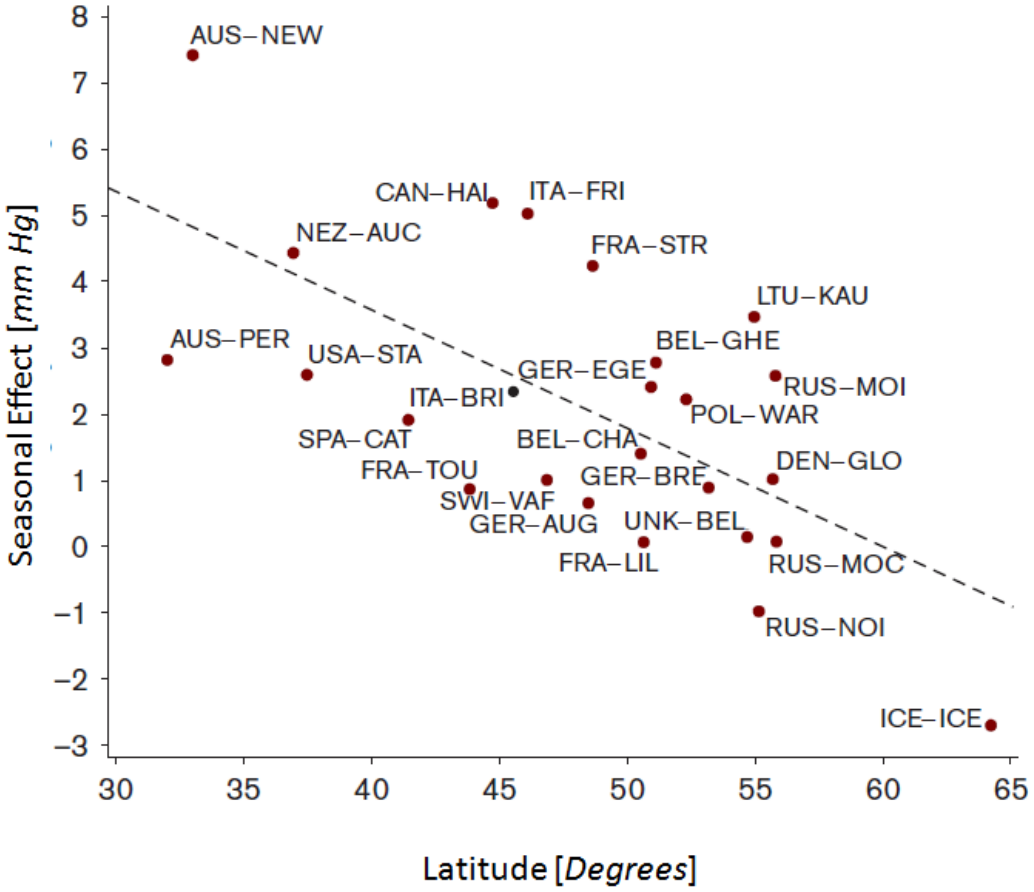
Seasonal effect is defined as the difference between the winter peak and summer trough of the population averaged annual cycle. Horizontal bars represent 95% confidence intervals.
The first letters of the study code indicate the geographical location: AUS = Australia, BEL = Belgium, CAN = Canada, DEN = Denmark, FRA = France, GER = Germany, ICE = Iceland, ITA = Italy, LTU = Lithuania, NEZ = New Zealand, POL = Poland, RUS = Russia, SPA = Spain, SWI = Switzerland, UNK = United Kingdom, USA = United States of America.
Adapted from Barnett et al. [167]

was 2.93 $mmHg$ and 1.32 $mmHg$ respectively for systolic and diastolic blood pressure. In the southern hemisphere, the values were 3.44 $mmHg$ and 0.86 $mmHg$.

Studies which reported separate estimates for age categories have also shown consistently that the seasonal effect tends to increase with age.[171, 174, 177, 182, 183]

Gender differences have also been repeatedly observed, with varying patterns by population, clinical status and age, but generally showing a slightly higher seasonal effect in men.[174, 176, 177]

Figure 2.11: Population specific seasonal effects on systolic blood pressure vs. latitude of the study location in the MONICA project.



Seasonal effect is defined as the difference between the winter peak and summer trough of the population averaged annual cycle.
The dashed line is the linear regression estimate of the seasonal effect against latitude.
The first letters of the study code indicate the geographical location (see Figure 7.1).
Adapted from Barnett et al. [167]

The causal mechanisms underlying these variations remain unclear, but substantial evidence points to the seasonal variation of outdoor temperature as the main driver of the seasonal variability of blood pressure, possibly accompanied by an independent effect of the varying number of daylight hours.[184–186]

Also poorly understood are the factors that, beyond climatic differences, explain the large variations observed in seasonal effect across and within populations. Among other biological, environmental, and behavioral factors, various authors have suggested that individual socioeconomic status may play a sizable role as an effect modifier of the relationship between season and blood pressure. In particular, it has been suggested that individuals with low so-

cioeconomic status may have both a restricted access to adequate means of protection from low temperatures (e.g. sufficient heating at home and adequate clothing) and working conditions which require more time outdoors than subjects with higher socioeconomic status. This would translate into a higher exposure to winter– summer temperature differences and, consequently, higher variations in blood pressure.[177, 187] A plausible hypothesis which finds some support by a few studies which show that the availability of indoor temperature control attenuates the difference between winter and summer blood pressure.[182, 188]

2.1.4.1.9 Circadian variations

Results of studies using both intra-arterial and noninvasive 24-hour ambulatory monitoring have consistently shown that BP and RHR follow a typical circadian pattern, which is well reproducible when evaluated in standardized conditions.[189]

Typically, in normotensive subjects the highest levels of SBP and DBP are measured in the early morning hours, then the blood pressure remains relatively stable until the early evening when it starts to decline progressively to reach a trough value at about midnight. The average magnitude of the rise in the morning is usually between 15 to 25 $mmHg$, and the fall during sleep is between 10% and 20% of the average daytime level[20].[190–194]

Superimposed on this circadian rhythm, fluctuations occurs in response to various psychologic stresses and physical activities, and BP trends to be higher during working hours and lower at home.[189]

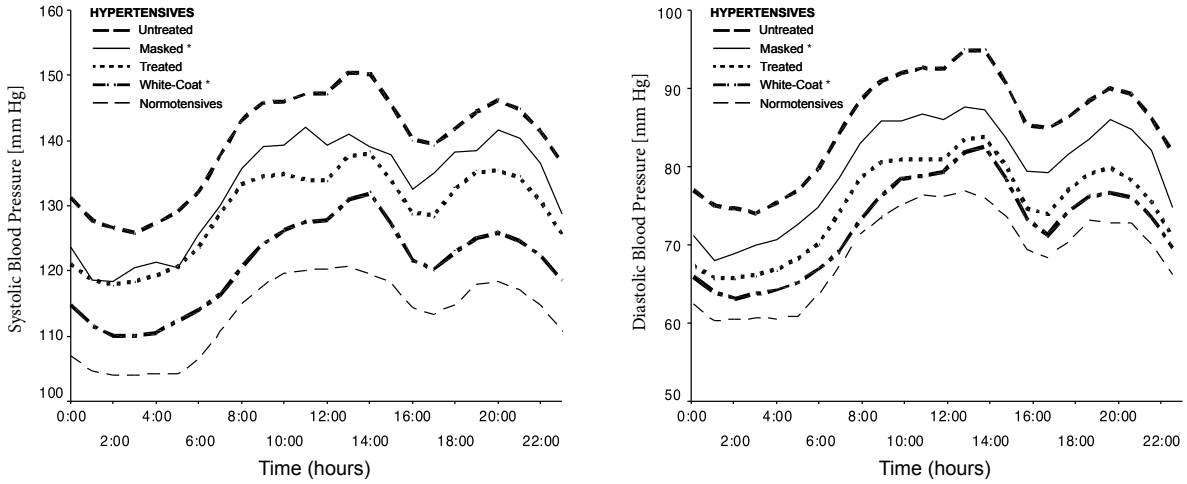
RHR usually follows a similar pattern, with the lowest values observed during sleep, but the higher values are reached later in the afternoon, rather than in the early morning hours as in BP.[195]

In hypertensive subjects with uncomplicated essential hypertension, the circadian pattern of BP is usually similar, but the magnitude of the variation and/or the 24 hours mean is abnormally elevated. In secondary hypertension, frequently both SBP and DBP are not far from normal during the day but remarkably high during sleep.[190]

Examples of 24-hour variation of BP and RHR in healthy and hypertensive individuals are depicted in Figures 2.12 and 2.13.

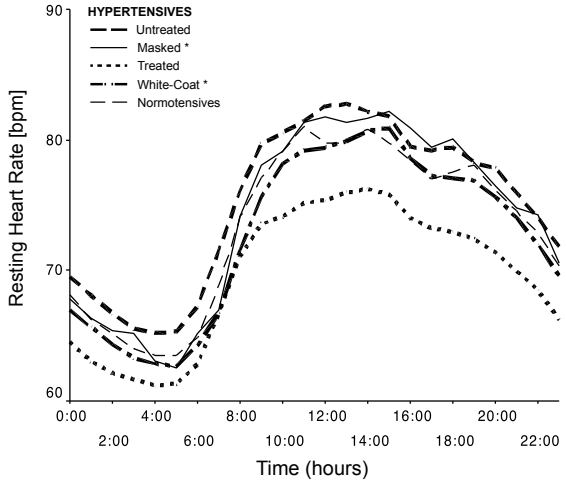
The magnitude of the morning rise in BP when a subject awakes and the magnitude of the decrease during sleep (*nocturnal dip*) have attracted growing attention in the last years, because of their association with cardiovascular risk. Specifically, growing but still controversial evidence associates a higher morning rise and/or a reduced nocturnal dip with increased cardiovascular risk, independently of the average BP value and hypertensive status.[197–199]

Figure 2.12: Example of circadian variation of systolic and diastolic blood pressure in normotensive and hypertensive subjects.



* For definition, see p. 51-52.
Adapted from Koroboki et al. [196]

Figure 2.13: Example of circadian variation of resting heart rate in normotensive and hypertensive subjects.



* For definition, see p. 51-52.
Adapted from Koroboki et al. [196]

Wang et al. [200] analysed the effect of age on the circadian rhythm of BP on a sample of 312 African Americans and 351 European Americans aged 7 to 30 years, repeatedly assessed over

a 15 years period. Results showed that daytime and nighttime SBP increase significantly with age in all gender and race groups. The increase was faster at younger age than later in life, and among males. Both daytime and nighttime SBP were higher among African Americans, and the latter increased faster with age in the same group. The racial ascription difference in nighttime SBP levels and its increase with age were significantly larger than those in daytime SBP. For daytime and nighttime DBP, African American had higher levels than European Americans, and this difference was significantly larger at night. From late adolescence onward, males showed a greater increase in diastolic blood pressure with age than females.

2.1.4.1.10 Emotional status

Emotional stress can produce marked elevations of BP with rapid onset but, generally, slow return to baseline values.

The average magnitude of the response varies in relation to the stimulus, and the inter-individual variability for a given emotional stressor is large.[37] Increases by 6 to 12 $mmHg$ in SBP have been observed both in normotensive and hypertensive individuals performing mental arithmetic tasks.[201]

In a study by Glynn et al. [202] where 72 young normotensive subjects were asked to recall a situation that made them angry, the results showed an average acute increase of SBP/DBP by 16.2/6.2 $mmHg$ and an average decrease in RHR by 4.7 bpm, with recovery times of more than 10 minutes. Compatible effects have been observed in other investigations on the relationship between BP and self-reported status of happiness, anger, or anxiety.[203, 204]

A few studies have analysed the effect of large scale traumatic events on blood pressure. A sample of hypertensive subjects living within 50 km of the epicenter of the 1995 Hanshin-Awaji earthquake in Japan showed average increases by 11/6 $mmHg$ (SBP/DBP) the day following the quake, with return to baseline values only after about a week.[205] A direct effect of the 9/11/2001 terrorist attacks on the World Trade Center Towers in New York has also been observed. An increase by 30 $mmHg$ in SBP has been observed in a hypertensive subject whose office was immediately opposite one of the towers, with recovery time of several days.[206] In a sample of subjects who were tele-monitoring their BP in four sites in the United States, a 2 $mmHg$ increase in SBP was observed between the two months before and two month after the attack.[207]

A well known emotion-related phenomenon which has been proven to have a significant effect on measurement of blood pressure and important epidemiological and clinical consequences is the *white coat effect*, usually defined as the elevation of BP when measured in clinical settings compared to the average daytime BP measured by ambulatory monitors[21]. The opposite

phenomenon (a *decrease* of BP when measured in clinical settings) is less common, but, nevertheless, observed in many studies.

The magnitude of both effects can be substantial, and in some patients it leads to the misclassification of their hypertensive status. This kind of misclassification is known as *white coat hypertension* or *masked hypertension* depending on the direction of the misclassification. White coat hypertension occurs when a subject's BP is higher than 140/90 $mmHg$ when measured in clinical settings but the daytime ambulatory BP is lower than the diagnostic threshold, and, as a consequence, he or she is incorrectly classified as hypertensive. Masked hypertension, conversely, occurs when an hypertensive subject is classified as normotensive[22]. Masked hypertension has been associated with negative clinical consequences[23].

Many studies have assessed frequency, magnitude and factors affecting white coat and masking effects. The difference between clinical and daytime ambulatory BP varies across populations and studies, and examples of this variability are shown in Table 2.7, which summarises, with no pretence of exhaustiveness, the results of studies carried out in a variety of populations.

Table 2.7: Average magnitude of the white coat effect observed studies in populations with different characteristics.

Reference	Sample	WCE	
		Systolic $[mmHg]$	Diastolic $[mmHg]$
Elijovich and Laffer [208]	51 treated and untreated hypertensives	13.0	9
Khoury et al. [209]	131 untreated hypertensives	14.4	2.9
Gosse et al. [210]	143 treated and untreated hypertensives	23	7
Myers and Reeves [211]	114 untreated hypertensives	34	13
Tanner et al. [212]	257 hypertensives aged 60 years or older	12.2	3.0
	257 hypertensives aged less than 60 years	8.4	6.2
Manios et al. [213]	2004 normotensives and hypertensives	9	7

WCE = White coat effect as the difference between clinical and average daytime blood pressure.

The prevalence of masked hypertension has been analysed by Verberk et al. [214] in their systematic review and meta analysis. The pooled prevalence estimate from studies including adult subjects was 19%. The prevalence found in some special populations is reported in Table 2.8.

Table 2.8: Prevalence of masked hypertension in special populations.

Reference	Sample	Prevalence [%]
Kawabe et al. [215]	700 adult workers	14
Ben-Dov et al. [216]	1007 treated hypertensives	12
Palatini et al. [217]	871 untreated hypertensives	14
Lurbe et al. [218]	592 untreated normotensives	8
Leitão et al. [219]	135 untreated normotensives with diabetes	30

Differences across studies are partly explained by different characteristics of the samples. The magnitude of the white coat effect on both SBP and DBP has been shown to be associated with gender (higher effect among women), smoking (higher among smokers), baseline BP and hypertensive status (increasing with increasing BP, and higher among hypertensives), body mass index (BMI) (increasing with increasing BMI), race (greater effect among Whites than among individuals of other racial ascription). The white coat effect has also been shown to increase with age for SBP, while results of different studies are less consistent regarding DBP .[209, 211, 213, 220] In most cases the white coat effect is considerably reduced, but not eliminated, in subjects taking antihypertensive drugs.[221] Reductions by more than 50% have been observed.[222]

Various studies have also associated the magnitude of the white coat effect with the characteristics of the person taking the measurement (observer). Results point consistently to the conclusion that the higher the perceived status of the observer (e.g. physician vs. medical student or nurse), the higher the magnitude of the effect.[138, 223, 224]

In a recently published study, Sheppard et al. [225] obtained a linear regression model predicting the difference between home and clinic BP using candidate predictors identified from a literature review of studies which reported data on white coat/masking effect. The model was built using two large datasets including 991 subjects and its validity assessed using 4 further datasets including 1172 subjects with different characteristics. It showed good calibration across samples and was able to reliably predict home BP (as a proxy of the 'gold standard' daytime ambulatory BP) using only a set of repeated office readings in a single visit and a set of the subjects' background characteristics (namely age, sex, BMI, use of antihypertensive drugs, previous diagnosis of hypertension and history of cardiovascular disease). Used a triage tool, the model performed well in predicting ambulatory hypertension and improving the classifi-

cation of individuals in hypertension categories compared with other guideline recommended approaches.

Strictly related to the white coat effect — and often difficult to distinguish from — is the *alerting reaction* which occurs when the patient is not familiar with the observer[24]. Typically, the alerting reaction manifests itself as a temporary increase in both SBP and DBP soon after a unfamiliar observer enters the room when the examination takes place.[37] The magnitude of the effect can be considerable, and average peak increases by 30/18 $mmHg$ have been observed.[224] The elevation has usually short duration (minutes), but it can occur in repeated visit with the same observer over a short period of time.[37] Unlike the white coat effect, it subsides when the subjects sees the same observer regularly.[224, 226]

2.1.4.1.11 Effect of treatment

Antihypertensive drugs are purposely prescribed to produce stable changes in the long term averages of the subjects' BP. From this point of view, their effect does not introduce measurement error in epidemiological studies when the objective is the estimation of the actual distribution of long term averages of BP.

However, when studying time trends in BP and their determinants from observational studies, it is often of interest to consider as the main outcome not the observed distributions of BP, but the the hypothetical (*counterfactual*) distribution that we would have observed in the absence of antihypertensive treatment. This is, for example, the case of studies of genetic susceptibility to hypertension, or when the research interest lies in the effectiveness of public health policies aimed at improving access to treatment.

In these cases the effect of treatment becomes a source of error, and this is the reason why a review of the observed effects from population studies is included in this section.

The effect of treatment varies widely across individuals, and average values have been shown to be influenced, among other factors, by class of medication, gender, age and race an their interaction.[227–229]

Average effects across different classes of antihypertensives have been reviewed by Wu et al. [230] in their meta-analysis of the results of 165 clinical trials reporting results on average treatment effects. For monodrug treatments they found pooled effects varying from -12.5 $mmHg$ (ACE inhibitors) to -15.8 $mmHg$ (loop diuretics) for SBP and from -8.2 $mmHg$ (loop diuretics) to -12.5 $mmHg$ (β-blockers) for DBP. The effect of a second medication was 84% of its effect as monodrug therapy for SBP, and 65% for DBP.

In US studies ACE inhibitors, α-blockers, β-blockers have been shown to be less effective in African Americans than in non-African Americans, whereas calcium channel blockers, thi-

azide diuretics, and loop diuretics were more effective in African Americans than in non-African Americans. Racial differences in the effect of hypertensives have been subsequently found in various other studies[227] and the overall evidence on the subject deemed strong enough to be incorporated in clinical practice and formalised in guidelines for the treatment of hypertension, including those by the Southern African Hypertension Society, which recommend that the choice of first line antihypertensive drugs should take into account the race of the patients.[231, 232]

Gender and age differences in the response to antihypertensives have also been observed in many studies across various classes of drugs. Overall, the results of these studies are consistent in reporting greater effects among women than among men, and among older than among younger subjects.[228, 233–235] Some longitudinal studies also noted a decreasing average effect over time in a given population, at least for some classes of drugs.[235]

While all antihypertensive medications lower blood pressure, the effects on RHR differ remarkably across the various classes of drugs. Materson et al. [236] analysed data from a clinical trial of 1292 men with stage I or II hypertension randomly assigned to different treatments. They found average changes in RHR between -12.2 bpm among subjects treated with β-blockers and +3.8 bpm among subjects treated with α-blockers). Large variations across antihypertensive classes have been confirmed by the recent meta-analysis by Iftikhar et al. [237] on the effect of a large variety of drugs on RHR and other haemodynamic parameters. Similarly to the study by Materson et al. [236], they found that use of β-blockers is consistently associated with lower RHR (pooled effect -12 bpm, 95% CI: -14 to -10), while other drugs were associated with smaller lowering effects or no effect at all. The only class of substances that showed some evidence of an increasing effect on RHR was the class of ACE inhibitors, with pooled effect of +0.8 bpm (95% CI: -0.4 to 2).

It is worth noticing, in conclusion, that the fact that treatment of subjects depends on the pre-treatment values of their BP, implies that treatment status cannot be considered independent from the counterfactual, untreated, BP. This makes it impracticable using the common method of statistical adjustment consisting on introducing treatment status as a binary predictor, among the other confounders, in linear regression equations with BP as outcome. The non-independence of treatment status from the outcome, in fact, violates the basic assumption underlying the ordinary least square estimator of linear regression, with the result of producing *biased* estimates of the regression coefficients.

The magnitude of this bias can be large and its effects on the conclusions of etiological studies are well known.[238, 239] For example, in observational studies where the variable of interest is the effect of treatment itself, it is common to find that this effect (incorrectly estimated by the observed regression coefficient β_o of treatment status as binary predictor) is an *increase* in BP. Because of the non-independence of treatment status from the pre-treatment BP, in fact,

the *observed* association between BP and the binary predictor has two components:

$$\beta_o = \beta_t + \beta_s$$

where β_t represent the average effect of treatment on BP (and is typically negative), while β_s reflects the fact that patients with higher underlying BP are more likely of being treated than those with lower BP. This second component is therefore positive in sign and its magnitude is often sufficient to offset the value of β_t.[240]

2.1.4.2 *Measurement devices and procedures*

2.1.4.2.1 Devices and methods

Various methods are used in clinical and epidemiological practice to measure BP. The *auscultatory* and *oscillometric* methods are, by far, the most common techniques. Other less common methods are the *finger cuff method* (or *Penaz method*), and the *applanation tonometry*. A summary description of each of these techniques is presented below.

- **Auscultatory method**

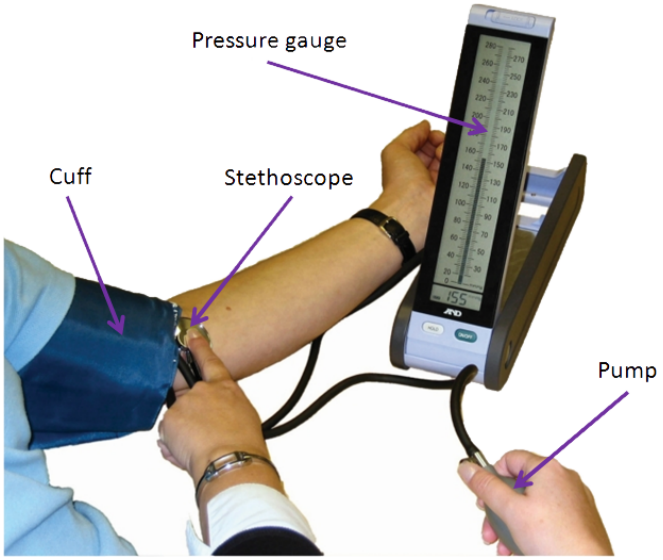
  With the auscultatory method, a cuff containing an inflatable bladder connected to a pressure gauge is placed around the upper arm of the subject, and a stethoscope[241] is placed under the cuff in correspondence with the brachial artery. The typical setup for the measurement is shown in figure 2.14.

  Initially the cuff is inflated to a level higher than the systolic pressure, so that the artery is occluded, there is no blood flow, and no sounds are heard from the stethoscope. The cuff pressure is slowly decreased, and the blood flow is gradually reestablished. This process is accompanied by sounds that can be heard with the stethoscope. These sounds (*Korotkoff sounds*[243]) are traditionally classified into five phases (see Figure 2.15) as described by Pickering *et al*:

  > *Phase I, appearance of clear tapping sounds corresponding to the appearance of a palpable pulse; phase II, sounds become softer and longer; phase III, sounds become crisper and louder; phase IV, sounds become muffled and softer; and phase V, sounds disappear completely. The fifth phase is thus recorded as the last audible sound.*
  >
  > "Recommendations for Blood pressure Measurements..."[34, p. 701]

  SBP is estimated as the pressure measured in the cuff at the onset of phase I, and DBP the pressure at the onset of phase V (i.e. when the last sound is heard).

Figure 2.14: Auscultatory method for the measurement of blood pressure: setup.



Adapted from HCE Healthcare Equipment Website [242]

Figure 2.15: Auscultatory method for the measurement of blood pressure: measurement.

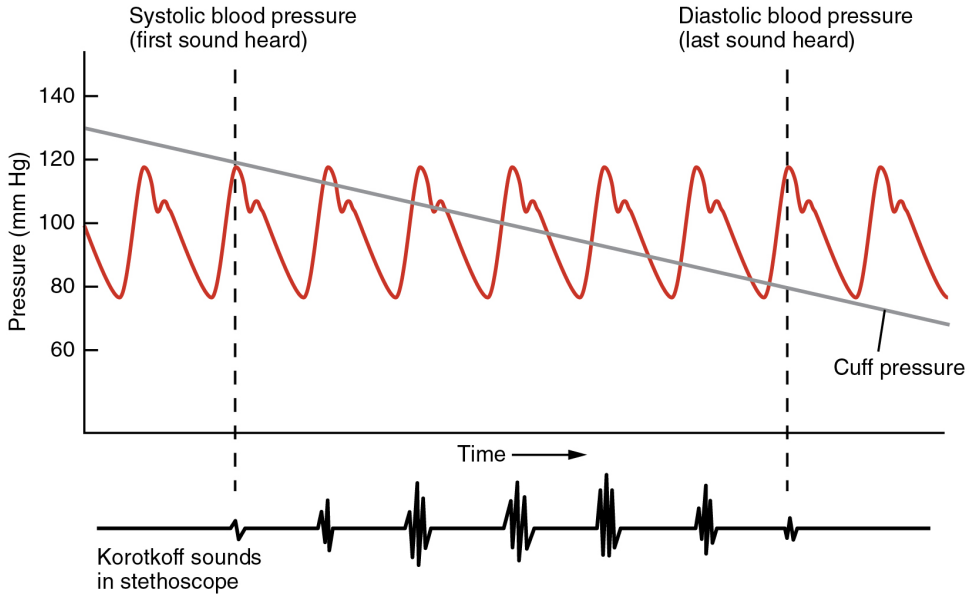


Figure from OpenStax CNX [32]

The various devices used in the auscultatory method differ mainly for the pressure gauge. Traditionally, the pressure in the cuff is measured by means of a *mercury sphyg-*

momanometer, where the reading is done by observing the height of a column of mercury.[244] Environmental concerns about mercury contamination are removing this kind of device from clinical practice, but they are still the reference instruments for the evaluation of accuracy of other measurement devices, especially because of their modest requirements in terms of periodical recalibration.[34, 198] Other pressure gauges commonly used are *aneroid sphygmomanometers* (where the pressure is registered by a mechanical system consisting of a metal capsule that expands as the cuff pressure increases, and a series of levers that indicate the pressure on a scale) and *hybrid sphygmomanometers* (where the pressure is measured by an electronic transducer).

A variation of the auscultatory method is the *ultrasound technique*, implemented in some automatic devices.[245] With this method, an ultrasound sensor, rather than a stethoscope, is placed under the cuff to detect variations in the blood flow during the deflation of the cuff. The output of the sensor is used, in place of the Korotkoff sounds, to identify the different phases of the BP variations during the cardiac cycle, and to estimate SBP and DBP.

- **Oscillometric methods**

  The oscillometric method uses a similar setup as the auscultatory method, but does not require the use of the stethoscope. The cuff is directly connected to an electronic pressure gauge, and the oscillations of the pressure during the deflation period (the *cuff deflation curve*) are used to estimate SBP and DBP by means of various empirically derived algorithms.

  The principles underlying the functioning of the oscillometric devices have been known since the 19^{th} century,[25] but the practical applications became common only in the last decades, with the availability of electronic systems able to automate the procedure.

- **Finger cuff method**

  With the finger cuff method[246], the arterial pulsation in a finger is detected by a photoplethysmograph[247] positioned under a small pressure cuff. The output of the plethysmograph is used to command a servo-mechanism able to change the pressure of the cuff and keep the output of the sensor constant. The oscillations of pressure in the cuff are measured and used, by means of empirical algorithms, to derive estimates of SBP and DBP.

- **Applanation tonometry**

  The tonometry method[248] measures the pulsation of an artery partially compressed against a bone, which are proportional to the pressure within the vessel, to derive algorithmically SBP and DBP. The radial artery in the wrist is usually used at this end, because it lies just over the radius bone and it is easily accessible.

Different methods provide different levels of accuracy and repeatability.

The Korotkoff sound method gives BP values that are highly correlated with the true intra-arterial pressure measured with invasive methods, but biased. More precisely, the literature is consistent in reporting that the Korotkoff method produces SBP measurements that are lower that the intra-arterial ones, and DBP measurements that are higher.[249] Typical mean discrepancies are -5/-10 $mmHg$ for SBP and +2/+5 $mmHg$ for DBP.[250–252] The level of bias can be much higher in some categories of subjects, when pathological conditions make it difficult to hear the Korotkoff sounds, such as older subjects with wide PP and patients with aortic insufficiency.[34, 253] The error in measurement can be especially high in obese subjects, where underestimations of the SBP by more than 50 $mmHg$ has been observed, together with a reversal of the usual overestimation of DBP.[254]

Similarly to the auscultatory method, oscillometric measurements usually underestimate intra-arterial SBP and overestimate DBP.[255–257] In general, studies comparing oscillometric with auscultatory measurements have found a good level of agreement.[258] A systematic review by Skirton et al. [259] concluded that oscillometric devices were less accurate, but the difference were not significant for routine clinical use, with the exception of some specific categories of patients. However, in currently available commercial instruments, the algorithms used for the estimation of SBP and DBP are proprietary, not in the public domain, and highly variable from manufacturer to manufacturer. This fact may partly explain the variability of the performances of oscillometric devices across studies, and the inadequacy of their accuracy found in some cases, even with devices which passed international validation protocols[26].[260–263]

A study which compared BP measurements obtained by oscillometric devices with those obtained by the auscultatory method in a large sample from general population found that oscillometric readings were systematically lower than auscultatory measurements, both for SBP and DBP. The average underestimation was by 1.6 $mmHg$ and 0.6 $mmHg$, respectively.[264] The results were consistent across subgroups defined by gender, age, race and BMI categories. However, all measurements in the study were performed with the same model of oscillometric device, and, for the reasons above, their generalizability to other devices applying different algorithms is not granted.

The oscillometric technique has become widespread because of some important advantages compared to the auscultatory method. Mostly, because its accuracy is less dependent on the exact placement of the cuff, on the presence of environmental noise, and on the ability of the observer in identifying the Korotkoff sounds. It is also applicable with patients for whom the Korotkoff sounds are inaudible. On the other side, oscillometric devices are very sensitive to artifacts due to movement, and, consequently, the arm must be immobile during measurement. Moreover, the amplitude of the oscillations from which BP is estimated depends on several factors other than blood pressure (especially the stiffness of the arteries), and therefore os-

cillometric measurements are particularly vulnerable to error in some categories of subjects, especially elderly patients and patients with arrhythmia.[34, 262, 265]

The finger cuff method has been shown to produce accurate estimates of *changes* of BP, which closely approximate measurements taken with invasive methods, while the accuracy in the measurements of *absolute* values of SBP and DBP is still controversial.[34] In a 1998 review on the accuracy of finger cuff devices compared to invasive methods, Imholz et al. [246] estimated a pooled bias (average bias across 43 studies, weighted for the number of subjects included in each study) of -0.8 $mmHg$ (standard deviation (sd) = 11.7 $mmHg$) for SBP and -1.6 $mmHg$ (sd = 7.7 $mmHg$) for DBP. Even though the point estimate of the pooled bias was low, the large standard error in the measurement of SBP and the extreme heterogeneity across and within studies led the authors to conclude that the precision of the method did not fully meet common standards and it was insufficient for the assessment of absolute blood pressure levels in individual patients. However, recent advances in the devices and the estimation algorithms have significantly improved the precision of the measurement, and some commercially available devices based of this method have shown full compliance with the accuracy requirements established by international guidelines.[266, 267]

Similarly to the Penaz method, measurements of BP based on the applanation tonometry method (which also relies on empirical algorithms) appear to produce accurate estimates of changes in blood pressure, while the estimation of absolute values requires calibration, and the accuracy of the results depends on the quality of the source for calibration.[268] Because of the need of individual calibration, sensitivity to sensor positioning, motion artefacts, the tonometric method is almost exclusively used in experimental studies which require continuous registration of the arterial pressure waveform, and rarely in clinical practice and population studies.[269]

2.1.4.2.2 Location of measurement

The location of the cuff affects remarkably the measured value of SBP and DBP — and, to a lesser extent MAP — for the combined effect of two phenomena: (1) the fact that BP differs in different parts of the arterial system (see Section 2.1.1.2), and (2) the hydrostatic effect when the relative levels of the measurement point with respect to the heart are different.

The standard location for blood pressure measurement is the upper arm at the level of brachial artery. The literature is controversial regarding the existence of systematic differences between the two arms. Many studies that measured BP simultaneously in the two arms found significant differences —both in SBP and DBP— but no clear pattern has emerged.[148] The most consistent results is that the inter-arm difference is extremely variable between subjects, and, even though for most people the differences have no practical significance, for some can

be as large as 20/10 $mmHg$.[270–272] For these reasons, current clinical guidelines suggest that patients' BP should be measured in both arms at the first occasion and when the differences are clinically significant, the arm with the higher measurement should be used in successive consultations[27].[34, 148, 232]

Other than in the upper arm, measurements at the level of the radial artery in the wrist are also becoming common, for practical reasons. Measurement on the finger are also possible, both using the oscillometric method and other more complex techniques, chiefly the Penaz method. However, the oscillometric method has been proven to be inaccurate and it is discouraged by international guidelines[34, 273], while the Penaz method is of limited applicability for the reasons summarised above.

Wrist devices are generally less accurate than arm devices, and only a small minority of them have passed clinical validation according to established standards.[273, 274] Studies in general population samples show that wrist measurements overestimate BP measured in the brachial artery, and the differences can be large (> 15/12 $mmHg$).[275–277] However, studies in hypertensive patients have found the opposite result of an underestimation of both DBP, and especially SBP, by wrist measurements. These contradictory results are, however, coherent with the validation study of one of the commercially available devices which also shows a tendency of the device to underestimate SBP at the higher pressures.[278]

Because of the sensitivity of the measurements to the positioning of the wrist in relation to the heart[279], wrist devices that incorporate position sensors to ensure a correct positioning of the wrist have been developed.[278, 280] However, the improved accuracy of these devices that has been proven in validation studies in controlled conditions[281] does not seem to translate into significant improvement in epidemiological studies.[282]

2.1.4.2.3 Procedures

Incorrect application of standardized measurement procedures is a common cause of discrepancies between observed and true values of BP, and an important source of variation in large scale epidemiological surveys.[38, 283]

Standardized protocols define in detail the measurement procedure with regard to:[34, 148, 232]

- body and arm position;
- level of comfort of the room (including temperature and noisiness);
- subject's and observer's behaviour and attitude during measurement (including avoiding talking);

- subjects' behaviour in the period immediately preceding the measurement (including avoiding physical exercise, eating, smoking and not consuming caffeine or other vasopressors; and having the bladder emptied);
- resting time (usually at least 5 minutes) before taking the measurement (in order to reduce the alerting effect due to the presence of the observer, and the effect of movement).

These prescriptions, if correctly followed, contribute substantially to the reduction of the variability of BP and RHR due to the factors reviewed in the previous sections, and to the improvement of the inter-survey comparability in epidemiological studies. [283, 284]

All protocols dedicate a special attention to the size and positioning of the measurement cuff. In particular, the optimal dimensions of the bladder (the inflatable bag inside the cuff) have been widely discussed in literature, and the use of incorrect sizes has long since been identified among the most common and important sources of procedural error in measurement of BP.[285, 286] Recent studies have substantially confirmed this fact.[287, 288]

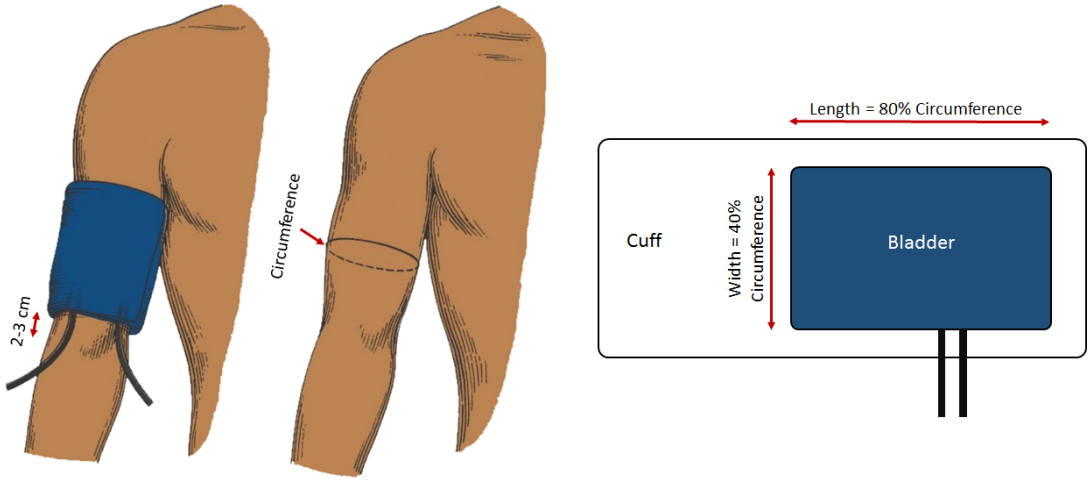
The variables relative to the cuff that have been shown to influence measurement error are: (1) the ratio between length and width of the bladder; (2) the relation of the width of the bladder to the length of the upper arm; and (3) the relation of both the width and the length of the bladder to the circumference of the arm.[289]

Rastam et al. [290] showed that, for any arm circumference, as the bladder size increases the blood pressure reading is progressively lower, until a plateau is reached at which no further increase in cuff size results in any further reduction of the blood pressure measurement. This plateau occurs approximately when the width of the bladder is 40% of the circumference of the upper arm at the midpoint and the length of the bladder is 80% of the circumference of the arm. More recent studies substantially confirm these results, even though they suggest a slightly higher ratio of 0.46 between width of the bladder and arm circumference.[291]

Based on this and other studies, the guidelines of the American Heart Association for the measurement of BP (and many other) recommend that the bladder width should be 40% of the arm circumference, and its length double than that, as shown in Figure 2.16.[34]

The error introduced by using incorrect cuff (or, more precisely, bladder) size can be large, and results of many studies indicate that undersized cuffs cause falsely high BP readings and oversized cuffs cause falsely low readings. It is generally acknowledged that the magnitude of the error caused by undersized cuffs is greater than the error caused by oversized cuffs.[289, 292–297] The average magnitude of the error produced by the use of a cuff one size larger/one size smaller than the correct one[28] was estimated by Sprafka et al. [296] in a sample of 181 adult aged 25 to 74 years. For undersized cuffs, SBP and DBP were overestimated by an average 2-6 $mmHg$ in men and by 3-4 $mmHg$ in women. For oversized cuffs, the average decrease

Figure 2.16: Optimal cuff bladder size in relation to arm circumference in adults according to the American Heart Association†.



† Pickering et al. [34]

was by 3-5 $mmHg$ in men and 1-3 $mmHg$ in women. Other studies in special populations have found even greater effects, with extremes of ± 30 $mmHg$.[285] The use of undersized cuffs is much more common that the use of oversized cuffs, and because of the significant and growing prevalence of obesity in many populations (not accompanied by greater availability of adequate cuffs) it has been indicated as a possible reason of overestimation of the prevalence of hypertension in such populations.[286, 294, 298, 299]

Another common procedural error is the positioning of the cuff over clothing (or with tight clothing pushed up on the arm) rather than on the bare arm as prescribed by standardized procedures. The average effects reported in literature are modest and of scarce clinical significance, usually not exceeding 1 $mmHg$ for measurements taken with clothes. However, the inter-individual differences (especially among hypertensive patients) can be very large, and effects greater than ± 20 $mmHg$ have been observed.[300, 301]

2.1.4.2.4 Number of measurements

Because of its large and rapid intra-individual variability, repeated measurements of blood pressure in the same occasion (multiple *readings*) are ubiquitous both in clinical practice and epidemiological studies.[302] The average of multiple readings is considered a better approximation of the true BP that a single reading, more strongly correlated with clinical outcomes, and recommended by scientific organizations and clinical guidelines.[2, 34, 148, 303]

A large literature shows that multiple readings on BP taken even at a short interval (even less than a minute) cannot be considered equivalent replicates. That is, they differ *systematically*, and the differences depend on the position of each reading in the sequence of measures. Results of many studies consistently show that both SBP and DBP tend to decrease in successive readings. The differences are usually greater between the first and the second reading than between the second and the following. [36, 304–311]. The first reading is also usually the most variable.[308]

Typical differences between successive readings in general population have been estimated by Schulze et al. [311] in a large sample of 25891 subjects from the EPIC-Postdam study. The results of the study are summarised in table 2.9.

Table 2.9: Average decrease in systolic and diastolic blood pressure in repeated measurements in the EPIC-Posdam study, by gender. Estimates and 95% confidence intervals.

		SBP Mean difference (95% CI) $[mmHg]$		DBP Mean difference (95% CI) $[mmHg]$	
Gender	n	First-second measurement	Second-third measurement	First-second measurement	Second-third measurement
Men	10 124	5.0 (4.8; 5.2)	0.9 (0.7; 1.1)	1.5 (1.4; 1.6)	0.3 (0.2; 0.4)
Women	15 767	4.9 (4.8; 5.0)	0.8 (0.7; 0.9)	1.9 (1.8; 2.0)	0.5 (0.4; 0.6)

n = sample size; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure.
Data from [311]

Exceptions to this trend have been observed in limited groups of subjects, among which the first reading is lower than the second, and this characteristic has been associated with the presence of masked hypertension.[215, 312]

Some studies have estimated the effects separately in subgroups, or explicitly studied factors associated with difference between successive readings. Schulze et al. [311] found that differences between successive readings tended to increase with age, BMI, baseline BP, and were higher among hypertensive rather than normotensive subjects, and among those on antihypertensive treatment. The drop in DBP was also more pronounced in women.

The study by Cheung and Cheung [313] on 4943 participants from the 2007-2008 edition of the United States National Health and Nutrition Examination Survey (NAHNES) reached similar conclusions regarding the effect of age and baseline BP, but did not found significant effects for gender, body weight, hypertensive status and use of antihypertensive drugs.

The epidemiological consequences of these systematic differences between successive readings have been analysed in various studies. Considering the non negligible magnitude of the differences, the choice of how many measurements are taken in population surveys — and which of them are averaged to approximate the 'true' BP of the participants — has a large influence on the estimated population values of BP and hypertension prevalence. Examples are the studies by Wietlisbach et al. [307] in Switzerland (hypertension prevalence between 9% and 14%, depending on which combination of readings were used for classification), the study by Handler et al. [302] in the United States (differences of classification in as much as 35% for some categories of subjects[29]), and the cited study by Schulze et al. [311] (prevalence of normotensives ranging between 48.5% and 58.1%).

In general, studies indicate that the lowest prevalence of hypertension is reached when the estimation is based on the average of multiple readings excluding the first, compared to any other reading alone or in combination.[314]

2.1.4.2.5 Subject anthropometric characteristics

As detailed in Section 2.1.4.2.1, in both the auscultatory and oscillometric methods, the values of SBP and DBP are indirectly determined by inflating a cuff around the arm until the pressure produces the closure of the underlying arteries and slowly releasing the pressure until the arteries are completely open. Unlike invasive methods, therefore, what it is actually measured is the pressure in the cuff needed to close and open the arteries[30]. This pressure is affected not only by the underlying BP and — as reviewed in Section 2.1.4.2.3 — by the size of the cuff, but also by the size and shape of the arm, the quantity of adipose and muscle tissue, and the structure of the walls of the arteries themselves.[315, 316]

Among the factors above, inter-subjects differences in arm circumference are probably the most common causes of differential measurement error both in clinical settings and, especially, in population surveys.

The first reason that explains the relevance of arm circumference among other anthropometric characteristics is the large error introduced by the use of cuffs of incorrect size, in particular by the use of undersized cuffs (see Section 2.1.4.2.3). Because even in clinical settings (and, a fortiori, in large scale surveys) the range of available cuff size is limited, it is often not possible to approximate the correct ratio between arm circumference and cuff size. This is especially true for large arm circumferences (typical of overweight or obese patients), where, in addition, the length of the upper arm might pose a limit to the use of correct cuffs[31]. As a result, it is well known that BP measurements in obese subjects tend to overestimate the true blood pressure.[285]

The second reason is that, even when the correct cuff size is used, a residual positive relationship between arm circumference and BP still exists, and subjects with smaller arms show lower measurements compared to those with larger circumferences.[317] The effect of arm circumference on BP measurements seems to be independent on the effect of BMI, as found by the study by Ulijaszek and Henneberg [316] in a sample of 802 adults, chosen to represent a broad range of variation in body-size, shape, and BP. The results of the study indicate a direct and statistically significant correlation between arm circumference and both SBP and DBP, after controlling for age, sex and BMI. The adjusted linear regression coefficients quantifying the association between arm circumference and BP were 0.41 $mmHg/cm$ for SBP and 0.51 $mmHg/cm$ for DBP, and were statistically significant in each of the population subgroups that were analysed. In the same study, the authors assessed the correlation between skinfold thickness[32] (as a measure of the subcutaneous fat deposit) and BP, controlling for the same variables as above. The results confirmed a significant direct correlation (partial correlation coefficients r = 0.08 and r = 0.14, respectively for SBP and DBP). After further adjustment for arm circumference the effect persisted for DBP (r = 0.09), but became non-significant for SBP.

Besides the circumference and the thickness of the subcutaneous fat deposit, the *shape* itself of the arm has been indicated as a possible source of measurement error. More precisely, some studies have found that when the shape of the subject's arm deviates substantially from the 'standard' cylindrical shape in relation to which commercial cuffs are designed, this fact can influence the possibility of accurate positioning of the cuff and its correct adherence to the arm. If the cuff does not adhere properly to the arm for its full length, when the bladder is inflated it expands in multiple irregular directions, making it uncertain the correct identification of the Korotkoff sounds in the auscultatory method.[318, 319] Current guidelines suggests, in these cases, to take the measurement in the forearm.[318] From the point of view of large scale epidemiological research, where oscillometric devices are most commonly used, the problem can assume special relevance. With the use of these devices, in fact, the fieldworkers (either health professionals or lay personnel) have no direct way to assess the 'quality' of the pressure signal coming from the cuff, and, while the device can still be able to produce a BP reading, the values can be inaccurate when based on pressure waveform that are not the standardized ones upon which the empirical estimation algorithms are calibrated.

The elasticity of the arterial walls is another source of error in the non-invasive measurement of SBP, but not DBP. The mechanism through which it affects the discrepancies between intra-arterial and non-invasive measurements of BP is directly linked to the occlusion of the arterial lumen implied in both the auscultatory and the oscillometric method. With these methods, SBP is read after occluding completely the arterial lumen with a pressure that compensates not only the BP within the artery, but also the elasticity of the arterial wall. Therefore, the pressure indicated by the pressure gauge connected to the cuff is higher than the true blood pressure, and the difference tends to increase with the elasticity of the arteries. Conversely,

DBP is measured when the artery completely relaxed, and the characteristics of the arterial wall play no role in determining the observed differences.[249]

2.1.4.3 *Data processing*

2.1.4.3.1 Cleaning procedures and treatment of outliers

Data cleaning procedures are commonly applied to the 'raw' datasets resulting from the fieldwork in epidemiological studies.

For example, individual values are often checked for plausibility (e.g., "*is the value within physiological limits?*") and consistency with other variables (e.g., "*is the value consistent with the subject's age and gender?*") and recordings not fulfilling the criteria established by the researchers are deleted or substituted with more plausible values (*imputation*). After the values of all respondents are recorded, further editing of data frequently occurs. The researchers may also examine the full distribution of values of the variables across all subjects, looking for atypical patterns.[78] Again, values that do not fit into the overall distributions according to some criterion (*outliers*) might be imputed or deleted from the final dataset.[320]

These and other editing procedures are performed with the explicit objective of reducing the overall error in the final estimate referred to the population (the total survey error, TSE). However, the editing may itself introduce some error in the estimation process, which may or may not be compensated by the reduction in other components of the TSE. This aspect is especially of concern when survey data are used for comparative purposes: in this case, differences in editing procedures between surveys may introduce bias in the comparisons, even when they are individually beneficial in reducing the TSE within each survey.

2.1.4.3.2 End digit preference, selective recording and other informal data editing procedures

The differences between recorded and measured BP due to the formal data editing procedures cited in the previous section often adds to the difference due to informal, undocumented (and, most often unwanted) editing procedure performed by the clinician or fieldworkers taking the actual measurements.

For example, a very common type of 'informal editing' of BP data is the consequence of the well known preference of human observers for numbers that end with some digits (even numbers, especially 0) rather than with other. This phenomenon, known as *end digit preference (EDP)* is hardly exclusive to BP measurements, and often results in non negligible differences between the true value of the variable of interest and those actually recorded.[321–326]

Digit preference in blood pressure values is well documented in literature, both in clinical and epidemiological settings, and regardless of the the qualification of the observers (physicians, nurses, lay fieldworkers).[327–333] Studies are consistent in finding that 0 is, by far, the most commonly preferred end digit, followed by even numbers. Some studies found also a preference for 5 compared to other odd numbers, but this is not always the case.

The magnitude of the EDP can be large. In a series of studies cited by Ayodele et al. [327], the proportion of readings ending with 0 ranged from 22% to 90%[33]

The effect of EDP on the estimated values of BP treated as a continuous variable and on its relationship with other risk factors is usually modest, if any. A slight reduction in the precision of the estimates due to the extra variability caused by the rounding has been observed by some authors, but in general this phenomenon is negligible compared to the variability from other sources.[332, 333] A slight change in the shape of the distribution has also been observed in a simulation study by Hense et al. [334].

However, when the main interest is the classification of individual into hypertension categories (in clinical settings) or the estimation of the prevalence of hypertension (at population level), the effect of EDP can be large. The current guidelines prescribe that individual whose SBP (DBP) values are *equal* to 140 $mmHg$ (90 $mmHg$) should be categorised as hypertensives. If we can assume that the observer's propensity for rounding to 0 is the same regardless of the direction (from above or from below), this leads to an overestimation of the true prevalence of hypertension, because rounding to 140 $mmHg$ values that are greater than that does not produce a change in the classification, while rounding values that are smaller changes the classification of the individual from normotensive to hypertensive. However, assuming the same propensity regardless of the direction of the rounding or, more in general, assuming that the propensity of rounding depends *only* on the last digit is generally unwarranted. In fact, frequently the knowledge of the classification threshold (and the observer's propensity to classify borderline subjects in one category rather than in another) influences the choice of rounding. The preference for particular values at or near the treatment cut-off point is sometimes called *selective recording*, and it is also well documented.[335, 336] At clinical level, the tendency to *reduce* BP readings just above the thresholds for hypertension diagnosis to values below the thresholds might be related to the avoidance of the cost (economic and/or in terms of personal effort) of treatment initiation or referral for further evaluation, and has been associated with negative effects for the patients.[335]

As a consequence of these combined phenomena, in practical circumstances EDP can lead to both over- and under-estimation of the prevalence of hypertension in population studies and to over- or under-diagnosis in clinical settings.[327]

An example of the effect that EDP can have in large surveys is provided by Wright [337], who

compared the age-adjusted prevalence of hypertension in the United States adult population between 1976-80 and 1999-02 and found that more than 15% of the observed decline could be explained by EDP error.

Another type of informal editing of BP data that has been repeatedly observed, is the propensity of some observers to report identical results when performing multiple measurements. Because, as discussed above, the values of BP from repeated measurements in the same individual differ systematically, a high proportion of identical readings is an indication of inaccuracy.[338–341]

Because of the predictable direction of the differences between successive readings (in average), high proportion of duplicate readings can result in a shift of the whole estimated distribution of BP in the population. This consideration is supported by the results of the simulation study by Hense et al. [334].

2.1.4.4 *Representation*

The problem of 'how well' a sample represents the population to which the results of a study aim to be generalised is a crucial element of any epidemiological investigation.

Incomplete and/or incorrect sampling frames and problems in data collection that result in biased samples are common to all studies. These problems assume particular relevance in large scale surveys, where explicit sampling frames at individual level are usually not available and where the realization of the sampling procedure as per study protocol faces practical difficulties that make some form of deviation a common, if not ubiquitous, occurrence.

Errors of representation — and in particular those caused by differential response rates, varying depending on the characteristics of the respondents — not only hinder the generalizability of the results of a study, but also bias the estimates of the relationships between variables and reduce the comparability between surveys.[342]

The direction and magnitude of the error introduced in the estimation of population parameters vary depending on the context and the specific characteristics of the study, and no generalization is possible. This fact makes it especially important that a careful evaluation of the sampling protocol and its practical realization precedes the data analysis. It also requires that the possible consequences of the representation error are made explicit, discussed and, when possible, quantified through some form of bias analysis.[343]

2.1.4.5 *Data analysis*

2.1.4.5.1 Distributional assumptions

Statistical methods used to estimate population parameters from measurements taken in a sample are based on assumptions which are most of the time not directly testable. Violations of these assumptions introduce error that can affect both the estimated values of the parameters and their precision.

In the analysis of blood pressure data, very often the analytical methods assume, explicitly or implicitly, that both SBP and DBP are normally distributed in the target population[34].[344]

In large scale surveys this assumption is often reasonable.

In the general population both SBP and DBP usually follow a smooth distribution, moderately skewed to the left.[239, 345–348] This is, for example, evident from Figures 2.17 and 2.18, which approximate the worldwide distribution as estimated by Wolf-Maier et al. [349].

Because of this skewness, the distribution of BP in general population is usually better approximated by a log-normal than a normal distribution. This approximation, besides being empirically supported, has also found some theoretical motivation.[350] The departures from normality are typically small and often can be taken into account by choosing appropriate statistical methods, which — despite still assuming normality of the distributions — are robust to moderate violations of this assumption.

Figure 2.17: Typical distribution of systolic blood pressure values in the general population.

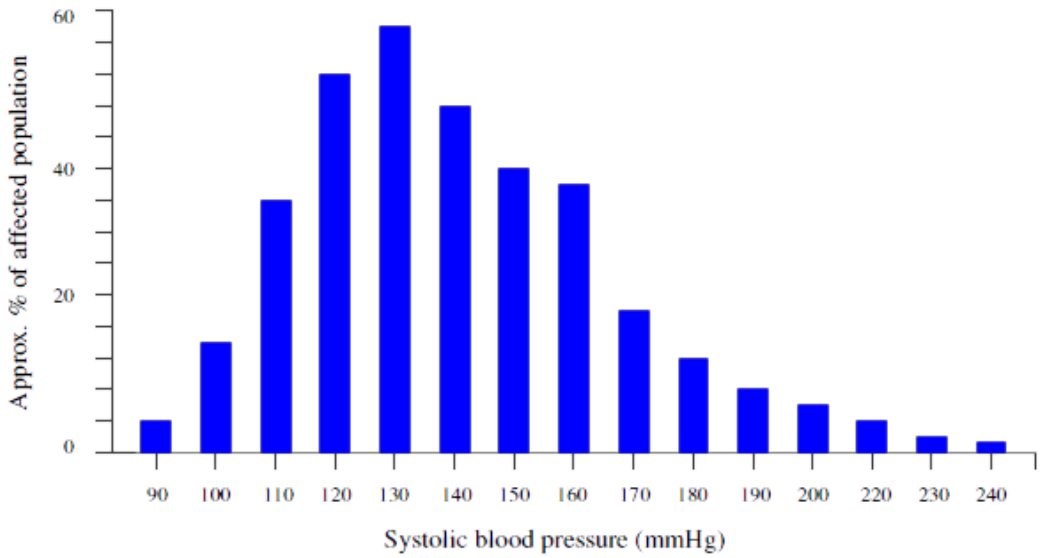


Figure adapted from Pater [351]

Figure 2.18: Typical distribution of diastolic blood pressure values in the general population.

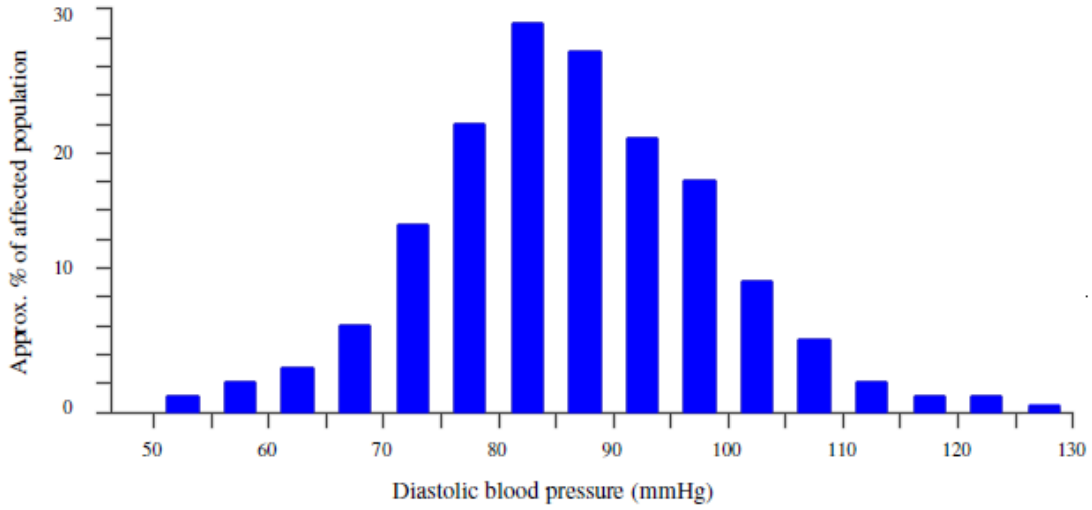


Figure adapted from Pater [351]

However, quasi-normality cannot be assumed in all circumstances, and there are many cases where the assumption is severely violated and ignoring this departure can introduce non-negligible error in the estimates.[352] An example is when the analysis is restricted to specific subpopulations, such as only to older people. In fact, it has been repeatedly observed that the distribution of SBP tends to be more right-skewed and flatter with increasing age (especially among women), leading to significant departures from the normality assumptions in the oldest age groups[35]

Another example is when the population under study is actually the result of two — or more — different groups (for example a urban and a rural community). In this case it is well possible that, even assuming normality within each subpopulation, the overall distribution is severely non-normal and, for example, bimodal.[347]

2.1.4.5.2 Missing data

The presence of missing data is ubiquitous in epidemiological research, in both observational and experimental studies. Data are missing for a variety of reasons, both pertaining to the data collection (e.g. a participant erroneously skips an item when filling a questionnaire) and to the data processing phase (e.g. errors in data entry procedures, or treatment of the outliers). In surveys involving anthropometric measurements it is not unusual for some participants who agree to fill a questionnaire and/or participate to an interview, to refuse the measurement pro-

cedure perceived as invasive. In other cases the measurement procedure might be impossible for technical reasons, e.g. the participant's arm circumference is to small or too large for the available cuffs, and BP measurements cannot be performed.

The presence of missing data is always undesirable because it reduces the *effective* sample size available for the analyses, negatively affecting the power of the study. However, in general, even large proportions of missing data do not necessarily produce bias in the study results. The best case scenario is when data are missing completely at random (MCAR), i.e. the probability of data being missing is unrelated to any observed or unobserved information. In this case individuals with complete data are a random sample of the originally identified set of cases, and no bias is introduced in the point estimates. The only undesired effect of the presence of missing data is the reduction of the precision of the estimates.

If, however, the probability that a value is missing from the dataset (missingness) depends on observed and/or unobserved variables, the individuals with complete data are a non-random sub-sample of the original set of cases, and, therefore, of the target population. If the variables that affect the probability of missingness are associated with the variables of interest in the study, the presence of missing data may bias the study results. When the probability of missingness depends *only* on observed variables data are said to be missing at random (MAR), and the available values can be considered a random sample of the original set of cases, *conditional on these observed variables*. In this case a series of effective statistical methods are available to reduce the possible biasing effect and the certain loss of power.

When the probability of missingness depends also on unobserved variables (or, in other words, it depends on the value that would have been observed if it was not missing) the data are said to be missing not at random (NMAR), and their statistical treatment requires explicit modelling of the mechanism that gave origin to the missingness. That is, the adjustment requires additional information not included in the incomplete dataset or untestable assumptions to describe the relationship between the probability of a datum being missing and its unseen value.

MCAR is a special case of MAR, and it is possible to distinguish between the two looking only to the observed data. However, whether data are MAR or NMAR cannot be concluded only observing the incomplete datasets. Because of the need of modelling the mechanism originating missing data in each specific case, no general method for handling NMAR exists, and the approach depends on extra-statistical considerations. Moreover, because the assumptions regarding the missing data mechanism are not testable with the data at hand, sensitivity analysis is usually required to assess the effect of possible violation of these assumptions.[353]

A general introduction on methods for handling missing data is provided by Ahrens and Pigeot [354, Chapter II.6] and Schafer and Graham [355], and details on the approach used in this thesis are presented in Chapter 3.

In surveys including BP measurements, the MCAR hypothesis is almost never plausible, for various reasons, including commonly found different refusal rates across genders and socioeconomic strata; and problems related to body shape. For example, Table 2.10 report the proportion of missing data on SBP in the adult subsample of the third wave of the National Income Dynamics Study (NIDS), a panel survey on a large representative sample of the South African population[80], across gender, race and BMI categories. The results clearly show that the proportion of missing data varies remarkably across categories, making the MCAR assumption untenable.

Table 2.10: Proportion of missing data in systolic blood pressure among adult participants in the third wave of the NIDS survey, by gender, race and BMI category.

Variable	n	Proportion of missing data
Gender:	21 821	
Men		20.9%
Women		12.2%
Race:	21 821	
Black		14.6%
Coloured		20.3%
Asian		29.1%
White		26.6%
Body Mass Index:†	18 336	
Underweight (BMI<18 Kg/m^2)		1.52%
Normal weight(18 Kg/m^2 ≤BMI<25 Kg/m^2)		0.31%
Overweight (25 Kg/m^2 ≤BMI<30 Kg/m^2)		0.41%
Obese (BMI≥30 Kg/m^2)		1.12%

NIDS = National Income Dynamics Study; BMI = Body Mass Index; n = number of non-missing values in the classification variable.
Figures represents the proportion of missing data in the first systolic reading.
† = Proportions are much lower compared to the other categorizations because the majority of subjects with missing data on blood pressure also had missing data on BMI, and the these subjects are excluded from the calculations.

The MAR hypothesis could be tenable is some circumstances, but it is often the case in BP studies that the probability of observing the value of BP depends heavily on the unobserved value, i.e. the data are NMAR. For example, a common occurrence in observational longitudinal studies is that individuals with high blood pressure are more likely to have their BP checked than normotensives. Another case that is discussed in detail in Chapter 3 is the case, common in genetic studies, when the variable of interest is the '*natural*' BP in absence of treatment. In these circumstances, the BP values of subjects on antihypertensive treatment are to be considered as missing, but the probability of missingness is clearly related to the underlying

natural BP prior to treatment.

Again, depending on the study objectives, the fact that data are NMAR does not necessarily lead to bias, but it is responsibility of the researcher either to give reasons why this is not the case, or to implement adequate methods to reduce this eventuality.

2.1.4.5.3 Adjustment for representation error

The use of *sampling weights* is a common method used in survey research to reduce the biasing effect of a sample that deviates from being representative of the target population[36]. The method consists of assigning to each individual i in the sample a number w_i representing the inverse of the probability of being selected in the sample. In the hypothetical case of 'perfect' simple random sampling of n individuals from a population of size N, each individual in the population has the same probability $p = n/N$ of being selected (and a sampling weight $w = 1/p = N/n$). In practical circumstances, however, the probability of selection differs across population groups and so the sampling weight varies across individuals: individuals that are under-represented in the sample have larger weights, and those in over-represented groups have smaller weights. Appropriate statistical methods are used to adjust all estimates and take into account these differences.[356]

The concept behind the use of sampling weights is simple, but the application is complex, mainly for two reasons:

- the probabilities of selection are not known, but must be estimated according to auxiliary information on the population (for example the demographic composition as assessed by a census);
- The statistical methods used to incorporate sampling weights in the analyses are also based on assumptions which most of the time are not directly testable.

Both these aspects are likely sources of error and between-survey incomparability. In extreme cases the introduction of sampling weights to improve the representativeness of the sample can produce final estimates that are more biased than those that ignore the unequal sampling probability across individuals.

A source of error of special relevance in longitudinal analyses when multiple cross-sectional datasets are compared to estimate trends over long periods of time — as in this thesis — is the incongruence of the *post-stratification* procedures commonly used in the calculation of sampling weights.

Briefly, post-stratification is used to adjust the so called *design weights* (i.e. the inverse of the probability of inclusion calculated *only* based on the sampling design) to account for sampling

errors (out of date sampling frame and non response) with the aim of improving the representativeness of the sample. This adjustment is done by organising data into homogeneous groups post data collection[37] and modifying the design weights so that their sum across each group matches as closely as possible the population totals, *supposedly known from external sources.*[357]

The results of post-stratification, however, depends heavily on the quality of the external information used. Population totals at the group level may be unavailable or unreliable. Post-stratification adjustments are based on adjusting the sample estimates to what is assumed to be the *true population.* If the population data available (usually coming for censuses) are unreliable or out of date, the adjustment is made to incorrect frequencies and can introduce bias, rather than reducing it. Moreover, when the auxiliary data form an inconsistent series over time, the comparison of the estimates between surveys carries out in different periods can be hindered. This latter case is quite a common occurrence, and it is certainly a real problem for the South African data that are analysed in this thesis, where sub-population census totals released by Statistics South Africa during the time span of interest have been already shown to be not completely consistent.[358]

2.2 Trends in blood pressure and hypertension prevalence in sub-Saharan Africa

Hypertension was at one time considered as a disease affecting prevalently the more affluent regions in the world, and of marginal, if any importance in LMICs and in sub-Saharan Africa (sSA) in particular, where infectious diseases and maternal, perinatal and nutritional causes accounted for the greatest burden of morbidity and mortality.[359]

The last decades, however, have seen a dramatic change in this perspective and the result of many studies and meta-analyses have consistently shown that in sSA hypertension is far more common than previously though and a major contributor to the overall burden of disease.[20, 359–365] The Global Burden of Disease Study 2010 indicated high blood pressure as the 6th contributor to the total number of DALYs in West Africa, the 5th in Central and East Africa, and the 2nd (after alcohol use) in Southern Africa.[366, 367] The overall prevalence of hypertension among adults (15 years and over) in the region has been estimated at 16.2% in 2008 (95% CI 14.2% to 20.3%)[38], with a total number of 74.7 million individuals affected (95% CI 65.2 to 93.4 million).[368]

The literature is also consistent in reporting that the rank of hypertension among the contributors to the burden of death and disease, the number of individuals affected and the total number of DALYs rose substantially in sSA in the last 3 decades and it is projected to further increase in the next.[366, 367] A recent meta-analysis by Twagirumukiza et al. [368] has estimated that the number of hypertensive individuals (15 years or older) in the region will rise to 125.5 million by 2025. This number is lower than the previous prediction by Kearney et al. [360] (150.7 million, adults 20 years or older), but still indicative of a considerable growth.

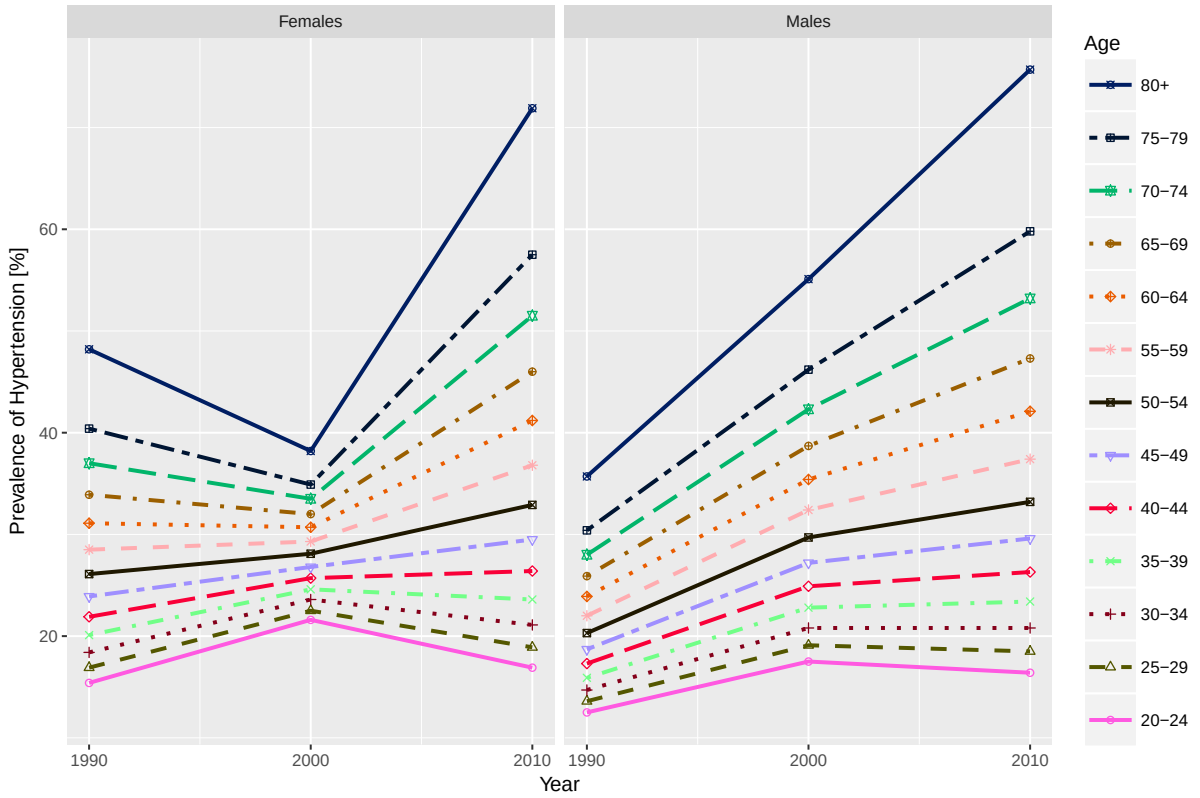
However, if we shift our interest from absolute indicators of burden of disease — the increasing trend of which is mainly driven by growth and ageing of the population[39] — to the analysis of age-specific trends in prevalence of hypertension and underlying distribution of BP, the evidence is much more controversial.

Limited surveillance and reporting, and lack of large-scale longitudinal studies make reliable data about trends in the African region scarce compared to those in high-income countries, with most of the evidence coming from comparisons of cross-sectional estimates — often carried out with different methodologies and in different settings, and reported inconsistently — or by extrapolating results of studies conducted in other regions of the world.[20, 359, 369, 370] In both cases, the estimates depends heavily on untestable assumptions underlying the statistical models used to overcome the lack of direct observations. This reliance on arguable modelling assumptions is reflected in the inconsistency of the estimates published by different authors, even when they access the same data sources.

A few recent reviews have analysed data of studies in the African region and produced estimates of the prevalence of hypertension among adults[40] at different time points and/or directly estimates of trends.

Adeloye and Basquill [363] reviewed the findings of 91 population studies carried out in Africa between 1980 and 2013. The results of their meta-analysis (summarised in Figure 2.19) suggest that the prevalence of hypertension has increased between 1990 and 2010 in all age classes. Compared to the previous period, in the decade 2000-2010 the rate of growth seems to have decreased or reversed among men in all age groups, except among subjects 80 years or older. Among women the reduction or reversal is only present in the younger age groups (< 45 years), while among older subjects the rate of growth was actually greater than in the previous decade.

Figure 2.19: Estimated age-specific prevalence of hypertension in Africa in 1990, 2000 and 2010.



Data from Adeloye and Basquill [363]

The review did not calculate age-specific trends separately for sSA. Estimates are available for the year 2000 and 2008 from two independent studies, unfortunately with a different age grouping which makes it impossible to compare directly their results.[360, 368] However, the

overall pattern of differences between the two sets of estimates (shown in Table 2.11) clearly indicates a remarkable *decrease* in the prevalence of hypertension in the region.

This large decrease is in contradiction with the results by Adeloye and Basquill [363] and has been highlighted as implausible by some authors. Specifically, it has been observed that the review by Twagirumukiza et al. [368] only included studies from 11 countries (which casts doubts about the representativeness of the whole sSA population) and the mean age of the samples included was relatively low, which can partly explain the surprisingly low prevalences.[363, p. 13]

Table 2.11: Estimated age-specific prevalence of hypertension in sub-Saharan Africa in 2000 and 2008.

2000: Kearney et al. [360]			2008: Twagirumukiza et al. [368]†		
Age [Years]	Females [%]	Males [%]	Age [Years]	Females [%]	Males [%]
20–29	9.9	10.5	15-24	4.0	5.8
30–39	22.7	22.7	25-34	8.1	10.2
40–49	39.5	38.5	34-44	15.6	17.2
50–59	50.1	48.1	45-54	28.5	26.4
60–69	61.0	57.4	55-64	45.4	38.6
70+	62.3	58.5	65+	49.5	50.3

† The original article only presented estimates of the number of hypertensive subjects. The prevalences in the table have been calculated by using the absolute numbers from the article and the 2008 total population estimates by gender from [371].

Indications about long-term trends in hypertension in sSA are indirectly provided also by Danaei et al. [17]. In their study, the authors pooled data from a large number of epidemiological studies and, rather than estimating trends in hypertension prevalence, they studied the underlying trends in SBP. Using a complex modelling strategy to overcome methodological differences among studies, they estimated age-adjusted regional trends in SBP between 1980 and 2008, for adults 25 years and over.

Their results for different sSA sub-regions are shown in Table 2.12, and indicate that the assumption of an overall positive trend in age-adjusted mean SBP is only supported (at the usual level of confidence) for males in East Africa. In all other regions the estimates are not statistically significant and, more importantly, of inconsistent sign. In other words — assuming that trends in SBP correspond to analogous trends in prevalence of hypertension[41] — the analysis does not offer evidence that age-specific prevalences of hypertension in sSA are higher now

than they were three decades ago, with the possible exception of the East African region.

Table 2.12: Average rate of change in systolic blood pressure between 1980 and 2008 in various African sub-regions, by gender.

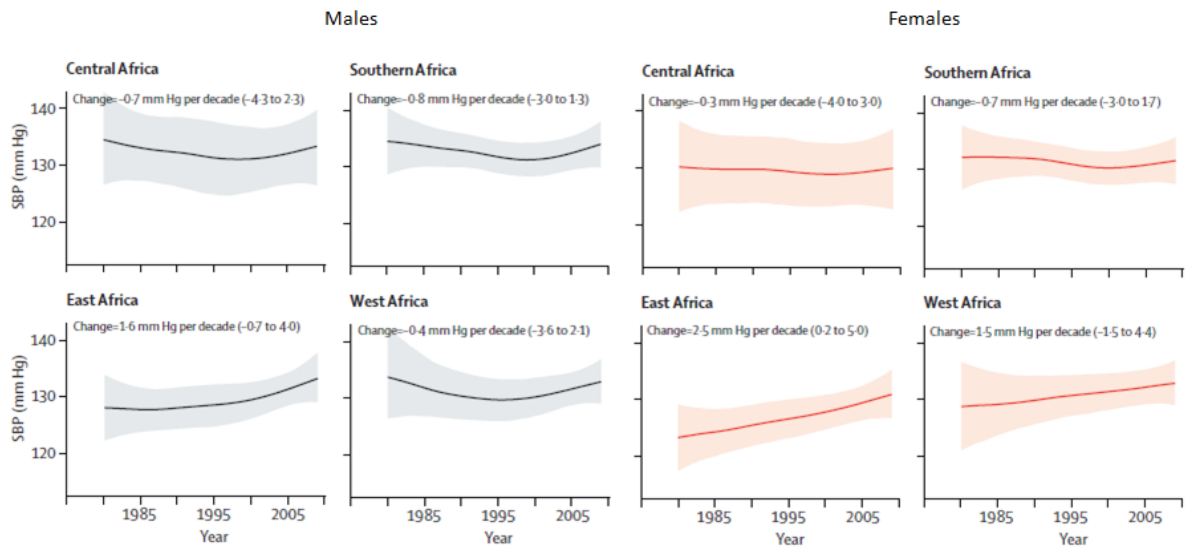
	Females		Males	
Region	Estimate [$mmHg$/dec]	95% BCI [$mmHg$/dec]	Estimate [$mmHg$/dec]	95% BCI [$mmHg$/dec]
Central Africa	-0.3	-4.0 ; 3.0	-0.7	-4.3 ; 2.3
East Africa	2.5	0.2 ; 5.0	1.6	-0.7 ; 4.0
West Africa	1.5	-1.5 ; 4.4	-0.4	-3.6 ; 2.1
Southern Africa	0.7	-3.0 ; 1.7	-0.8	-3.0 ; 1.3

BCI = Bayesian Credibility Interval; dec = decade.
Data from Danaei et al. [17]

In addition to average rates of changes between 1980 and 2008, Danaei et al. [17] also estimated more detailed trajectories, which are reproduced in Figure 2.20. These estimated trajectories are compatible with the results of the meta-analysis by Adeloye and Basquill [363] in suggesting that period 1990-2008 has seen an increase in mean SBP in all sSA sub-regions, opposed to the decrease observed in the previous decade.

Taken together, the findings from the reviews above support the hypothesis that trends in BP and prevalence of hypertension in sSA are complex, far from linear or homogeneous across sub-regions, and that the simplified and common assumption that there is a general positive trend in mean BP and prevalence of hypertension in the region is not supported by the available data.

Figure 2.20: Trends in age-standardised mean systolic blood pressure in sub-Saharan Africa between 1980 and 2008. Estimates and 95% Bayesian uncertainty intervals.



Adapted from Danaei et al. [17, p. 571]

2.2.1 Trends in South Africa

Compared to other countries in sSA, a relatively high number of studies have estimated prevalence of hypertension and/or average BP in the South African adult population in the last 20 years.

Four large scale surveys on representative samples of the whole population have been carried out between 1998 and 2014-2015 which included direct[42] measurements of BP. Three of them — two editions of the South Africa Demographic and Health Survey (SADHS) and the South Africa National Health and Nutrition Examination Survey (SANHNES) — were cross-sectional and produced estimates for 1998, 2003-2004 and 2012 respectively.[372–374] The fourth — the already cited NIDS — is an ongoing panel study with baseline data collection in 2008 and re-contacts in 2010-2011, 2012 and 2014-2015, so far. A fifth survey, the Study on Global Ageing and Adult Health (SAGE) in 2007-2008, also estimated hypertension prevalence and BP values at national level, but limited to subjects aged 50 years and over.[375]

Based on these data, various authors have produced estimates of BP and hypertension prevalence in the different years. Their findings are summarised in Table 2.13 and Figure 2.21.

The comparison of these estimates — which are not age-adjusted, and, therefore include also variations due to the changing age-structure of the population — seems to indicate a consis-

Table 2.13: Estimated prevalence of hypertension and average values of systolic and diastolic blood pressure in the South African adult population, by gender.

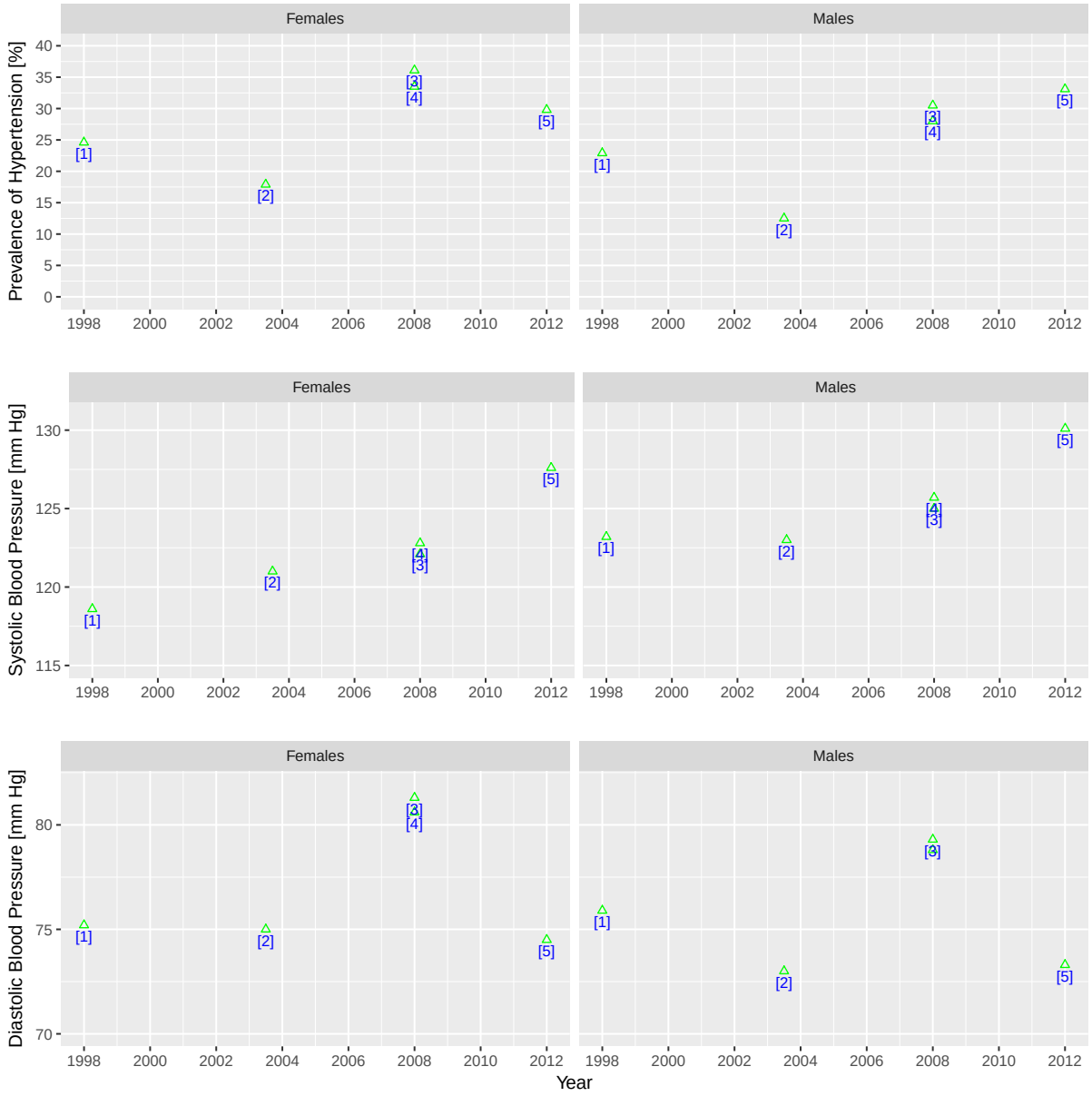
Study	N	Source of data	Year	Age range	HTN [%]	SBP [$mmHg$]	DBP [$mmHg$]
Females							
[372]	8155	SADHS	1998	15+	24.6 (0.48)	118.6 (0.36)	75.2 (0.20)
[373]	4693	SADHS	2003-4	15+	17.9 (0.56)	121 (0.40)	75 (0.23)
[375]	2098	SAGE	2007-8	50+	72.4 (0.97)†	146.8 (na)	96.6 (na)
[376]	2139	SAGE	2007-8	50+	80.3 (0.87)	(na)	(na)
[377]	8341	NIDS	2008	15+	36.1 (0.53)	122.1 (na)	81.3 (na)
[19]	7592	NIDS	2008	15+	33.5 (0.99)	122.8 (0.43)	80.6 (0.33)
[374]	4556	SANHNES	2012	15+	29.8 (0.69)	127.6 (0.56)	74.5 (0.32)
Males							
[372]	5671	SADHS	1998	15+	22.9 (0.56)	123.2 (0.37)	75.9 (0.25)
[373]	3442	SADHS	2003-4	15+	12.5 (0.56)	123 (0.46)	73 (0.36)
[375]	1644	SAGE	2007-8	50+	70.2 (1.12)†	144.1 (na)	96.1 (na)
[376]	1681	SAGE	2007-8	50+	74.7 (1.07)	(na)	(na)
[377]	5492	NIDS	2008	15+	30.5 (0.62)	125.0 (na)	79.3 (na)
[19]	NIDS	6260	2008	15+	28.0 (1.02)	125.7 (0.48)	78.8 (0.36)
[374]	2475	SANHNES	2012	15+	33.1 (0.94)	130.1 (0.58)	73.3 (0.42)

N = Sample size; Year = Year(s) of data collection; SBP, DBP = Average values of systolic and diastolic blood pressure; HTN = Prevalence of subjects with BP in the hypertensive range and/or taking antihypertensive drugs, except † where hypertensive treatment is not included; na = data non available.

Standard errors (in brackets) when not directly reported, are calculated from the confidence intervals (assuming normal approximation) of from sample size and prevalence estimates.

tent increasing trend in the average SBP in both genders, and large oscillations of DBP around a quite constant value. The prevalence of hypertension seems to have consistently increased from 1998 to 2008/2012. The estimates from the 2003 SADHS survey, however, are in countertendency, because they are remarkably lower (especially in men) compared to both the 1998 and the 2008 estimates. This drop is the result of a decrease of the average DBP, not accompanied by a similar trend in SBP, the latter being more congruent with the results of the other surveys. While inconsistent trends between SBP and DBP are not unusual and have been observed in various populations[378, 379], the magnitude of the reduction in the prevalence of hypertension (6.7 percentage points among women and 10.4 percentage points among men) not accompanied by reductions in SBP has been judged as implausible by the research team who carried out the survey and — after excluding other possible sources of error — attributed to incorrect application of measurement procedures by the fieldworkers.[373, p. 238]

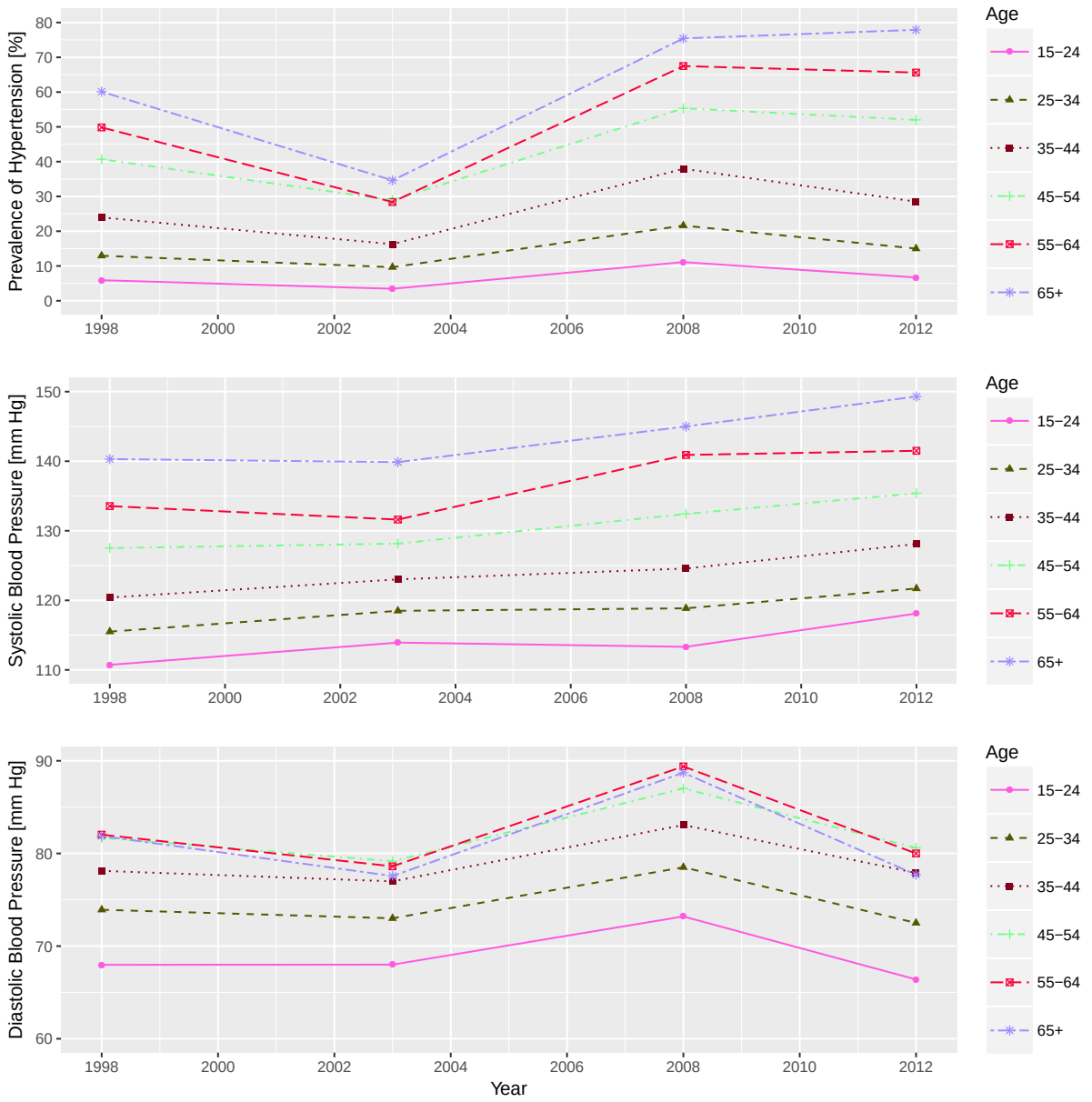
Figure 2.21: Prevalence of hypertension and average values of systolic and diastolic blood pressure in South Africa. Published estimates for the general population 15+ years old.



[1] = Department of Health - Medical Research Council [372]; [2] = Department of Health et al. [373]; [3] = Ardington and Case [377]; [4]= Cois and Ehrlich [19]; [5] = Shisana et al. [374].
Estimates from the SAGE survey are excluded because they refer only to subjects 50+.

Age-specific estimates from some of the sources cited above are compared in Figure 2.22.

Figure 2.22: Prevalence of hypertension and average values of systolic and diastolic blood pressure in South Africa. Age-specific estimates for the general population 15+ years old. Both genders combined.



Estimates for 1998, 2003-2004 and 2008 are calculated by weighting the published sex-specific values with the population structure from [380].
Blood pressure and hypertension estimates from [372], [373], [377], [374]

The prevalences of hypertension and mean SBP and DBP are consistently higher in 2008 than in 1998 across all age classes. SBP has consistently and similarly increased during the 14 years period across all age classes. DBP, however, seems to have reversed its increasing trend in the last 4 years period, again in all age classes. The combined effect on hypertension prevalence — taking into account the data quality issues regarding the 2003 estimates — is an age pattern which agrees with the regional estimates by Adeloye and Basquill [363], and suggests that, in

recent periods, the prevalence has decreased among younger subjects but it is still on the rise among older people.

The estimates from the SAGE are not shown in the graph because of the incompatibility of the age classification used in the published studies. However, it is worth pointing out the large differences between estimates referred to approximately the same period. The prevalence of hypertension in 2007-2208 estimated by Lloyd-Sherlock et al. [376] from the SAGE data (77.9% for subjects *50 years and older*, both gender combined) is almost 8 percentage points higher than the value estimated by [377] from the 2008 NIDS data in the population *55 years and older*[43]. These large incongruencies despite similar target populations, methods of sampling and measurement are, unfortunately, not uncommon in literature (see, for example Nguyen et al. [381]) and their magnitude has clearly the potential of producing inconsistent estimates of secular trends, depending to which data are accessed.

Other than in nationally representative surveys, the prevalence of hypertension and/or the average BP have been estimated in many other small scale studies.

Without claim of completeness, Tables 2.14 and 2.15 summarise the results of some of them, identified by querying some of the major electronic search engines (namely Pubmed and Google Scholar) for articles published between 1980 and 2015 and reporting estimated of SBP and/or SBP from general population samples (excluding studies in clinical settings and special populations) in South Africa[44]. Articles reporting only prevalence of hypertension have been excluded to avoid the problem of incomparability of results arising from the incongruent definitions of hypertension over time[45].

The populations under study are categorised by gender, age and also as urban/rural because of the well established evidence that urban populations in Africa tend to have significantly different BP profiles from rural populations.[361, 370]

Table 2.14: Published estimates of mean systolic and diastolic blood pressure in adult samples from urban and rural communities in South Africa.

Ref.	Year	Sample Size	Location	Sex	Age (sd) / range [$years$]	SBP (se) [$mmHg$]	DBP (se) [$mmHg$]
Urban							
Seedat and Seedat [382]	1975-76	459	Urban	m	15-90	122 (1)	78.1 (0.7)
Seedat and Seedat [382]	1975-76	535	Urban	f	15-90	122.8 (1)	77.9 (0.7)
Seedat and Seedat [382]	1976-77	476	Urban	m	15-90	122.1 (0.9)	75.8 (0.6)
Seedat and Seedat [382]	1976-77	524	Urban	f	15-90	124.1 (1)	76 (0.6)
Seedat and Seedat [382]	1977-78	487	Urban	m	15-90	128.9 (0.8)	83.5 (0.5)
Seedat and Seedat [382]	1977-78	503	Urban	f	15-90	112.5 (1)	80.7 (0.5)
Mollentze et al. [383]	1989-90	290	Urban	m	25+	138.1 (1.2)	83.0 (0.8)
Mollentze et al. [383]	1989-90	468	Urban	f	25+	144.8 (1.3)	82.6 (0.8)
Vorster et al. [384]	1996-98	207	Urban	m	37.6 (1.0)	128 (1.3)	77 (0.8)
Vorster et al. [384]	1996-98	54	Urban	m	31.0 (2.1)	122 (2.3)	79 (1.5)
Libhaber et al. [385]	2002-07	377	Urban	m+f	42.5 (17.7)	130 (1)	84 (0.6)
Pisa et al. [386]	2005	399	Urban	m	35+	137.5 (1.5)	87.9 (0.8)
Pisa et al. [386]	2005	605	Urban	f	35+	136.7 (1.1)	89.5 (0.7)
Matsha et al. [387]	2008	664	Urban	f	52.7 (13.9)	123 (0.8)	76 (0.5)
Matsha et al. [387]	2008-09	195	Urban	m	54.5 (14.6)	127 (1.4)	77 (0.9)
Peer et al. [388]	2008-09	552	Urban	m	25-74	129.7 (1.3)	81.4 (0.9)
Peer et al. [388]	2008-09	577	Urban	f	25-74	121.6 (1)	81.1 (0.6)
Lategan et al. [389]	2009	76	Urban	m	44.3 (10.6)	134.8 (2.6)	86.6 (1.7)
Lategan et al. [389]	2009	263	Urban	f		135.7 (1.5)	90.7 (1.1)
Cooper et al. [390]	2010-11	232	Urban	m	33.7 (17.1)	129 (1.1)	79.6 (0.9)
Cooper et al. [390]	2010-11	268	Urban	f	33.1(6.0)	118.2 (1.1)	76.3 (0.7)
Rural							
Seedat et al. [391]	1975-76	327	Rural	m	15-70	123.9 (1.2)	80.2 (0.9)
Seedat et al. [391]	1975-76	660	Rural	f	15-71	127 (1)	81 (0.6)
Daniels et al. [392]	1989	1240	Rural	m+f	14+	130 (0.7)	79 (0.4)
Mollentze et al. [383]	1989-90	279	Rural	m	25+	137.2 (1.4)	81.4 (0.8)
Mollentze et al. [383]	1989-90	574	Rural	f	25+	143.1 (1.1)	83.6 (0.7)
Steyn et al. [393]	1990	442	Rural	m	15-64	117 (0.7)	75 (0.6)
Steyn et al. [393]	1990	544	Rural	f	15-65	114 (0.7)	73 (0.5)
Vorster et al. [384]	1996-98	175	Rural	m	42.4 (1.2)	125 (1.3)	75 (0.8)
Vorster et al. [384]	1996-98	100	Rural	m	36.1 (1.5)	125 (1.5)	76 (1.3)
Vorster et al. [384]	1996-98	119	Rural	m	35.5 (1.4)	131 (1.5)	80 (1.5)
Motala et al. [394]	1999	999	Rural	m+f	15+	126.3 (0.6)	80 (0.4)
Thorogood et al. [395]	2002-03	95	Rural	m	35+	136 (2.8)	81 (1.5)
Thorogood et al. [395]	2002-03	307	Rural	f	35+	132 (1.8)	80 (1)
Barnighausen et al. [396]	2003-04	2207	Rural	m+f	36.87 (0.6)	125.19 (0.4)	79.47 (0.2)
Alberts et al. [397]	2004	499	Rural	m	30+	134.7 (1)	86.3 (0.6)
Alberts et al. [397]	2004	1563	Rural	f	30+	136.1 (0.6)	85.6 (0.3)
Pisa et al. [386]	2005	347	Rural	m	35+	132.2 (1.3)	84.9 (0.8)
Pisa et al. [386]	2005	659	Rural	f	35+	127.8 (1)	86.4 (0.6)
Gaziano et al. [398]	2007-08	1072	Rural	m+f	25-68	131.8 (na)	na
Malaza et al. [399]	2010	†	Rural	m	15+	119.5 (0.1)	76.5 (0.1)
Malaza et al. [399]	2010	†	Rural	f	15+	117 (0.1)	80 (0.1)

Year = Year(s) of data collection; SBP, DBP = Average values of systolic and diastolic blood pressure; m = male; f = female; se = standard error; sd = standard deviation.
When not reported directly, values for the standard error are calculated from the width of the confidence intervals (normal approximation) or by dividing the standard deviation by the square root of the sample size.

Table 2.15: Published estimates of mean systolic and diastolic blood pressure in adult samples including both urban and rural communities in South Africa.

Ref.	Year	Sample Size	Location	Sex	Age (sd) / range [$years$]	SBP (se) [$mmHg$]	DBP (se) [$mmHg$]
Rossouw et al. [400]	1979	1082	Mixed	m	15-64	135.7 (0.6)	85.5 (0.4)
Rossouw et al. [400]	1979	1208	Mixed	f	15-64	137 (0.6)	86.5 (0.3)
Rossouw et al. [400]	1979	1224	Mixed	m	15-64	134.7 (0.6)	86.4 (0.3)
Rossouw et al. [400]	1979	1396	Mixed	f	15-64	134.6 (0.6)	85.3 (0.3)
Rossouw et al. [400]	1979	1051	Mixed	m	15-64	138.3 (0.6)	86.4 (0.4)
Rossouw et al. [400]	1979	1227	Mixed	f	15-64	135.8 (0.6)	84.3 (0.3)
Steyn et al. [401]	1982	478	Mixed	m	15-64	131.5 (0.8)	83.1 (0.5)
Steyn et al. [401]	1982	498	Mixed	f	15-64	130 (0.9)	84 (0.6)
Rossouw et al. [400]	1983	595	Mixed	m	15-68	139.9 (0.8)	87.7 (0.6)
Rossouw et al. [400]	1983	710	Mixed	f	15-68	132.1 (0.9)	85.8 (0.5)

Year = Year(s) of data collection; SBP, DBP = Average values of systolic and diastolic blood pressure; m = male; f = female; se = standard error; sd = standard deviation.
When not reported directly, values for the standard error are calculated from the width of the confidence intervals (normal approximation) or by dividing the standard deviation by the square root of the sample size.

The findings in the tables are not directly comparable across studies because they refer to populations with different characteristics, in some cases not clearly specified in the published reports.

However, most of the studies reported details on the age structure of their samples and on the study setting (urban vs. rural), and separate estimates for males and females. Because age, gender and setting are acknowledged as three main factors associated with BP, this information offers the opportunity of increasing the comparability of the estimates, by considering separately males and females and by adjusting statistically for the difference in age and urban/rural setting. A similar meta-regression approach has been previously used to reduce comparability problems and estimate prevalences and trends from heterogeneous data. It is, for example, the approach underlying the trend estimates by Adeloye and Basquill [363] cited above.

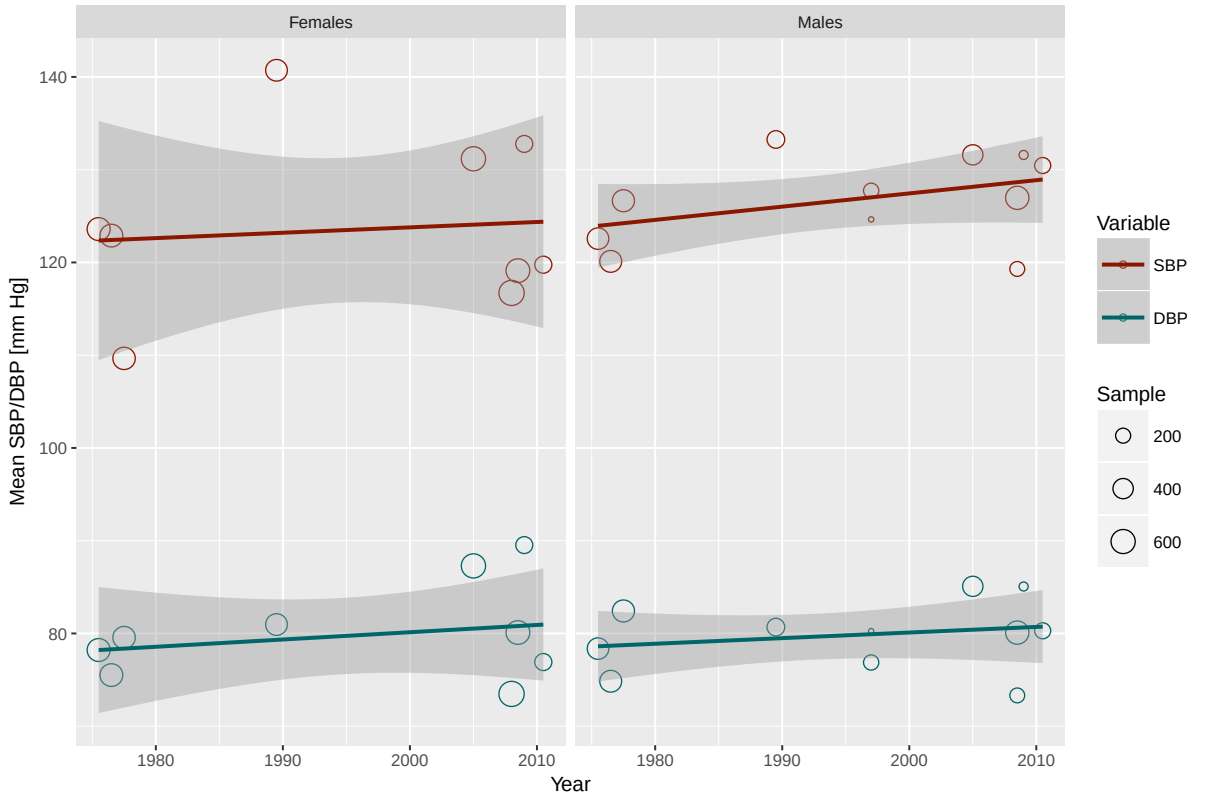
Figures 2.23 and 2.24 show the results of the analysis I applied to the studies in Table 2.14, separately for urban and rural communities. Each data point represents a study in a specific population, with SBP/DBP in the vertical axis and the average year of data collection in the horizontal axis. The size of the data points is proportional to the sample size. The solid lines represent the best-fit linear trend, calculated by weighting each study according to the sample size. The grey areas represent 95% confidence bands, which do not take into account the extra-uncertainty due to the adjustment for age and setting.

The studies in Table 2.15 have been excluded because they did not provide results separated by setting, together with five further studies (described in Libhaber et al. [385], Daniels et al.

[392], Motala et al. [394], Barnighausen et al. [396], Gaziano et al. [398], and Malaza et al. [399]) which did not report separate estimates by gender and/or adequate information regarding the age structure of the sample. This resulted on the availability of data for 20 urban communities (9 female samples and 11 male samples) and 15 rural communities (6 female samples and 9 males samples) studied between 1975-76 and 2010-2011.

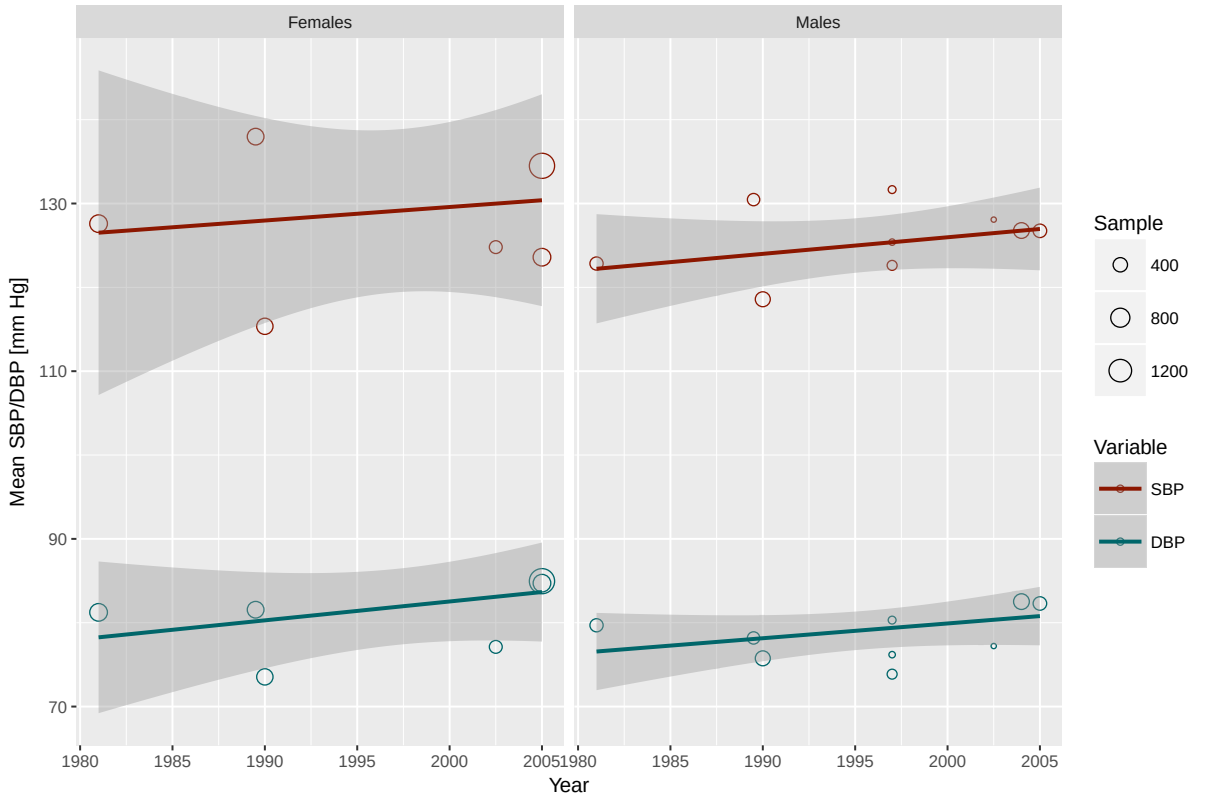
Mean values of SBP and DBP were linearly regressed on the mean age of the sample[46], separately for males and females, and the estimated regression coefficients used to adjust the observed values to the mean age of 37 years, which is the average of the South African population 15+ according to the Census 2011[402][47].

Figure 2.23: Age-adjusted estimated mean systolic and diastolic blood pressure from studies in urban communities in South Africa, by gender.



SBP, DBP = Average values of systolic and diastolic blood pressure.
Estimates are statistically adjusted to a mean age of 37 years. See text for details.

Figure 2.24: Age-adjusted estimated mean systolic and diastolic blood pressure from studies in rural communities in South Africa, by gender.

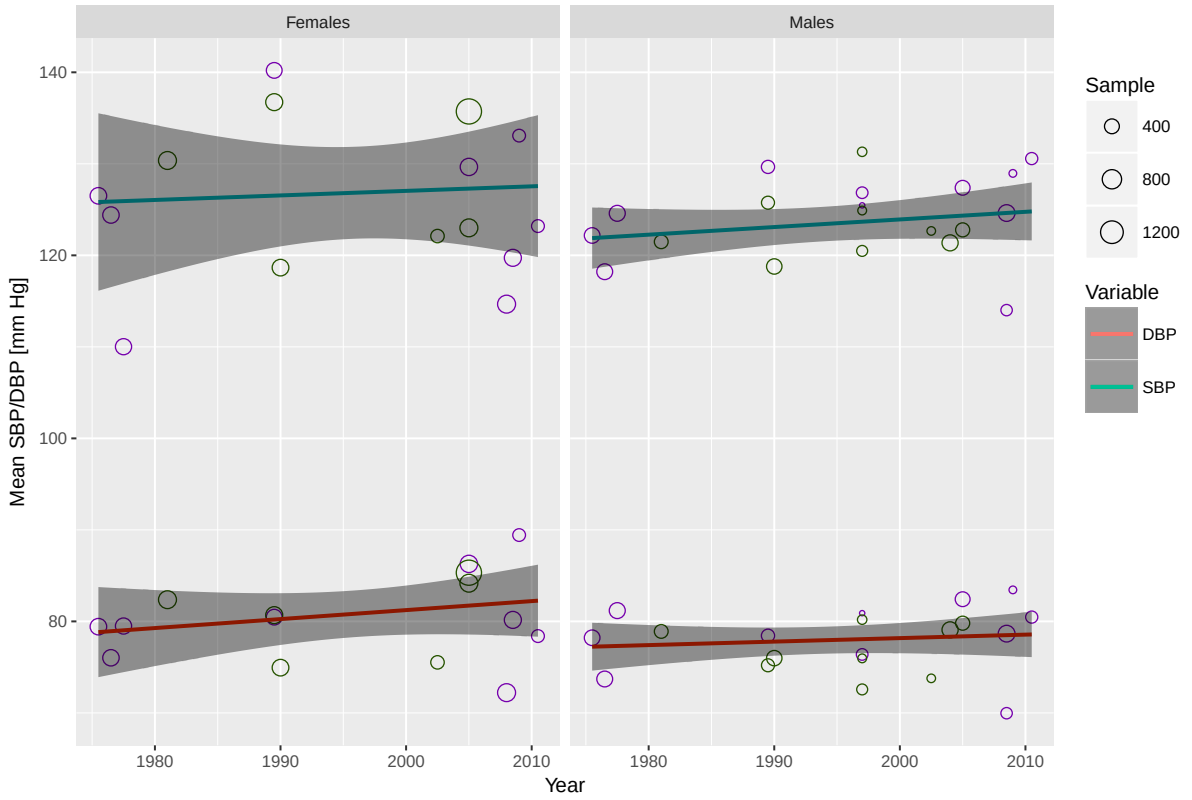


SBP, DBP = Average values of systolic and diastolic blood pressure.
Estimates are statistically adjusted to a mean age of 37 years. See text for details.

Figure 2.25, show the combined analysis of the results from studies in both urban and rural communities, and includes further adjustment, with the same procedure, for setting of the study. The reference value for the adjustment is a proportion of 62% of the population living in urban areas (average of the South African population according to the Census 2011).

Within the limitations of the crude adjustment method, which does not consider many other factors likely to influence the comparability of the estimates (including sampling strategies and differences in measurement instruments and protocols), the results seem to agree with those from the large scale surveys cited above, that shown an increase in the age-specific mean values of SBP and DBP in the decade 1998-2008. This result is also substantially consistent with the country-specific results of the study by Danaei et al. [17] cited above, which show (Figure 2.26) an overall increase (albeit small for men) in the average value of SBP between 1998 and 2008, opposite to the substantial decrease in the two preceding decades.

Figure 2.25: Age-adjusted estimated mean systolic and diastolic blood pressure from studies in South Africa, by gender. Studies in urban and rural communities combined.

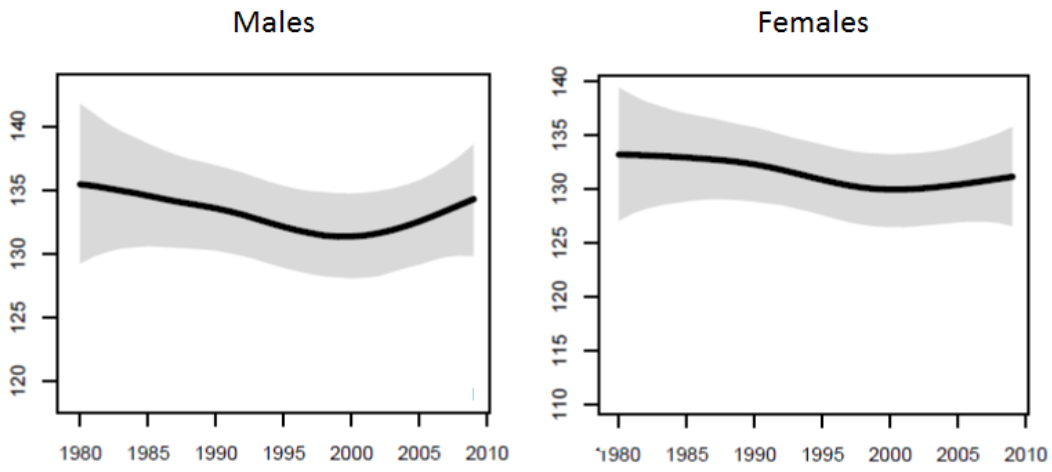


SBP, DBP = Average values of systolic and diastolic blood pressure.
Estimates are statistically adjusted to a mean age of 37 years and for a proportion of 62% of urban dwellers. See text for details.

Overall, the results of the literature review suggests the following general conclusions:

- Average values of SBP and prevalence of hypertension have increased in the South African population in the period 1998-2010, especially among older subjects. This trend might have been reversed in the following period for younger subjects, more so among women.
- Trends in DBP are not consistent with those for SBP. The evidence of any defined trends in DBP is contradictory and the published results from large scale surveys points more to large variations around stable long-term values than to any overall growing or decreasing trend.
- Discrepancies between estimates theoretically referring to the same population in the

Figure 2.26: Trend in age-adjusted mean systolic blood pressure for the South African adult population (25 years and over) between 1980 and 2008. Estimates and 95% Bayesian uncertainty intervals.



Adapted from Danaei et al. [17, Webappendix 1]

same period are large, and potentially able to reverse conclusions regarding the sign of medium- and long-term trends.

2.3 Blood pressure, socioeconomic variables and biobehavioural risk factors

2.3.1 Socioeconomic status

Socioeconomic disparities in the distribution of BP have long been observed in high income countries, where sound epidemiological evidence associates higher socioeconomic status (SES) — defined, for the purposes of this review, as the set of *"socially derived economic factors that influence the positions held by individuals or groups within the stratified structure of a society"*.[11, p. 335][48] — with a lower prevalence of hypertension and cardiovascular disease. [403, 404]

A clear association between SES and BP is well documented also in LMICs and in sSA in particular, with the notable difference that the pattern of association appear diverse in these regions, where a mix of positive and negative gradients has been found across studies, in some cases distinct by gender.[19, 405–408]

South Africa is no exception, and the pattern of association between SES, BP and hypertension in its population is more diversified and complex than the pattern observed in high-income countries. A few large-scale surveys have explicitly addressed the subject and reported data on the distribution of BP and/or prevalence of hypertension in population strata defined according to some of the most commonly used indicators of SES, namely educational attainment, income, and wealth/assets ownership. A summary of the results is shown in Table 2.16.

The results of the studies are not directly comparable, because of heterogeneity of the samples, differences in study designs and adjustment techniques, methods of BP measurement and definition of hypertension and, especially, differences in measurement of SES. However, all studies agree on the notable results that, in men, the relationship between SES and BP/hypertension is *direct*, opposite to the inverse relationship consistently found in high-income countries. On the contrary, with the only exception of the study by Schneider et al. [411], all studies which produced estimates separately by gender found an *inverse* relationship among women[49].

Observing gender differences in the relationship SES/BP is quite common in epidemiological studies in any setting, but what is usually observed is an inverse relationship in both sexes, only stronger among women.[404] However, in South Africa both the analyses by Norman et al. [407] of the data collected in 1998 during the first edition of the SADHS and those by Cois and Ehrlich [19] of the data collected ten years apart during the first wave of the NIDS, agree in suggesting opposite relationships in the two sexes. Norman et al. [407] used an asset index and educational attainment as SES indicators and hypertension prevalence as outcome, and Cois and Ehrlich [19] household income per capita and again education as SES indicators

Table 2.16: Selection of studies reporting data on the relationship of socioeconomic status indicators with blood pressure and/or hypertension in South Africa.

Study Country *Sample*	SES measure	Adjustments	Association with SBP	Association with DBP	Association with HTN
Scotch[409] South Africa *505 urban Zulu*	Income	None	-	-	Inverse in females
Steyn *et al.*[410] South Africa *13 803 adults*	Assets Education	Age Gender Race	-	-	Inverse (education)
Norman *et al.*[407] South Africa *13 803 adults*	Assets Education	Age Race	-	-	Direct in males Inverse in females
Schneider *et al.*[411] South Africa *13 803 adults*	Assets	Age	-	-	Direct
Ardington & Case[377] South Africa *13 843 adults*	Assets	Age Education Race Urban/Rural	-	-	Inverse in females (education)
Egbujie[412] South Africa *2000 adults*	Income	Age Sex	-	-	Direct
Cois & Ehrlich[19] South Africa *13 843 adults*	Education Income	Age Race Treatment	Inverse in females (education)	Direct in males Inverse in females (education)	-

SBP = Systolic blood pressure; DBP = Diastolic blood pressure; HTN = Hypertension.
- = No association or not tested.

and SBP and DBP as outcomes.

The results of the Cois and Ehrlich [19] study, which is the only one that used SBP and DBP as outcome rather than hypertension prevalence (which collapses the two values into a single indicator) also suggest the possibility of different relationships between SES and SBP/DBP. Different patterns of association of SES with DBP and SBP have been found elsewhere, including in the study by Lang et al. [406] in Senegal and the one by Gulliford et al. [413] in a representative sample of the population of Trinidad and Tobago. In particular, the findings of the latter study agree with the results of the study by Cois and Ehrlich [19] that, in men, DBP is more strongly associated with SES than SBP. Other studies also support the hypothesis that different blood pressure indices have different biobehavioural and psychological determinants.[414]

All the studies summarised in Table 2.16 above were cross-sectional. Recently, the association between SES and BP in young adults has been studied by Kagura et al. [415] in the Gauteng Province, using a longitudinal dataset including data on 838 black urban subjects followed from birth to the age of 18 years (the 'Birth to Twenty' cohort in Soweto, Johannesburg).

In their study, the authors analysed the relationship between SES in infancy and at the age of 16 years (measured by means of a household asset index) and BP at the age of 18 years. The results, presented combined across genders, support the hypothesis of a protective effect of high SES in adolescence and infancy against high blood pressure in young adulthood. In particular, the results show that, compared to subjects constantly belonging to the lowest SES tertile during infancy and adolescence, those who improved their SES had a significantly lower SBP at 18 years. Differences in BP at 18 years were not significant when the comparison was done between subjects with constantly low SES and those with constantly medium or high SES, but the point estimate of the difference was still negative and large. No effect was observed on DBP (i.e. results not statistically significant and negligible effect sizes).

2.3.2 Urban vs. rural dwelling

Differences in prevalence of hypertension between urban and rural areas (with the higher values in the former) have been consistently reported in studies in sSA, and, despite some evidence that the gap might be diminishing, it is still clearly present.[361, 416–418]

South Africa follows the general trend from this point of view, as consistently indicated by the results of large-scales surveys in the last two decades, summarised in Table 2.17. The only general population survey which does not support these findings is the SAGE. Its prevalence estimates are higher in rural than in urban areas (73.9% vs. 70.1%). However, they only refer to the population 50 years and older, and are, therefore, not comparable with those in Table 2.17.

Table 2.17: Prevalence of hypertension the South African adult population (15+ years), by area of residence. Estimates from population surveys.

Area	SADHS 1998		NIDS 2008		SANHANES 2012
	f [%]	m [%]	f [%]	m [%]	m + f [%]
Urban	27.3 (0.68)	24.6 (0.76)	38.1 (0.79)	32.4 (0.91)	
Rural	24.1 (0.72)	21.5 (0.85)	33.2 (0.72)	27.7 (0.83)	
Urban Formal					34.4 (1.60)
Urban Informal					22.1 (1.70)
Rural Formal					35.7 (2.19)
Rural Informal					29.5 (1.48)

m = Males; f = Females. Standard errors in brackets.
Estimates are weighted and unadjusted. Data from [372, 374, 377].

2.3.3 Racial ascription

A large number of studies have examined racial differences in BP, prevalence of hypertension and other CVD risk factors.[3]

In the US, where most of the studies have been carried out, the prevalence of hypertension greatly differs across racial ascriptions, and African Americans of both sexes and in all age classes tend to have higher levels of hypertension than White Americans. Other differences between individuals of different racial ascriptions have been observed[50], but the findings are less consistent across studies, genders and ages.[3, 419]

Studies in sSA also agree that people of African ancestry ('*Blacks*') are at higher risk of hypertension than those of European ancestry ('*Whites*'), and various explanations — involving differences in genetic predisposition, autonomic nervous system and cardiac function, and environmental/socioeconomic factors — have been proposed.[361, 420] The relative contribution of these factors is still unclear, but the current literature tends increasingly to emphasise environmental rather than genetic factors to explain the higher incidence of hypertension in black subjects.[361]

In South Africa, the distribution of hypertension by racially defined population groups was analysed, among others, by Steyn et al. [410] in the results of the first South Africa Demographic and Health Survey. Using multiple logistic regression, the authors estimated the odds ratios (ORs) for hypertension in the four population groups defined according to the traditional classification formalised during the apartheid era: Asian (or Indian), Black (or African),

Coloured (wide grouping of people of mixed ancestry) and White (or European). They showed that racial differences were large and significant in the crude data, with the black rural population at the lowest level of risk and Whites at the highest. Nevertheless, after adjusting for age, gender and basic socioeconomic variables, the differences in the odds of hypertension among population groups became smaller and, except in the rural African group, not statistically significant.

These results are not surprising considering the South Africa's long history of institutionalized segregation of the population on the basis of race, resulting in a strong association between socioeconomic characteristics and race.[421] An association which is still evident after more than 20 years from the formal end of the apartheid regime, as showed by the results of the 2001 population census which clearly indicates that the distribution of many of the SES indicators is persistently skewed in favour of the White minority group [51].[402] For these reasons — in South Africa more than in other countries — the racial categorization of the individuals acts very often as a reliable proxy for socioeconomic patterns, overshadowing its obvious association with phenotipic and putative genetic characteristics.

2.3.4 Age and gender

A number of studies in countries with diverse cultures and at different stages of economic development have documented a consistent relation between age and BP. The great majority of studies have demonstrated a general tendency of both SBP and DBP to rise during childhood and adulthood, with a rate consistently greater for the former than for the latter. Systolic pressure maintains this trend until the eighth or ninth decade, albeit with a lower gradient after the sixth decade. Diastolic pressure tends, by contrast, to remain constant or decline after the age of 55/60 years.[3] The typical association of BP with age calculated from a large scale population study are shown, for example, in the article by Wright and Østbye [345].

A few exceptions have been observed to this almost universal pattern. Namely, it has been observed in some isolated populations with dietary habits characterised by extremely low sodium intake, that both SBP and DBP do not show any rising trends, and remain stable (and low) until old ages.[422] These findings, interpreted together with the results of migration studies which consistently show the tendency of migrants to assume quickly the BP pattern of the country of arrival, supports the hypothesis that age-related changes in blood pressure are not a biological necessity, and environmental/lifestyles factors play a major role in shaping this relationship.[3, 422, 423]

Gender differences in the relationship between age and BP are also well documented. From birth though infancy men and women tend to have similar values of BP, but from adolescence onwards men tend to display higher average levels. Discrepancies are most evident in

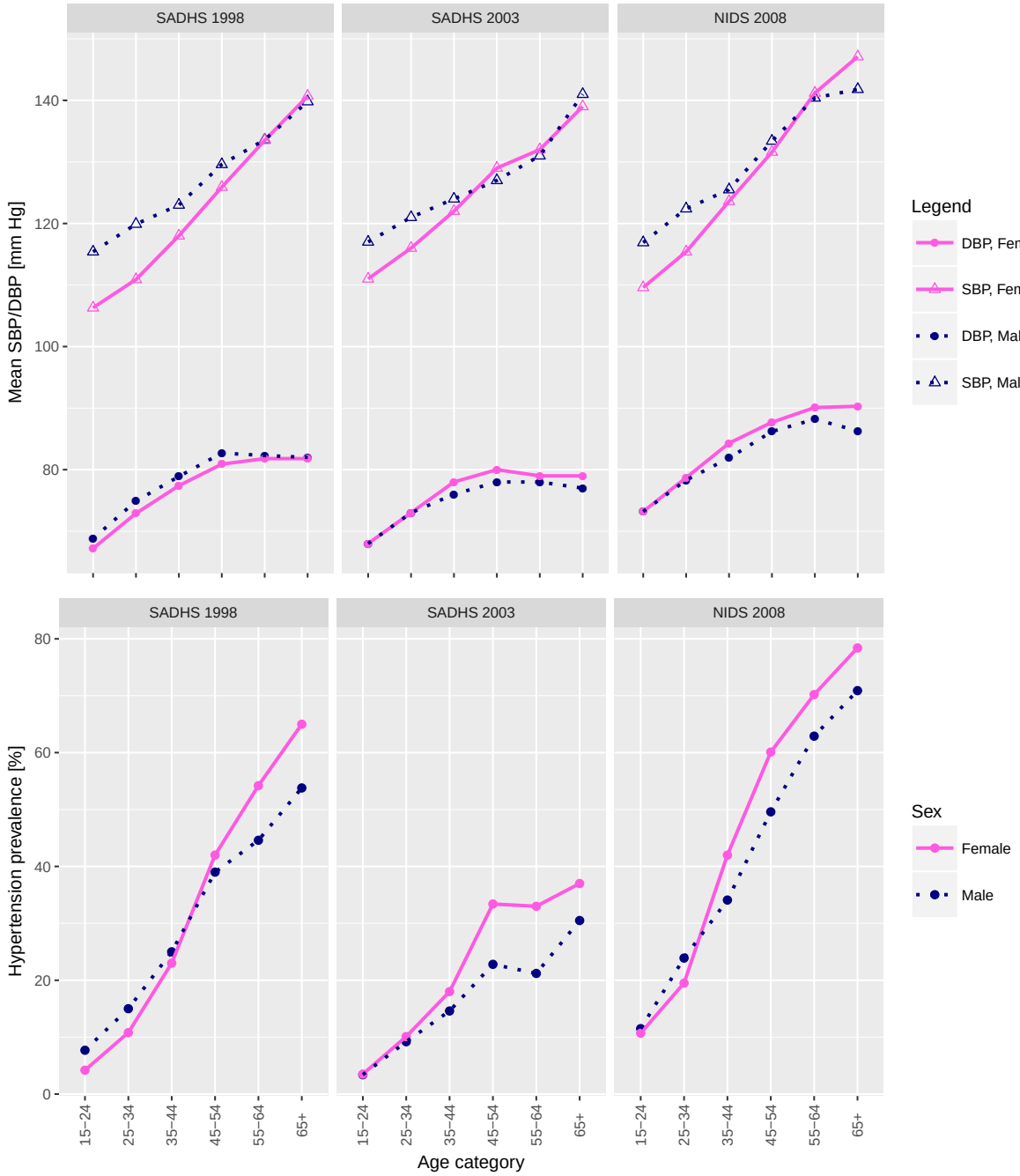
young and middle-aged adults. Later in life the difference narrows again and the pattern often reverses, mostly because of the higher rate of premature death of hypertensive men in middle-age.[422, 424–426]

The incidence and the progression rate of hypertension reflect the same trend: both are remarkably higher in men than in age-matched women until middle-age, when this gender relationship no longer exists, and the incidence as well as the rate of progression of hypertension and other cardiovascular diseases are very similar in both sexes.[427, 428]

The results of large population studies in the South African population (graphically depicted in Figure 2.27) confirm the general findings summarised above. Both SBP and DBP tend to increase with age, but the rate of increase in DBP is reduced after middle age, while is almost constant for SBP.

The figure also show that women have a steeper increase in DBP and in the older age groups their average BP is higher than males. These gender differences in the rate of increase of BP (especially SBP) correspond to the known fact that the prevalence of hypertension is higher among men at younger age, but higher among women later in life. This ‘inversion’ of the relative prevalence of hypertension between men and women does not seem to happen in the estimates from the 2003 edition of the SADHS, but this inconsistency might be another consequence of the unreliability of DBP data in that survey.

Figure 2.27: Age- and gender-specific mean values of blood pressure and prevalence of hypertension in the South African population. Results from large scale population surveys.



SBP, DBP = Average values of systolic and diastolic blood pressure; SADHS = South Africa Demographic and Health Survey; NIDS = National Income Dynamics Study.

2.3.5 Diet

The relationship between dietary factors and BP has been examined in a large number of studies, and, even though various aspects are still unclear, some findings can be considered well established. The most relevant among these are:[429–431]

- Lowering the intake of sodium produces a decrease in BP in hypertensive subjects and, to a lesser extent, in normotensive individuals.

  Evidence of this association has been found in observational and experimental studies, and it is consistent across different geographical and socioeconomic contexts.[432] In South Africa, a randomised study in a natural urban environment confirmed the positive effect of a low-sodium diet in lowering blood pressure in drug- treated mild-to-moderate hypertensive subjects.[433]

  On the contrary, increased dietary potassium intake seems also to reduce the risk of hypertension, but results are less established than those relative to the effect of sodium;

- Increased protein, fibre, monounsaturated fat and fish oil is associated with a decrease in BP, even though the effect in normotensive patients is less established;

- A diet high in fats is generally associated with raised blood pressure. However, conflicting results have been found in studies which have taken into account the increase in body weight/BMI usually associated with high-fat diets.

Besides these results referring to broad categories of foods, the literature offers evidence on the hypertensive (or hypotensive) effects of a large variety of specific substances/products which are part of the diet of many people. The analysis of these specific effects is beyond the scope of this review, but it is important to highlight that the hypertensive/hypotensive effects of some products can be large, certainly worth consideration at clinical level, and might be also of epidemiological interest when it refers to products in widespread use. For example, a series of studies have analyses the effects on BP of the regular consumption of liquorice, the root of the *Glycyrrhiza glabra* commonly used for its taste and as a thirst-quencher, and contained as a flavourant in many foods (especially candies), drinks and tobacco preparations[52]. The studies have clearly documented large hypertensive effects. For example, the studies by Sigurjonsdottir and colleagues found average increases by 6.5 $mmHg$ for SBP and 3.4 $mmHg$ for DBP after consumption of moderate quantities of licorice, with a clear dose-response relationship and values as high as 15 $mmHg$ in SBP for higher doses.[434, 435] The mechanism underlying this effect is also known, and related to the ability of licorice to inhibit the peripheral metabolism of cortisol with consequent retention of sodium and water.[436]

2.3.6 Chronic alcohol use

Long-term elevation of blood pressure among heavy drinkers has been repeatedly found in large scale population studies[437, 438], and the results of a recent systematic review[439] of studies using mendelian randomization to take into account confounding factors[53] strongly support the hypothesis of a direct relationship between alcohol consumption, blood pressure and the risk of hypertension.

The relationship has been demonstrated in both sexes and among several racial groups and independently of the type of alcoholic beverage and the presence of common confounding factors such as smoking and salt intake.[437, 438]

The dose-response relationship between alcohol consumption and hypertension has also been analysed repeatedly. In their meta-analysis Taylor et al. [440] found evidence for a linear dose-response relationship in men, with a relative risk for hypertension of 1.57 at 50 g pure alcohol per day (equivalent to 3.5 glasses of wine) and 2.47 at 100 g per day, compared to non drinkers. Among women, they found a modest protective effect for consumption below 5 g per day, and a linear dose-response relationship thereafter, with a relative risk for hypertension of 1.81 at 50 g per day and of 2.81 at an average consumption of 100 g per day.

Analogous results of increased risk of hypertension with increased used of alcohol have been found in various studies in sSA. In South Africa, a significant relationship between problem drinking (measured by the CAGE questionnaire[441]) and increased odds of hypertension has been confirmed in the first edition of the SADHS.[410] Other smaller-scale studies also found similar relationships between alcohol and blood pressure.[442–444] The analysis by Cois and Ehrlich [19] of the baseline data from the NIDS found that, among women, alcohol use was associated with a significant increase in DBP, independent of its effect on BMI. The same effect was not significant among men and, in both genders, for SBP.

2.3.7 Chronic use of tobacco

Acute effects of smoking, in Section 2.1.4.1.2, result in a transient rise of the blood pressure, usually lasting less than 30 minutes, and some studies suggest a positive interaction with coffee drinking.[445, 446].

However, the evidence that this acute hypertensive effect translates in an increased risk of hypertension in chronic users of tobacco products is scarce.[447] On the contrary, most observational studies show that habitual smokers have lower blood pressures than non-smokers.[448, 449] This seeming contradiction has been explained mainly by the inverse relationship of smoking with body weight, and by the vasodilator effect of cotinine, the major metabolite of

nicotine.[450, 451]

Evidence from South Africa is contradictory. For example, the *Transition and Health during Urbanisation of South Africans (THUSA)* study reported a direct association between smoking and both systolic and diastolic blood pressure in women, but no association in men,[452] while the analyses by Cois and Ehrlich [19] of the NIDS database offered evidence of a protective effect of smoking (mediated mainly by a decrease in BMI) on BP.

2.3.8 Body weight and obesity

The link between obesity (defined, in adults, as having a BMI $\geq$ 30) and hypertension — and, more generally, between BMI and blood pressure — has been documented in many large epidemiological studies, and the burden of hypertension attributable to obesity has been found high both in men and women. Some studies have also documented the independent effect of waist circumference (a measure of central adiposity) on BP.[453]

Population-based studies consistently demonstrate an increased risk of hypertension among overweight and obese people. Compared with normal weight cohorts (BMI $<$ 25), obese individuals have a 2- to 3-fold risk for developing high blood pressure. The mean systolic and diastolic blood pressure values were estimated to be 9 and 7 $mmHg$ higher in obese men and 11 and 6 $mmHg$ higher in obese women compared to cohorts with normal BMI.[454]

A meta-analysis by Neter et al. [455] of the results of 25 randomised controlled trials published between 1978 and 2002 on weight reduction in racially diverse populations, showed an average reduction of 4.4/3.6 $mmHg$ for an average 5 kg weight loss obtained by energy restriction, physical activity, or both. Larger reductions were achieved in populations that included subjects in antihypertensive treatment. Other studies have found evidence regarding the non-linear shape of the relationship body weight/BP. In particular, the meta-analysis by Cappuccio et al. [456] of the results of 13 studies in populations of African descent, show that the strength of the association tends to decrease as BMI increases.

In South Africa, various studies have confirmed this general finding of a positive association between BMI (or obesity) and hypertension. Among these the studies by Mollentze et al. [383] in the Free State, Steyn et al. [443] in the Cape Peninsula, and, more recently, the THUSA study in the North West Province[452, 457].

2.3.9 Physical activity

Observational and experimental studies have provided consistent evidence of an inverse relationship between regular physical activity and blood pressure, including studies carried out

in sSA.[458–460] The reductions associated with physical activity can be large (6 -7 $mmHg$ for both SBP and DBP) and comparable with the hypotensive effect of pharmacological treatments.[461]

While the main mediator of the hypotensive effect of physical activity seems to be the reduction in body weight, there is evidence that other independent mechanisms are involved. Various studies have found, in fact, that the relationship physical exercise/BP persists after adjustment for body weight and the phenomenon of the rapid (and of long duration) post-exercise decrease in blood pressure discussed in Section 2.1.4.1.3 is also not explained by changes in body weight.

The exact nature of the alternative mechanisms underlying the hypotensive effect of physical exercise not mediated by body weight is still unclear, but it might be related to the reduction of the RHR constantly observed in athletes and individuals who exercise regularly.[462] The mediation study by Cois and Ehrlich [19] on data from the South African NIDS found that the protective effect of physical exercise on DBP (but not on SBP) was partly mediated by a reduction in RHR, thus offering some support to the hypothesis above.

2.3.10 Stress

By definition, stress is any uncomfortable "*emotional experience accompanied by predictable biochemical, physiological and behavioural changes*".[463] As reviewed in Section 2.1, it has long been acknowledged that among these "physiological changes" we must include short-term variations in BP.

Chronic exposure to a variety of psychological stressors (including job strain, social isolation, marital conflicts, and racial discrimination) have been associated with increases in long-term average of BP and risk of hypertension,[464] and the positive results of some clinical trials on the effects of relaxation techniques in the treatment of mild hypertension seem to support the hypothesis of a causal link.[431].

The causal mechanism underlying these associations is not completely clear, but is generally believed to involve a sympathetic nervous system response, in which release of catecholamines leads to increased RHR, cardiac output, and BP. However, even though sympathetic responses to acute stress are well documented, the process by which stress contributes to *sustained* BP elevation over time is not well understood. Hypotheses (not mutually exclusive) are the repeated activation of this system, failure to return to resting levels following stressful events, failure to habituate to repeated stressors of the same type.[464, 465]

2.3.11 Early life determinants

A growing literature shows how the risk of developing hypertension and cardiovascular disease (in particular haemorrhagic stroke, strongly related with BP) is directly associated with early-life or pre-birth factors such as a greater number of siblings, low birth weight, and socioeconomic disadvantage.[466–469]

The causal pathways explaining these findings are only partly known. Among others, the cumulative effects of inter-generational changes in nutritional habits and food availability has been often cited as a possible explanation of the unequal distribution of hypertension across individuals belonging to different birth cohorts, though mechanisms of genetic programming also advanced to explain other changes in health profiles. There is evidence, for example, that relates early-life undernutrition and rapid compensatory growth in children previously undernurished to higher BP and risk of hypertension during adolescence and adulthood.[470–472] Breast-feeding has been also found directly associated with lower offspring blood pressure, with a possible physiological explanation in the fact that sodium levels are lower in breast milk than in most formula feeds.

2.3.12 Relationships between risk factors: an ecosocial perspective

A large body of research has analysed the complex relationships between socioeconomic variables, biological and behavioural risk factors, and health.

The prevalent interpretative models which have guided this research is the eco-social perspective, where individual lifestyle variables are embedded in social relationships and "fundamentally" shaped by contextual socioeconomic factors at different levels.[473] In this perspective, cross-sectional differences in BP across population strata (e.g. between rural and urban dwellers, or between subjects with different education) and temporal trends are seen as the result of a causal chain in which changing environmental conditions (cultural, social, economic) play the role of fundamental determinants and behavioural variables (e.g. physical activity and salt consumption) and biological factors (e.g. body weight) the role of proximal mediators.[370, 473, 474]

The specific elements of this causal chain have been increasingly studied in high-income countries in the last decades and — despite the fact that the picture is far from complete — some consistent relationships between socioeconomic indicators and BP distribution through biobehavioural risk factors have been identified.[9–11]. In particular, research in various populations has shown quite consistently that the unequal distribution of a relatively small number of risk factors (namely body weight/shape, level of physical activity, stress, smoking and nutritional habits) explain a sizeable part of the differences in BP across population strata.[2]

However, the literature regarding possible mediators of the observed relationship between socioeconomic variables and BP in LMICs and in sSA in particular is limited and the results much less consistent.

The identification of the possible mediators of the observed relationship between socioeconomic variables and BP is not among the objectives of this study. However, for completeness, this section presents a brief summary of evidence regarding the association between the biological and behavioural factors reviewed above and indicators of SES in the South African population, and their potential role in explaining the observed difference in BP and prevalence of hypertension across socioeconomic strata.

Age and gender:

Age and gender are often associated with socioeconomic indicators in many contexts, and this is certainly the case of South Africa. For example, Figure 2.28 shows mean age and proportion of males across quintiles of household income per capita, and indicates a clear direct association between income and mean age, as well as between income and male gender.

The existence of established associations of age and gender with both SES indicators and BP, make these variable likely candidates for confounders of the observed association between SES and BP.

Diet

A growing literature shows that 'healthy' dietary habits (from a cardiovascular point of view) are clearly positively associated with socioeconomic status, with a likely causal relationship: lower SES entails restricted access to healthy food both because of economic reasons — processed food high in fat, calories and salt is usually cheaper and more available in underserviced areas than healthier food — and because of lower levels of health-consciousness in the lowest SES strata of the population.[475–477]

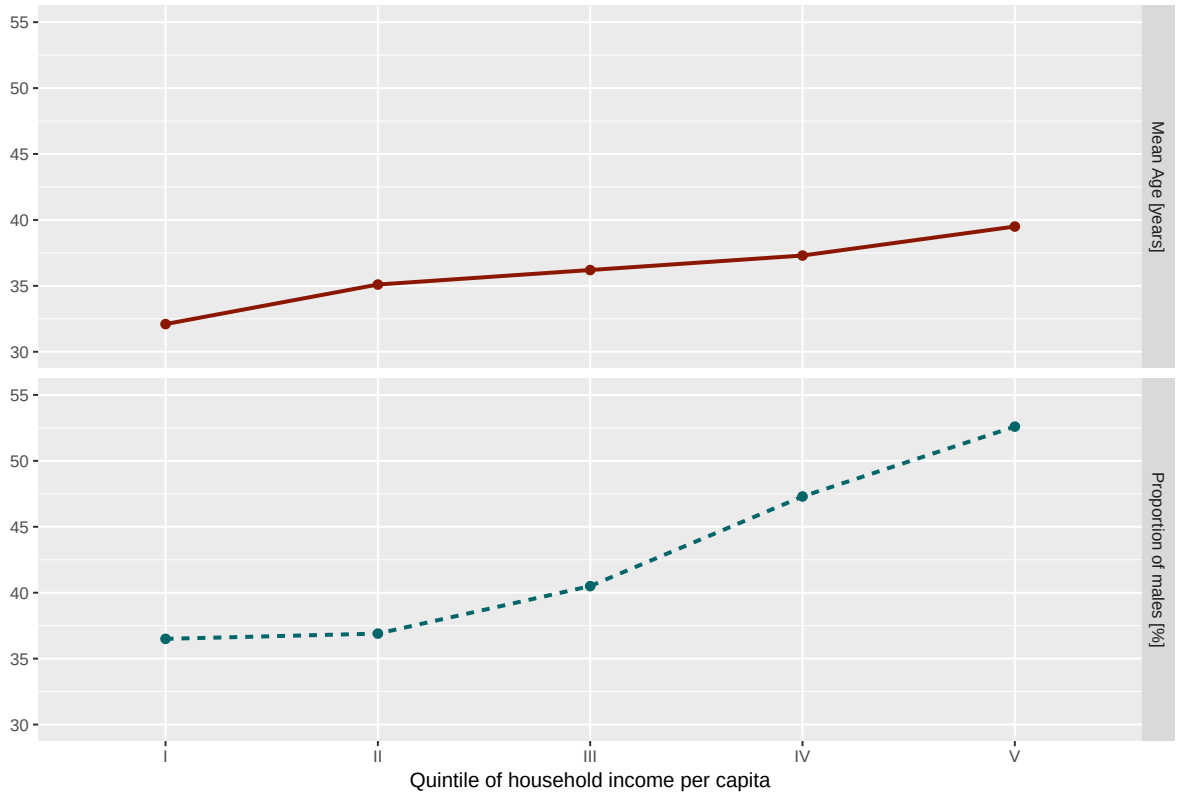
Various studies conducted in South Africa largely confirm this relationship, opening the door for a role of diet as an important mediator of the observed SES/BP association.[478–482] More precisely, they suggest that dietary habit may partly mediate a protective effect of high SES against elevated BP.

However, considering that, beyond SES, dietary habits are strongly determined by cultural factors, their plausible mediating role does not exclude the possibility that in some cases diet may act as confounder, as well as mediator.

Alcohol

Evidence exists that the prevalence of alcohol use — and especially of problem alcohol use — is significantly influenced by socioeconomic factors.[483] The pattern of this association

Figure 2.28: Mean age and proportion of males by quintile of household income per capita. Estimates for the South African adult population (15+ years) in 2008.



Estimates based on data collected during the baseline wave of the National Income Dynamics Study.

is, however, complex and different types of associations are shown in different studies, depending on gender, race, context, SES indicators and outcome metrics (alcohol use, misuse, or dependence).[484]

In South Africa the analyses of the data from population surveys support in general the hypothesis of an inverse association between problem drinking and SES, while no consistent association has been found between amount of alcohol used in itself and socioeconomic variables (excluding race, when considered as a proxy for SES).[411, 485–487]

Smoking

The association of smoking with SES, on the contrary, is well established both in general, in sSA, and in South Africa in particular. Population-based data from 16 Demographic Health Surveys in 14 countries have been reviewed by Pampel.[488] Among men aged 15 to 54 years,

higher prevalence of cigarette smoking was significantly related to lower education and lower occupational status. Results for women (aged 15 to 49 years) showed much a lower smoking prevalence than men but similar socioeconomic patterns of use. Similar inverse relationships between SES and smoking has been found by Bovet *et al* in Tanzania.[489] Overall, these findings are consistent with the research results in high-income countries.[484]

South Africa does not differentiate itself from this general trend. Data from the SADHS in 1998 show that people in the lowest wealth quintile have the greatest overall prevalence of smoking.[411] The study by Mfenyana et al. [490] in the Northern Province show, similarly, an inverse relationship between education and smoking, after adjustment for age and gender. The same results were found in the 2003 wave of the SADHS.[373]

Taken together, the findings above suggest smoking as a possible mediator of the association between SES and BP, even though the magnitude of the mediating effect (and the direction of it itself) is probably context-dependent.

Body weight and shape

Various studies have found a significant association between SES and body weight, BMI, obesity and measures of central obesity, like waist or waist-to-hip ratio.[489–491] In affluent countries, these associations are typically inverse,[492] whereas in sSA in many cases a direct relationship between measures of SES and weight/obesity have been found.

In South Africa, an analysis of the 1998 South Africa Demographic and Health Survey found that both BMI and waist circumference were directly associated with education in men, while the relationship was U-shaped in women: subjects with either no education or with tertiary education showed significantly higher values of BMI and waist circumference than those with primary or secondary education.[493] Multivariate analyses of the NIDS survey, done a decade later (and adjusted for age, sex and race) showed yet a different pattern of association between the socioeconomic variables and obesity in men and women. In both genders household wealth (measured by number of assets) was directly associated with BMI and obesity (although each *additional* asset had a larger effect on the odds of being obese among women than among men), but a statistically significant, direct, relationship with education was only found in men.[377]

Taken together, the results above strongly suggest obesity as a possible mediator of the association between SES and BP in the South African population, even though — as commonly happen in LMIC — the magnitude and direction of the effect do not match those most consistently found in high-income countries.

Physical activity

The association of physical exercise with SES has been analysed in various studies, whose findings are difficult to summarise because of the variety of SES indicator and, especially, of

measures of physical activity. In particular, studies differ according to whether they measure the *total* physical activity (i.e. including occupation, commuting and recreational activities) or only *leisure-time/sports* activity. It is often acknowledged that an active lifestyle tends to be a necessity for those with very low SES, while adoption of more sedentary, westernised, lifestyles is a privilege affordable only among those with medium-high socioeconomic position.[494] Therefore, measures of physical activity based only on leisure time tends to be less representative of the global level of physical activity with decreasing SES, thus biasing observed relationships between SES and total physical exercise (the plausible determinant of the health effect).

In sSA published research on the socioeconomic determinants of physical activity in adult is quite sparse. The 2006 systematic review by Gidlow et al. [494] on studies that reported data on physical activity in relation to socioeconomic status only include a study from Africa. The study was carried out on 799 Nigerian civil servants, and its results indicated a lower level of physical activity among senior staff (a marker of higher socioeconomic status) compared to junior staff, in most age classes.[458] The cited analysis by Cois and Ehrlich [19] of South African general population data estimated the association of education and household income per capita as SES indicators with a self-report measure of leisure-time physical activity, and found a significant direct association between income (but not education) and physical activity, in both genders.

No other study, in my knowledge, has explicitly addressed this aspect among *adult* South Africans, while it has been studied among children/adolescents. The findings of the studies in this younger population seems to support the existence of a direct relationship between SES indicators and measures of physical exercise.[495, 496] However, the comparability of these results with those in adult populations is questionable, both because of the different age-range and because of the different measures of physical activity.

In any case, the results summarised above suggest that physical activity should be considered among the possible mediators between SES and BP.

Stress

Numerous studies — recently reviewed by Spruill [464] — have explicitly analysed the relationship between BP and indicator of SES, and have generally demonstrated a graded relationship between SES and risk of hypertension. Various indices of SES have been studied, the most common being educational attainment, occupational status, and income; others include social class, social status, and neighbourhood characteristics. Moreover, low SES has also been associated with characteristics of the circadian rhythm of BP associated with hypertension and increased CVD risk, namely reduced nocturnal dipping and delayed recovery of BP following acute stress.[497, 498]

The involvement of the sympathetic nervous system in the response to stress has led some studies to analyse the role of RHR (which is a known and easily measurable marker of the activation of the sympathetic system) as a possible proxy for chronic stress. Some of the studies on the subject have been conducted in Africa. Among these the THUSA migrant study,[452] investigated the relationship of RHR and level of urbanization. The study found that, among males, subjects living in informal shacks in peri-urban areas had the highest age-adjusted RHR, while the lowest levels belonged to farm-workers and to the urban upper class[54]. The authors interpreted these results on the light of the finding that among subjects recently moved to the city from rural areas the prevalence of systolic, but not diastolic, hypertension was particularly elevated. They suggested a "s*tress-mediated*" explanation: because of the large load of unfamiliar stimuli that they need to process "*their cardiovascular system is in a hyperkinetic state where the cardiac output and heart rates are high with high systolic pressure and normal vascular resistance*".[452, p. 784] A possible mediating role of chronic stress between socioeconomic variables and BP is also supported by the results of the cited mediation study conducted on the population data from the NIDS baseline survey.[19], at least if we accept the assumption that RHR is a marker of activation of the sympathetic nervous system, and thus of stress. The study, in fact, found that, both among men and women, RHR was involved in a significant mediation path between education and DBP.

Urban vs. Rural dwelling

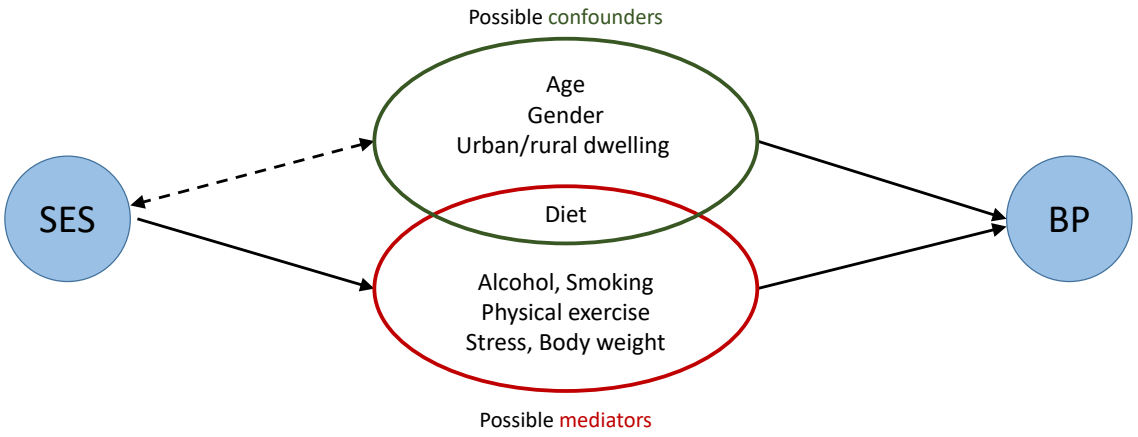
There is no doubt that the distribution of many SES indicators is remarkably different between rural and urban areas, and this inequality favours urban areas (see, for example, the data on poverty level from Statistics South Africa[499]).

Despite the fact that the interpretation of statistics regarding the urban/rural divide is complex[55], the evidence clearly supports the need to consider the urban/rural variable as a plausible confounder of the SES/BP relationship.

Relationships between risk factors: a graphical summary:

The path diagram of Figure 2.29 summarises graphically the results discussed above, and shows the possible role of the factors above in the relationship between socioeconomic status and BP.

Figure 2.29: Possible mediators and confounders of the relationships between SES and blood pressure. Summary path diagram.



Single-headed solid arrows indicate hypothesised causal relationships; Double headed dashed arrow represent associations of unspecified nature.

2.4 Conclusions

Various considerations can be drawn from the overall interpretation of the results of this literature review. They can be summarised in five main points:

1. **The operational definition of blood pressure is complex.**

   Despite its seeming simplicity, the concept of blood pressure is operationally complex and the literature abounds with alternative definitions often only implicitly (and, sometimes, ambiguously) present in the methods section of scientific articles and research reports.

   Different operational definitions result in observational and experimental datasets with different characteristics. Variables that represent BP data collected according to different definitions have different distributions within and across populations and different associations with other variables of interest. The literature is consistent in showing that these differences can be extreme and of substantial importance from a clinical and/or epidemiological perspective: for example, while *ambulatory* BP is strongly associated with a host of cardiovascular outcomes, single-visit *office* BP shows almost no relationship with CVD risk.

   The use of inconsistent definitions of BP in different studies has profound consequences for the comparability of their results, upon which the estimation of long-term trends in South Africa BP relies, given the lack of on longitudinal data. The problem is, moreover, exacerbated when the research question concerns temporal trends in the prevalence of hypertension — rather than the underlying distributions of SBP and DBP — because of the changes in classification thresholds over time.

2. **Estimating blood pressure is an error-prone operation, both at individual and population level.**

   The second element that clearly emerges from the review is that both the actual measurements of BP in individual participants in a survey and the subsequent estimation of population means and descriptive parameter are difficult and extremely error-prone operations.

   Large biological variability of BP and extreme sensitivity of the readings to the characteristics of the instruments and to the implementation of the measurement procedures are sources of potentially severe bias in individual measurements. And, even though for some of these sources of error the epidemiological investigation can rely on plausible assumptions of randomness and, therefore, reasonably assume small bias in large samples, this is not the case for many of them. Seasonal and circadian variations, for example,

are clearly not random and their effect on the measurement cannot be ignored, neither at individual nor at population level, especially when the interest is the comparison between separate estimates. Lack of representativeness of the samples and unwarranted assumptions in the analysis phase are other potential sources of large errors, which add to the aforementioned ones.

These considerations are backed by various examples (in South Africa and elsewhere) of estimates of BP-related quantities carried out by different authors in the same target population with contrasting results.

3. **The evidence about long- and medium-term trends in blood pressure and prevalence of hypertension for the South African population is complex and partially inconsistent.**

   The overall evidence from large-scale studies seems to point to the conclusion that, on average, the prevalence of hypertension in the South African adult population as a whole has been on the rise between 1998 and 2012. Age-specific prevalences seems also to show a growing trend, more pronounced among older subjects and possibly reversed in recent years among those in the youngest age categories.

   However, when the analysis includes a broader variety of studies and a separate consideration of the underlying distribution of BP, the picture becomes more variegated, and inconsistencies related to study design, data collection, measurement procedures and modelling assumptions become apparent. Trends in SBP and DBP do not match, results from surveys carried out in the same period are significantly different from each other, and rates of changes seem to reverse in some periods.

   All published studies estimated trends by comparing sequences of cross-sectional estimates from independent studies, relying on statistical adjustment to overcome methodological differences. This adjustment certainly included some of the major factors that can hinder the comparability between study, chiefly age, gender, rural vs. urban place of residence and a few others.

   However, the results of the first part of literature review show that many other factors have a substantial influence in the results of inter-survey comparison (e.g. inconsistent sampling frames, type of measurement instruments and procedures). How much neglect of these possible sources of bias has affected the estimated trends is a completely open question[56].

4. **The distribution of blood pressure and prevalence of hypertension in South Africa differ across socioeconomic strata.**

   The pattern of association between socioeconomic variables and BP is more complex and variegated than those observed in high-income countries. However, there is consistent

evidence that individual BP values and hypertension risk are significantly affected by indicators of SES, including education, income and wealth.

5. **Some biological and behavioural risk factors have the potential to be important drivers of the observed variations of BP over time.**

   Age, gender, race, diet and nutrition, chronic use of alcohol and tobacco, body weight and other related variables, physical activity, stress and heart rate, place of residence are all factors for which there is consistent evidence of a causal association with blood pressure/hypertension. Their variations over time, therefore, may play a non-negligible role in explaining changes in the distribution of BP.

Notes

[1] The concept of basal blood pressure has seen a renewed interest only in the last years, when the availability of automatic devices has made it relatively easy to obtain multiple readings of blood pressure when subjects are relaxed and without the need of extraneous presences. In particular, ambulatory monitoring devices provide the opportunity of collecting multiple readings of blood pressure during sleep. Nightime ambulatory pressure shows clear conceptual similarity with the Smirk's basal pressure, being the blood pressure during deep sleep, when the patient's 'mental, physical and emotional activity' is supposedly minimal, if not absent.[55]

[2]The two conceptualizations are similar, in the sense that both decompose the casual blood pressure into an underlying slow-varying component and a further component rapidly varying because of accidental factors. However, while Smirk's supplemental pressure is always a positive quantity because the basal pressure is the lower limit of the casual pressure when all 'disturbances' are removed, the 'nuisance' component can be both positive and negative, because it is simply defined as the deviation from the mean of the casual pressure.

[3]Including the current edition of the *South African hypertension guidelines*.[232]

[4]Minutes vs. hours

[5]Among these measures, the difference between daytime and nightime ambulatory blood pressure (*nocturnal dipping*) seems to be the most promising, and there is some evidence that lack of nocturnal dipping may be associated with increased cardiovascular events.[34, 197–199]

[6]The Guyton model has undergone various modifications since its original formulation, but it is still considered conceptually valid and shows good agreement with experimental results. See, for example, the 'exchange of views' at this regard in the April 2009 issue of Experimental Physiology.[500, 501]

[7] In a small proportion of subjects, however, the mean ambulatory BP is higher than to the office BP, consistent with the less widespread phenomenon of *masked hypertension*. A formal definition and discussion of the characteristics of white coat effect and masked hypertension is provided in Section 2.1.4.1.10

[8]In the following exposition, examples and considerations refer to the estimation of the average value $\bar{\mu}$ of blood pressure in a population from individual readings y_i obtained by some kind of device in a subset of population members. When not otherwise stated, the same considerations are in principle valid for any other population parameter related to blood pressure, such as medians and other quantiles, or regression coefficients summarising relationships between blood pressure and other variables.

[9]The term *inferential process* is used here in the general sense of the process of drawing conclusions in the presence of uncertainty, as opposed to a *deterministic process*, were no uncertainty is present or taken into account.

[10]Cardiac output is the volume of blood pumped by the heart per minute, and it is usually measured in ml/min. Cardiac output is the product of heart rate and *stroke volume*, i.e. the volume of blood pumped out of the heart with each beat.

[11]A degenerative disease of the autonomic nervous system also known as *idiopathic orthostatic hypotension*, that occurs in middle age or later in life, more frequently in men.

[12]Five systematic reviews have been carried out between 1999 and 2012 on the the effect of caffeine on blood pressure and risk of hypertension, and their discordant conclusions confirm this lack of strong evidence. Among the four reviews including studies on healthy subjects: (1) two meta-analyses of randomised controlled trials

(RCTs) concluded a slight increase in both SBP and DBP associated with chronic caffeine intake; (2) a meta-analysis of six prospective cohort studies found an inverse 'J-shaped' relationship with high BP risk increasing with up to 3 cups of coffee per day compared with less than 1 cup, and then decreasing with higher intakes; (3) a meta-analysis of ten RCTs and five cohort studies did not show any association between coffee intake and BP or risk of hypertension.[502–505] A fifth review meta-analysed RCTs that examined the effect of habitual coffee intake on BP among hypertensive individuals and did not find any association.[506]

[13]Which is associated with a reduced tolerance to alcohol because of the impaired ability to metabolise acetaldehyde, a highly active and toxic intermediate element in the metabolic pathway of ethanol.

[14] Chronic effects are of no interest in this review of sources of *measurement error* because they produce variations in the long-term averages of BP, which is the quantity of interest. On the contrary, acute effects creates differences between long-term averages and the values at the moment of measurement, i.e. measurement error by definition.

[15]University of Cape Town, Medicines Information Centre. Personal communication 17 March 2016.

[16]Numbers are approximate, recovered from Figure 2 in the article by Wolthuis et al. [132]

[17]These two positions are, by far, the most common. Standing measurements are uncommon both in clinical practice and epidemiological investigation. An exception to this practice is represented, in clinical settings, by measurements in patients who manifest reduced ability to adjust BP when moving from sitting to standing position (*postural hypotension*). In these cases, guidelines prescribe that BP is measured with the patient both lying and standing.[148]

[18]The difference Δp in pressure for a change h in vertical position is approximately given by: $\Delta p = \rho g h$, where ρ is the blood density, and g is the acceleration of gravity.

[19]The exceptions of the finding that blood pressure is higher during cold months than in warm months are rare, and usually consist in finding non-significant variations, which might be related to insufficient power. A notable example of a statistically significant but reversed seasonal effect (higher values in summer) is reported for Iceland by Barnett et al. [167] in their analysis on the data from the WHO's MONICA project ($\approx 3\ mmHg$ difference between mid-summer and mid- winter)

[20]These rhythms may be reversed in people working during the night and sleeping during the day, such as shift workers.[507]

[21]This is the most widely used method to define and quantify the white coat effect, but is is not the only one. Other methods include taking the difference between clinic and home pressure, analysing the differences between the first and the last hour of a 24-hour ambulatory recording, or taking the differences in BP before and after the observed enters the examination room.[221]

[22]A more detailed definition, including the thresholds currently used, is reported and discussed by Gorostidi et al. [508].

[23]For example, a 10-year longitudinal study of a sample of 1332 subjects (representative of the general population 40 years and older in a Japanese community) found that the relative hazard of stroke and death from cardiovascular problems were significantly higher among subjects with masked hypertension.[509]

[24]Or, similarly, when he/she is not familiar with the environment/context in which the measurement takes place

[25]In 1876 the French physiologist Etienne Marey observed that, if he placed a patient's arm in a pressure chamber the pressure of the chamber would fluctuate with the pulse and the magnitude of the fluctuation would vary with the pressure of the chamber. These fluctuations correspond to the occluding effect on the artery of pressure applied uniformly to the arm and the same effect can be observed in the pressure of an occluding cuff.[510]

[26]The problem is less evident for the determination of the MAP, for which there is general agreement in the literature on its relationship with the oscillometric waveform.[261]

[27]Excluding extreme differences, larger than 20/10 $mmHg$, that require specialist evaluation for exclusion of arterial disease.[148]

[28]The sizes of the 4 different cuffs used for the study, and the rules of assignment according to arm circumference are reported in the cited reference. In average, the width increased by $\approx$ 20% from one size to the next.

[29]Namely, those categorised as stage 1 hypertension based on the first reading.

[30]Because of their almost exclusive use in large scale surveys, I focus the discussion on the effects of anthropometric characteristics on the accuracy of auscultatory and oscillometric measurements only.

The finger cuff and applanation tonometry methods have in common with the auscultatory and oscillometric techniques the fact that what it is actually measured is the pressure in the cuff and not the pressure within the arteries. However, neither of them requires the complete obliteration of the arterial lumen and, more importantly, the sensors are applied in different locations (finger and wrist, respectively). Therefore, even though some of the general considerations discussed for the oscillometric and auscultatory methods apply to the other methods as well, the actual consequences on magnitude and characteristics of measurement error are substantially different.

[31]This is because the arm circumference dictates the correct width of the cuff (see figure 2.16). For very large arm circumferences, the length of the upper arm might be smaller than the width of the cuff with the correct bladder size.

[32]Precisely, the averaged biceps and triceps skinfold thickness.

[33]Versus an expected value of 20%, because the studies registered BP values at intervals of 2 $mmHg$.

[34]At least conditionally on the observed covariates.

[35]A similar effect, but less pronounced, is present for DBP.[511, 512]

[36]More precisely, from being representative of the target population *with respect to the variables of interest.* Differences in characteristics unrelated to the phenomenon under study do not affect the estimates.

[37]For example, in groups homogeneous regarding gender, age category, place of residence.

[38]Wich becomes 23.3% when adjusted to the WHO standard population.

[39] A positive relationship between age and both SBP and DBP is well established, and this phenomenon justifies — in regions where the mean age of the population is growing, as in sSA — increasing prevalences of hypertension even in populations with stable age-specific prevalences.[513] Similarly, growing life expectancy increases the number of DALYs even with stable prevalence.

[40]Defined either as subjects 15 years and over or 20 years and over.

[41]This is not exactly the case, because the prevalence of hypertension also depends on trends in DBP and on

possible changes in the distribution of BP values in the population. However, on the reasonable hypothesis of an approximately constant shape of the distribution of BP in the population and in the association between DBP and DBP, the two trends can be considered similar.

[42]As opposed to self-report data, where the hypertensive status is determined by asking the participants.

[43]To calculate the prevalence among the subjects aged 55+ years, I have combined the estimates by Ardington and Case [377] using population data from [380].

[44]The search strings used for querying the search engines were the following:

PUBMED: *("South Africa/epidemiology"[Mesh]) AND ("Blood pressure" OR "Hypertension")*
Restricted to articles published between 1980 and 2015 and to adult human subjects.

SCHOLAR: *allintitle: "Blood pressure" OR "Hypertension" "South Africa"*
Restricted to documents published between 1980 and 2015.

The first search returned 302 articles, and the second 115. Non relevant articles and duplicates were excluded by a preliminary screening by title and abstract. The articles which passed this first screening were examined in detail to assess eligibility and extract the data of interest. The references cited in the selected articles were examined to find further studies.

[45]Studies carried out in the '80s and '90s usually report the prevalence of hypertension calculated using the thresholds 160/95 $mmHg$, rather than the current thresholds of 140/90 $mmHg$.

[46]Either directly provided by the study or calculated from the age structure by assuming a uniform distribution within each age category.

[47] The coefficients used for the adjustment are the following:

BP reading	Gender	Linear regression coefficient $[mmHg/year]$
Systolic	Female	0.40
Systolic	Male	0.44
Diastolic	Female	0.16
Diastolic	Male	0.21

The use of a more flexible functional form for the relationship between age and BP has been considered, but tests with polynomial functions did not produce meaningful differences in the results of the adjustment procedure.

[48]The concept of SES refers to a finely graded hierarchy of social positions which can be used to describe a person's overall social status. It is a complex, multidimensional and abstract concept, in the sense that it cannot be directly measured but only indirectly observed through a series of *indicators*. Among those, the most commonly considered are employment status, type of occupation, educational attainment, income, and wealth. The exact definition of SES and its quantification is a complex subject which embodies a series of methodological and

analytical issues for which no general consensus exists.[514] The discussion of these issues is beyond the scope of this review.

[49]Schneider et al. [411] analysed the same SADHS dataset as Norman et al. [407] with a different method, and found a direct relationship in both genders. The discrepancy between the findings of the two analyses highlights the relevance of modelling assumptions (including the choice of potential confounders to be considered for inclusion in the models) in determining the results of the analyses. It calls, therefore, for a careful justification of the assumptions underlying any analysis and for the routine use of sensitivity analysis when these assumptions cannot be adequately supported on substantive grounds.

[50]For example, between non-Hispanic whites and Mexican Americans.

[51]The consequences of this historical discrimination for the health of its citizens and on the distribution of both communicable and non-communicable disease are well known.[515]

[52]Licorice extracts and its active ingredient (glycyrrhetinic acid) have also a number of medical uses, and they are used in herbal and folk medications.[516]

[53] The studies reviewed by Chen et al. [439] used a common polymorphism in aldehyde dehydrogenase 2 (ALDH2) as a surrogate for measuring alcohol consumption. ALDH2 encodes a major enzyme involved in alcohol metabolism. Individuals homozygous for the null variant experience adverse symptoms when drinking alcohol and consequently drink considerably less alcohol than wild-type homozygotes or heterozygotes.

[54]The differences were similar, but not statistically significant in women.

[55] The interpretation of statistics on urban-rural differences is complex in general and in South Africa in particular for a series of reasons. Among these is the different meaning that many SES indicators assume in the different settings (see, for example, [517] for a discussion of the availability of infrastructure on the interpretation of household assets) and the legacy of the race-based restrictions to the freedom of movement created during the apartheid regime, which has resulted in the persistent existence of sub-areas with completely different sociodemographic profiles. For example, urban centres were declared by apartheid to be the domain of Whites, while Black workers were not allowed to reside there and were located in 'townships' in close proximity the urban centres but physically separated. Therefore, at that time and still largely today, the term 'urban' might refer to extremely different social, economic and cultural contexts.[518]

The classification criteria to define an area as 'urban' or 'rural' are an open subject of discussion in themselves, and have changed between the 1996 and 2001 censuses, for example.[519] The current classification of the South African territory used by Statistics South Africa is the following:

- **Urban formal areas**

  Comprising planned settlements in areas formally declared as residential.

- **Urban informal areas**

  Comprising unplanned settlements on land which has not been surveyed or proclaimed as residential, consisting mainly of informal dwellings (shacks).

- **Rural formal areas**

  Planned settlements in rural areas, mainly commercial farms..

- **Tribal areas and rural informal settlements**

  Comprising rural areas under the jurisdiction of a traditional tribal authority, and informal settlements outside those areas.

[56] Among the studies reviewed, only the meta-analysis by Danaei et al. [17] — which is also the one that adjusted for the greatest number of possible confounding factors — published as additional material a detailed sensitivity analysis regarding the likely effects of the violation of their modelling assumptions.

Chapter 3

Methods

This chapter describes methods and procedures used for data management and analysis. It includes three main sections:

1. **Data sources**

   This first section provides a description of the data sources used in the secondary analyses which form the object of this thesis. For each dataset, details are provided on the characteristics of the primary data collection, namely target population, sampling strategy, period of data collection, response rates and protocols and devices used for measurement of BP.

2. **Data management**

   The second section describes the procedures used to import data from the different sources, select and recode uniformly the variables of interest, screen anthropometric variables for implausible values, generate derived variables and produce a single consolidated dataset.

   A reference table with the formal definition, scale of measurement and coding of each of the variables used for the analyses is also provided.

3. **Statistical analyses and models**

   The third section of the chapter is the most extensive, and includes a description of the general approach and details on procedures, assumptions, estimation methods and software used for the analyses.

   Given that one of the aim of the thesis was the exploration of potential and limits of latent variable techniques and structural equation modelling (SEM) applied to the joint analysis of multiple datasets to recover BP trends, most of this section is dedicated (1)

to description of the general characteristics of the SEM approach to data analysis and highlight their potential utility for the objectives above, and (2) to present and justify the specific models and techniques — within the general SEM framework — that have been applied in this study to produce trend estimates while minimising the possible negative effects (in bias and unreliability) of between-surveys methodological differences .

3.1 Data sources

While self-report data on the prevalence of hypertension in the South African general population are available from different sources[1], five surveys have collected direct measurements of BP in representative samples of the whole population:

- the two editions of the SADHS in 1998 and 2003-2004;
- the SAGE in 2007-2008;
- the NIDS panel survey with four waves of data collection between 2008 and 2014-2015;
- the SANHNES in 2012.

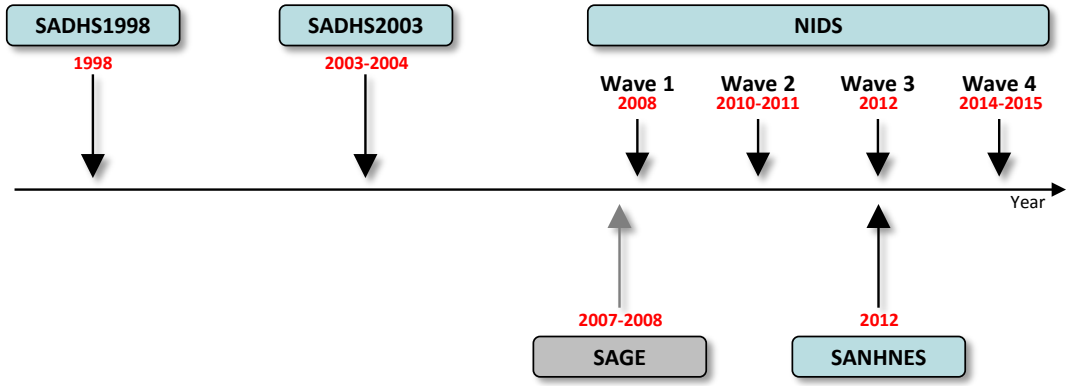
As indicated in Chapter 2, a series of other datasets are available, which include direct measurements of BP in community samples, i.e. in samples not representative of the whole population but rather of a sub-population defined either geographically and/or by other characteristics. These datasets have not been included in the analyses to eliminate a further source of uncertainty in the comparisons (in addition to the other reviewed and, when possible, taken care of in this thesis) represented by differences in the target population.

The SADHS, NIDS and SANHNES surveys targeted the whole South African general population at different points in time, thus potentially providing a set of comparable data to track changes in the distribution BP between 1998 and 2014-2105 in the *adult* subpopulation 15 years and older of interest in this thesis[2]. The SAGE also targeted the general population, but focused specifically on subjects 50 years and older with only a small comparison sample of those between 18 and 49 years, and no representation of the age category 15-18 years. Its data, therefore, are not directly comparable with the remaining surveys, but are included in our preliminary analyses as a potential source of extra information regarding the older age classes.[3].

Figure 3.1 summarises the available datasets and their temporal distribution.

The following subsections 3.1.1 to 3.1.4 summarise the general characteristics of each surveys regarding target population, sampling strategy and response rates, while subsection 3.1.5 presents details on BP measurement methods and devices.

Figure 3.1: Population surveys including measured blood pressure data in representative samples of the South African population.



3.1.1 South Africa Demographic and Health Survey

The SADHS is a repeated cross-sectional survey based on an international methodology with the primary objective of providing data on population, health and nutrition in developing countries.[520]

A variety of demographic and health indicators were collected in the two editions of the SADHS carried out so far (in 1998 and in 2003-2004). Among others, of interest for this study were:

- sociodemographic characteristics of respondents, including urban/rural place of residence and indicators of socioeconomic status;
- chronic health conditions, including past diagnoses and current treatment status for hypertension;
- behavioural and lifestyle indicators, including tobacco and alcohol use;
- clinical and anthropometric variables, including SBP and DBP, RHR, height, weight and waist circumference.

In both editions, the datasets of which are publicly available for research purposes,[521] a large nationally representative sample of the South African population was selected using a multistage random sampling design. The country was stratified into the nine provinces and each province was further divided into urban and non-urban areas[4]. The sampling frame for

the survey was provided by Statistics South Africa[5] based on the list of the approximately 86 000 census enumeration areas (EAs) created during the 1996 census for the first edition, and for the 2001 census for the second edition. Within each stratum a two-stage sampling strategy was applied. In the first stage a set of EAs — the primary sampling units (PSUs) — were selected with probability proportional to size, the size being the number of census visiting points in the EA. The second stage of selection involved the systematic sampling of households from the selected EAs. Among these, every second household was considered for the adult health survey. In this second household, all adults aged 15 years and over were eligible to be interviewed with the adult health questionnaire, from which the data of interest for this study were collected.

The period of data collection was January-September 1998 for the first edition of the survey (SADHS 1998) and October 2003 to September 2004 for the second edition (SADHS 2003).

The official reports for the two editions of the survey present the details of the sampling procedure, including the methods of calculation and calibration of the sampling weights provided with the datasets to take into account the sampling design and the unequal response rates across population strata.[372, 373] Response rates for the adult sub-sample are summarised in Table 3.1.

Table 3.1: Response rates for the two editions of the South Africa Demographic and Health Survey.

	1998		2003-2004	
	N	%	N	%
Households				
Selected	12 860	100.0	10 214	100.0
Interviewed	12 247	95.2	7 756	75.9
Adults 15+ years				
Eligible	14 928	100.0	9 614	100.0
Interviewed	13 827	92.6	8 115	84.4
Overall response rate				
Adults 15+ years		**88.2**		**64.1**

Data from [372, p. 7] and [373, p. 10]

3.1.2 Study on Global Ageing and Adult Health

The WHO's SAGE is a longitudinal study which collects data on adults aged 50 years and older from nationally representative samples of the population in China, Ghana, India, Mexico, Russian Federation and South Africa. Data on a smaller sample of adults aged 18–49 years are also collected for comparison purposes.

Primary objectives of the study are:[375]

- To obtain nationally representative, reliable, valid and comparable data on levels of health for adult populations aged 50 years or older;
- To examine patterns and dynamics of age-related changes in health and well-being, and investigate socioeconomic consequences of these health changes;
- To supplement and cross-validate self-report measures of health to improve their comparability;
- To collect data on health examinations and biomarkers to assess reliability of data on morbidity and risk factors, and monitor the effect of interventions.

The first (and unique, so far) wave of the South African leg of the study (SAGE 2007) was carried out between January 2007 and October 2008

The SAGE sampling strategy was a two-stage probabilistic sampling designed to yields national and sub-national estimates to an acceptable precision at provincial level, by residence (urban and rural), and by population group according to the traditional racially defined classification used in South Africa (see Section 2.3.3).

In the first stage 600 PSUs were randomly selected from the Human Sciences Research Council master sample of 1000 EAs,[522, p. 48] stratifying by province, residence and population group. The EAs were selected with probability proportional to size, with the estimated number of people aged 50 years or older in each EA as a measure of size. In the second stage, 30 households were selected within each PSU and screened for the presence of members 50 years or older. All households with at least one person 50 years or older were included and all individuals in that age range considered eligible for interview. Of the remaining households, two were randomly selected and, in each of these, one respondent aged 18–49 years randomly selected to constitute a cohort of younger adults for comparison purposes.

Of the 600 PSUs originally selected, only 396 were visited owing to time and financial constraints (62% average coverage, ranging from 50% to 82% across provinces).

Details on design, coverage and implementation of the sampling strategy are presented in the official survey report and in the documentation provided with the dataset,[375, 523] and a summary is shown in Table 3.2.

Table 3.2: Response rates for the Study on Global Ageing and Adult Health.

	N	%
Households		
Selected	6 000	100.0
Interviewed	4 020	67.0
Adults 18+ years		
Eligible	5 490	100.0
Interviewed	4 227	77.0
Overall response rate		
Adults 18+ years		**51.6**

Data from Phaswana-Mafuya and Peltzer [523].
Details on response rates across demographic strata are reported in [375] and [524]. However, the three documents show some minor incongruencies in the absolute numbers of observations.

Because of the focus on older subjects and the consequent undersampling of younger subjects and exclusion of minors 15-18 years, the SAGE data can provide estimates only for the South African population 50 years or older.

The SAGE is committed to the public release of study instruments, protocols and micro-data: access is provided upon completion of a user's agreement available through WHO's SAGE website.[525]

3.1.3 National Income Dynamics Study

The NIDS is a panel survey of a representative sample of the South African population, randomly selected in 2008 and subsequently re-interviewed approximately every two years. The data analysed in this study are those collected at baseline (wave 1) and during the subsequent three waves, in 2010-2011, 2012 and 2014-2015.

Despite the name of the survey, the emphasis in NIDS is not on income but on a wide range of measures of well-being. Similarly to the SADHS, information is gathered on sociodemographic variables, chronic health conditions, lifestyle indicators and a set of anthropometric indicators, including blood pressure.

During the baseline data collection, a two-stage cluster sampling design was used to identify about 7300 households across 400 PSUs randomly selected by Statistics South Africa from a master sample of 3000[6]. The sample was stratified by district council (a second level administrative division of South Africa's territory into 53 areas at the time where the sample was drawn). Trained fieldworkers were instructed to interview and collect anthropometric data on all available subjects belonging to the selected households. The same individuals were re-contacted in the subsequent waves and administered the same questionnaire.

Data collection took place between February and December 2008 for the first wave (NIDS 2008), between May 2010 and August 2011 for the second wave (NIDS 2010), between April and December 2012 for the third wave (NIDS 2012) and between October 2014 and August 2015(NIDS 2014) for the fourth wave.

Details of the design and implementation of the sampling procedure and on the calculation of the different sets of sampling weights included in the datasets are provided in the methodological papers by Woolard et al. [80] and Wittemberg [526], and in the survey user manuals[527, 528].

At baseline, the overall response rate for the adult subsample was 63.0% (see Table 3.3).

Table 3.3: Response rates for the baseline data collection of the National Income Dynamics Study.

	N	%
Households		
Selected	10 858	100.0
Interviewed	7 301	67.2
Adults 15+ years		
Eligible	18 617	100.0
Interviewed†	17 372	93.3
Overall response rate		
Adults 15+ years		**63.0**

Household response rates from Southern Africa Labour and Development Research Unit [529]. Individual adult response rates calculated from the dataset.
† Including 1753 proxy interviews

Attrition in the *stable* part of the cohort (consisting of the individuals who were successfully interviewed at wave 1) was relatively low. Of the 17 372 adults interviewed in wave 1, 13 133 (76%) were re-interviewed at wave 2, 13 136 (76%) at wave 3 and 12 553 (72%) at wave 4.[530, p. 7].

In the present study, however, I considered the *unbalanced* panel as consisting not only of these individuals (Continuing Sample Member, CSM) but also of the individuals who joined the panel in successive waves, either being born of a female CSM or temporarily present in the household but not part of the original sample (Temporary Sample Member, TSM)[7]. Moreover, because of our interest in the estimation of BP trends in the *adult* population, CSMs were excluded from the analyses until they turned 15 years.

Table 3.4 summarises cross-sectional response rates for the unbalanced panel defined as above. Further details on the characteristics of the attrition in the whole NIDS panel (including children) are provided by Villiers et al. [528] and Chinhema et al. [530].

Table 3.4: Number of adult individuals successfully interviewed in the four waves of the National Income Dynamics Study.

		Interviewed in wave 1 (2008)	Interviewed in wave 2 (2010-2011)	Interviewed in wave 3 (2012)	Interviewed in wave 4 (2014-2015)
First present in wave 1	CSM	17 372	14 509	15 595	16 370
	TSM	-	-	-	-
First present in wave 2	CSM	-	822	687	662
	TSM	-	3 401	1 862	1 421
First present in wave 3	CSM	-	-	189	147
	TSM	-	-	3 081	1 516
First present in wave 4	CSM	-	-	-	42
	TSM	-	-	-	4 195
Total successful interviews		17372	18732	21414	24353
CSMs attempted		18 617	20 335	21 555	23 200
TSMs attempted		-	3 533	7 540	13 323
Individual response rate (%)		**93.3**	**78.5**	**73.6**	**66.7**

CSM = Continuing Sample Member; TSM = Temporary Sample Member.

Various versions of the NIDS datasets are freely available for research purposes. This study uses data from wave 1 dataset v.6.1, wave 2 v.3.1, wave 3 v.2.1 and wave 4 v.1.1.[529, 531–533]

3.1.4 South Africa National Health and Nutrition Examination Survey

The SANHNES is a continuous population health survey designed to asses periodically the health status of the South African population and provide information to map the emerging epidemic of non-communicable diseases and analyse its social, economic, behavioural and environmental determinants.[374]

At present, only one edition of the survey has been carried out (SANHNES 2012), between January and December 2012. Data collection focused mainly — but not exclusively — on characterising the health of South Africans with respect to:

- Prevalence of cardiovascular disease, diabetes and hypertension and their major risk factors, namely diet, physical activity and tobacco use;
- Knowledge, attitudes and practices related to both non-communicable and infectious diseases;
- Nutritional status, including alcohol consumption and body weight management;
- Demographic, socio-economic and geographic factors affecting health behaviour and outcomes.

The target population of the SANHNES is the whole South African population living in occupied households, without age restriction. The sampling frame excludes, similarly to the NIDS, individuals living in educational institutions, old-age homes, hospitals and other collective living, as well as homeless people.

A multi-stage, stratified cluster sampling design was implemented, with PSUs represented by EAs from the 2001 population census, and province, locality type (urban vs. rural) and race as stratification variables. EAs were sampled with probability proportional to the number of visiting points (households) in the EA. In each area, over-sampling of the least represented race group was implemented if necessary to ensure the minimum required sample to obtain race-specific estimates. A total of 500 EAs were selected and a random sample of 20 households was extracted from each EA, for a total number of 10 000 households.

Response rates at household and individual levels are summarised in Table for the adult subsample.

Unlike the previous tables, Table 3.5 shows separate response rates for the interview and the clinical examination, which includes the replicated measurements of BP and RHR used in this thesis.

Table 3.5: Response rates for the baseline data collection of the South Africa National Health and Nutrition Examination Survey.

	N	%
Households		
Selected	10 000	100.0
Valid	8 166	81.7
Interviewed	6 307	63.1
Adults 15+ years		
Eligible	18 201	100.0
Interviewed	16 780	92.1
Clinical Examination	7 436	40.8
Overall response rate		
Adults 15+ years (Interview)		**58.1**
Adults 15+ years (clinical)		**25.7**

Data from Shisana et al. [374].

The reason for this separation is related to the particular characteristic of the SANHNES study design, unique among all nationally representative population surveys in South Africa, which is the inclusion of a comprehensive clinical examination performed by health professionals (medical doctors and nurses) rather than lay fieldworkers, and the collection of a relatively large set of biomarkers.[374] Differently from the other surveys, where clinical data were collected at the participants' homes, during the interview, in the SANHNES the clinical examination took place in a clinic, where the participants were invited to travel successively to the interview. While this procedure might have increased the quality of measurements — both because of the qualification of the personnel and the more controlled environment — for the purposes of our analysis it carried two important drawbacks:

- a dramatic increase in missing data on blood pressure, owing to the fact that a sizeable proportion of respondent agreed to participate to the interview at their home, but missed the subsequent appointment at the clinic. For these respondents (about 60% of the number of eligible adults) *all* clinical data are missing, including basic anthropometric measurements such as weight and height.

  Besides the obvious consequences for precision, this proportion of missing data makes room for a potentially large amount of bias in the population estimates, because the mechanism that generates the missing data (i.e. lack of presentation of participants to the clinic) makes the assumption that the data are missing at random hardly tenable,

and the absence of other anthropometric data also makes the introduction of sensible forms of statistical adjustments difficult;

- the possibility of an artefactual average increase in the observed blood pressure compared to the measurement taken at the participants' homes. This is because of the well-known phenomenon of the white-coat effect which is typically more pronounced in clinical than in more familiar environments, and which tends to increase with the perceived status of the observer (see Section 2.1.4.1.10)

The exploratory data analysis confirmed these doubts and ultimately led to the exclusion of the SANHNES data from the analyses.

The dataset of the SANHNES is not in the public domain, but has been provided, for the purpose of the analysis presented here, by the Human Sciences Research Council, which conducted the survey. The terms of the agreement are included in Appendix A.

3.1.5 Measurement of blood pressure

In all surveys, repeated measurements of blood pressure and heart rate were taken, after the participant was seated for at least 5 minutes, by using an automatic oscillometric device. All devices met internationally accepted validation criteria.[534–537][8] and were factory calibrated. In all surveys except the SANHNES the monitors were used with their standard multi-size cuffs. In the SANHNES, clinicians were instructed to use different cuffs according to the participant's arm circumference. The criteria for the selection of the correct cuff size are indicated in Table 3.6[9]. Note that the standard cuff used in the SADHS surveys was not able to adequately accommodate subjects with very large arms.

In the SADHS, NIDS and SANHNES the measurements were taken on the left (or non-dominant) arm resting at the level of the heart, while in the SAGE measurements were taken on the right wrist. Two successive measurements were taken in NIDS, and three in the remaining surveys. Table 3.6 compares the main characteristics of the devices (as reported in their respective user manuals) and measurement procedures, and Table 3.7 provides details on the results of the validation studies.

Despite the fact that the results of the validation studies are specific to the sample used for validation[10] and cannot be directly generalised to the South African population, the figures in the table clearly indicate that the fact that a field device has passed internationally accepted validation criteria does not exclude the possibility of a large amount of bias.

For example, let us suppose that two studies are carried out in a population with the same BP distribution of the samples used for the validation studies, one (*Study A*) using the same

Table 3.6: Comparison of blood pressure measurement methods.

Survey	Device	Device Specifications	Measurements	
			Position	N
SADHS	OMRON M1	*Range*: BP: $0 - 280\ mmHg$ Pulse: $40 - 200\ bps$ *Accuracy*: BP: $\pm$ 3 $mmHg$ or 2% Pulse: $\pm$ 5% *Cuff Range*: Arm 22 to 33 cm circumference	Left arm	3
SAGE	OMRON R6	*Range*: BP: $0 - 299\ mmHg$ Pulse: $40 - 180\ bps$ *Accuracy*: BP: $\pm$ 3 $mmHg$ or 2% Pulse: $\pm$ 5% *Cuff Range*: Wrist 13.5 to 21.5 cm circumference	Right wrist	3
NIDS	OMRON M7	*Range*: BP: $0 - 299\ mmHg$ Pulse: $40 - 180\ bps$ *Accuracy*: BP: $\pm$ 3 $mmHg$ Pulse: $\pm$ 5% *Cuff Range*: Arm 22 to 42 cm circumference	Left arm	2
SANHNES	OMRON M2	*Range*: BP: $0 - 299\ mmHg$ Pulse: $40 - 180\ bps$ *Accuracy*: BP: $\pm$ 3 $mmHg$ Pulse: $\pm$ 5% *Cuff size*: Small: Arm 22 to 26 cm circumference Medium: Arm 27 to 34 cm circumference Large: Arm 35 to 32 cm circumference Thigh-sized: Arm 45 to 52 cm circum.	Non-dominant arm	3

oscillometric device as in the SANHNES and the other (*Study B*) using the same device as in the NIDS. For this reason alone we can expect that Study A's mean SBP estimate could exceed by 3.4 $mmHg$ Study B's estimate, and Study A's mean DBP estimate would be 2.7 $mmHg$ lower than Study B's estimate. The implication of this possibility for comparative surveys is, clearly, important.

Table 3.7: Mean difference between blood pressure measurements taken with various devices and a reference mercury sphigmomanometer. Estimates and standard error from the validation studies.

Survey	Device	ΔSBP (se) $[mmHg]$	ΔDBP (se) $[mmHg]$
SADHS	OMRON M1	+1.25 (4.7)	+0.51 (3.9)
NIDS	OMRON M7	-0.75 (6.5)	+1.35 (5.0)
SAGE	OMRON R6	+0.2 (4.2)	+0.2 (2.9)
SANHNES	OMRON M2	+2.7 (5.0)	-1.4 (3.2)

ΔSBP = Mean difference in systolic blood pressure; ΔDBP = Mean difference in diastolic blood pressure; se = Standard error.
Source: [534], [535], [536], [537].

3.2 Data management

All data were acquired from the data holders in Stata format,[538] and the variables of interest uniformly recoded, renamed, and consolidated into a single dataset. Inconsistencies and obvious coding mistakes were corrected when more accurate values could be plausibly recovered; otherwise the inconsistent values were set to missing. Namely:

- hypertensive medication use was set to 'no' for subjects with no diagnosis of hypertension and, in the NIDS, for those for whom a response (either 'yes' or 'no') was recorded for the question "*do you still have high blood pressure?*" because the question was not asked to subjects on medication;
- day and month of measurement outside the admissible ranges 0-31 and 1-12 were set to missing;
- a few missing values for the stratum variables were recovered, when possible, by combining information from district council, EA and population group;

Outliers in the univariate distribution of the anthropometric variables[11] were identified using the cutoffs shown in 3.8. Values outside the specified range, although not biologically impossible, were deemed to be more likely the result of recording mistakes than actual measurements and set to missing. The cutoffs for blood pressure and heart rate reflect those used by the *Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group* for their worldwide collection of anthropometric data to track trends in metabolic risk factors.[539]

Table 3.8: Plausible values for anthropometric data.

Variable	Unit	Lower limit	Upper Limit
Height	cm	60	250
Weight	kg	30	250
Waist circumference	cm	30	200
Systolic blood pressure	$mm\ Hg$	70	270
Diastolic blood pressure	$mm\ Hg$	30	150
Heart rate	$mm\ Hg$	40	180

For blood pressure, a further cleaning rule was applied, consisting of the exclusion of SBP/DBP pairs when their difference was less than $15\ mmHg$.

Tables 3.9 and 3.10 show the number and percentage of values set to missing because of the procedures described above.

Table 3.9: Absolute number and proportion of values in anthropometric variables excluded from the SADHS, SAGE and SANHNES datasets because of the cleaning rules.

	N = 13826		N = 8115		N = 4223		N = 16941	
	SADHS 1998		SADHS 2003		SAGE 2007		SANHNES 2012	
Variable	n	%	n	%	n	%	n	%
Height	0	0.00	0	0.00	49	1.21	47	0.63
Weight	4	0.03	3	0.04	0	0.00	20	0.27
Waist circumference	0	0.00	28	0.36	162	3.99	36	0.49
Systolic BP	857	2.12	297	1.25	242	1.98	39	0.20
Diastolic BP	817	2.02	298	1.25	336	2.76	87	0.44
Heart rate	142	0.35	34	0.14	23	0.19	35	0.18

N = Total sample size of the study; n = Number of excluded values; BP = Blood pressure.
Proportions refer to the total number of nonmissing values for the relevant variable before cleaning.

Table 3.10: Absolute number and proportion of values in anthropometric variables excluded from the NIDS datasets because of the cleaning rules.

	N = 18617		N = 19307		N = 21810		N = 24856	
	NIDS 2008		NIDS 2010		NIDS 2012		NIDS 2014	
Variable	n	%	n	%	n	%	n	%
Height	0	0.00	0	0.00	6	0.02	0	0.00
Weight	4	0.01	6	0.02	2	0.01	8	0.02
Waist circumference	19	0.07	2	0.01	0	0.00	1	0.00
Systolic BP	468	1.67	726	2.41	12	0.03	26	0.06
Diastolic BP	392	1.40	674	2.24	7	0.02	6	0.01
Heart rate	27	0.10	447	0.15	23	0.06	19	0.04

N = Total sample size of the study; n = Number of excluded values; BP = Blood pressure.
Proportions refer to the total number of nonmissing values for the relevant variable before cleaning.

A series of derived variables was created using information from one or more variables in the original datasets. Namely:

- Two binary variables indicating any self-reported current smoking or alcohol use, respectively, regardless of frequency and quantity;
- A categorical education variable with 4 classes, corresponding to the following number of completed years of schooling as self-reported by participants[12]:

  None $< 1\ year$

Primary	1-7 $years$
Secondary	8-12 $years$
Tertiary	13+ $years$

- A BMI continuous variable, calculated as the ratio between the average of the available repeated measures of weight (in kg) and the square of the average of the available repeated measures of height (in m).

  The variable was cleaned for biological plausibility and extremely unlikely values (BMI<10 or BMI>80[539]) were set to missing. The procedure resulted in the elimination of 3 values from the SADHS 1998 edition; 32, 22 and 30 from the three waves of NIDS; and 4 from the SAGE.

  The variable was categorised using the common WHO cutoffs:[540]

Underweight	$<$ 18 kg/m^2
Normal weight	$\geq$ 18 and $<$ 25 kg/m^2
Overweight	$\geq$ 25 and $<$ 30 kg/m^2
Obese	$\geq$ 30 kg/m^2

- A binary variable indicating self-reported previous diagnosis of hypertension by a health professional.
- A binary variable indicating history of CVD, i.e. any self-reported episode of stroke or heart attack.
- A binary variable indicating self-reported current use of antihypertensive drugs.

The categorization by racial group ('race') applied by all surveys and kept in our analyses was the classification codified in South Africa under apartheid and continued by state practice for certain public purposes. It comprises four group ascriptions: Asian (or Indian ancestry), Black (or African ancestry), Coloured (wide grouping covering multiple ancestries) and White (or European ancestry).

Table 3.11 shows the complete list of the variables considered in the analyses, accompanied by a short description and some coding details.

Table 3.11: Variables used for the analyses.

Variable	Description	Scale	Unit/Coding
CS	Source of data	CAT	1=SADHS 1998, 2=SADHS 2003, 3=SAGE 2007, 4=NIDS 2008, 5=NIDS 2010, 6=SANHNES 2012, 6=NIDS 2012, 8=NIDS 2014
pid	Subject unique identifier	CAT	
psu	Primary Sampling Unit	CAT	
stratum	Stratum	CAT	
csweight	Sampling weight	CON	
day	Day of interview	DIS	
month	Month of interview	DIS	
year	Year of interview	DIS	
sex	Gender	BIN	0=Female, 1=Male
race	Population group	CAT	1=Black, 2=Coloured, 3=Asian, 4=White
age	Age in completed years	DIS	$years$
educat	Categorical education	CAT	1=None, 2=Primary, 3=Secondary, 4=Tertiary
prov	Province of residence	CAT	1 =WC, 2=EC, 3=NC, 4=FS, 5=KZN, 6=NW, 7=GT, 8=MP, 9=LI
urban	Urban vs. Rural residence	BIN	0=Rural, 1=Urban
height (1,2,3)	Multiple readings of height	CON	cm
weight (1,2,3)	Multiple readings of weight	CON	kg
waist (1,2,3)	Multiple readings of waist circumference	CON	cm
sys (1,2,3)	Multiple readings of SBP	CON	$mmHg$
dia (1,2,3)	Multiple readings of DBP	CON	$mmHg$
pul (1,2,3)	Multiple readings of RHR	CON	$mmHg$
htnd	Diagnosis of Hypertension	BIN	0=No, 1=Yes
cvdhist	CVD history	BIN	0=No, 1=Yes
treat	Antihypertensive treatment	BIN	0=Not treated, 1=Treated
smok	Current smoking	BIN	0=No, 1=Yes
alc	Current alcohol use	BIN	0=No, 1=Yes
bmi	Body mass index	CON	kg/m^2
bmicat	Categorical bmi	CAT	1=Underweight, 2=Normal weight, 3=Overweight, 4=Obese

CAT = Categorical; DIS = Numerical discrete; CON = Numerical continuous; BIN = Binary.
WC = Western Cape; EC = Eastern Cape; NC = Northern Cape; FS = Free State; KZN = Kwa-Zulu Natal; NW = North West; GT = Gauteng; MP = Mpumalanga; LI = Limpopo.
CVD = cardiovascular disease.

The scripts used to import, recode, clean and consolidate the various data sources are attached as Appendix C.

3.3 Statistical analyses and models

This section includes three subsections.

Subsection 3.3.1 describes procedures and indices used in the preliminary data analysis, with special focus of the assessment and comparisons of the quality of BP and RHR data (as determined by a series of empirical indices) and their distributional characteristics in each sample.

Subsection 3.3.2 introduces the general analytical approach of this thesis, gives reasons for its choice, and provides details on the specific techniques applied to reach the various study objectives taking into account the characteristics of the data.

Subsection 3.3.3, finally, describes graphically and analytically the specific set of models used in the various steps.

3.3.1 **Exploratory data analysis**

3.3.1.1 *Sample characteristics*

Socio demographic, behavioural and anthropometric characteristics of each sample were summarised in tables as median and interquartile range[13] for continuous variables and frequency for categorical measures. The period of data collection and the distribution of the sample per month of interview was also tabulated and graphically depicted, given its relevance in relation to adjustment for the seasonal variation in BP.

3.3.1.2 *Data on blood pressure and resting heart rate*

Univariate and multivariate distributions of individual readings of BP and RHR in each sample were analysed in detail by means of graphical representation (boxplots and histograms) and tables of summary statistics.

The level of departure from normality of the univariate distribution was assessed by visual inspection of histograms and boxplots and by calculating the usual indices of skewness and kurtosis. Mardia's indices of multivariate skewness and kurtosis[541] were calculated to analyse the 'shape' of the multivariate distributions.

Multivariate outliers were identified by plotting the Mahalanobis distance of each observation and visually identifying an appropriate cut-off. Values of BP/RHR above the cutoff were set to missing.[542]

3.3.1.3 *Quality indices*

In the absence of a generally accepted 'gold standard', various empirical indices and procedures have been proposed for the assessment of the quality of blood pressure data collected in population surveys.[339, 341, 543, 544]

In our study, I assessed the overall quality of the available data in each survey by calculating and comparing:

1. **Proportion of missing values in each variable and proportion of complete measurements**.

   That is, the proportion of values that were missing after the cleaning procedure, and the proportion of observations for which a valid value was available for all three (or two) measurements indicated in the study protocol.

   Low proportions of missing data and high proportions of complete readings are an indirect indication that the measurement instruments and procedures were adequate to collect valid data, and that the measurement protocol has been correctly followed during the fieldwork.

2. **Proportion of identical readings**.

   Because of the large short-term variability of blood pressure, high proportions of identical readings are suspect and might indicate some degree of manipulation or forgery in reporting data.

3. **Digit preference score**.

   The digit preference score (DPS) is a measure of how much the distribution of the last digits in the measurements differs from the expected, uniform, one. It is calculated by the formula:[339]

   $$DPS = 100\sqrt{\frac{\chi^2}{df\,N}}$$

   where N is the number of observations, χ^2 is the chi-squared statistics for the test of homogeneity between the observed and expected distribution of last digits, and df are the respective degrees of freedom, which equal the number of possible end digits minus one, 9 in our case[14].

   The DPS ranges from 0 to 100, with low values indicating better agreement with the uniform distribution, i.e. low levels of digit preference.

For all these indices, no absolute thresholds exist to indicate which values are acceptable and which are not, even though some indication can be drawn by comparison with the result of large epidemiological studies, such as the WHO's MONICA project.[339, 545] They can be, however, used to compare the quality across different surveys.

3.3.2 Analytical methods

3.3.2.1 *Structural equation modelling*

This study took a SEM[15] approach to the analysis of the relationships between the variables involved and to the estimation of and adjustment for measurement error.

In its most general formulation, SEM can be defined as "*an inference method that takes three inputs and produces three outputs*":[546]

The inputs are:

1. **A set of qualitative causal hypotheses based on theory or results of empirical studies**.

   These hypotheses are typically formalised by means of a *directed graph (DG)* or, equivalently, by a set of equations (*structural equations*) with free parameters.

   The use of DGs[16] is widespread in epidemiology to represent qualitative causal knowledge.[547] For example, the simple DG in Figure 3.2 below

Figure 3.2: A simple directed graph.

   expresses the belief that the value of the variable X 'affects' in some way the value of Y (i.e. that changing the value of X will cause some change in Y) and, similarly, that the value of Y affects Z.

   The type of causal knowledge depicted in a DG is *qualitative* because the details on how X affects Y and Y affects Z are left (partly or completely) unspecified: the DG above, for example, does not indicate how much Y is expected to increase (or decrease) if we change the value of X from, say, 1 to 2.

Sets of structural equations are an equivalent way of formalising causal hypotheses. Causal effects are represented by equations which express the *expected*[17] change in the values of an outcome when the value of one or more exposures change.

Traditional SEM assumes that all relationships between variables are linear with parameters that are constant over individuals. Under these assumptions (*linear SEM*), the structural equations assume the form of a set of linear regression equations. An equivalent representation of the DG in Figure 3.2 becomes, therefore:

$$Y = \beta_x \cdot X + \tau_y + \mathcal{E}_y \tag{3.1}$$

$$Z = \beta_y \cdot Y + \tau_z + \mathcal{E}_z \tag{3.2}$$

where $\mathcal{E}_x$ and $\mathcal{E}_z$ are two random variables which represent the regression residuals. In the linear regression framework residuals are usually assumed to be normally distributed with mean 0 and constant variance:

$$\mathcal{E}_y \sim N(0, \theta_y^2)\ ,\ \mathcal{E}_z \sim N(0, \theta_z^2) \tag{3.3}$$

Note that the values of the *model parameters* β_x, β_y (*regression coefficients*), τ_x, τ_y (*intercepts*), θ_x^2 and θ_y^2 (*residual variances*) are left unspecified.

Most of the models in this study fall in the category of linear SEMs and, for simplicity, in this brief presentation of the general principles of structural models I refer to this subset of models without further specification.

However, it is important to highlight the fact that SEM is not restricted (neither in principle nor in practice) to linear models. The principles presented here are equally applicable to more general forms of SEM which assume neither linearity of the relationships nor homogeneity of the parameters.

For example in the *generalised SEM framework* the assumption of linearity of the relationships is replaced with the less stringent assumption that the expected value of the outcome variables can be expressed by means of generalised linear regression equations, thus allowing for an efficient treatment of some categories of limited dependent variables (categorical, censored, truncated).[548, Chapter 2]

Completely non parametric structural equation models (NPSEMs) are also possible, where the functional relationships between variables is formulated via unspecified smooth functions. See, for example, Pearl [549] and Bollen and Pearl [550] for a general introduction and a discussion on the conditions under which these models are identifiable, and Song et al. [551] and Song and Lee [552] for possible approach to their estimation within the Bayesian framework.

2. **A set of queries concerning causal relationships among variables of interest**.

   These queries typically concern the magnitude of the parameters that define the functional form of the causal relationships between variables (e.g., the *structural coefficients* β and τ, and the error variances θ^2 in equations 3.1 to 3.3), and this is the case of the models considered in our study. More general queries are, however, possible.[546]

3. **A set of data**.

   The data are characterised by a joint probability distribution supposedly generated by the causal process hypothesised in point 1.

The outputs of a SEM are:

1. **A set of logical implications of the causal hypotheses**.

   The implications are independent of the data, and follow directly from the hypothesised causal relationships. For example, if the causal assumptions formalised in the DG of Figure 3.2 (or in equations 3.1 to 3.3) hold, X has no effect on Z if we hold Y constant. In epidemiological language, Y is a *total mediator* of the effect of X on Z. This conclusion is a direct consequence of the qualitative hypotheses, and holds regardless the actual values of the structural coefficients and the residual variances.

2. **A set of data based claims concerning the magnitude of the model coefficients, conditional on the causal hypotheses**.

   These claims assume typically the form of a set of point *estimates* for the model parameters, accompanied by a quantification of their precision (e.g. *confidence intervals* and *p-values*).

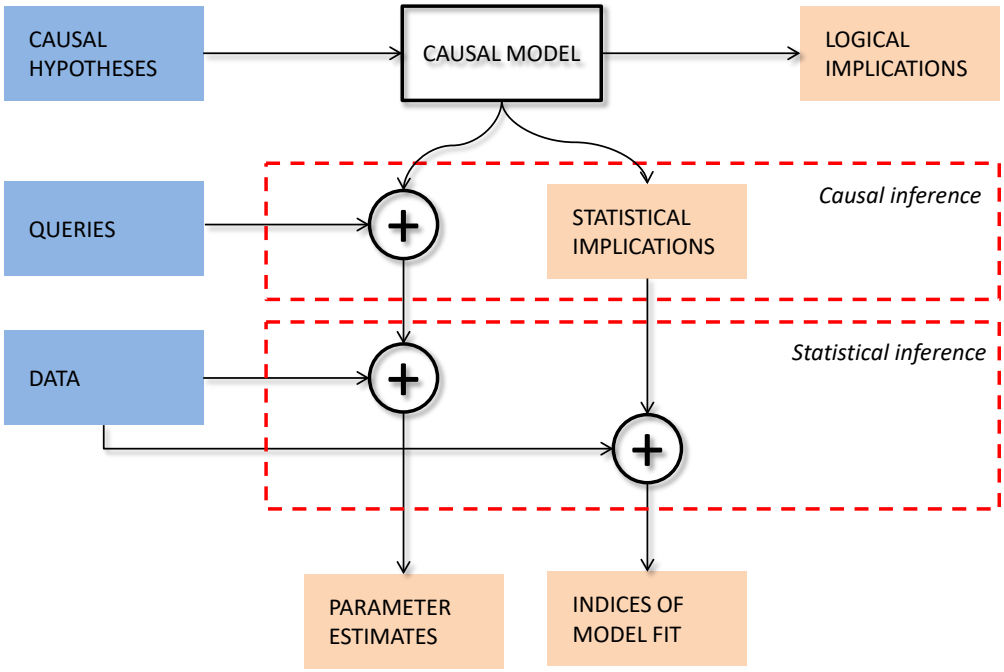
3. **A set of testable statistical implications of the casual hypotheses, and the degree to which the data agree with each of those implications**.

   For example, the linear SEM expressed by 3.1-3.3 implies that the partial correlation between X and Z is zero, after adjustment for the total mediator Y: this implication can be tested in the data and accepted/rejected at a given level of significance as a result of adequate hypothesis testing procedures.

   Often the overall congruence of the set of causal hypotheses with the data is statistically assessed using a series of *indices of model fit* (see Section 3.3.2.5).

Figure 3.3 summarises the inferential process underlying SEM described above.

Figure 3.3: SEM as an inferential process.



3.3.2.1.1 Why SEM?

SEM has been increasingly used in the past decades in social science and psychology, while its relative complexity compared to other widespread multivariate techniques such as linear and logistic regression, and its limitations in dealing with binary and other limited dependent variables have until more recent times hindered its applications in epidemiology.

Recent developments have removed most of the limitations on the use of non-continuous variables, and this fact — together with the growing availability of user-friendly computer packages which do not require advanced knowledge of matrix algebra, characteristic of the first software implementations — have fostered the use of SEM among epidemiologists to deal with the increasingly complex theoretical models which characterise contemporary research in the field.

Even though their use is still limited, SEM techniques have been repeatedly used and are increasingly applied for the analysis of population data on blood pressure. Examples are the quantification of the magnitude and characteristics of measurement error[553–556]; the analysis of the role of biological and behavioural mediators in explaining the observed socioeconomic disparities within populations[9, 10, 19, 408, 557]; the study of the relations between

blood pressure in adolescence, foetal development, and maternal characteristics[558]; and, more generally, the modelling of complex interrelation between high blood pressure, genetic traits and other elements of the metabolic syndrome[559–562].

The specific characteristics of the SEM approach that are especially appealing for the objectives of this thesis are:

- The ability to model and estimate jointly multiple relationships.

  This allows for the direct comparison of the association between different variables without relying on indirect inference obtained by comparing estimates from multiple models.

- The ability to deal efficiently with variables which are conceptualised but not directly observed (*latent variables*), the realization of which can only be inferred from the observed values of other variables.

  The use of latent variables, often with different denominations, is anything but unique to SEM, but a special strength of the SEM approach is the flexibility with which latent variables can be introduced into the models to deal with a plurality of issues, and the freedom with which their relationships with other observed and latent variables can be specified.[563]

- The availability of measures of global fit that provide an overall evaluation of 'how well' the model represents the data.

  Most alternative procedures that can be used in place of SEM to analyse complex relationships (such as sequences of multiple regression equations, independently fitted) provide only separate tests of model components that are conducted on an equation-by-equation basis.[564] When, as in the case of the models developed for this study, multiple relationships are involved, the overall fit of the model can be extremely difficult to assess from the analysis of a long succession of separate tests for each model component.

- The ability of incorporating into the models qualitative knowledge regarding causal relationships between variables.

  Given a general set of assumptions regarding the distribution of the variables involved and the broad nature of their relationships (their *functional form*[18]), the translation of a DG into a SEM is a mechanical procedure, that most modern software packages perform thus automatically. From this point of view SEM offers a 'natural' way of representing substantive knowledge on the phenomenon under study and incorporating it into the statistical model.

- The possibility of separating the *measurement model* (i.e. the model for the relationships between the imperfectly observed values of the variables of interest with their 'true'

unobserved values) and the *structural model* (i.e. the model for the relationships between the 'true' values of the variables of interest).

This separation has a series of advantages. Under certain conditions — such as the availability of multiple sets of imperfectly observed values for the same 'true' variables —, this separation allows for the explicit estimation of the magnitude of measurement error, and the recovering of structural relationships that are 'cleaned' of the biasing effect of it[19].

- The possibility of joint estimation of multiple models, using data from different samples (*multiple-group modelling*).

  The joint estimation of the parameters in each group allows for the direct estimation of inter-group differences, including their standard error, taking into account measurement error, possibly differential.

In the next sections some of the above characteristics are presented with greater detail and their direct relevance for this study made explicit.

3.3.2.2 *Latent variables*

It is common practice in statistics to resort to variables that are not directly observed as an integral part of models and estimation procedures.

One of the most basic illustrations of this widespread use is to represent residuals in regression models. For example, in the simple linear regression model

$$Y = \beta X + \tau + \mathcal{E}$$

the outcome Y is a linear function of the exposure X (defined by the *slope* β and the *intercept* τ) and of an 'extra' random variable $\mathcal{E}$ (the *residual*). The realizations of $\mathcal{E}$ are not directly observed but only inferred from the observed values of X and Y, given an appropriate set of assumptions (e.g. $\mathcal{E} \sim N(0, \theta^2)$ and $\mathcal{E} \perp\!\!\!\perp X$ in ordinary least squares regression).

Depending on the tradition of the field of study and the specific context, these 'utility' variables that are not actually present in the dataset are referred to with different names: *residuals* (as in the previous example), *unmeasured* or *unobserved variables*, *factors*, *constructs*, *true scores*, *random coefficients* to name only a few.

Their formal definition also reflects this plurality of points of view and uses, and many different terms are reported in the literature. Each definition highlights different aspects, resulting in a non complete equivalence (see [565] and [548, chapter 1] for a non exhaustive review of the most common formal definitions found in the literature).

In this thesis I take a broad approach to the definition of this family of variables and, following Skrondal and Rabe-Hesketh [548], the term *latent variable* (in contrast to *observed* or *manifest variable*) is used to refer to "*any random variable whose realizations are hidden from us*"[548, p. 13], regardless of the reasons behind this lack of observability.

When necessary or useful, specific terms are used to refer to defined subcategories (e.g. the common term 'residuals' is used to indicate the latent variables representing differences between predicted and observed values in our models), but the term 'latent variables' encompasses all these subclasses.

Latent variables played a central role in the statistical analyses of this study, and their properties were exploited for different purposes:

- To represent 'true' variables measured with error.

  In particular, given the considerations in Chapter 2 about the ubiquitous presence of non negligible measurement error in the observed values of blood pressure, I assume that the true values of SBP and DBP are unobservable and, therefore, according to our definition, have the status of latent variables.

- To directly represent measurement error.

  By definition, measurement error is the difference between observed and true values. Given that true values are unobservable, the result of the subtraction cannot be calculated directly from observed values, and therefore has again the status of latent variable.

- To represent differences between predicted and observed values in regression equations.

  As indicated above, I refer to this specific subclass of latent variables as *residuals*, as per common practice.

- To represent unobserved continuous variables underlying the observed values of *partially observed variables*.

  Part of this study deals with the estimation and interpretation of the effect of antihypertensive treatment on the observed population trends of BP, which implies recovering the hypothetical (*counterfactual*) distribution of BP in absence of treatment. This counterfactual distribution was conceptually represented by a latent variable, the values of which determined the observed values of BP in the population, which are only observed (with error) for the untreated subjects and missing for those on treatment (*partially* observed).

  This approach is a generalization of the so called *Tobit model*, originally proposed by James Tobin to describe the relationship between a non-negative dependent variable and one or more independent variables,[566] and belongs to the same family of the *logistic*

and *ordered logistic* models commonly used in epidemiology to deal with categorical outcomes[20].

- To represent *unobserved heterogeneity*.

  Unobserved heterogeneity, in opposition to *observed* heterogeneity, is the variability in the outcome variables that is not explained by other variables present in the model. It can originate from a multiplicity of phenomena, including the ubiquitous presence of unmeasured confounders. Latent variables (usually designated as 'random effects' in this context) are commonly used in statistics to represent this type of heterogeneity.

  In these analyses I exploited this possibility to take into account the interdependence of repeated measurements of BP in the same subjects across the subsequent waves of NIDS in the analysis of seasonal effects.

3.3.2.3 *Directed graphs and the causal interpretation of SEMs*

The general equivalence between directed acyclic graphs (DAGs) and recursive SEMs (and more in general, DGs and SEMs) for the representation of causal hypotheses has long been established.[546, 567, 568] SEMs use a system of simultaneous equations to represent causal knowledge about the relationships between a set of variables, in the same way as DGs use a set of nodes connected by arrows.

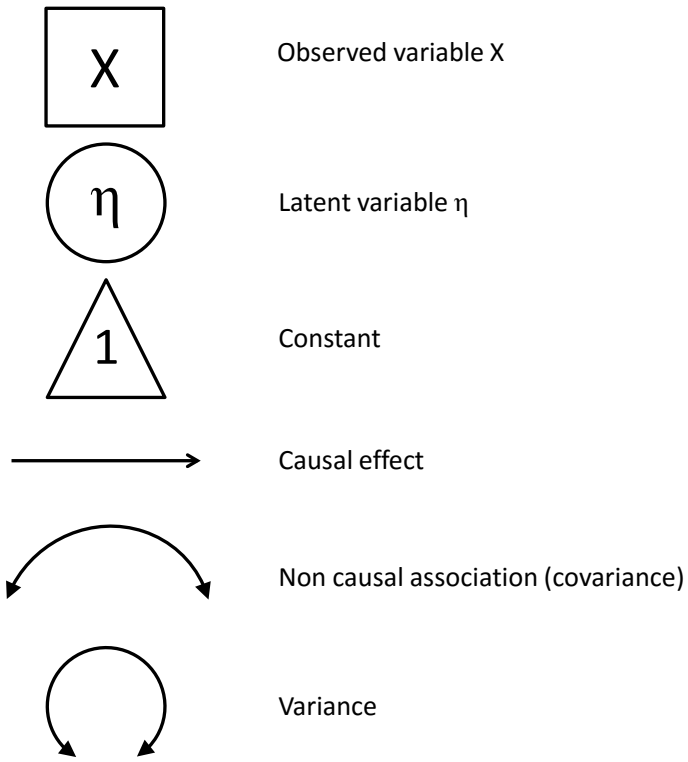
The equivalence of the two representations is the justification of the use of the alternative name of *causal modelling* to indicate SEM[21]. This use is formally correct, but has nevertheless generated a long-lived and sometimes heated debate about its appropriateness among scholars with different background. The origin of the controversy revolves around the widespread misinterpretation of the name 'causal modelling' as the statement that SEM aims to establish causal relationships from association alone (see Bollen and Pearl[550, p. 310] for a short but enlightening summary on the subject). This interpretation is, clearly, incorrect.

The causal relationships to which the denomination of causal modelling refers are *not* inferred from the available data (i.e. from their pattern of covariance), but are hypothesised *a priori* (from non-statistical, substantive knowledge on the phenomenon under study) and 'embedded' in the set of equations that constitutes a SEM. As made clear by the general definition illustrated in Section 3.3.2.1, SEM does not infer casual relationships from observational data (and neither from experimental data, for that matter), but it uses causal hypotheses as an 'input', together with the observed values of a set of variables ('data') to draw a series of consequences. These consequences, usually in the form of estimates of model parameters with associated level of uncertainty, are valid to the extent to which the original hypotheses are valid.[569, p. 369-374] In some circumstances, the interpretation of these consequences in

terms of statistical and/or substantive plausibility can lead to the rejection or modification of the original hypotheses, thus contributing to the development of causal knowledge.

Throughout this thesis, the substantive knowledge (reviewed in Chapter 2) on both the mechanisms responsible of the changes in 'true' blood pressure (e.g. the aging process) and those responsible for the discrepancy between true and observed values (measurement error) is represented by means of DGs. More precisely, following a consolidated habit in the SEM literature, I use a 'specialised' version of DG, the *path diagram*, which integrates the causal hypotheses represented in a DG with other modelling details, such as the status (observed or latent) of each variable and the presence of constraints in the values of the model parameters.[570] Similarly to DGs, path diagrams use single- or double-headed arrows to represent relationships, while variables are depicted as squares or circles/ellipses depending on their status. A summary of the various symbols used in path diagrams together with their meaning is shown in Figure 3.4.

Figure 3.4: Symbols used in path diagrams.



The values of the model parameters are indicated in proximity to the relative symbol, and their meaning depends on the element represented, as in Figure 3.5. Values are interpreted as regression coefficients when referred to casual effects (directed arrows), as covariances when

referred to non causal associations (double-headed arrows), and variances when referred to the semi-closed circles in the figure.

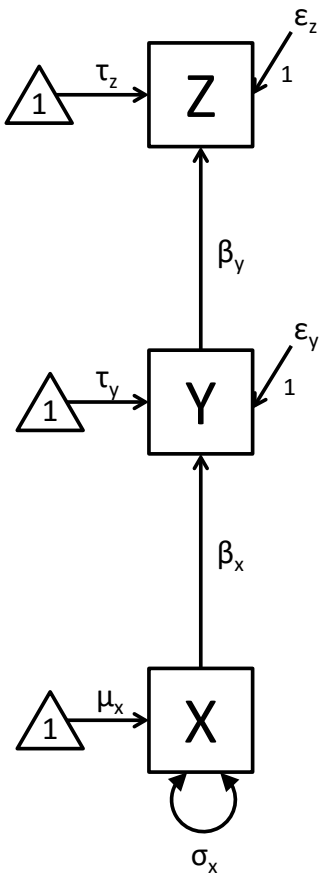
Intercepts and means can also be indicated as labels in proximity to the symbol of the variable to which they refer, but in this thesis I adopt the reticular action model (RAM) notation by McArdle and McDonald [571], where means and intercepts are explicitly represented as the regression coefficients of the variable on the constant '1'.

When the latent variable represents a residual/error term, the circle is often omitted, and only the name assigned to the residual is indicated. The coefficient of the path connecting error terms to their associated variables are most commonly fixed to 1 for identification purposes, and the indication of the constant is omitted. I use the same convention in this thesis, but it is important to highlight that this is only a representation convention to avoid excessive 'clutter' in the path diagrams: from a substantive and statistical point of view no difference exists between error terms and any other latent variable in the model. The directed path which connects error terms to the outcome variable to which they refer further indicates that they have the same characteristics of the other variables in the models, including the ability to causally affect other variables.

The variance symbol is also often omitted from path diagrams, and the name (or value) of the corresponding model parameter is directly indicated in proximity to the symbol of the variable.

An example of a path diagram representation of the SEM model formalised by equations 3.1 to 3.3 is depicted in Figure 3.5.

Figure 3.5: Path diagram for the model represented by equations 3.1 to 3.3.



3.3.2.4 *Measurement vs. structural model*

In their most general form, SEMs are the combination of two logically distinct part: a *measurement model* and a *structural model*. Special cases of SEMs are:

- models which only includes the measurement part.

  These models are known with different names depending on the nature (continuous or discrete) of the observed and latent variables: *factor analysis (FA)* models, where both observed and latent variables are continuous; *item response theory (IRT)* models, where latent variables are continuous and observed variables discrete; *latent class (LCA)* models, where both observed and latent variables are discrete; and *mixture models (MMs)*, where observed variables are continuous and latent variables are discrete.[572]

  In all these models the focus in on the measurement process itself, and it is not a coincidence that they are especially common in psychology and in the social sciences, where

many of the variables of interest are represented by theoretical constructs that can only be observed indirectly and where, consequentially, measurement problems have a special relevance.

- model which only include the structural part.

  The implicit assumption in the models of this category (*path analysis* models) is that the variables of interest are measured without error, or, at least, that the magnitude and characteristics of the measurement error are such that they do not produce substantial bias in the estimates of interest.

  Generalized linear regression methods are special cases of path analysis that include one or more predictors but a single outcome. As such, all of them implicitly assume absence of measurement error[22].

An example of a SEM including both a measurement and a structural model is presented in Figure 3.6. The causal hypothesis underlying the model (adapted from Hox and Bechger [573]) is that quality of sleep in children (variable *S*) is directly affected by the presence of neurotic symptoms (*N*): this is represented by the arrow connecting the two variables, which constitutes the *structural model*.

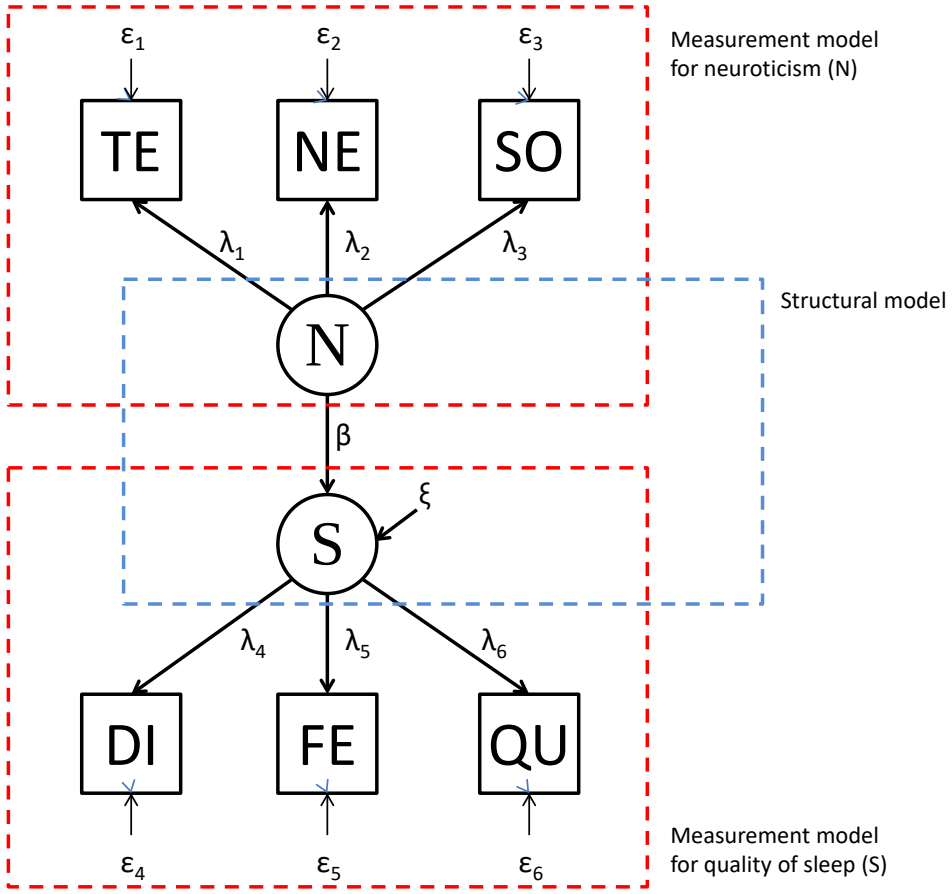
Both neurotic symptoms and quality of sleep are 'conceptual' variables non directly observable: therefore they are represented in the model by latent variables (circles). The unobservable latent variables are hypothesised to affect a set of variables whose values are observed (squares)[23]. These variables directly affected by the latent variables are its *indicators*. Under certain conditions ('identifiability', see below) the knowledge of the values of the indicators allows for the estimation of the distribution of the underlying latent variable. The set of indicators and their relationships between the latent variable is the *measurement model* for the latter.

In our example the measurement model for *N* comprises the three observed variables '*test attitude*' (*TE*), '*neuroticism*' (*NE*), '*somatic symptoms*' (*SO*). Their values are predicted by the underlying latent variables, but the model allows for this prediction to be imperfect, and this is represented by the error terms ($\mathcal{E}_1$, $\mathcal{E}_2$, $\mathcal{E}_3$) that also affect the indicators. Similarly, the measurement model for *S* included three observed variables — '*difficult*' (*DI*), '*feeling rested*' (*FE*), '*quality*' (*QU*) — imperfectly predicted by the underlying latent variable.

It is worth noticing that the error terms $\mathcal{E}_i$, which in the regression framework are defined as the difference between observed and predicted values (residuals), assume in SEM a *causal meaning* as unobserved factors that effect the observed values of some variables.

In our linear framework, arrows represent linear regression equations. This type of measurement model is indicated as a FA model and the regression coefficients are known as *factor*

Figure 3.6: An example of structural equation model.



Adapted from Hox and Bechger [573, p. 161]

loadings and usually indicated with the Greek letter λ. The structural coefficient β is also a linear regression coefficient, not different from the λs, and it is only to acknowledge its different substantive interpretation that it is usually indicated with a different letter.

In the structural model, the error term ξ affects the values of the outcome variable S together with the latent predictor N. As such, it coincides with the difference between the values of S predicted by N through the structural equation and its (indirectly) measured value. Similarly to $\mathcal{E}_1 ... \mathcal{E}_6$ it can be interpreted as a regression residual, with the only difference that both the predictor and the outcome are unobserved.

In algebraic notation the model of Figure 3.6 is equivalently expressed as:

$$\begin{aligned} TE &= \lambda_1 \cdot N + \mathcal{E}_1 \\ NE &= \lambda_2 \cdot N + \mathcal{E}_2 \\ SO &= \lambda_3 \cdot N + \mathcal{E}_3 \end{aligned} \tag{3.4}$$

$$\begin{aligned} DI &= \lambda_4 \cdot S + \mathcal{E}_4 \\ FE &= \lambda_5 \cdot S + \mathcal{E}_5 \\ QU &= \lambda_6 \cdot S + \mathcal{E}_6 \end{aligned} \tag{3.5}$$

$$S = \beta \cdot N + \xi \tag{3.6}$$

$$\mathcal{E}_i \perp\!\!\!\perp \mathcal{E}_j, \forall\, i \neq j \tag{3.7}$$

where equations 3.4 and equations 3.5 represent the measurement model for *N* and *S*, respectively; and equation 3.6 represents the structural model[24].

Equations 3.7 represent the assumption that the correlation between the observed variables is not explained by extraneous factors (graphically: no double-headed paths connecting the error terms). In epidemiological language, this corresponds to the fact that the model makes strong assumptions regarding the unconfoundness of the observed associations[25]. More in general, it is important to point out that the *absence* of double-headed arrows between residuals in path diagrams carries an important substantive meaning that cannot be ignored.

Under the hypothesis (1) that the model represented by Figure 3.6 and Equations 3.4 to 3.7 is correct, and (2) that it is identifiable (see section 3.3.2.5), the separation of the structural from the measurement part of the models has important consequences:

- it allows for the evaluation of the characteristics of the measurement.

  The variances θ_i^2 of the residuals $\mathcal{E}_i$, together with the magnitude of the loadings λ_i and intercepts τ_i of the measurement equations allow us to estimate the validity of each of the observed measures and their relative bias.

- it allows for the estimation of the structural coefficient β avoiding the negative effect of measurement error on both the point estimate and its standard error.

  These effects are well known and predictable in case of simple regression equations such as 3.6: the β coefficients are biased downwards by the presence of measurement

error in the predictor, and their standard error are inflated by measurement error in both the predictor and the outcome.[574] In case of regression equations with multiple predictors, such as our structural model, the effects of ignoring measurement error on the point estimates of the β coefficients are unpredictable, but in general their precision is reduced.

Both these characteristics are exploited in this thesis.

Chapter 5 presents the results on the analysis of the measurement model and its consistency across surveys. The observed variance of each multiple reading of BP and RHR is decomposed in 'true' and 'error' variance and validity coefficients and relative bias of each reading calculated and compared across surveys.

Chapters 6 and 7 focus on the structural part of the model. Structural parameters representing the effect of a series of biological, behavioural and socioeconomic factors, seasonal effects and differences in BP and RHR distributions across surveys are estimated, adjusted for the negative effects of measurement error, which is taken care of by the measurement model.

3.3.2.5 *Estimation*

SEMs, similarly to DGs, represent causal hypotheses qualitatively, i.e. they formalise the presence of relationships between variables ("A affects B") and some of their characteristics (e.g. "the relationship between A and B is linear"), but, in general, they do not specify all the details of the hypothesised relationships. In the context of linear SEM, this means that the functional form of the relationships is established (linear, precisely) but the actual model parameters (the λs, βs, τs and θs in the examples above) are left unspecified.

When a SEM is used to analyse a specific sample s from a population P, the actual values of the parameters are chosen ('estimated') in order to minimise the discrepancies between the relationships observed in the sample and those estimated by the model for the population.

This procedure is called *estimation*, and the specific method used to perform it is indicated as *estimator*.

3.3.2.5.1 Assumptions

Estimators base the choice of the 'best' parameters on a series of assumptions, which vary depending on the specific estimator. These assumptions are *statistical assumptions*, of a different nature from the *causal assumptions* represented by the path model.

Other than as observed (or manifest) and latent, variables in a SEM are classified as:

- *Endogenous* variables

  Endogenous variables are predicted by other variables in the model. In the path diagram they are recipients or one of more single-headed arrows.

- *Exogenous* variables

  Exogenous variables are the independent variables of the model, sources but not recipients of single-headed arrows in the path diagram. Exogenous *observed* variables are also indicated as *covariates*.

The most common assumption in linear SEM is that *the joint distribution of the endogenous variables, conditional on the covariates, is multivariate normal.*

If this assumption holds with reasonably approximation, many estimation procedures simplify and become computationally much lighter. This assumption is, however, not necessary in all cases, and estimators exist that either assume normality but are fairly insensitive to reasonable deviations for this ideal situation (*robust* estimators), or relax completely this requirement. The latter category includes estimators that can handle non-continuous variables such as binary/categorical and other types of limited dependent variables (e.g. censored).

It is worth noticing that SEMs are estimated *conditional on the covariates*, and, similarly to regression models, no assumptions are made regarding the distribution and covariance of the latter. The covariates are technically not part of the model[26] and an important consequence of this fact is that no measurement process is modelled, and they are *implicitly assumed to be measured without error*[27].

3.3.2.5.2 Identification

A SEM is said to be *identified* if, given a set of data and an estimator, the estimation procedure produces a unique set of numerical values for the parameters in the model.

Owing to the flexibility in model specification provided by the SEM framework, a variety of models can be conceived. However, not all conceivable models can be estimated. Identification of SEMs is a complex issue, and, even though methods to check *a priori* the identifiability status of a model have been developed (see for example Pearl [549] and Bollen and Davis [575]), none of them provides necessary and sufficient conditions of general applicability, and the area is still in active development.[576–579]

However, two basic necessary (but not sufficient) conditions for the identification of a generic SEM exist and are well known in literature:[580, chapter 6] [581, 582]

1. The model *degrees of freedom* must be non negative.

Similarly to solving equations in algebra where the number of unknowns cannot be greater than the number of independent equations, a basic principle of identification in SEM is that a model cannot have a number of unknown parameters greater than the number of unique pieces of information provided by the data. The difference between number of unique pieces of information and number of parameters is indicated as the degrees of freedom (df) of the model, and this first condition of identifiability is expressed as:

$$df \geq 0 \tag{3.8}$$

In linear SEM with all continuous variables, and under the hypothesis of multivariate normality, all the information contained in a dataset with v observed variables is subsumed in a vector of v means plus a symmetrical matrix representing the variances and covariances of the v variables. The total number unique pieces of information is, therefore:[580, p. 303]

$$\frac{v(v+3)}{2} \tag{3.9}$$

and the number of degrees of freedom is:

$$df = \frac{v(v+3)}{2} - p \tag{3.10}$$

where p is the number of parameters in the model[28].

Models with $df < 0$ are said to be *underidentified*, models with $df > 0$ are said to be *overidentified*, and models with $df = 0$ are said to be *just-identified*.

Parameter estimates of both overidentified and just-identified models are unique, given a certain estimator. Just-identified models fit the data perfectly and this is not necessarily desirable in SEM, because (1) sample data contain random error and a model with a perfect fit may be fitting sampling error; (2) given that very different just-identified models produce the same perfect empirical fit, the models cannot be evaluated and compared each other.

In underdidentified models, multiple sets of parameters produce the same level of model fit: these models are not interpretable and require respecification. The number of parameters needs to be reduced, e.g. by fixing some of them to specific values or introducing constraints involving more than one parameter.

2. Every latent variable must be assigned a *metric*.

   Latent variables are, by definition, unobserved, and their metric is arbitrary and needs to be fixed to allow identifiability. Fixing the metric of a latent variable means deciding

the unit of measurement (the *scale*) and the position of the 'zero' point (the *location*).

The scale of a latent variable is commonly fixed by setting one of its loadings to 1 (which is equivalent to assuming for the latent variable the same scale as that of the associated indicator) or by fixing its variance to 1 (which is a form of standardization). The location is usually fixed by setting the intercept of one of its indicators to 0, or by setting the mean of the variable to 0.

Alternative identification strategies can be applied in specific circumstances, and this is the case of the models in this study, where the set of constraints proposed by Little et al. [583] is applied in order to improve the interpretability of the model results. The details of this identification method are presented in Section 3.3.3.2.

As previously pointed out, even in the simplest case of linear models with multivariate normal distribution of the variables, the global identifiability conditions above are necessary but not sufficient. A model (especially a complex one) can be globally identified according to these rules, but some of its parts may be not, thus hindering the ability of the estimators in recovering the values of the parameters.

Also, a model can be theoretically identified, but *empirically underidentified*[29], i.e. the overall model has positive degrees of freedom, but there is insufficient covariance information in a portion of the model for the computing algorithm to generate valid estimates. Some of the conditions that make empirical underidentification more likely are known,[584, 585] and I took advantage of this knowledge in our analyses by introducing appropriate remedies.

3.3.2.5.3 Estimators

Many different estimators are used in SEM,[586] and they differ regarding:

- The *criterion* used to measure the discrepancies between the relationships observed in the sample and predicted by the model.

  Most estimators assess the discrepancies by calculating some monotonic function of the probability of observing the actual data given the model and a set of parameters (the *likelihood function*). Higher values of the likelihood function indicate better correspondence between predicted and observed values, and therefore the estimators work by selecting a set of parameters that maximise this function (*maximum likelihood estimators*).

  However, this is not the only possibility. For example, another family of estimators of widespread use measures discrepancies as the sum of the squared differences between observed and predicted values. In this case lower values indicates better model fit and the estimators work by selecting a set of parameters that minimise this function (*least squares estimators*).[548, Chapter 6]

- The type of variables (e.g., continuous, binary, categorical) they can handle.
- The assumptions underlying their applicability.
- Their level of *biasedness* and *efficiency*.

  An estimator is said to be asymptotically unbiased (or consistent) if it produces estimates that converge to their true value in the population as the sample size tends to infinity. For simplicity, in the rest of this thesis the term 'unbiased' is used to refer to asymptotic unbiasedness. The efficiency represents the 'speed' of this convergence: the more an estimator is efficient, the faster the parameter estimates reach their true values as the sample size increases. A measure of efficiency is the standard error of the estimates, with lower values (given a sample size) representing greater efficiency.[587]

- The type of treatment applied to missing data

  Some estimators exclude observations with missing data in any variable, while others are able to take into account the partial information provided by incomplete records.

- Their *computational complexity*.

  Given a model and a sample, the requirements in computational power (i.e. computing speed and memory size required by the computer) vary between estimators. Even though no general rule exists (because the characteristics of the model influence heavily the performances of the estimators), usually estimators based on maximum likelihood tend to have higher computing requirements than least-squared estimators.

The main variables of interest in our analyses (SBP and DBP, and, to a lesser extent, RHR) are continuous variables with distributions that are not far from normal (see section 2.1.4.5.1 in Chapter 2) and, moreover, our samples are fairly large. In these conditions, the common implementation of maximum likelihood (ML) estimators in SEM software is known to have favourable properties and to provide asymptotically unbiased estimates with greater efficiency than other estimation methods.[586] The basic assumption underlying the statistical properties of ML estimators (other than large samples[30]) is, in fact, the correct specification of the model including the distribution of variables (conditional on the covariates), and this distribution is commonly assumed to be multivariate normal.

Conditional multivariate normality is difficult to test empirically and, therefore, it is usually assumed, supporting the hypothesis with substantive (and not only statistical) reasons. Its plausibility can be evaluated *post hoc* (i.e. after the estimation) by adequate model checking procedures.

Fortunately, a large literature shows that ML estimators are robust to violations of the assumption of multivariate normality, in the sense that even with large levels of skewness and

kurtosis, they still provide relatively unbiased parameter estimates.[588, 589] However, this favourable property does not extend to other aspects, in particular ML estimators applied to non-normal data tend to produce biased estimates of standard errors and of the χ^2 statistic of model fit.[590, p. 417] [588, 591] In general, the distributional characteristic that more directly affects the estimation of standard errors and χ^2 is kurtosis rather than skewness: leptokurtic distributions tend to inflate the χ^2 statistics and bias downwards standard errors, while the opposite is true for platikurtic distributions.[542, 592, 593] A well-known approach to avoid this form of bias (*robust ML estimation*) consists of estimating the model parameters using a standard ML estimator, but correcting the standard errors and the χ^2 statistic to take into account skewness and kurtosis of the data. This approach, first proposed by Satorra and Bentler [594, 595] has been shown to work well even in relatively small samples[31].

There are no established criteria to judge which values of skewness and, especially, kurtosis of the multivariate distribution of the variables are to be considered 'too large' for the application of ML estimation methods.

Two common statistics used to quantify skewness and kurtosis in the multivariate case are the Mardia's multivariate skewness and kurtosis coefficients.[592, p. 148] Their asymptotic distribution is known and so they can be used to formally test the null hypothesis of no departure from the normality assumption. However, formal testing has little use both because in large samples (above 500-1000) almost inevitably produce significant results, and because 'strict' normality is not required. A frequently reported 'rule of thumb' for the most critical kurtosis parameter states that a normalized Mardia's multivariate kurtosis coefficient lower than 5 or 6 is an indication of 'acceptable' departures from normality, compatible with ML estimators.[596] No rule seems to exist to quantify the level of departure that is acceptable when robust estimators are used, and often multivariate normality is assumed rather than investigated. However, among the relatively rare SEM studies that provide information on the multivariate distribution of the variables, examples exist of successful analyses with levels of multivariate kurtosis >200.[597, p. 607]

The robust estimator used for our analyses is the robust maximum likelihood (MLR) estimator by Asparouhov and Muthén [598], which is based on the pseudo maximum likelihood (pseudo-ML) method of Skinner et al. [599] and uses adjustments similar to those of Satorra and Bentler [594] for standard errors and χ^2 statistics.

Besides being robust to relatively large departures from multivariate normality (especially when applied to large samples), the MLR has two other important properties:

1. It is applicable even when *complex sampling designs* are used for data collection.

   Standard ML estimators assume independently and identically distributed (i.i.d.) observations, a condition which is in most (if not all) cases violated in large-scale surveys,

where complex sampling designs involving clustering and stratification are used for logistic and other practical reasons.

Moreover, sampling schemes often involve oversampling of some population strata in order to recover reliable estimates for specific areas and/or population groups, and this, together with the ubiquitous presence of differential non-response rates, results in unequal probability of selection of the different individuals in the sample.

Both the observations above apply to all data sources analysed in this study.

Clustering, stratification and unequal probability of selection, if not taken properly into account, are known to produce severe bias in statistical estimates with many techniques. SEM is no exception, and this is well documented in literature.[600]

Various methods have been proposed to produce valid estimates in the presence of complex survey designs, and these fall in two main categories: *disaggregated* and *aggregated* methods. Disaggregated methods (e.g. multilevel analyses) model directly the structure of the data, and estimate the within-cluster parameters *conditional* on cluster membership. In contrast, aggregated analyses take a *marginal* approach and estimate directly the average of the parameters across all clusters with the usual procedures, adjusting standard errors and model fit statistics to take into account the departure from the assumption that the observations are i.i.d.[601] The MLR estimator used in our analyses belongs to this latter category, and its properties and performances in various settings are discussed, among others, by Asparouhov and Muthén [602], Yuan and Bentler [603] and Asparouhov and Muthén [604]

2. It deals efficiently with the presence of missing data.

   The MLR estimator takes a full information maximum likelihood (FIML) approach to the treatment of missing data.

   Standard implementations of ML estimators (i.e. those used in the majority of the SEM software) only work with complete data. That is, if an observation has missing data in any of the variables, the whole observation is excluded from the dataset (*listwise deletion* or *complete-case analysis*). Besides the loss of power consequent on the reduction on the effective sample size, this procedure may produce biased estimates if the assumption that data are MCAR does not hold.[605, p. 41-44]

   On the contrary, FIML estimators do not discard observations with missing data on *endogenous variables*, with obvious advantages in efficiency. Moreover, it can be shown that, if the model is correctly specified, it produces parameter estimates that are asymptotically unbiased under the assumption that data are missing at random conditional on the observed covariates (MAR). This assumption is milder that the MCAR assumption underlying complete-case analyses[32].[606], [605, Chapter 6]

> In the analyses of this thesis, this property of the MLR estimator is exploited to deal with the non negligible presence of missing blood pressure data in the datasets.

ML estimators are not free from drawbacks. In particular, the maximization of the likelihood function is not a trivial task and the iterative procedures used at this end are computationally heavy when models include many variables and sample size increases, especially when the characteristics of the models (e.g. the presence of limited dependent variables or other forms of non-linearity) make a closed form for the likelihood function unavailable, and numerical integration is necessary to calculate its value at each iteration[33].

The difficulties in the maximization procedures leads in some cases to the estimation of inadmissible values for models parameters, i.e. negative values for variances or correlations greater than 1, known as *Heywood cases*. In other cases the maximization procedure can converge on a local rather than overall maximum, thus leading to sets of parameter estimates that vary depending on the initial values used in the optimization.[584, 607–609]

The problem of inadmissible values for some parameter estimates (namely residual variances) was present in some models used for this study, and it has been addressed on an *ad hoc* basis with the usual techniques used in SEM, i.e. either by constraining the offending model parameters (when possible and coherent with the substantive theory) and/or by modifying starting values.[589, 608]

3.3.2.6 *Model checking and model fit*

Classical diagnostics for SEMs are based on aggregate forms of the data and on overall measures of fit. A wide variety of 'measures of model fit' is available and commonly reported in literature.[580, p. 193-209][610] Despite having different statistical properties and incorporating different forms of adjustment (e.g. for model complexity or sample size), the starting point is common: they are all measures of the discrepancy not between observed and predicted individual values, but between observed and predicted variances and covariances of the variables, summarised by the *observed covariance matrix* Σ and the *estimated covariance matrix* $\hat{\Sigma}$[34].

The literature agrees that, because of the limitations of each of the available indices in the different contexts and the fact that each of them reflects different aspects of model fit, good practice requires reporting more than one index, even though less agreement exists on which of them should be reported.[611–613] Moreover, for most of the indices the statistical distribution is unknown and, therefore, the decision on what represents a 'good' or a 'bad' fit is based on a series of conventional cut-offs derived from simulation studies, often limited in scope. These cut-off are, understandably, another source of disagreement in the literature.[612, 614–616]

In the analyses, I followed the general guidelines of Hooper et al. [612] and reported[35] the following indices of model fit:

- **χ^2 index of model fit**.

  The χ^2 index of model fit is defined as:[617, p. 17]

  $$\chi^2 = F_{ML}(\Sigma, \hat{\Sigma}) \cdot (n-1) \tag{3.11}$$

  where $F_{ML}(\Sigma, \hat{\Sigma})$ is the minimum value of the statistical criterion minimized in ML estimation,[36] and n is the sample size.[37]

  When the data are multivariate normal and the model is correctly specified, the product in expression 3.11 is asymptotically distributed as χ^2 with degrees of freedom df defined in equation 3.10. It can be therefore used for formal testing of the null hypothesis that there is no discrepancy between the observed and estimated covariance matrices ($H_0 : \Sigma = \hat{\Sigma}$). Non-significant p-values are an indication that the null hypothesis cannot be rejected. From this point of view, the χ^2 statistic is more precisely an index of lack-of-fit, and large values correspond to bad fit.

  A well known problem of this statistic is that it is very sensitive to sample size, which directly multiplies the minimum value of the fitting function. With large samples, even trivial differences between Σ and $\hat{\Sigma}$ lead to the rejection of the model. It is commonly acknowledged that with samples much greater than 200, the χ^2 statistic is often significant even in well-fitting models, and must be integrated with other indices to asses the fit of the model.[611, 618, 619]

  To overcome this extreme sensitivity, a 'scaled' version is sometimes used, obtained by dividing the χ^2 by its degrees of freedom. However, the statistical distribution of the scaled χ^2 is unknown, and its interpretation is based on cut-offs, for which different values are proposed in literature, ranging from 2 to as much as 5,[612] with some consensus reached in the psychometric literature of a value ≤ 3 indicating an acceptable fit .[613, p. 91]

- **RMSEA**.

  The Root Mean Square Error of Approximation (RMSEA) is a χ^2-based index which represents an approximate measure of the *lack* of fit of the specified model to the population. It is defined as:

  $$RMSEA = \sqrt{\frac{(\chi^2/df) - 1}{n}} \tag{3.12}$$

  where df indicate the model degrees of freedom and n the sample size.

The RMSEA takes into account sample size, and for this reason it performs better than χ^2 in large samples. It is also adjusted for the number of degrees of freedom of the model. This is another desirable property, considering that introducing more parameters into a model always produces a decrease in the χ^2, regardless of their appropriateness.

Besides the χ^2 statistic, the RMSEA is the only model fit index that provides a confidence interval around its calculated values. This confidence interval is asymmetric around the point estimate and ranges from 0 to $+\infty$. A *close-fit* test for the null hypothesis that RMSEA< 0.05 can be conducted.[617, p. 20].

In well fitting models, there is relative agreement in the contemporary literature that the 90% confidence interval for the RMSEA should have a lower limit close to 0 and an upper limit lower than 0.08, and that the p-value for the close fit test should be greater than 0.05.[612, 614]

- **SRMR**.

  The Standardized Root Means Residual (SRMS) is a residual-based index. It corresponds to the square root of the of the average difference between predicted and observed standardised covariances between the variables:

$$SRMR = \sqrt{\frac{\sum_j \sum_k r_{jk}^2}{(p+1)/2}} \tag{3.13}$$

  where r_{jk} is the standardised covariance residual between variable j and k, and p is the number of observed variables.

  A value of SRMS < 0.08 is usually considered a good fit and a value < 0.10 acceptable.[580, p.], [614]

- **CFI**

  The Comparative Fit Index (CFI) belongs to the category of comparative indexes, which compare the model of interest with a 'null model' which assumes zero covariances among the observed variables [617, p. 18]. It is defined as:

$$CFI = \frac{d_{null} - d_{mod}}{d_{null}} \tag{3.14}$$

  where d_{null} and d_{mod} represent the difference between the χ^2 statistics and the degrees of freedom, respectively for the null model and the model to be assessed.

  The values of CFI range from 0 to 1 (if out of range, it is set to 0 or 1), where higher values indicated better fit.

A common cut-off for a CFI indicating good fit is 0.95, but values above 0.9 are also used to indicate an acceptable fit.[614].

When the interest is in comparing the fit of different models, the previous indices are integrated with the one of the information criteria indices and by the McDonald's NCI:

- **AIC**, **BIC** and **aBIC**.

  The Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and sample size-adjusted Bayesian Information Criterion (aBIC) belong to the class of *information criteria indices*, that are *relative* model fit indices, commonly used in statistical modelling to compare the relative agreement with the data of different models.

  These indices share a general form $-2ln(L) + P$, where L is the value of the model likelihood function and P is a penalty added to model complexity.

  The three indices differ only for the penalty for sample size and model complexity:

$$AIC = -2ln(L) + 2m \tag{3.15}$$

$$BIC = -2ln(L) + ln(n)m \tag{3.16}$$

$$aBIC = -2ln(L) + ln(n + 2/24)m \tag{3.17}$$

  where n is the sample size and m is the number of free parameters.[617, p. 21] For all these indices, lower values indicate better fit.

- **NCI**

  The Noncentrality Index (NCI) is another adaptation of the AIC to reduce its dependence on sample size. It is defined as

$$NCI = exp\left(-\frac{1}{2}\frac{-2ln(L) - df}{n - 1}\right) \tag{3.18}$$

  The NCI varies theoretically from 0 to 1, with larger values indicating better fit. However, this results is only asymptotically valid, and, because of sample variability, it can assume in some cases values > 1.

  Independent simulation studies by Cheung and Rensvold [620] and by Meade et al. [621] have shown that the NCI performs in general better than all other indices in detecting misspecification during the assessment of measurement invariance in multiple group modelling (see below).

All these indices provide an overall evaluation of model fit, which 'averages' the fit of all parts of the model to produce a single value. Because of this, it is possible that relatively severe deficiencies in some parts of the model (especially if complex) are 'masked' by the excellent fit of other parts. To exclude this possibility, the whole *residual matrix* (i.e.the matrix of the differences between estimated and observed covariances between variables) is examined. More precisely, the normalised[38] matrix is calculated and the distribution of residuals is checked for large departure from normality and the presence of (absolute) values $>> 2$, which are both indications of localised misfit.

3.3.2.7 *Multiple group analysis and measurement invariance*

The main objective of this study is to analyse changes in the distribution of blood pressure in the South African population across time, using the series of samples described above and adjusting for various sources of error that may introduce artifactual differences (or, conversely, mask real ones) when comparing estimates in different periods.

When comparing estimates from multiple samples, two broad alternative approaches exist: (1) to regard the groups as fixed, focusing the inferences on the particular groups in the data, or (2) to regard them as random, that is, a sample drawn from a population of groups and focusing the inferences on this population.[622] Classical examples of the two categories of methods are fixed- and random-effects generalised linear regressions, respectively. Both approaches are widely used in general statistics and also applied within the SEM framework, and both have pros and cons that must be weighted in the specific context.

With the exception of the sub-study on seasonal effects on *individual* BP (see Chapter 7), this thesis follows a fixed-effect approach, and applies the subset of SEM techniques known an *multiple group modelling*.[617, Chapter 5]

In its most general form, multiple group modelling consists of the simultaneous estimation of a set of models (a multiple group model (MGM)), each in a different sample, while constraining some parameters to be equal (or in a specified relationship) across models[39]. In a MGM the estimation is performed by maximising a single 'discrepancy' function (likelihood or sum of squared residuals) calculated over all models and samples.

There are two main reasons why in this study a MGM approach is preferred to the alternative multilevel approach that would have considered the groups (i.e. each surveys) as a random sample from an hypothetical 'population' consisting of all possible surveys that could have been carried out in South Africa in the period of interest:

1. Theoretical considerations.

From a theoretical point of view, considering the surveys in this study as a random sample representative of all surveys that could have been carried out is a very implausible assumption, if only because the year when each survey has been carried out has been purposely chosen taking into account the period of the previous ones.

2. Sample size at group level.

   No absolute lower limit exists for the number of groups needed for multilevel models with random effects and the rules of thumb reported in literature vary widely from a minimum of about 10 to 30, 50 or more.[623–628] However, a number of groups equal to 6^{40} is difficult to defend in a random effects framework, especially when, as in our case, the interest is on the group differences rather than on the within-group parameters.[629, Chapter 12]

Moreover, a multi-group approach is more flexible regarding which parameters can be different across groups, and this is of special importance in our study, where one of the research hypotheses is that measurement and representation error are different across surveys.

In our study, multiple group modelling is applied both to comparing the characteristics of measurement across surveys and to estimating changes over time of the true distributions of blood pressure, adjusting for differential measurement error.

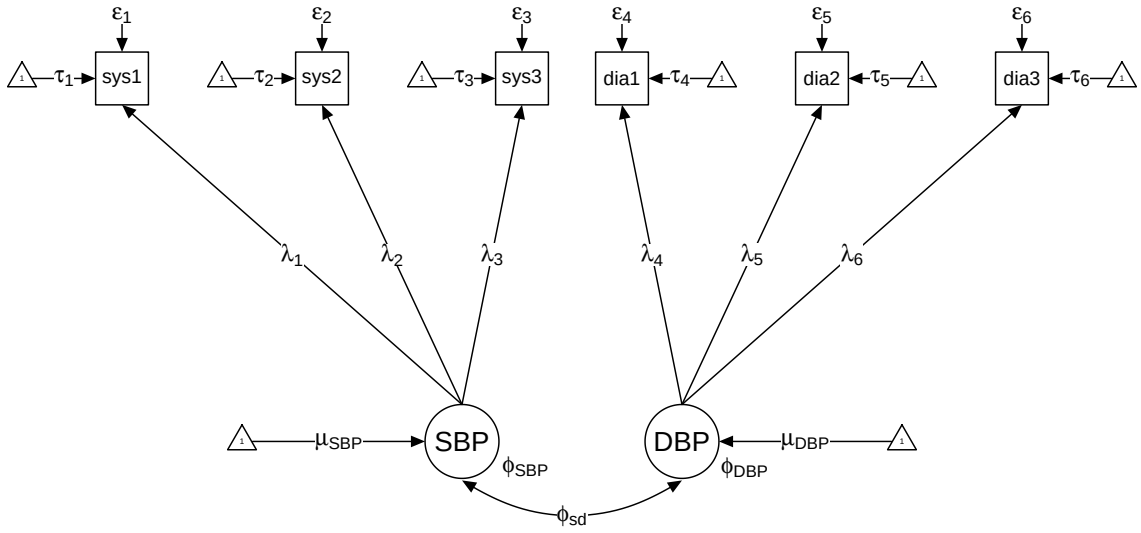
3.3.2.7.1 Measurement invariance

A preliminary condition for a meaningful estimation of the structural parameters in a MGM and, in our case, for the comparison of the distribution of blood pressure across surveys is the congruence of their measurement models. In our study, the 'true' blood pressure distribution is represented by latent variables (one for SBP and one for DBP), the values of which are indirectly inferred from observed values, using a measurement model. Before estimating changes over time in blood pressure, we must ensure that the same measurement model is applicable across all surveys. If this is not the case, in facts, the estimated changes include not only 'true' differences, but also artifactual differences due to discrepancies in the measurement models.

The problem of assessing the compatibility of the measurement models across groups and/or across time (*measurement invariance*) has long been addressed in the SEM literature, and the basic methodology is well established.[630]

A precise hierarchy of measurement invariance exists, illustrated below with reference to the example measurement model in Figure 3.7. In this model, two latent variables (representing SBP and DBP) are measured by three observed variables each (e.g. three sequential measurements taken with an automatic device).

Figure 3.7: An example of measurement model.



If this measurement model is applied to data from two different surveys (say survey **A** and survey **B**) in order to compare the latent values of SBP and DBP we must ensure that:

1. The *structure* of the measurement model is the same in A and B. That is, the measurement model is represented in both surveys by the same graph of Figure 3.7.

   This first level of measurement invariance is indicated as *configural invariance*.

2. The relationship between each latent variable and its observed indicators is the same across group.

   That is, the linear regression coefficients λ_i (*factor loadings*) must be equal in A and B:

   $$\lambda_i^A = \lambda_i^B \quad \forall\, i \in 1:6$$

   This level of measurement invariance (which assumes the previous) is indicated as *metric invariance*.

3. The numerical values of the latent variables are the same for individuals with the same values for the observed indicators, regardless of which group they belong to. This is equivalent to adding to the previous level of equivalence the further requirement that the intercepts τ_i are equal in A and B:

$$\tau_i^A = \tau_i^B \quad \forall\, i \in 1:6$$

This level of measurement invariance is indicated as *scalar invariance*, and it is required for a meaningful comparison of the means of the latent variables.

4. A further levels of measurement invariance (*full invariance*) requires that the residual variances θ_i are equal across groups[41]:

$$\theta_i^A = \theta_i^B \quad \forall\, i \in 1:6$$

This level of invariance — with substantively means that we are measuring with the same precision across groups — is not required for meaningful comparisons of the distributions of latent variables across groups, and often is not even expected theoretically. This is, for example, the case in our study, where there is no reason to hypothesise that measurements carried out in different surveys, by different fieldworkers and with different methods, should have the same level of measurement error, and many reasons to think the opposite.

The equalities above, that express the requirement for the different levels of measurement invariance are to be interpreted as referring to the population, and not to the sample. Therefore, their assessment is done via statistical testing, where the null hypothesis is the absence of differences in the source population.

The testing procedures vary depending on the models, the estimator and the sample size, but they are based on the same principle. They consist in comparing the overall fit of a MGM where some parameters (e.g. loadings for metric invariance and intercepts for scalar invariance) are constrained to be equal across groups with the same model where the parameters are free to vary: if the fit of the constrained model is not significantly worse than the fit of the unconstrained model, the corresponding level of invariance is supported; otherwise it is not.[631]

When an estimator of the ML family is used, the most traditional procedure compares the values of the χ^2 indices of fit between the constrained and unconstrained models[42]: under relatively broad conditions their difference (or some 'scaled' version of it) is distributed as χ^2 with degrees of freedom equal to the number of constrained parameters, and therefore its statistical significance can be assessed in the usual way. However, similarly to what happens with the assessment of the absolute fit of a model, the power of the χ^2 test for difference becomes excessive with large samples, with the consequence that the hypothesis of measurement invariance is almost always rejected even when the difference in fit is trivial.

Therefore, it is common practice in literature to asses the relative fit of the progressively constrained models by comparing the values of other indices of model fit, less sensitive to sample

size. Various indices of model fit are used to this end, but all share the undesirable property that the statistical distribution of their difference is unknown. The decision about accepting or rejecting the hypothesis of measurement invariance is based on the application of empirical cut-off, derived from simulation studies.[620, 621, 632]

In this study I report, for completeness, the results of the scaled χ^2 difference test[43], and base the decision regarding invariance on the comparison of the difference in CFI and and mcDonald's NCI, using the cut-off provided by Meade et al. [621].

3.3.2.8 *Quantile estimation with skewed distributions*

As previously stated, the estimator of choice for fitting the models in this thesis is the MLR estimator. This estimator is 'robust' to deviation from normality in the observed variables, in the sense that it adjusts the standard errors and the fit indices to take into account this eventuality, but the distribution of latent variables is still supposed to be multivariate normal. This is not a problem in general, both because ML point estimates of model parameters (especially means) are relatively insensitive to the exact distribution of the latent variables[44], and also because in general populations the distribution of BP is not too far from normal.

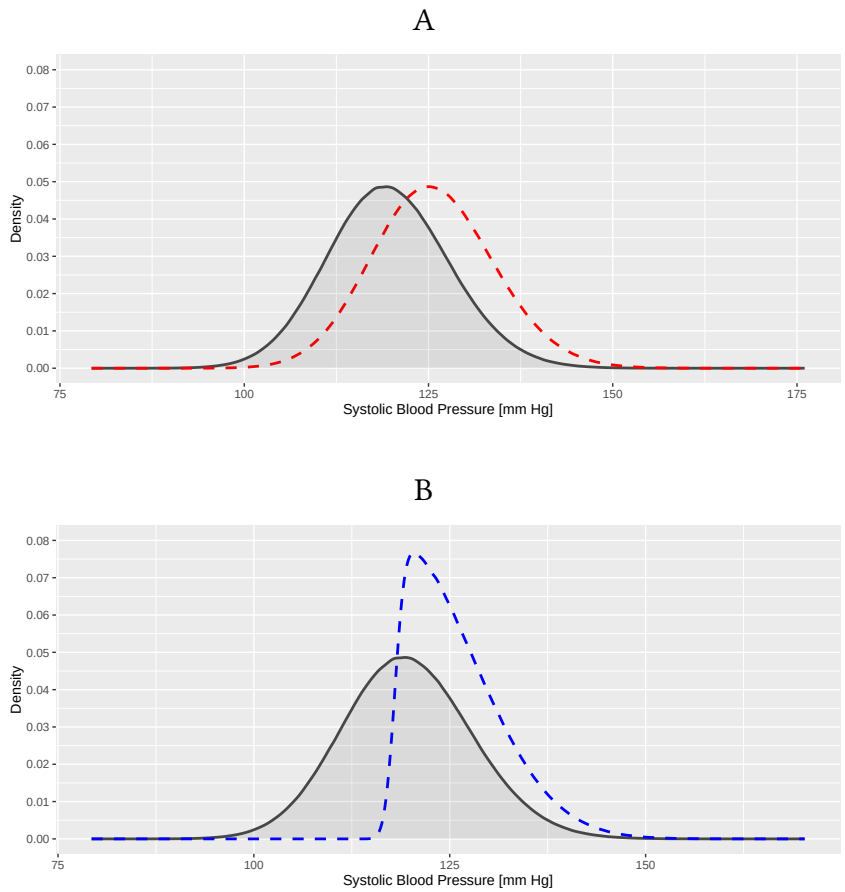
However, in the analysis of the changes in the distribution of BP over time, it is of interest to go beyond analysing trends in mean values and studying in more details the whole distribution. This is because the same change in the mean may be the result of very different phenomena, and having an indication of which phenomenon (or phenomena) are involved may have important substantive consequences.

For example, Figure 3.8 compares two hypothetical situations where a 'baseline' SBP distribution with mean 120 $mmHg$ is shifted to the right.

Both the final distributions (dashed lines in panel *A* and *B*) have the same mean of 126 $mmHg$, but the changes from baseline represent very different phenomena. The first represent a homogeneous shift of the whole distribution, where the 6 $mmHg$ increase of the mean is the result of an increase which affects similarly individuals with low and high baseline BP. In the second case, on the contrary, the increase in mean is substantially due by a large increase in the BP of low-risk individuals with low baseline BP, while the right tail of the distribution does not change much. The different implications of the two cases in a public health perspective are evident.

To explore this phenomenon with our data, I re-fitted some of the models relaxing the assumption of multivariate normal distribution of the latent variables and the observed endogenous variables. At this end, I applied the methodology described by Asparouhov and Muthén [633] and implemented in the Mplus statistical software. The method allows the variables to follow

Figure 3.8: Different ways of shifting the mean of a distribution: an example.



See text for a detailed description of the figure.

either a *skew-normal* distribution or a more general *skew-t* distribution.[634] The latter allows for any level of skewness, while the skew-normal only allows for moderate levels of skewness ($-1 \leq univariate\,skewness \leq +1$). Because the expected values of skewness of the BP distribution is relatively small, I chose the skew-normal distribution, less prone to convergence problems and computationally less demanding.

The parameters of the distribution of both SBP and DBP estimated with this method were then used to analyse graphically the change of the distribution over time and to calculate some statistics to better describe its characteristics. Formulæ that allow for the calculation of the moments of the skew-normal distribution from the estimated model parameters are described in [633], while quantiles were calculated using the R package *mntnorm*[635].

3.3.2.9 *Dealing with different numbers of measurements*

A computation problem that arises in this study is the consequence of the fact that the different surveys use a different number of measurements of BP, namely two in the NIDS and three in the remaining. As a result, the different groups have a different number of observed variables. While this is not a problem from a theoretical point of view[45], the traditional ML estimation for multi-group analysis implemented in the available software requires the presence of a complete covariance structure in all groups. That is, if the covariance structure for one or more group cannot be fully specified because of the absence of some observed variables, the estimation fails.[636]

To deal with this problem without recurring to the obvious (and wasteful) solution of discarding the third measurement in all samples, I applied the procedure proposed by Baumgartner and Steenkamp [637], consisting of:

1. introducing in the group with missing measurements imaginary observed variables that have means of zero, variances of one, and covariances of zero with all other variables;
2. re-specifying the model in the the group with missing measurements by fixing the factor loadings and intercepts of the imaginary variables to zero and their residual variance to one;
3. estimating the model in the usual way.

The presence of the imaginary variables makes the estimation possible, because the number of 'observed' variables becomes equal across groups. The overall fit of the model and the estimation of the parameters of interest are not affected, because the 'imaginary' part of the model is fitted perfectly by the chosen values. The only adjustment which is needed to to obtain correct results is the correction to the number of degrees of freedom, which must be reduced to take into account that the imaginary variables do not add any information. The reduction in the degrees of freedom equals the number of arbitrary entries in the sample covariance matrices and mean vectors of the groups with incomplete measurements, and is given by the general formula:

$$\Delta df = \sum_{i=1}^{k} q_i \left(p - \frac{q_i - 3}{2} \right) \tag{3.19}$$

where p is the total number of variables in each of the k groups and q_i is the number of missing variables in the i^{th} group.

To generate the 'imaginary' variables with the characteristics above, I applied the algorithm proposed by Scholtus et al. [638, p. 28]. With this two step procedure, the missing variables

are first imputed as random normal variates with mean 0 and variance 1, and then iteratively substituted with the residual of their regression on all observed variables in the dataset. Regression residuals are, by definition, uncorrelated with all the predictors, and only need to be rescaled to have variance = 1 and fulfil the requirements above.

An alternative solution to the problem of incomplete covariance structure has been more recently proposed by Kim et al. [636]. Briefly, it consists of fitting the models as mixture models (i.e. models where the membership to a group is not known but 'latent', estimated from the data), and then forcing the membership to correspond to the known one. The procedure gives identical results as the procedure above, with the only drawback that mixture estimation does not provide the usual range of model fit indices, and this is the reason why I preferred to proceed with the inclusion of imaginary variables. I have, however, applied the latent class procedure in some cases, namely when fitting the models with skewed distribution where the mixture estimation was in any case a requirement.

3.3.2.10 *Sample dependency*

Multigroup analysis assumes that each group is an independent sample of the population. Among our datasets, this assumption of independence holds for the two SADHS, the SAGE and SANHNES datasets, but not for the four waves of the NIDS survey, where the samples are largely — albeit not totally — overlapping and the same individuals are repeatedly interviewed.

The consequences of the violation of this assumption are known, and the main aspects of interest for our study can be summarised as follows:

1. If the model is otherwise correctly specified, the correlation between samples does not affect the point estimates of the model parameters, i.e. standard estimation procedures still produce valid results even if the independence assumption is violated.[639]

   This result, which is valid under broad assumptions, ensures that the point estimates of parameters in all our models are still valid.

2. Standard errors of the estimates are in general affected, and in most cases neglecting an existing correlation leads to values that are smaller than they should be.[640]

   However, a series of interesting studies by Papadopoulos and Amemiya [641] and Papadopoulos [639, 642] have shown that for a large class of SEMs (the so-called *error-in-variables models*, where no restrictions are imposed on the covariance matrix of the latent variables) standard errors of loadings, intercepts, residual errors and latent means estimates (but not variance-covariances of latent variables) are asymptotically correct even in presence of sample dependency. The results of the simulation study by Perdomo et al. [643] also confirms these findings.

Our base measurement models belong to the category of error-in-variables models, and our samples are large. Therefore, we can assume that estimates of standard errors of factor loadings, intercepts, error variances and latent means are still valid and can be reliably compared across surveys.

This property does not extend formally to the estimation of the standard errors of validity coefficients, because this computation requires the estimates of the standard error of the variances of the latent variables, which are not guaranteed to be unbiased. Neither is applicable to the estimates of the variances of the latent BP.

3. χ^2 and other measures of model fit are in general affected. Usually, neglecting group dependency lead to the underestimation of the χ^2 and, consequently, almost all other measures of (mis)fit.

   This result means that ignoring sample dependency might lead to an increased type II error when assessing model fit. Results from simulation studies in the literature, however, shows that this overestimation tends in general to be quite small.[643, 644]

4. Likelihood Ratio tests (or, equivalently, χ^2 difference tests) to assess measurement invariance are very robust to sample dependency, and this property extends to other common indices of model fit. That is, group dependency has a negligible effect, if any, on the Likelihood Ratio and, similarly, on the difference in CFI, SRMR, RMSEA and other indices between nested models.[643, 644]

   This result means that the standard procedure for assessing measurement invariance can be applied, from a practical point of view, even in our case where the formal assumption of independence is not met.

Overall, the considerations above are reassuring regarding the applicability of the standard procedure (ignoring dependency) for:

1. Assessing model fit and measurement invariance across surveys;
2. Estimating the unstandardised parameters of the base measurement model and the mean difference in latent means across groups with no adjustment for covariates.

Doubts, however, remain regarding estimating standard errors of means, variances and covariances of the latent variables (i.e. the 'true' values of BP according to our model) when adjusting for possible confounders (such as seasonal effect) or other explanatory variables (such as BMI or smoking status).

Methods to properly take into account sample dependency in a multi-group framework without imposing constraint on the structure of the model and taking into account complex sampling designs are an active area of research.

Compared to conventional methods for the analysis of correlated data (such as longitudinal models with random effects) these methods do not require explicit modelling of the relationships between variables across groups, and may address effectively a series of scenarios where direct modelling of inter-group relationships is difficult or impossible.[640, 641] This is the case of the analyses in this thesis, where explicit modelling of the relationships between variables across groups is not straightforward because of (1) the highly unbalanced nature of the dataset (which is a combination of a series of independent cross-sections with an unbalanced panel where some, but not all, individuals are repeatedly interviewed) and (2) the small and unequally spaced number of time points.[639] Moreover, modelling the relationships of the variables across groups while ensuring that the estimates are applicable to the whole South African population (with its changing structure) at the different time points, would require *explicit* information regarding the realization of the complex sampling scheme in each survey [46]. However, all available datasets provide only *implicit* information at this regard, in the form of sets of sampling weights, which *differ across waves even for the same individual*, when he/she is repeatedly interviewed in the NIDS, and this makes the conventional longitudinal approach non applicable in our case.

Recently, two articles have been published with examples of procedures to adjust indices of model fit and standard error of the estimates to take into account sample dependency.[638, 640] The two articles utilise a similar approach, based on the modification of the pseudo-ML procedure commonly used to adjust standard errors for within sample dependency and departure from multivariate normality. Briefly (see [638, p. 26-27 and 30] for details) the standard pseudo-ML procedure adjusts standard errors and measures of fit using correction factors calculated as a function of the estimated asymptotic sample covariance matrix $\hat{\Gamma}$. In a multi-group framework with k independent groups, the $\hat{\Gamma}$ matrix is block-diagonal, with structure:

$$\hat{\Gamma} = \begin{bmatrix} \frac{n}{n_1}\hat{\Gamma}_1 & & & \\ & \frac{n}{n_2}\hat{\Gamma}_2 & & \\ & & \cdots & \\ & & & \frac{n}{n_k}\hat{\Gamma}_k \end{bmatrix} \tag{3.20}$$

Where $n_1 \cdots n_k$ are the sample sizes in each group, n is the total sample size, and $\hat{\Gamma}_1 \cdots \hat{\Gamma}_k$ are estimates of the asymptotic sample covariance matrices in each group.

When some groups are dependent, the matrix $\hat{\Gamma}$ is substituted by a matrix $\hat{\Gamma}^d$, where the off-diagonal blocks corresponding to non-independent groups i and j are not zero any more, but are the estimated asymptotic between-group covariance matrix $\hat{\Gamma}_{ij}$ and $\hat{\Gamma}_{ji} = \hat{\Gamma}'_{ij}$. For

example, if we suppose that group 1 and group 2 are now dependent, the matrix $\hat{\Gamma}$ becomes:

$$\hat{\Gamma}^d = \begin{bmatrix} \frac{n}{n_1}\hat{\Gamma}_1 & \frac{n}{\sqrt{n_1 n_2}}\hat{\Gamma}_{12} & & \\ \frac{n}{\sqrt{n_1 n_2}}\hat{\Gamma}_{21} & \frac{n}{n_2}\hat{\Gamma}_2 & & \\ & & \cdots & \\ & & & \frac{n}{n_k}\hat{\Gamma}_k \end{bmatrix} \tag{3.21}$$

The remaining pseudo-ML estimation procedure stays the same.

The problem of estimating the matrices $\hat{\Gamma}_{ij}$ with $i \neq j$ is an open area of research. Deng and Yuan [640] proposed a procedure adequate for samples with no missing data and when the multivariate distribution of the dependent variables is not too far from normal. Scholtus et al. [638] took into account a complex sampling design, but their solution is based on an *ad hoc* adjustment, valid for that specific case which is not comparable to the case examined in this thesis.

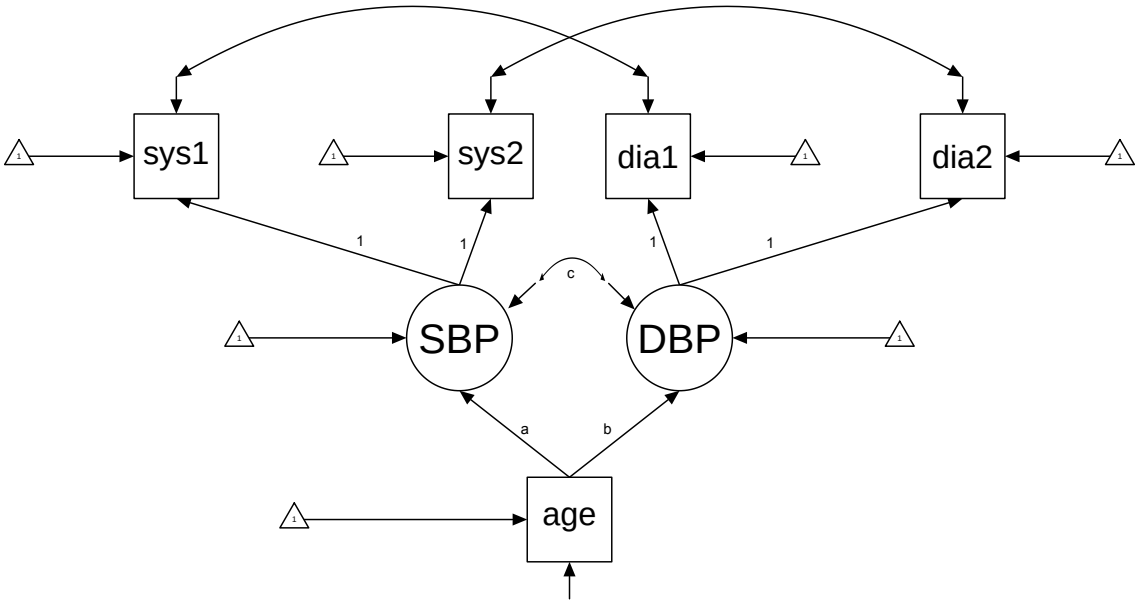
Outside the context of MGMs, Cessie et al. [645] proposed a general method to approximate the correlation between parameter estimates (odds ratios in their case) in dependent groups, by bootstrapping. As a form of sensitivity analysis, and without claim of completeness, I adapted their method to the estimation of the off-diagonal elements of the $\hat{\Gamma}^d$ matrix to assess the effect of neglecting the sample correlation between the waves of the NIDS on the parameter estimates.

The example MGM model in Figure 3.9 has been used for the analyses. It has been fitted on different combinations of the four waves of the NIDS: (1) first and second; (2) second and third; (3) third and fourth and (4) first and fourth. Each estimation has been carried out twice, the first time ignoring sample dependency, and the second adjusting standard errors and measures of model fit using the procedure above. As a form of control, the same model was fitted considering the SADHS 1998 and the NIDS 2014 samples, which are independent.

Note that in the model the regression coefficients **a** and **b** representing the effects of age on SBP and DBP, and the residual covariance **c** have been constrained to be the same in the two groups. This imposes constraints on the latent covariance matrix, and, therefore, our model is outside the scope of validity of the reassuring results from the studies by Papadopoulos and Amemiya.

The R packages *Lavaan*[646] and *Lavaan.survey*[647] have been used for the estimation, because of the possibility of accessing the internal objects needed for the modification. This possibility is restricted in the commercial Mplus software used in the rest of this thesis. The

Figure 3.9: Model for sensitivity analysis for sample dependency: path diagram.



Note: For simplicity, parameter labels are omitted for residuals and means/intercepts.

code used to access the Lavaan internal objects and modify the $\hat{\Gamma}$ matrix is based on the code kindly provided by Sander Scholtus (personal communication, July 2016) and described in [638]. The bootstrap procedure used to approximate the $\hat{\Gamma}_{ij}$ matrix is, however, an original contribution of this thesis.

The results of the sensitivity analysis showed that taking into account the sample dependency produced negligible changes in both the major indices of model fit and the standard errors of all parameters estimates. As expected, the differences between adjusted and unadjusted estimates in the NIDS were higher when the two samples were closer in time (e.g. were higher when comparing the first and second wave of the NIDS than when comparing the first and the fourth). Differences were zero (within the numerical precision of the calculations) when comparing the SADHS 1998 and NIDS 2014 sample, actually independent.

A more detailed description of the results and the R code used for the calculations is reported in Appendix G.

Given the results of this sensitivity analysis — and the fact that the differences were likely to be even smaller when all samples are considered together, because the dependency only affects 4 samples out of 6 — *the adjustment for sample dependency was not applied to the analyses.*

3.3.2.11 *Treatment effects*

As already pointed out in Chapter 2 the binary variable indicating whether or not a subject is on treatment with antihypertensive drugs has peculiar characteristics, which make it impossible to treat it as an ordinary predictor in relationships involving the observed values of BP as outcomes.

To circumvent this problem and avoid the bias that ignoring it would introduce into ordinary estimates of the treatment effect itself and into the relationships between BP and other risk factors, various methods have been proposed. Among those, (**a**) the addition of a constant to the value of the observed BP of the treated subjects, and (**b**) the use of a censored normal regression rather than ordinary linear regression.[240]

Method **a**, which is easy to apply and has been shown to provide good results, has been used for the analyses in Chapter 7, where the interest was on the estimation of seasonal variations on BP adjusted for confounding factors including treatment, but not on the estimation of treatment effects themselves.

For the analysis of BP trends, however, the estimation of the treatment effect itself was of interest, in order to determine the extent to which it explained the observed variations of BP over time, and method **a** was not applicable, because with that approach the magnitude of treatment effect is assumed rather than estimated.

Therefore, for those analyses, I took a two-steps approach, that can be considered a modification of the censored normal regression method. This approach consists in (1) predicting, by means of a censored normal regression model, the values of the *untreated* BP for the treated participants, i.e. the values of BP that would have been observed in absence of treatment, and (2) using these values, rather than the observed ones, in the following analyses. With this method, treatment effects among the treated and in the population can be directly recovered as the difference between the observed and the predicted values, and the remaining analyses can be conducted with the usual method (multiple group SEM in our case) without the need of introducing the 'problematic' binary treatment variable as regressor.

Clearly, because the untreated values are unobserved, their prediction requires some assumptions. The assumption underlying the censored normal regression used to this end are:

1. The values of BP that would have been observed in treated individuals in the absence of treatment is at least as high, and probably higher, than their observed BP;
2. The observed distribution of BP among untreated individuals and the unobserved distribution of BP in absence of treatment among treated individuals are similar and approximatively normal, conditional on the observed covariates.

The first assumption is quite mild, and corresponds to the reasonable substantive hypothesis that antihypertensive treatment does not increase BP among the treated. The second assumption is, on the contrary, more arguable not so much because it requires approximately normal distributions, but because it corresponds to assuming that the fact that an individual is treated says nothing about his or her underlying BP (*non-informative censoring* in statistical terms). However, there are reasons to believe that the violation of this assumption does not have a substantial effect of the estimates, i.e.: (1) the requirement only applies to the *conditional* distributions and, therefore, the BP distributions of treated and untreated subjects can actually differ, provided that we have information on the variables that influence this difference; and (2) the method has previously been used and performed well in simulation studies.[240, 648]

Given these assumptions the method consists in representing the (common) underlying distribution of BP among treated and untreated subjects with a latent variable, the realization of which is only observed for the untreated individuals, but missing for the treated subjects.

Formally, a regression model is fitted, in the form:

$$bp_i = \mu + \beta X_i + \epsilon_i \tag{3.22}$$

were X_i is a vector of covariates (e.g. age, sex, BMI or any other observed factor that might influence BP values) in the i^{th} individual, μ is the population mean, β is a vector of regression coefficients, ϵ_i is the regression residual and bp_i is the latent value of BP, which is assumed to be associated to the observed value bp_i^o with the relation:

$$\begin{cases} bp_i \geq bp_i^o & if\ the\ subject\ is\ treated \\ bp_i = bp_i^o & if\ the\ subject\ is\ not\ treated \end{cases} \tag{3.23}$$

The model in equation 3.22 and 3.23 can be efficiently fitted by ML and the estimated coefficients β and μ used to predict individual values of the unobserved untreated BP for the treated subjects.

In this study, I applied the estimation procedure above (as implemented in the R package *survival*[649]) to each individual multiple reading of SBP and DBP, separately for each survey, and I substituted the predicted values for the observed one in the multi-group SEM used to recover population trends. The covariates (X) introduced into the model were: age, BMI and waist circumference (continuous); season of data collection (*cosinor* representation, see Section 3.3.3.2); province of residence, urban vs. rural dwelling, education, race, alcohol use, smoking, history of cardiovascular disease (categorical/binary).

The model described above is a latent variable model itself, and, potentially, it can be integrated in the larger multiple group SEM models used for the other analyses. That is, in the measurement model for the latent variables SBP and DBP, each of the observed indicators (repeated measurements) can be substituted by the latent variable representing the untreated BP, the distribution of which is estimated by a censored regression model. With this approach, all model parameters — including those of the censored regression part — are estimated jointly, thus avoiding the two-step procedure with the advantage that the estimates of SBP and DBP take into account the fact the values of the untreated BP are estimated and not observed. The main reason why I did not apply this procedure but rather the two-step procedure described above is because this would have implied the introduction of 9 censored variables into the model[47]. The ML estimation of models with censored variables is one of the cases where numerical integration is required, and each variable represents a dimension of integration. A multiple group model with $9 + 3 = 12$ dimensions of integration[48] (and a total sample size exceeding 50 000) is, unfortunately, numerically intractable.

3.3.2.12 *Estimating prevalence of uncontrolled hypertension*

The analyses in this thesis focused on modelling directly the distribution of blood pressure, rather than the prevalence of hypertension. The main reason for this choice are:

1. avoiding the loss of information due to the discretization of a pair of continuous variables (individual SBP and DBP) into a binary one (hypertension status);
2. avoiding the drawbacks related to modelling discrete rather than continuous variables. In the former case, in fact, ML estimators require numerical integration (computationally heavy) and switching towards least square estimators (computationally simpler) has a cost in efficiency and cannot be applied to some sub-analyses[49];
3. avoiding the use of totally arbitrary cut-offs as fundamental elements in the modelling procedure;
4. avoiding (or at least reducing) the effects of digit preference because of the smoothing process implicit in the ML estimation.

However, for the reasons made explicit in Chapter 2 a secondary objective of the analyses was the estimation of the proportion of subjects with BP values above the threshold of 140/90 $mmHg$, i.e. the prevalence of *uncontrolled* hypertension across time.

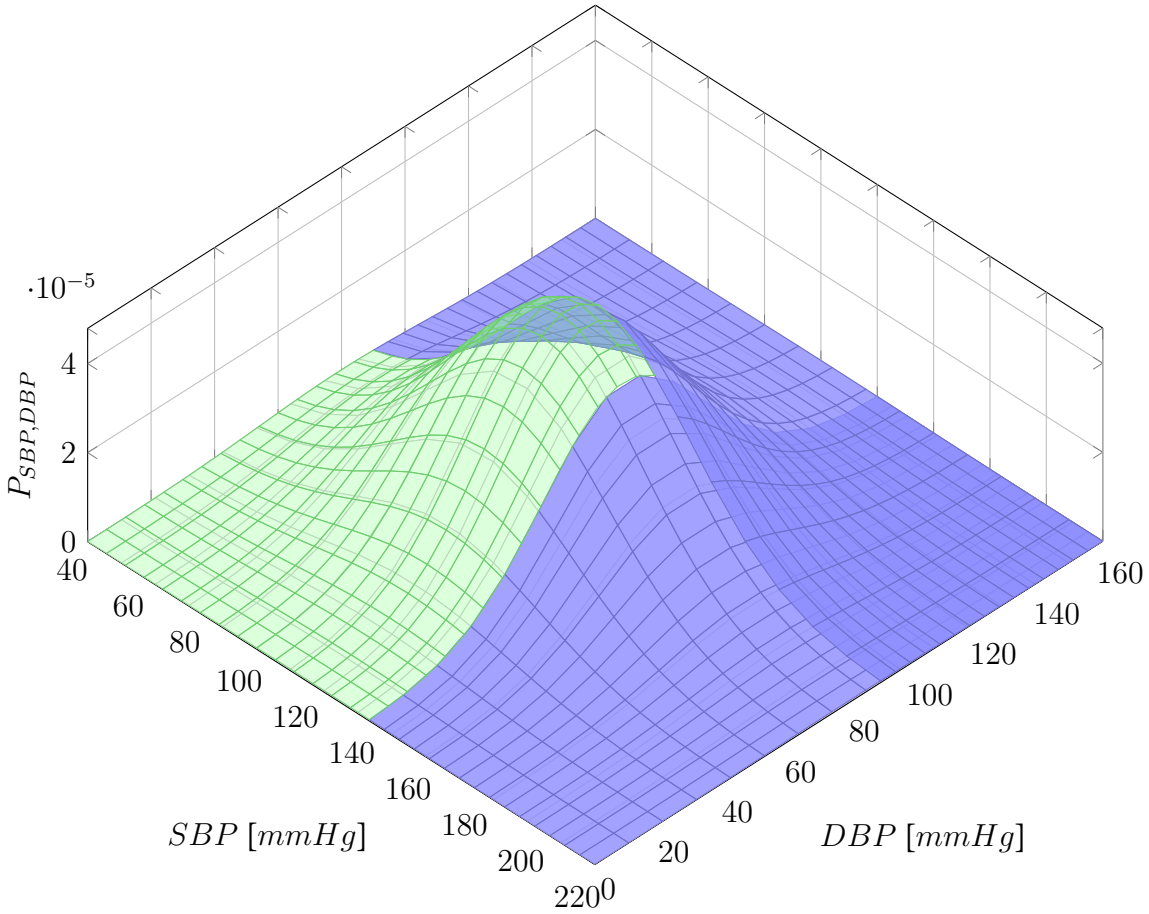
These values are obtained indirectly, from the joint distribution of SBP and DBP estimated in the model.

According to this approach and the cut-off adopted in this study, the prevalence of uncontrolled hypertension P_{hyp} is defined as the probability that either the *latent* value of SBP ≥ 140 or the *latent* values of DBP ≥ 90, or both:

$$P_{hyp} = Pr(SBP \geq 140) + Pr(DBP \geq 90) - Pr(SBP \geq 140|DBP \geq 90) \tag{3.24}$$

Graphically, in the example of Figure 3.10, depicting the joint distribution of systolic and diastolic blood pressure in a hypothetical population, the prevalence P_{hyp} is represented by the volume under the dark surface, while the volume under the lighter surface on the left represents the complementary proportion of normotensives.

Figure 3.10: Joint distribution of systolic and diastolic blood pressure in a hypothetical population.



If the joint distribution of SBP and DBP is assumed bivariate normal, P_{hyp} is completely defined

by the values of the estimated model parameters μ_{sbp}, μ_{dbp},ψ_{sbp}, ψ_{dbp}, and $\psi_{sbp,dbp}$, respectively means, variances and covariances of the latent variables SBP and DBP:

$$P_{hyp} = P_{hyp}(\mu_{sbp}, \mu_{dbp}, \psi_{sbp}, \psi_{dbp}, \psi_{sbp,dbp}) \tag{3.25}$$

In the more general case of the skew-normal distributions, variances and covariances are not sufficient statistics, and other parameters are needed to define the distribution[50], but in any case P_{hyp} is a unambiguous function of the estimated model parameters.

The calculation of the cumulative probability P_{hyp} requires numerical approximation, because a closed form does not exist even in the simpler case of bivariate normal distribution.[650] The R package *mnormt*[635] (for the normal case) and *sn*[651] (for the skew-normal case) have been used to this end.

3.3.2.13 *Dealing with the complex survey design and representation error*

All surveys considered in this study collected data using a multi-stage clustered sampling design and included stratification and oversampling of sub-populations of specific interest. The MLR estimator used for fitting all models in this thesis takes into account this departure from simple random sampling, incorporating sampling weights in the maximization of the likelihood function, and adjusting standard errors for clustering and stratification.[598, 652]

Variables indicating clusters and stratum (defined in geographic terms) were provided in each survey and incorporated in the analyses. For the NIDS survey — where the panel structure created some ambiguity regarding which cluster/stratum had to be assigned in the following waves to individuals who moved from an area to another — the analyses followed the approach suggested by Wittemberg [653] and all individuals were assigned in the following waves to the same cluster and stratum where they were originally sampled.

The treatment of sampling weights deserves a more detailed description. All surveys provided sampling weights calculated in order to inflate the sample and represent the target population, taking into account not only the survey design (i.e. the inverse of the probability of being included in the sample, given the survey design) but also (as far as possible) non-response and coverage errors. To obtain the latter result, the weights provided with the surveys were *calibrated*, i.e. adjusted so that their sum across specific population strata (defined by sex, age category, race and province in our datasets) matched externally supplied population totals.

When data are used cross-sectionally, this procedure ensures — assuming that the statistical model used for calibration and the totals are correct — that the estimates are internally consistent and represent unbiased estimates at the population level. However, the main aim of this

thesis is to jointly analyse and compare data from the different surveys and recover trends and longitudinal relationships. In this case, consistency of the estimates is not ensured both because of differences in the calibration procedure[51] and, mostly, because population totals used as a reference changed over time and do not represent a consistent temporal series[52].

To reduce the bias introduced in estimates of longitudinal relationships, I re-calibrated the sampling weights in each survey using a consistent series of population totals over time. The procedure has been previously applied for the purpose of comparing data across the different editions of the South African National Household Survey.[358]

The population totals used for calibration were provided by the Actuarial Society of South Africa Demographic and AIDS (ASSA) model, in its 2008 version, published in 2011.[654] The model is the latest of a series of mathematical models developed to assist the actuarial profession and the Actuarial Society of South Africa in assessing and addressing the impact of the HIV and AIDS epidemic in South Africa. The models have been developed by the AIDS Committee of the Society and the Center for Actuarial Research (CARe) at the University of Cape Town, and provide, *inter alia*, a consistent series of population totals by sex, race, age group and province.

The re-calibration has been done using a cross-entropy procedure implemented by the Stata user-written program *maxentropy*[655], using the original calibrated sampling weights as the input.[53]

The sum of sampling weights was constrained to match the corresponding population totals in each of the 48 age-sex-race groups (5 ten-years age groups, plus a sixth group including subjects 65 years and older) and in each of the nine provinces. The total number of subjects with missing information in any of the race, age and race variables were considered as a separate group. A further constraint was that the proportion of urban dwellers matched the country proportion as published in the United Nation's World Population Prospects.[371]

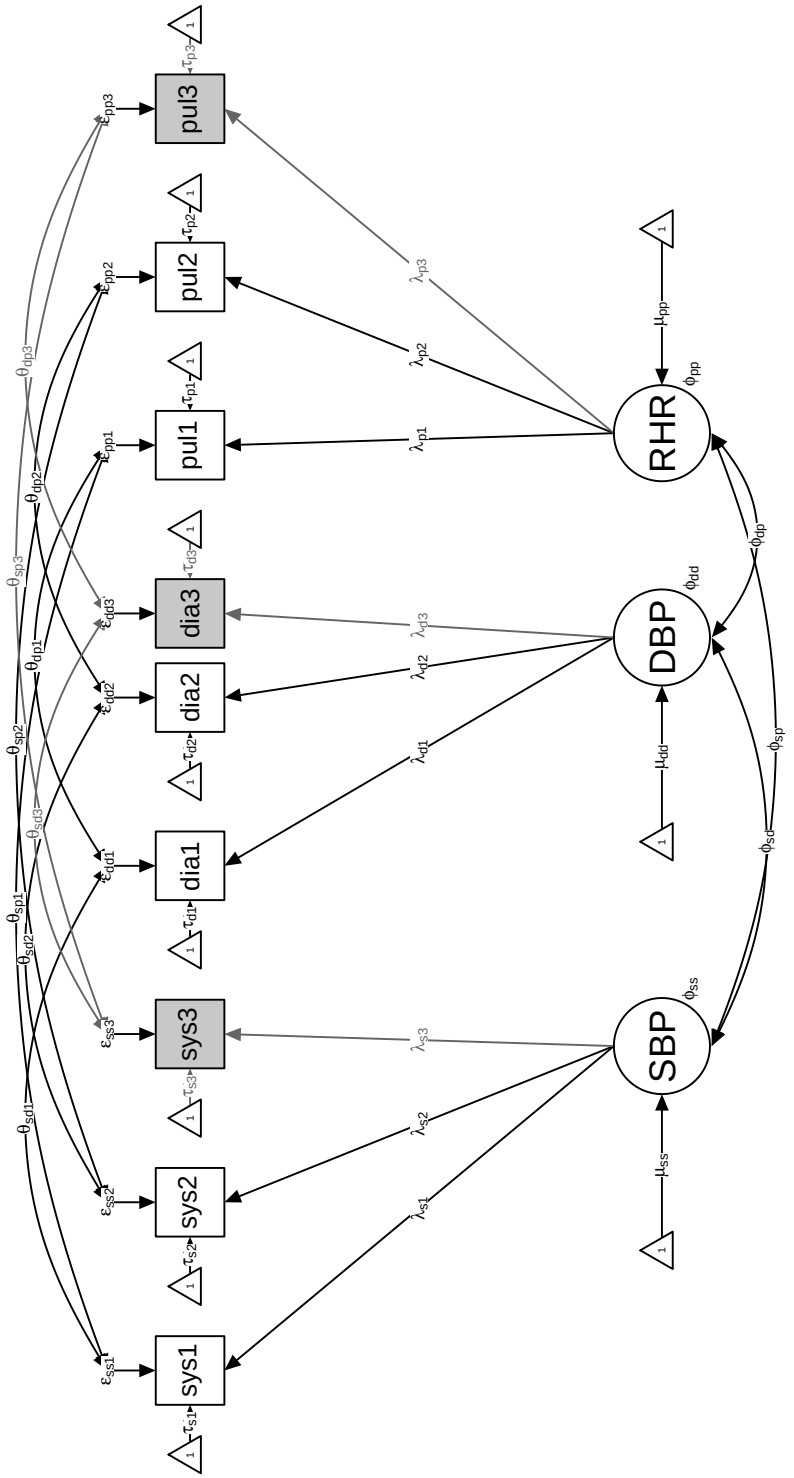
Examples of the inconsistency of the original sampling weights and of the beneficial effects of the re-calibration process on the group-specific population totals are shown in Chapter 4.

3.3.3 Models

3.3.3.1 *Measurement models*

The measurement model used in our analyses to estimate the latent true distributions of BP is represented by the path diagram in Figure 3.11.

Figure 3.11: Base Measurement model: path diagram.



sys1, sys2, sys3 = multiple readings of systolic blood pressure; dia1, dia2, dia3 = multiple readings of diastolic blood pressure; pul1, pul2, pul3 = multiple readings of resting heart rate; SBP, DBP, RHR = latent systolic and diastolic BP, and resting heart rate.
Gray arrows and squares represent the part of the model absent in the analyses of the NIDS samples.

Despite our main interest in the estimation of the 'true' values of systolic and diastolic blood pressure (represented by the latent variables SBP and DBP), the model also includes the observed multiple measurements of resting heart rate, as well as its underlying latent value (RHR). The reason for considering RHR an integral part of the model is twofold. First, because BP and RHR are correlated[656], introducing into the model the extra information coming from the multiple measurements of heart rate may improve the precision of the estimates of SBP and DBP. For the same reason, its introduction may improve the numerical stability of the estimation procedure, especially in the NIDS datasets where only two measurements were available[54]. Second, because RHR has been repeatedly proposed as an indicator of chronic stress and a possible mediator of the observed effect of socioeconomic factors on BP,[19] estimates of RHR may be of value *per se* for the interpretation of BP trends and their determinants.

The model in Figure 3.11 is known as a *correlated uniqueness model*, where — in contrast with the more common *congeneric* measurement model — the residual errors ϵ are allowed to correlate freely between measurements of BP and RHR taken at the same time.[657]

From a substantive point of view the model embeds the hypothesis that an observed value (say $sys1$, the first reading of SBP) is the results of the causal effect of two different variables:

1. the 'true' SBP, the effect of which on $sys1$ is represented by the path λ_{s1};
2. an error term ϵ_{ss1} which subsumes all sources of variability beyond the true SBP, i.e. the combined effect of all biological and methodological sources of measurement error reviewed in Chapter 2[55]. The effect of the error on the observed values is represented by the path connecting ϵ_{ss1} to $sys1$.

   Without loss of generality, this error term is hypothesised to have mean 0, and any systematic difference between the mean of ϵ_{ss1} and the mean of SBP (*bias*) is accounted for by the intercept τ_{s1}.

The presence of the double-arrow paths $\theta_{\cdot 1}$ means that the error term ϵ_{ss1} cannot be regarded as independent from the error terms ϵ_{dd1} and ϵ_{pp1} corresponding to the measurement of diastolic BP and RHR taken during the same procedure. On the contrary, part of the measurement error variance is common across measurements taken simultaneously. Substantively, this corresponds to the hypothesis that part of the variability in the observed values of BP and RHR is associated with the particular position of the reading in the sequence of the repeated measurements (*method effect*).[658] This is a plausible hypothesis, largely supported in literature, which has also testable statistical implications[56].

Allowing errors of measurements taken during the same procedure to freely correlate — as in the correlated uniqueness models — is not the only way to take into account (and, if of interest, quantify) method effects. Various other solutions are available in the SEM literature,

in most of which the effect of the different methods of measurement (in our case the same procedure but applied at three different points in time) are explicitly represented by a set of latent variables, in addition to the latent variables representing the true values of interest. For the purposes of our analyses, I chose the correlated uniqueness approach because of its known good properties in terms of convergence and fit, and its robustness to violations of the implicit assumption that effects attributable to different methods are uncorrelated [57].[659, 660]

The analytical expression of the model in Figure 3.11 is as follows:

$$
\begin{aligned}
sys1 &= \lambda_{s1} SBP + \epsilon_{ss1} + \tau_{s1} \\
sys2 &= \lambda_{s2} SBP + \epsilon_{ss2} + \tau_{s2} \\
sys3 &= \lambda_{s3} SBP + \epsilon_{ss3} + \tau_{s3} \\
dia1 &= \lambda_{d1} DBP + \epsilon_{dd1} + \tau_{d1} \\
dia2 &= \lambda_{d2} DBP + \epsilon_{dd2} + \tau_{d2} \\
dia3 &= \lambda_{d3} DBP + \epsilon_{dd3} + \tau_{d3} \\
pul1 &= \lambda_{p1} RHR + \epsilon_{pp1} + \tau_{p1} \\
pul2 &= \lambda_{p2} RHR + \epsilon_{pp2} + \tau_{p2} \\
pul3 &= \lambda_{p3} RHR + \epsilon_{pp3} + \tau_{p3}
\end{aligned}
$$

$$
\begin{aligned}
var(\epsilon_{ss1}) = \theta^2_{ss1} \; ; \; var(\epsilon_{ss2}) = \theta^2_{ss2} \; ; \; var(\epsilon_{ss3}) = \theta^2_{ss3} \\
var(\epsilon_{dd1}) = \theta^2_{dd1} \; ; \; var(\epsilon_{dd2}) = \theta^2_{dd2} \; ; \; var(\epsilon_{dd3}) = \theta^2_{dd3} \\
var(\epsilon_{pp1}) = \theta^2_{pp1} \; ; \; var(\epsilon_{pp2}) = \theta^2_{pp2} \; ; \; var(\epsilon_{pp3}) = \theta^2_{pp3} \\
cov(\epsilon_{ss1}, \epsilon_{dd1}) = \theta_{sd1} \; ; \; cov(\epsilon_{ss1}, \epsilon_{pp1}) = \theta_{sp1} \; ; \; cov(\epsilon_{dd1}, \epsilon_{pp1}) = \theta_{dp1} \\
cov(\epsilon_{ss2}, \epsilon_{dd2}) = \theta_{sd2} \; ; \; cov(\epsilon_{ss2}, \epsilon_{pp2}) = \theta_{sp2} \; ; \; cov(\epsilon_{dd2}, \epsilon_{pp2}) = \theta_{dp2} \\
cov(\epsilon_{ss3}, \epsilon_{dd3}) = \theta_{sd3} \; ; \; cov(\epsilon_{ss3}, \epsilon_{pp3}) = \theta_{sp3} \; ; \; cov(\epsilon_{dd3}, \epsilon_{pp3}) = \theta_{dp3}
\end{aligned}
\tag{3.26}
$$

$$
\begin{aligned}
var(SBP) = \phi^2_{ss} \; ; \; var(DBP) = \phi^2_{dd} \; ; \; var(RHR) = \phi^2_{pp} \\
cov(SBP, DBP) = \phi_{sd} \; ; \; cov(SBP, RHR) = \phi_{sp} \; ; \; cov(DBP, RHR) = \phi_{dp}
\end{aligned}
$$

$$
E(SBP) = \mu_{ss} \; ; \; E(DBP) = \mu_{dd} \; ; \; E(RHR) = \mu_{pp}
$$

The *effect coding* method by Little et al. [583] has been applied to set the metric of the latent variables and allow for the identification of the model. The method consists in imposing the

following set of constraints on the parameters in equations 3.26:

$$\lambda_{s1} + \lambda_{s2} + \lambda_{s3} = 3 \; ; \; \lambda_{d1} + \lambda_{d2} + \lambda_{d3} = 3 \; ; \; \lambda_{p1} + \lambda_{p2} + \lambda_{p3} = 3 \tag{3.27}$$

$$\tau_{s1} + \tau_{s2} + \tau_{s3} = 0 \; ; \; \tau_{d1} + \tau_{d2} + \tau_{d3} = 0 \; ; \; \tau_{p1} + \tau_{p2} + \tau_{p3} = 0 \tag{3.28}$$

With these constraints, there is no pre-defined choice of a 'reference' indicator as in the more common method of fixing the loading of an arbitrary indicator at 1 and its intercept at 0, and no individual loading or intercept is fixed. What the constraints require is that the average intercept is 1 and the average loading is 0. Quoting Little et al. [583, p. 63], we can say that: "*This method results in estimates of the latent variances that are the average of the indicators' variances accounted for by the construct* [latent variable], *and the latent means are estimated as optimally weighted averages of the set of indicator means for a given construct. In other words, the estimated latent variances and latent means reflect the observed metric of the indicators, optimally weighted by the degree to which each indicator represents the underlying latent construct.*"

By imposing these constraints the model is globally overidentified, with $p = 39$ free parameters, $\nu = 9$ observed variables and, consequently (formula 3.10), $df = 15$ degrees of freedom.

Using the estimates of the model parameters, it was possible:

- To decompose the observed variance of each individual measurement ($\sigma^2_{o,xj}$) as the sum of two components: the variance due to the variability of the 'true' BP/RHR (*true variance* or *trait variance* $\sigma^2_{t,xj}$) and the variance due to measurement error ($\sigma^2_{e,xj}$):

$$\sigma^2_{o,ij} = \sigma^2_{t,xj} + \sigma^2_{e,xj} \tag{3.29}$$

  where x indicates the latent variable ($x = s, d, p$ respectively for SBP, DBP and RHR) and j ($j = 1, 2, 3$) indicates the specific reading.

  The share of observed variance of an indicator that is due to the variability of the 'true' BP/RHR is given by:

$$\sigma^2_{t,xj} = \lambda_{xj}\phi^2_{xx} \qquad x = s, d, p \; ; \; j = 1, 2, 3 \tag{3.30}$$

  The share of observed variance due to error coincides with the residual error, because the loadings of the error terms are fixed at 1 for identification:

$$\sigma^2_{e,xj} = \theta^2_{xxj} \qquad x = s, d, p \; ; \; j = 1, 2, 3 \tag{3.31}$$

- To calculate the *indicator validity* (also known as the *standardised validity coefficient*

or *empirical validity*) of each of the nine individual measurements of SBP, DBP and RHR.[661].

The validity Q of an individual reading is defined as the proportion of variance of the reading which is explained by its true value:

$$Q_{xj} = \frac{\sigma^2_{t,xj}}{\sigma^2_{o,xj}} = \frac{\lambda_{xj}\phi^2_{xx}}{\lambda_{x}j\phi^2_{xx} + \theta^2_{xxj}} \qquad x = s, d, p\ ;\ j = 1, 2, 3 \tag{3.32}$$

It can be read directly from the standardised solution of the models, because it can be easily shown that it corresponds to square of the *standardised* loading of the indicator.

- To calculate the bias of each indicator relative to another (*relative bias*, δ).

  The relative bias measures the difference in the means of the indicators for a given value of the latent mean. The presence of relative bias significantly different from zero means that the indicators being compared are not interchangeable and lead to latent scores that are systematically different.

  The relative bias of between indicators i and j of the same latent variable x is calculated as:

$$\delta_{xij} = \mu_x(\lambda_{xi} - \lambda_{xj}) + \tau_{si} - \tau_{sj} \qquad x = s, d, p\ ;\ j, i = 1, 2, 3 \tag{3.33}$$

  Note that, while the indicator validity is a property of the indicator, the relative bias depends on which indicator is chosen as a reference.

Estimates of the standard error of the coefficients and indices described above (which are all linear combinations of model parameters) were obtained by introducing them as additional parameters into the models.[622] Their calculation was based on the delta method (first order approximation).

The same method was used to throughout the analyses to recover standard errors for all quantities that were not model parameters but could be expressed as a function of them. It is worth noticing that the procedure is not restricted to linear combinations of parameters and is it applicable to generic functions[58] of model parameters, such as, for example, the magnitude of the seasonal effect described below as a non linear function of two regression coefficients.

3.3.3.1.1 Composites

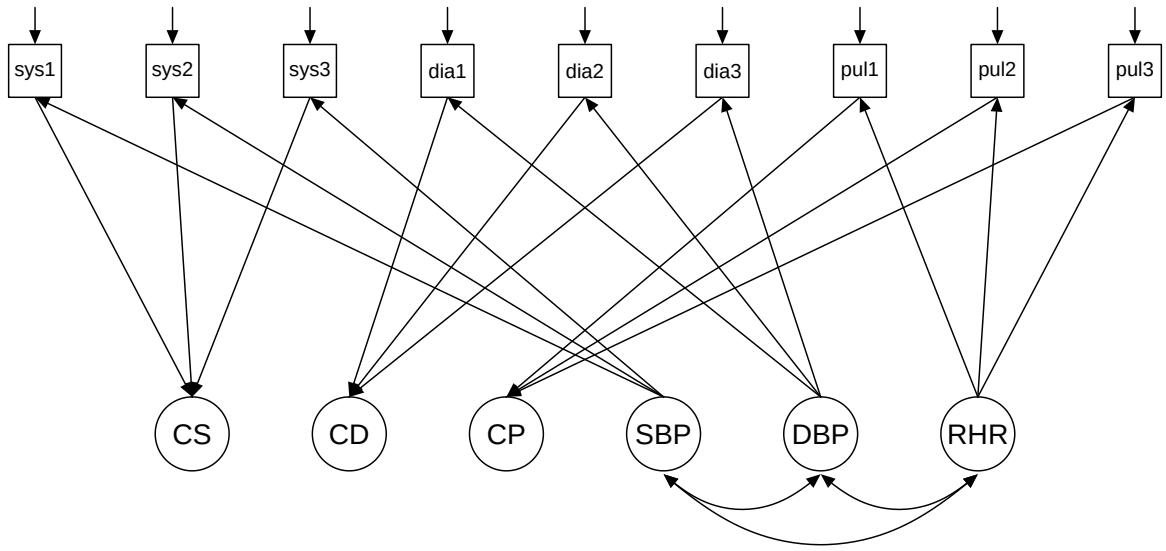
Besides the validity of individual readings, another quantity of interest is the validity of *composite measures*, i.e. measures obtained by linear combinations of multiple readings. Similarly

to the validity of individual readings, the validity of a composite measure is defined as the ratio between the true variance and the observed variance of the composite.

Among the composite measures, certainly the most common are the simple averages of repeated readings, which are commonly calculated because they have usually higher validity than any of their components taken alone.

To calculate *composite validity* Q_c, I used the approach proposed by Raykov and Shrout [662], consisting of introducing into the measurement model a set of *phantom latent variables* (with no indicators, and intercept and residual variances fixed to 0). The phantom variables are regressed on the indicators to be averaged with regression coefficient fixed at $1/n$ (n is the number of indicators) and are uncorrelated with any other variable in the model. The structure of this model for our case is shown in Figure 3.12.

Figure 3.12: Model for the calculation of composite validity: path diagram.



CS, CD and CP are the phantom latent variables representing the composite measures of SBP, DBP and RHR. Mean structure and model parameters labels are omitted for simplicity.

In these conditions, it can be shown that the square of the correlation between the latent variables CS (defined in Figure 3.12) and SBP equals the validity of the measure obtained by averaging the three readings. The correlation between CD and DBP, and between CP and RHR

have a similar meaning. This property was used to estimate the composite reliability in our models.

As already noted by Batista-Foguet et al. [553], the equally weighted averages of the individual readings of the same type (i.e. systolic readings for SBP, diastolic readings for DBP and pulse rate readings for RHR) do not necessarily produce a composite with the highest possible validity. Unequally weighted averages can further increase the validity of the composite, and it can be shown that the set of weights that ensures the maximum possible validity is given by the so-called factor score coefficients.[663] To asses the extent to which this occurred in our datasets, I calculated the validity Q_o of these *optimal composites* and compared it with the validity of the equally weighted composites. In principle, Q_o could be calculated with the same approach used for Q_c, by substituting the unit regression coefficients of the phantom variable with the factor score coefficients. However, the Mplus software used for the estimation of our models is able to directly produce the so-called *factor score determinacy* for each latent variable, which, by definition, corresponds to the correlation between the latent variable and the optimally weighted average defined above. By squaring the factor score determinacies we can obtain, therefore, the optimal validity coefficients. This approach was, therefore, used for our analyses.

3.3.3.1.2 Measurement model in the NIDS samples

In the four samples from the NIDS only *duplicate* measurements of BP and RHR were available, and therefore the part of the model indicated in grey in Figure 3.11 was missing. The number of free parameters in these models was therefore $p' = 27$, the number of observed variables was $\nu' = 6$ and the number of degrees of freedom $df' = 0$, implying that the model was globally just-identified. Moreover, each latent variable had only two indicators and in these cases the identification of the measurement parameters depends on its relationships with the other variables (local underidentification). This condition is a common source of empirical underidentification, quite likely in our case where the correlation between BP and RHR is known to be low[59]. To avoid this undesirable condition, when the model in Figure 3.11 was estimated in the NIDS samples, I imposed the further condition of the equality of the loadings:

$$\lambda_{s1} = \lambda_{s2} \; ; \; \lambda_{d1} = \lambda_{d2} \; ; \; \lambda_{p1} + \lambda_{p2} \tag{3.34}$$

With these constraints the number of parameters to be estimated decreased and the model gained 3 degrees of freedom, becoming overidentified, with the advantage that the fit with the data could be assessed with the usual methods. All considerations and definitions of measurement quality indices are still valid in the reduced models, with modest adaptations of the formulæ due to the absence of some parameters.

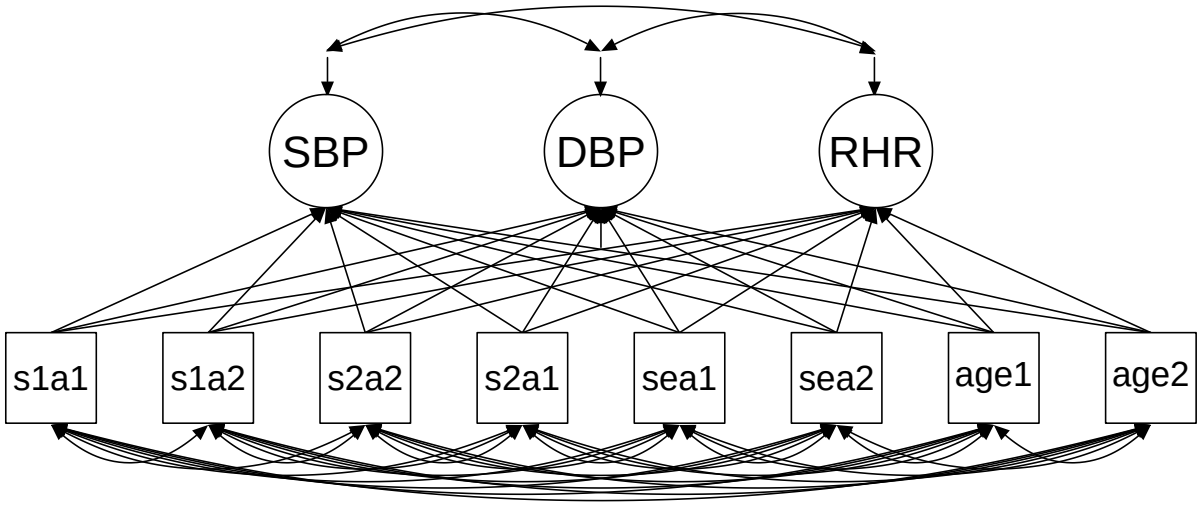
3.3.3.2 *Structural models*

The measurement models above were integrated with a structural part where a series of predictors were allowed to affect the values of the latent variables. All predictors were introduced as covariates, thus implicitly assuming that they were measured with negligible error. This is a reasonable assumption for some of them (such as age) but certainly less tenable for other (especially smoking status and alcohol consumption). However, in absence of multiple measurements for these variables or estimates of their reliability in the specific population[60], their introduction as latent error-free variables with the observed values as indicators was not an option, and this must be acknowledged as a limitation of the data.

A first structural model was used (1) to estimate the magnitude of seasonal effects on the latent BP and RHR taking into account the evidence that it is not constant with age, and (2) and to produce estimates of BP and RHR adjusted for inter-survey difference in the distribution of the data collection during the year.

The path diagram of this model is shown in Figure 3.13.

Figure 3.13: Structural model for seasonal effects: path diagram.



age1, age2 = elements of the linear spline for age; sea1, sea2 = elements of the cosinor function for seasonal effect; s1a1, s1a2, s2a1, s2a2 = interaction terms between season and age.
Intercept and means are omitted for clarity.

The structure of the model embeds the following causal assumptions, supported by the evidence reviewed in Chapter 2:

a Age linearly affects BP and RHR, but the magnitude of the effect can be different during youth/adulthood and later in life.

b BP and RHR follows an annual cycle with a single peak and a single through, approximately 6 month apart.

c The magnitude of the annual variation of BP and RHR might be different at different ages.

Assumption **a** is represented in the model by paths connecting the latent variables with *two* covariates (age1 and age2), which are the component of a linear spline with a single knot at the age of 55 years. Analytically, the effect of age on BP/RHR of individual i was thus modelled as:

$$a_i = \beta_{<55} \cdot age1_i + \beta_{\geq 55} \cdot age2_i \tag{3.35}$$

where $age1_i$ is the age of the individual i, $age2_i$ is 0 if $age1_i < 55$ and equals $age1_i$ if $age1_i \geq 55$, and $\beta_{<55}$ and $\beta_{\geq 55}$ are two regression coefficients estimated from the model.

Assumption **b** is represented in the model by paths connecting the latent variables with the covariates sea1 and sea2, which are the component of a *cosinor* function, frequently used in epidemiological studies to model seasonal patterns. [664]

Analytically, the cosinor function is expressed by the equations:

$$\begin{aligned} s_i &= \beta_A \cdot sea1 + \beta_B \cdot sea2 \\ \beta_A &= \sin \frac{2\pi day_i}{365} \\ \beta_B &= \cos \frac{2\pi day_i}{365} \end{aligned} \tag{3.36}$$

were day_i is the day of data collection (measured from the first of January) for individual i, and β_A and β_B are two regression coefficients estimated from the model.

Given the model in Equation 3.36, the magnitude S of the seasonal effect, defined as the difference between the maximum and the minimum value reach by BP (or RHR) during the year is calculated as:

$$S = 2 \cdot \sqrt{\beta_A^2 + \beta_B^2} \tag{3.37}$$

Finally, assumption **c** in embedded in the model by introducing four further predictors (s1a1,

s1a2, s2a1 and s2a2), representing the interaction between age and time of data collection:

$$\begin{aligned} s1a1_i &= sea1_i \cdot age1_i \\ s1a2_i &= sea1_i \cdot age2_i \\ s2a1_i &= sea2_i \cdot age1_i \\ s2a2_i &= sea2_i \cdot age2_i \end{aligned} \tag{3.38}$$

In the multiple group estimation, both seasonal and age effects are assumed to be stable during the study period. Analytically, this corresponds to constraining the regression coefficients $\beta_{<55}$, $\beta_{\geq 55}$, β_A and β_B and those of the interaction terms to be equal across groups.

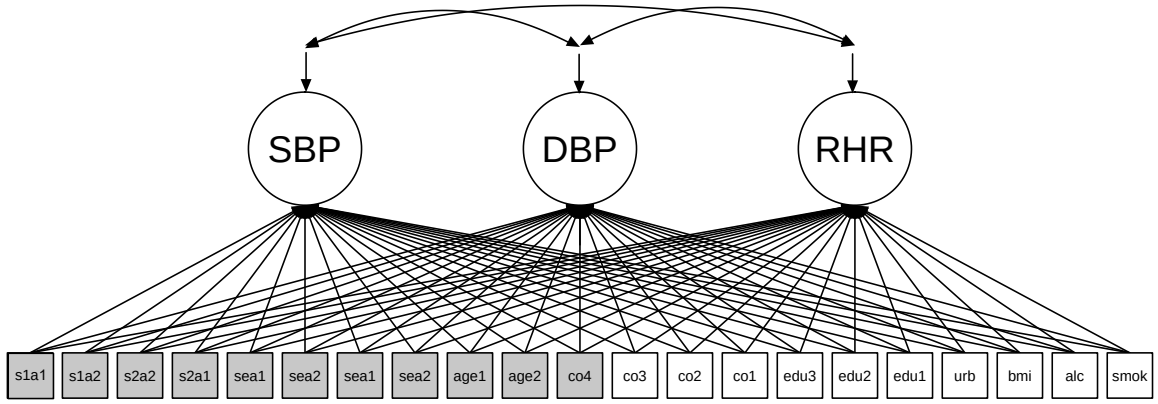
To produce BP and RHR estimates comparable across surveys despite the large differences in the seasonal distribution of data collection, the multiple group model was fitted with the variables sea1 and sea2 centred at a common value in all groups. With this operation, the means of BP/RHR that would have been observed in each period if all measurements had been taken in the same month coincide with the intercepts of the latent variables, which are model parameters. The overall weighted mean of sea1 and sea2 over the pooled dataset was used as a common value for centring. Given the actual distribution of measurements in the surveys, this corresponds — in the hypothesis that the model was correctly specified — to report all measurements as if they were taken approximately at the end of the month of June.

Conversely, the variables age1 and age2 were centred at their mean *in each group*, so that no adjustment for differences in the mean age of the population between surveys was applied to the estimates.

The same model in Figure 3.13, with the same centring of the components of the cosinor function, was refitted using the mixture procedure described in Section 3.3.2.8 which relaxed the assumption of multivariate normality of the distribution of the latent variables, and the results used for the estimation of the prevalence of uncontrolled hypertension as per Section 3.3.2.12.

A second structural model was used to estimate the effects of the biological, behavioural and socioeconomic factors on the *untreated* values of SBP, DBP and RHR, and explore the extent to which their variation explained the observed changes in the distribution of BP over time. This model is shown in Figure 3.14.

Figure 3.14: Structural model for the effects of bio-behavioural and socioeconomic factors: path diagram.



age1, age2 = elements of the linear spline for age; sea1, sea2 = elements of the cosinor function for seasonal effect; s1a1, s1a2, s2a1, s2a2 = interaction terms between season and age; smok = smoking (yes/no); alc = alcohol use (yes/no); bmi = Body Mass Index (continuous); urb = urban dwelling (yes/no) ; edu1-edu3 = education (dummy variables); co1-co4 = birth cohort (dummy variables).
Intercept, means and covariances between covariates are omitted for clarity.

The model included all the covariates of the previous one (with the same function and meaning), and a further set of 10 to jointly model tobacco and alcohol use, BMI, urban dwelling, education and cohort effects. As for the effects of age and season on the observed BP and RHR, stability of the relationships across the whole study period was assumed, and all parameters of the structural model were constrained to be equal across surveys.

To study the individual contribution of each of the risk factors above to the explanation of the changes in the untreated BP, the same model was repeatedly fitted. In all cases the covariates representing the component of the cosinor function were centred at the overall mean to adjust for artefactual differences due only to seasonal effects. All other covariates were centred at the group mean, except one at a time, so that the trend in intercept of the latent variables could be directly interpreted as the the trends adjusted for the relevant variable.

The simultaneous introduction in the multiple group model (where each group represents a different *period*) of the linear spline to model *age* effects and the four dummy variables to represent *birth cohorts* corresponds conceptually — but in a multiple group SEM framework — to a fixed effect Age–Period–Cohort analysis approach, as described by Yang and Land [665]. It is worth noticing that the separate identification of the three effects — which is a well known problem, given the perfect linear dependence of the three variables age, cohort and period — relies on extra-statistical assumptions, in this case the appropriateness of the linear spline to

define age effects and the arbitrary choice of the cut-off years to define birth cohorts.[666]

3.3.4 Software

SEMs were estimated, unless otherwise stated, using Mplus® statistical software v.7.4[667].

Stata® statistical software v.13[538] and R Statistical environment v.3.3[668] were used for other estimation procedures, graphing, and data management. The R base environment has been integrated with the following packages:

- Data Management:
  MplusAutomation, *foreign*.[669, 670]
- Graphics:
  ggplot2, *semPlot*, *tikzDevice*, *qgraph*.[671–674]
- Estimation:
  Survey, *mntnorm*, *sn*, *PairwiseCI*, *survival*, *Lavaan*, *Lavaan.survey*.[635, 646, 647, 649, 651, 675, 676]

Notes

[1]Among these sources, it is worth noticing the South Africa General Household Survey (GHS), which is conducted annually since 2002 by Statistics South Africa[677] in a representative sample of South Africa's households.

[2]According to the United Nation official classification of age groups,[678] this age range includes, more precisely, both youth and adults. For brevity, in this thesis I omit this specification and refer to all subjects 15 years and older as *adults*.

[3]After the exploratory data analysis, the SAGE dataset — together with the SANHNES one — was ultimately excluded from the comparative analyses because of doubts about data quality and sample representativeness. Details of the reason for these exclusions are provided in Section 4.3.4.

[4]Further stratification, different between the two surveys, was considered in order to ensure adequate representativity of specific sub-populations of interest. The details are provided in the official reports for each survey.[372, 373]

[5]Statistics South Africa, often abbreviated as *StatsSA*, is the official national statistical service of South Africa.

[6] The master sample is a sample drawn by Statistics South Africa based on information collected during the 2001 Population Census. The master sample was created for repeated use so as to avoid ad hoc sampling on each occasion. It was designed to be representative at the provincial level and within provinces at the metro/non-metro level. Within the metros, the sample was further distributed by geography type. The four geography types are: urban formal, urban informal, farms and tribal. This implies , for example, that within a metropolitan area the sample is designed to be representative at the different geography types that may exist within that metro.

[7] CSMs are all resident members of the original selected Wave 1 households (including children) and any children born to or adopted by female CSMs in subsequent waves; TSMs are persons who are not CSMs but are co-resident with a CSM at the time of the interview. See Villiers et al. [528] and Chinhema et al. [530] for details.

[8]The validation study by Topouchian et al. [536] refers to the Omron model 'R7' rather than model 'R6' used in the SAGE survey. The two monitors are equivalent for our purposes, and only differs for the possibility of the newer R7 model to interface with a computer through a USB port.

[9]In the SANHNES, the description of the measurement procedure in the survey report[374] contains some incongruencies and does not match the description in the fieldworkers manual[679]. The data in the table refer to the latter.

[10]The characteristics of the sample are specified in the validation protocol. There are some variations across protocols, but all required samples have in common the fact that they are strongly orientated towards subjects in the older age classes, compared to the general population of almost any country.

[11]SBP, DBP, RHR, waist circumference, height, weight and the derived variable BMI calculated as the ratio between weight in kg and the square of the height in metres.

[12]The various surveys used a different coding scheme for the educational level of participants. However, in all surveys the information was sufficient to unambiguously classify the individuals into one of the four categories used in this thesis.

[13]In the tables and throughout the thesis, a two-numbers notation is used to report the interquartile range of a variable, where the two numbers represents the 25th and the 75th percentile, respectively. The choice of this notation rather than the more common single-number notation (where the number represents the difference between the 25th and the 75th percentile) has been made to ensure coherence with a similar notation used for the range, and because the two-numbers notation provides, in conjunction with the value of the median, more information regarding shape of the distribution.

[14]The number of possible end digits is not always 10, because there are may examples of surveys where the observers are instructed to record the readings rounded to the nearest even number. This practice was common when manual mercury sphygmomanometers were in use, but it has been abandoned with the diffusion of automatic oscillometric devices.

[15]As per common practice, in this thesis the acronym SEM is used with reference both to the method itself (Structural Equation *Modelling*) and to its realization (Structural Equation *Models*).

[16]I refer here to 'directed graphs' (DGs) rather to the narrower class of 'directed *acyclic* graphs' (DAGs) more commonly used in epidemiology because SEM is not limited, in principle, to the representation and estimation of acyclic models (*recursive*, in SEM terminology). The distinction is often more philosophical than practical. Acyclicity corresponds in causal terms to the accepted principle that the future cannot cause the past, and "*apparent counterexamples are usually resolved by more finely articulating the temporal sequence of events*"[568, p. 249]. In any case, all the models considered in this study are recursive and their graphical representation is a DAG.

[17]The term *expected* is used here in its classical statistical meaning. The expected values of a generic quantity q (in our example the change in the outcome for a given change in the exposure) is the average of q over a large number of repetitions of the experiment giving origin to q.

[18] The term *functional form* refers the algebraic form of the relationship between dependent and independent variables in the equations that represent the hypothesised causal relationships. The functional form can be expressed either parametrically (the equation is completely specified except for the numeric value of a set of parameters, as in a linear regression equation where only the values of slopes, intercept and residual error are left unspecified and are estimated from the data) or non-parametrically (the 'shape' of the relationship itself is left unspecified, except for some general characteristics such a smoothness, and determined by the data).

In our SEMs, the functional relationships are specified parametrically as *linear regression equations*.[680]

[19]The biasing effect of measurement error on regression coefficients (known as *regression dilution*) is a well known phenomenon with substantive implications.[681] An example are the analyses by Elliott and colleagues on the INTERSALT study, which showed how correction for regression dilution bias resulted in markedly increased strength of association between salt intake and blood pressure.[682]

[20]In these models the observed categorical outcome is conceptualised as the 'coarse' version of an underlying continuous variable with logistic distribution, rather than normal distribution as implied by the Tobit model. Models that use the normal distribution also for categorical outcomes are common in economics, and are known as *probit* models. Because the logistic and normal distributions are very similar, except in some extreme cases, the substantive results of probit and logit analyses are generally the same, and the choice is a matter of computational convenience, ease of interpretation and tradition.[683]

[21]Other common names are *latent variable modelling* and *analysis of covariance structure*.

[22]This is not to say that the problem of the ubiquitous presence of measurement error is ignored by researchers

applying regression methods. On the contrary, the issue has long been a concern in many fields, including epidemiology (see for example Carroll [574]) and various *ad hoc* methods have been developed and applied to adjust regression estimates for the bias introduced by imperfectly measured variables. However, most of these methods represent situation-specific adjustments applied after the regression coefficients have been estimated, and are not integral part of the regression procedure itself.

[23]It is not essential for our reasoning to go in details on what these observed variables represent. We can, for example, assume, that they are the summary results of some questionnaire/psychological test.

[24]Note that, differently from the model in Figure 3.5, the model of Figure 3.6 and, equivalently, the equations 3.4 to 3.7, do not have intercepts. This is because in this model the interest lies only in the relationship between variables (i.e. in the magnitude and statistical significance of the regression coefficients λ and β), while means and intercepts do not have any particular meaning. In these cases the observed variables are commonly centred at their mean, the means of the latent variables (which are arbitrary) are fixed at zero, and all intercepts are, consequently, zero and not modelled.

[25]The discussion of the relationships between the topology of DGs (or path diagrams), identifiability of causal effects and their interpretation with regard to confounding is well beyond the scope of this exposition. See Greenland et al. [547] for a general introduction to the subject, and Pearl [549] and Pearl [684] for a more detailed discussion on the conditions under which the presence of extraneous, unmeasured, factors does not hinder the possibility of a correct identification of the causal effects of interest.

[26]For this reason often their covariance is not explicitly represented (with double-headed arrows) in path diagrams. However, this graphical omission does not mean that the model imposes restrictions on the relationships between covariates: they are free to covary, but their covariances are not model parameters and, when requested, can be estimated directly from the data, independently from the model.

[27]A second important consequence is discussed in Section 3.3.2.5.3.

[28] Similarly to what happens in regression analysis, in most SEMs the researchers' focus is on covariances or correlations between variables, while means and equation intercepts are of no interest. In such case (which is the 'default' in some SEM packages) the SEMs simplify, the variables are introduced in the models as deviations from their means, and means and intercept are not estimated. The expression 3.10 becomes:

$$df = \frac{v(v+1)}{2} - p \tag{3.39}$$

The above is not the case in our analyses, of which the estimation of means and intercepts (the *mean structure* of the SEM) forms an essential part. See Kline [580] and Bentler and Yuan [685] for an introduction to the treatment of means structure in SEM.

[29]The term was originally used by Bollen [590, p. 149].

[30]The properties of unbiasedness of ML estimators are derived from asymptotic theory and, therefore, formally valid only when the sample size tends to infinity.

[31]In the order of 200-500 observations. See Curran et al. [686] and Lei and Wu [586].

[32]As a consequence of the fact that exogenous observed variables are not part of the model, this appealing property of the ML estimator does not apply to observations with missing data on covariates; unless some remedy is taken, these observations are discarded from the analyses.

[33]See Skrondal and Rabe-Hesketh [548, Chapter 6] for a general presentation of the computational problems associated with the maximization of the likelihood function and an overview of the most common procedures.

[34]Formally speaking, the observed covariance matrix is only defined when all variables involved in the model are continuous. When this is not the case and all or some observed variables are categorical, the covariance matrix is substituted by a *polychoric* or *polyserial* correlation matrix, but the basic idea of comparing observed vs. estimated correlations stays the same.[687]

[35]When their calculation is possible, which is not always the case for all our models.

[36] For standard ML estimators, the expression of F is:[617, p. 28]

$$F_{ML}(\Sigma, \hat{\Sigma}) = ln|\hat{\Sigma}| + tr(\Sigma\hat{\Sigma}^{-1}) - ln|\Sigma| - p$$

where p is the number of observed variables in the model.

When estimators other than ML are used, the formula is modified accordingly, often using a scaling factor to correct for the discrepancies between ML and other fitting functions.

[37]This is the most commonly applied definition of χ^2 in SEM. Mplus, the software I used for the analyses, multiplies the fit function F by n rather than by $(n-1)$. Considering the order of magnitude of our samples, the difference has no practical implications.

[38]The *normalised*, rather than *standardised* residuals are considered in the analysis, because some of the former are not available due to known computational problems in estimating the denominator of their expression.[688]

Under the null hypothesis standardized residuals should have a standard normal distribution and any deviation from that would indicate model misfit. Therefore, standardized residuals can be used as tests of model fit, taking into account that the tests are not independent (for example, in our multigroup base measurement model there are 42 residuals: we can expect that 2 of them are above the 1.96 cut-off by chance alone).

The absolute value of normalized residuals is always smaller than the absolute value of standardized residuals, i.e., the normalized residual is a more conservative test. Under the null hypothesis the normalized residuals should have a distribution smaller than the standard normal distribution and any deviation from that would indicate model misfit.[688]

[39]The presence of constraints is not necessary for the estimation. However, if no constraint is applied the parameter estimates in each group are not different from those obtained by estimating separately each model. In this case the added complexity of the joint estimation is not justified.

[40]This is the final number of cross-sections used here, after the exclusion of the SAGE and SANHNES samples.

[41]The Greek letter θ indicates the variance of the residuals $\mathcal{E}$: $\mathcal{E}_i \sim N(0, \theta_i^2)$.

[42]Equivalently, the values of the likelihood function can be compared. The χ^2 difference test is formally equivalent to the likelihood ratio test.[689]

[43]The use of the scaled version of the test is necessary to take into account departure from normality and the complex sampling designs. In these circumstances, the difference of the χ^2 indices of model fit is not distributed as χ^2, and adjustments need to be made.[689]

[44]Within limits, i.e. for unimodal distributions with reasonable values of kurtosis and skewness.

[45]The decomposition of the total likelihood function under which the SEM multi-group theory is still valid when groups have different number of variables. It does not require that the same model is fitted across groups.

[46]Including oversampling of sub-populations, non-response at cluster and individual level, loss to follow-up and inclusion of new individuals in the NIDS panel

[47]Three systolic readings, three diastolic readings and, as explained in the following Section 3.3.3.2, three heart rate readings.

[48]The 9 latent variables underlying the partially observed readings, plus the 3 variables representing the latent SBP, DBP and RHR.

[49]For example, the procedure to relax the assumption of multivariate distribution of the variables described above requires the use of an estimator of the ML family.

[50]In the Mplus implementation, these supplementary parameters are the skew parameters δ.

[51]The procedure and the list of variables used for calibration were similar, but not identical, in the different surveys. For example, while NIDS used a procedure ensuring constant weights for all members of the same household, this was not the case in SADHS. Details are presented in the documentation of each survey.

[52]All surveys calibrated the sampling weights using population totals published by Statistics South Africa, which are periodically adjusted when more precise data become available from a census or other sources.

[53]Using design weights (i.e. the inverse of the probability of selection only according to the sampling design) would have been a better choice and avoided a double calibration. However, these were only available for the NIDS survey and, therefore, for sake of consistency, I opted for using calibrated weights in all cases.

[54]The model in Figure 3.11 is locally underidentified if only two measurements are available, i.e. the identification of each of the three latent variables relies on their correlation with the others.

[55]Note that the error terms are defined as *residuals*, i.e. they include all sources of variability that are *not explicitly modelled* and their estimation is possible because we make assumptions regarding their distribution. When information is available regarding some of these sources of of error, they can explicitly modelled and their effect unbundled from the generic measurement error terms. This is what, in these analyses, has been done for example with seasonal effects.

[56]One of these implications is that a model where the covariances θ_{ij} are constrained to be 0 does not adequately fit the data.

[57]Another model commonly applied to take into account method effects is the correlated traits uncorrelated methods (CTUM) model. Examples of its application to the study of measurement error in BP are reported in [553, 555, 556].

[58]Provided their first derivative exists and is continuous.

[59]When the correlation falls below a certain level, in fact, the measurement model of RHR becomes almost independent (from a practical point of view) from the rest of the model, and a two-indicator model considered alone is underdentified.[690]

[60]Multiple measurements were available for weight and height, used for the calculation of BMI. However, given the relatively small error associated with these measurements, the use of the average of the available readings was deemed sufficient for the purpose of the analyses.

Chapter 4

Exploratory data analysis

This chapter presents the results of the exploratory data analysis, and includes three main sections.

1. **Sample characteristics**

   This first section summarises, with a series of tables, the demographic and bio-behavioural characteristics of the sample and the temporal distribution of data collection.

2. **Sampling weights**

   The second section highlights the inability of the original set of sampling weights provided with the datasets to produce consistent time series of basic population demographics. The results of the analyses of the original weights are then compared with those carried out with the new set of weights re-calibrated according to the procedure described in Chapter 3.

3. **Blood pressure and heart rate data**

   The last section analyses BP and RHR data in greater detail. The characteristics of their univariate and multivariate distributions are described by means of tables of summary statistics and graphs. The values of a series of quality indices are presented for each dataset and interpreted to justify the choice of excluding some of the data sources from the trend analyses.

4.1 Sample characteristics

Socio demographic, behavioural and anthropometric characteristics of the samples (excluding data on BP and RHR which are examined in detail in Section 4.3) are summarised in tables 4.1 to 4.5.

Note that the total number of nonmissing values for some demographic variables exceeds the number of subjects actually interviewed reported in Chapter 3, because the NIDS and SANHNES datasets also incorporate information on the family structure from other household members.

Table 4.1: Descriptive statistics of the **SADHS 1998 sample**.

Variable		n	Median/percentage	IQR/frequency	Range
Men		13 826	41.6%	5753	
Age class		13 826			
	15-24		28.5%	3 946	
	25-34		19.7%	2 725	
	35-44		17.4%	2 412	
	45-54		13.0%	1 803	
	55-64		10.6%	1 467	
	65+		10.6%	1 473	
Race		13 801			
	Black		75.8%	10 456	
	Coloured		12.9%	1 780	
	White		8.0%	1 103	
	Asian		3.4%	462	
Education		13 760			
	None		16.5%	2 265	
	Primary		38.7%	5 330	
	Secondary		43.2%	5 950	
	Tertiary		1.6%	215	
Urban		13 826	56.1%	7 752	
Current smoking		12 953	26.7%	3 461	
Current alcohol use		13 786	28.4%	3 919	
Waist circ. [cm]		13 539	81.0	[72.5 ; 93.2]	[42.0 ; 180.0]
BMI [kg/m^2]		13 539	23.9	[20.7 ; 28.6]	[11.3 ; 78.8]
BMI category		13 539			
	Underweight		7.5%	1 013	
	Normal weight		49.3%	6 680	
	Overweight		23.2%	3 144	
	Obese		20.0%	2 702	
CVD history		13 861	5.5%	765	
Diagnosis of hypertension		13 596	14.2%	1 930	
Antihypertensive treatment		13 826	6.6%	915	

n = number of not missing values; IQR = interquartile range.

Table 4.2: Descriptive statistics of the **SADHS 2003 sample**.

Variable		*n*	Median/percentage	IQR/frequency	Range
Men		8 115	41.0%	3 328	
Age class		8 115			
	15-24		29.3%	2 376	
	25-34		20.5%	1 667	
	35-44		17.5%	1 418	
	45-54		14.6%	1 185	
	55-64		9.8%	793	
	65+		8.3%	676	
Race		8 090			
	Black		75.2%	6 081	
	Coloured		12.3%	995	
	White		8.9%	717	
	Asian		3.7%	297	
Education		8 076			
	None		12.6%	1 017	
	Primary		15.3%	1 234	
	Secondary		64.9%	5 238	
	Tertiary		7.3%	587	
Urban		8115	57.2%	4641	
Current smoking		8 089	26.8%	2 171	
Current alcohol use		8 104	22.5%	1 824	
Waist circ. [cm]		7 736	78.0	[69.7 ; 88.5]	[31.4 ; 198.0]
BMI [kg/m^2]		7 795	23.8	[20.6 ; 28.3]	[12.0 ; 59.2]
BMI category		7 795			
	Underweight		7.8%	607	
	Normal weight		49.6%	3 868	
	Overweight		24.0%	1 869	
	Obese		18.6%	1451	
CVD history		8 115	5.0%	408	
Diagnosis of hypertension		8 033	15.5%	1 246	
Antihypertensive treatment		8 115	7.5%	605	

n = number of not missing values; IQR = interquartile range.

Table 4.3: Descriptive statistics of the **SAGE 2007 sample**.

Variable		n	Median/percentage	IQR/frequency	Range
Men		4 223	42.5%	1 797	
Age class		4 223			
	15-24		1.4%	61	
	25-34		2.1%	88	
	35-44		3.5%	150	
	45-54		24.6%	1 038	
	55-64		33.2%	1 401	
	65+		35.2%	1 485	
Race		3 809			
	Black		61.5%	2 344	
	Coloured		19.7%	751	
	White		8.7%	330	
	Asian		10.1%	384	
Education		4 158			
	None		44.2%	1 840	
	Primary		24.0%	998	
	Secondary		26.2%	1 090	
	Tertiary		5.5%	230	
Urban		4 221	66.6%	2 810	
Current smoking		3 995	15.5%	619	
Current alcohol use		4 003	26.7	1 067	
Waist circ. [cm]		3 895	92.0	[80.2 ; 102.0]	[30.0 ; 200.0]
BMI [kg/m^2]		3 864	28.5	[24.0 ; 33.9]	[12.9 ; 80.0]
BMI category		3 964			
	Underweight		3.0%	118	
	Normal weight		27.4%	1 084	
	Overweight		27.6%	1 094	
	Obese		42.1%	1 668	
CVD history		4 223	8.3%	352	
Diagnosis of hypertension		4 019	28.5%	1 144	
Antihypertensive treatment		4 012	25.2%	1 012	

n = number of not missing values; IQR = interquartile range.

Table 4.4: Descriptive statistics of the **NIDS 2008 sample**.

Variable		n	Median/percentage	IQR/frequency	Range
Men		18 617	43.8%	8 143	
Age class		18 541			
	15-24		30.7%	5 690	
	25-34		19.7%	3 657	
	35-44		16.6%	3 082	
	45-54		13.8%	2 567	
	55-64		9.5%	1 766	
	65+		9.6%	1 779	
Race		18 617			
	Black		76.6%	14 254	
	Coloured		15.4%	2 859	
	White		6.3%	1 182	
	Asian		1.7%	322	
Education		18 510			
	None		13.1%	2 417	
	Primary		23.9%	4 434	
	Secondary		53.8%	9 950	
	Tertiary		9.2%	1 709	
Urban		18 617	50.5%	9 395	
Current smoking		15 507	21.1%	3 277	
Current alcohol use		15 504	24.3%	3 767	
Waist circ. [cm]		13 970	83.1	[74.2 ; 95.4]	[30.0 ; 200.0]
BMI [kg/m^2]		13 885	24.4	[20.9 ; 29.7]	[10.6 ; 74.8]
BMI category		13 885			
	Underweight		6.8%	947	
	Normal weight		47.2%	6 550	
	Overweight		22.1%	3 066	
	Obese		23.9%	3 322	
CVD history		18 617	3.7%	689	
Diagnosis of hypertension		17 141	15.7%	2 686	
Antihypertensive treatment		16 846	11.5%	1 936	

n = number of not missing values; IQR = interquartile range.

Table 4.5: Descriptive statistics of the **NIDS 2010 sample**.

Variable		n	Median/percentage	IQR/frequency	Range
Men		19 307	43.1	8 322	
Age class		19 293			
	15-24		33.1	6 387	
	25-34		20.1	3 884	
	35-44		15.4	2 967	
	45-54		13.1	2 525	
	55-64		9.4	1 815	
	65+		8.9	1 715	
Race		19 306			
	Black		81.8	15 793	
	Coloured		13.6	2 632	
	White		3.3	638	
	Asian		1.3	243	
Education		19 270			
	None		12.2	2 357	
	Primary		22.4	4 316	
	Secondary		55.8	10 744	
	Tertiary		9.6	1 853	
Urban		19 228	46.3	8 897	
Current smoking		16 775	15.8	2 645	
Current alcohol use		16 735	20.5	3 437	
Waist circ. [cm]		15 146	82.00	[72.0 ; 96.0]	[30.0 ; 200.0]
BMI [kg/m^2]		15 122	25.00	[21.4 ; 30.3]	[10.3 ; 76.2]
BMI category		15 122			
	Underweight		5.7	863	
	Normal weight		44.4	6 714	
	Overweight		23.9	3 614	
	Obese		26.0	3 931	
CVD history		19 307	2.5%	481	
Diagnosis of hypertension		18 480	12.0%	2 216	
Antihypertensive treatment		18 268	9.2%	1 690	

n = number of not missing values; IQR = interquartile range.

Table 4.6: Descriptive statistics of the **NIDS 2012 sample**.

Variable		n	Median/percentage	IQR/frequency	Range
Men		21 810	43.0	12 389	
Age class		21 780			
	15-24		32.4	7 052	
	25-34		21.2	4 620	
	35-44		15.2	3 309	
	45-54		12.9	2815	
	55-64		9.5	2 067	
	65+		8.8	1 917	
Race		21 810			
	Black		81.2	17 718	
	Coloured		14.4	3 133	
	White		3.2	694	
	Asian		1.2	265	
Education		21 725			
	None		10.8	2 358	
	Primary		20.9	4 529	
	Secondary		56.7	12 312	
	Tertiary		11.6	2 526	
Urban		21 810	47.4	10 342	
Current smoking		19 901	14.6	2 898	
Current alcohol use		18 664	23.5	4 386	
Waist circ. [cm]		18 262	86.0	[76.0 ; 98.7]	[42.6 ; 199.0]
BMI [kg/m^2]		18 317	25.0	[21.5 ; 29.9]	[11.8 ; 78.4]
BMI category		18 317			
	Underweight		3.9	722	
	Normal weight		46.0	8 428	
	Overweight		25.3	4 632	
	Obese		24.8	4 535	
CVD history		21 810	3.5%	757	
Diagnosis of hypertension		21 282	16.4%	3 496	
Antihypertensive treatment		21 005	12.0%	2 527	

n = number of not missing values; IQR = interquartile range.

Table 4.7: Descriptive statistics of the **NIDS 2014 sample**.

Variable		n	Median/percentage	IQR/frequency	Range
Men		24 856	43.15	10 725	
Age class		24 808			
	15-24		31.6	7 839	
	25-34		22.7	5 642	
	35-44		14.8	3 678	
	45-54		12.5	3 111	
	55-64		9.6	2 367	
	65+		8.7	2 162	
Race		24 856			
	Black		82.5	20 500	
	Coloured		14.1	3 509	
	White		2.4	606	
	Asian		1.0	241	
Education		24 763			
	None		8.8	2 185	
	Primary		19.0	4 706	
	Secondary		56.9	14 094	
	Tertiary		15.3	3 778	
Urban		24 856	49.4	12 287	
Current smoking		22 738	18.8	4 226	
Current alcohol use		22 737	28.7	6 532	
Waist circ. [cm]		22 402	84.8	[74.8 ; 98.9]	[33.0 ; 190.0]
BMI [kg/m^2]		22 324	24.8	[21.0 ; 30.6]	[11.3 ; 64.9]
BMI category		22 324			
	Underweight		5.3	1 193	
	Normal weight		45.6	10 171	
	Overweight		22.1	4 926	
	Obese		27.0	6 034	
CVD history		24 856	2.6%	649	
Diagnosis of hypertension		21 915	10.6%	2 330	
Antihypertensive treatment		23 659	13.9%	3 288	

n = number of not missing values; IQR = interquartile range.

Table 4.8: Descriptive statistics of the **SANHNES 2012 sample**.

Variable		n	Median/percentage	IQR/frequency	Range
Men		16 941	42.1%	7 134	
Age class		16 880			
	15-24		28.1%	4 743	
	25-34		20.0%	3 380	
	35-44		16.3%	2 747	
	45-54		15.0%	2 535	
	55-64		11.3%	1 915	
	65+		9.2%	1 560	
Race		16 741			
	Black		66.1%	11 069	
	Coloured		20.4%	3 411	
	White		4.6%	763	
	Asian		8.9%	1 498	
Education		14 320			
	None		8.0%	1 148	
	Primary		13.3%	1 907	
	Secondary		68.5%	9 807	
	Tertiary		10.2%	1 458	
Urban		16 338	66.3%	10 833	
Current smoking		15 267	18.4%	2 816	
Current alcohol use		15 274	24.5%	3 740	
Waist circ. [cm]		7 252	84.0	[73.0 ; 96.5]	[32.0 ; 195.5]
BMI [kg/m^2]		7 216	25.1	[21.0 ; 30.8]	[11.4 ; 77.6]
BMI category		7 216			
	Underweight		6.0%	436	
	Normal weight		43.6%	3 144	
	Overweight		22.3%	1 610	
	Obese		28.1%	2 026	
CVD history		16 941	6.7%	1 128	
Diagnosis of hypertension		15 146	20.4%	3 083	
Antihypertensive treatment		16 941	14.1%	2 386	

n = number of not missing values; IQR = interquartile range.

Tables 4.9 and 4.10 compare the age, sex and race distribution of each sample with the demographic composition of the South African adult population in the same period.

Table 4.9: Age, sex and race composition of samples vs. population: SADHS, SAGE and SANHNES samples.

	SADHS 1998		SADHS 2003		SAGE 2007		SANHNES 2012	
Variable	S [%]	P [%]	S [%]	P [%]	S [%]	P [%]	S [%]	P [%]
Men	41.6	47.7	41.0	47.6	42.5	47.6	42.1	47.5
Age class								
15-24	28.5	30.6	29.3	30.1	1.4	29.4	28.1	27.7
25-34	19.7	24.8	20.5	24.1	2.1	24.0	20.0	24.4
35-44	17.4	18.7	17.5	18.6	3.5	18.1	16.3	18.0
45-54	13.0	11.6	14.6	12.9	24.6	13.4	15.0	13.7
55-64	10.6	7.6	9.8	7.5	33.2	8.0	11.3	8.9
65+	10.6	6.8	8.3	6.9	35.2	7.1	9.2	7.3
Race								
Black	75.8	70.6	75.2	71.7	61.5	72.1	66.1	72.9
Coloured	12.9	8.6	12.3	8.6	19.7	8.7	20.4	8.7
White	8.0	12.2	8.9	11.1	8.7	10.5	4.6	9.8
Asian	3.4	8.6	3.7	8.6	10.1	8.7	8.9	8.7

S = Sample; P = Population.
Population distributions at the median point of data collection for each survey are calculated by linear interpolation from the mid-year population estimates produced by the Actuarial Society of South Africa.[654]

Table 4.10: Age, sex and race composition of samples vs. population: NIDS samples.

	NIDS 2008		NIDS 2010		NIDS 2012		NIDS 2014	
Variable	S [%]	P [%]	S [%]	P [%]	S [%]	P [%]	S [%]	P [%]
Men	43.8	47.6	43.1	47.5	43.0	47.5	43.1	47.5
Age class								
15-24	30.7	29.2	33.1	28.2	32.4	27.7	31.6	27.3
25-34	19.7	24.0	20.1	24.3	21.2	24.4	22.7	24.6
35-44	16.6	18.1	15.4	18.1	15.2	18.0	14.8	18
45-54	13.8	13.5	13.1	13.7	12.9	13.7	12.5	13.6
55-64	9.5	8.1	9.4	8.6	9.5	8.9	9.6	9.2
65+	9.6	7.1	8.9	7.2	8.8	7.2	8.7	7.4
Race								
Black	76.6	72.2	81.8	72.6	81.2	72.9	82.5	73.1
Coloured	15.4	8.7	13.6	8.7	14.4	8.7	14.1	8.7
White	6.3	10.4	3.3	10.1	3.2	9.8	2.4	9.5
Asian	1.7	8.7	1.3	8.7	1.2	8.7	1.0	8.7

S = Sample; P = Population.
Population distributions at the median point of data collection for each survey are calculated by linear interpolation from the mid-year population estimates produced by the Actuarial Society of South Africa.[654]

In all samples, females are moderately overrepresented compared to the estimated distribution in South African population in the year of data collection, which is a common result in many population surveys.

In the SADHS, NIDS and SANHNES, the age structure of the samples underrepresents younger age groups (less than 36 years) and overrepresents subjects 55 year old and over. Except for the oldest age group (65+) where all surveys oversampled by almost 100%, in the remaining groups the departures from the actual age structure of the population are moderate, and unlikely to introduce major bias in the analyses after adequate weighting. In the SAGE, older age groups (50+) were oversampled by design, and the number of younger subjects (18-49 years) is limited ($\approx$ 380 individuals, or 10% of the overall sample) and not meant to be representative of the general population.

Regarding the distribution of the samples across population groups defined by race, the surveys showed large differences. In two editions of the SADHS the samples match quite closely the racial composition of the South African population, with only a modest oversampling of the Asian group, by design. Things are, however, different for the SAGE, NIDS and SANHNES. The sample from the SAGE severely underrepresents Whites (8% of the sample vs. $\approx$ 19% in

the population 50+,[691] for a total of about 290 individuals) and overrepresents Asians and Coloureds. In the baseline NIDS and especially in the SANHNES Whites are also underrepresented by more than 50%. In these surveys, therefore, estimates specifically referred to the White group must be cautiously considered, especially in the SAGE where the absolute size of the White subsample is also small. Because race, as discussed in Chapter 2, is strongly associated with SES, and in particular White race is associated with higher SES, this fact may have consequences for the generalizability of the estimates to high-SES groups.

4.1.1 Period of data collection

The distribution of the sample during the period of data collection is summarised in Table 4.11. The median month of data collection indicated in the table is the reference used in the trend analyses and in the graphical representation of the results, i.e. the cross-sectional estimates for the South African population relative to each dataset are temporally located at the median month of data collection.

Table 4.11: Period and median month of data collection for the adult subsample of the SADHS, SAGE, NIDS and SANHNES studies.

	Data collection		
Survey	Inception	Conclusion	Median month
SADHS 1998	January 1998	September 1998	March 1998
SADHS 2003	October 2003	August 2004	February 2004
NIDS 2008	January 2008	December 2008	April 2008
NIDS 2010	May 2010	September 2011	September 2010
NIDS 2012	April 2012	December 2012	August 2012
NIDS 2014	October 2014	August 2015	January 2015
SAGE 2007	January 2007	November 2008	August 2007
SANHNES 2012	January 2012	December 2012	June 2012

Of particular interest for our analyses is the distribution of data collection by month, regardless of the year, within each survey. This is because of the possible role of the season as a confounder in inter-surveys comparisons and estimation of trends. The graphical representation of these distributions in the histograms of Figure 4.1 clearly supports the plausibility of this hypothesis, and shows large differences across the eight surveys.

Of particular interest for our analyses is the distribution of data collection by month, regardless

of the year, within each survey. This is because of the possible role of the season as a confounder in inter-surveys comparisons and estimation of trends, given the known phenomenon of seasonal variation of BP. The graphical representation of the distribution of the sample by month of data collection in Figure 4.1 (which shows large differences across the eight surveys), and the data of Table 4.12(which shows how mean values of glsSBP/DBP tend to be higher in winter than in summer) clearly supports the plausibility of this hypothesis.

It is worth highlighting the extreme cases of the SADHS 2003 and the SANHNES 2012. In the first survey, the graph shows than almost no data collection was conducted during winter months (June to August, in blue in the graph). On the contrary, in the SANHNES 2012 no data collection was conducted during summer (December to February, orange bars). The distribution in the SADHS 2003 is especially interesting, because the almost total absence of measurements in the coldest months (when BP tends to be higher) might partly explain the unexpected low prevalences of hypertension estimated from those data.[373, p. 238]

Figure 4.1: Distribution of the sample per month of data collection, by survey.

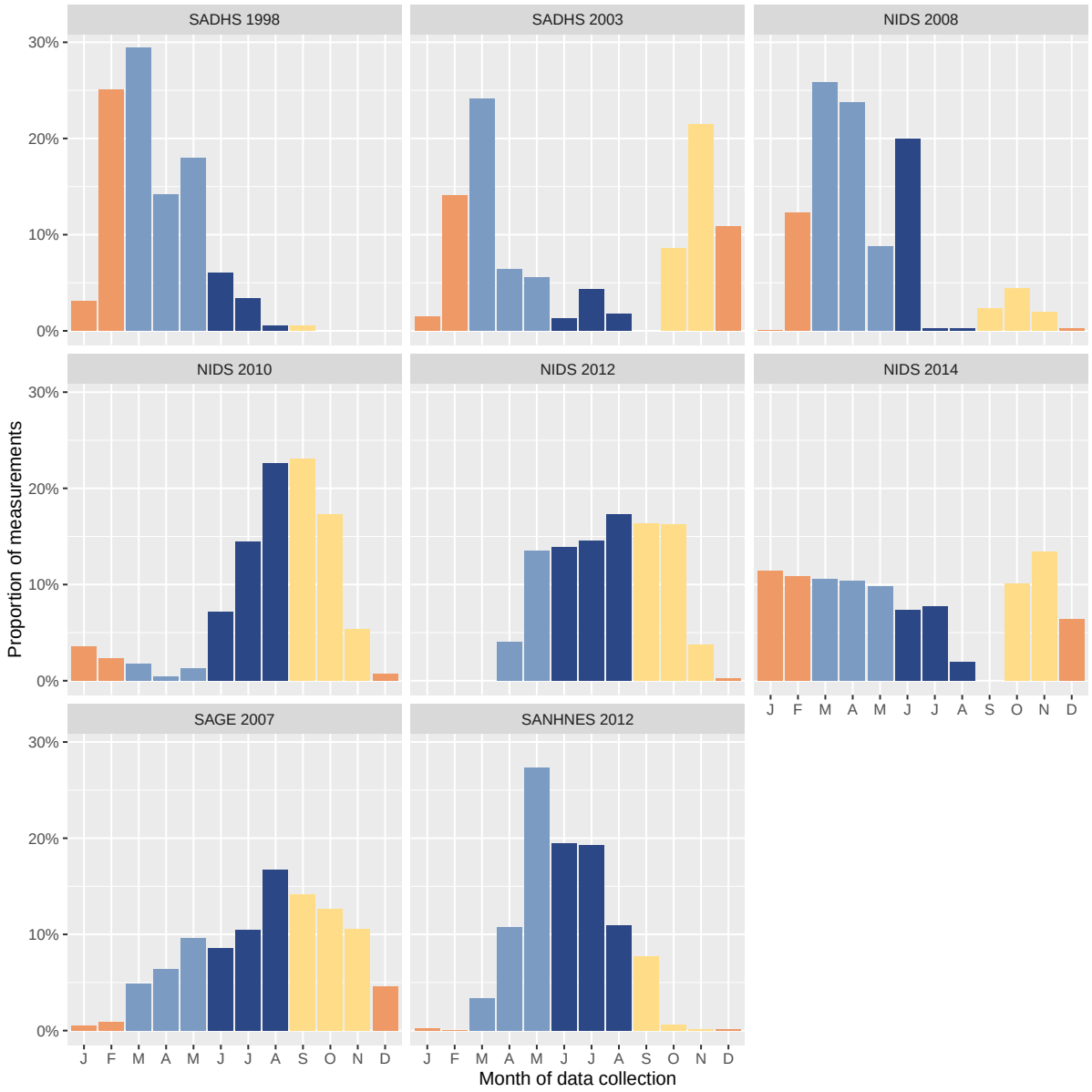


Table 4.12: Mean and standard deviation of the average of multiple readings of systolic and diastolic blood pressure for the adult subsample of the SADHS, SAGE, NIDS and SANHNES studies.

	SADHS		SAGE	SANHNES	NIDS			
	1998	2003	2007	2012	2008	2010	2012	2014
Month	est (sd)	est (sd)	est (sd)	est (sd)	est (sd)	est (sd)	est (sd)	est (sd)
Systolic Blood Pressure								
1	119.5 (21.8)	123.1 (19.3)	137.0 (25.7)	128.7 (18.0)	112.2 (22.1)	124.4 (23.5)		116.8 (19.9)
2	119.3 (20.5)	123.5 (19.8)	143.9 (23.3)	*	122.0 (22.8)	118.9 (18.9)		118.6 (20.3)
3	120.4 (20.9)	125.0 (20.1)	137.6 (24.5)	132.3 (23.6)	123.7 (22.5)	119.0 (18.3)		118.6 (20.5)
4	121.5 (20.6)	125.4 (18.6)	141.8 (26.1)	134.0 (22.9)	127.7 (23.7)	121.9 (22.1)	123.3 (22.6)	122.5 (21.9)
5	125.5 (21.4)	124.6 (18.8)	146.2 (27.8)	134.1 (24.0)	128.2 (23.5)	122.1 (19.9)	125.1 (23.0)	121.5 (20.8)
6	131.5 (23.4)	125.1 (18.6)	147.1 (25.8)	134.6 (22.5)	129.5 (24.3)	124.2 (22.2)	125.4 (22.6)	123.4 (21.1)
7	124.9 (21.9)	126.9 (17.8)	148.5 (26.1)	137.2 (23.4)	132.6 (24)	125.4 (21.2)	125.0 (21.3)	127.9 (22.9)
8	122.9 (16.6)	124.4 (15.2)	144.8 (25.1)	136.9 (24.1)	126.4 (23.7)	125.3 (21.6)	122.9 (21.4)	125.0 (20.5)
9	123.6 (18.2)	145.5 (26.2)	133.8 (22.9)	129.4 (22.8)	124.8 (21.8)	122.8 (21.0)		
10	125.2 (21.3)	148.5 (26.4)	136.9 (20.8)	124.6 (20)	124.0 (21.6)	122.7 (21.2)	117.3 (20.3)	
11	124.9 (20.7)	148.2 (23.7)	126.1 (12.3)	123.1 (14.9)	122.2 (20.2)	122.8 (20.4)	120.0 (21.6)	
12	123.4 (19.9)	149.3 (24.7)	133.4 (18.2)	128.1 (16.7)	121.6 (19.7)	115.4 (17.6)	118.5 (21.6)	
Diastolic Blood Pressure								
1	74.7 (13.3)	77.1 (12.9)	89.0 (18.0)	72.7 (10.5)	72.2 (10.5)	78.8 (14.2)		76.4 (12.8)
2	75.0 (12.8)	77.2 (12.4)	95.0 (18.4)	*	78.4 (14.7)	76.5 (13.0)		77.7 (12.9)
3	75.3 (13.1)	78.2 (12.4)	90.1 (15.9)	75.6 (12.9)	78.9 (13.7)	75.9 (13.3)		77.9 (12.9)
4	76.3 (12.5)	78.2 (12.3)	92.4 (16.2)	76.5 (13.2)	81.9 (13.9)	78.3 (12.5)	81.0 (14.0)	80.4 (13.4)
5	78.6 (12.9)	77.0 (12.9)	95.8 (18.6)	77.7 (12.9)	82.1 (13.9)	80.5 (12.4)	82.2 (13.6)	79.8 (12.8)
6	80.5 (11.9)	74.8 (15.7)	97.0 (15.3)	77.5 (12.5)	82.8 (14.4)	80.3 (13.2)	82.7 (13.6)	81.7 (13.1)
7	78.9 (12.9)	79.2 (11.0)	96.5 (16.9)	79.2 (13.4)	83.2 (11.8)	81.0 (13.3)	82.3 (13.1)	83.4 (13.5)
8	79.8 (12.6)	77.3 (9.6)	95.4 (16.3)	78.3 (13.6)	79.0 (14.2)	81.0 (13.6)	80.6 (13.3)	82.4 (11.7)
9	77.8 (11.2)	95.7 (17.5)	78.6 (13.0)	83.2 (13.3)	80.1 (13.9)	79.9 (13.5)		
10	77.4 (13.3)	97.5 (17.6)	79.2 (13.7)	80.5 (11.8)	79.2 (13.4)	80.0 (13.5)	77.8 (13.3)	
11	77.2 (12.7)	97.3 (16.6)	74.7 (7.6)	82.5 (11.7)	78.0 (13.1)	80.0 (12.9)	78.8 (13.0)	
12	76.4 (12.5)	97.5 (15.3)	75.8 (12.1)	87.2 (15.6)	80.2 (14.0)	76.4 (12.1)	78.0 (13.7)	

est = Estimate; sd = Standard Deviation. All values are expressed in mm Hg.
* All blood pressure measurements were missing for the few individuals interviewed in this month.

4.2 Sampling weights

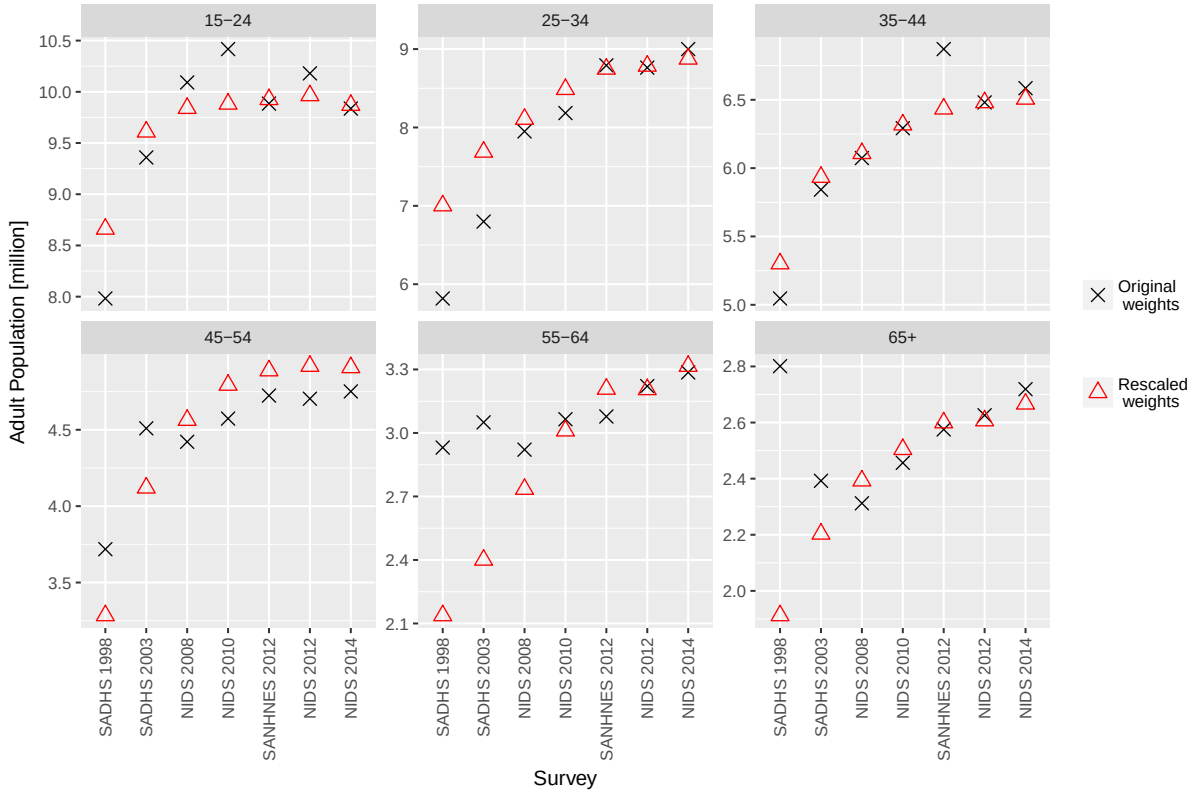
Figures 4.2 to 4.4 compare population totals calculated as the sum of the original sampling weights provided with the datasets (× markers) and as the sum of the recalibrated weights calculated as described in Chapter 3 (△ markers). The first figure refers to the whole adult population, and the following to the subgroups defined by gender, age category and race.

Figure 4.2: Comparisons of estimated population totals using the original vs. the recalibrated sampling weights, **by gender**.

As expected, the graphs show that the original weights did not produce consistent estimates of population totals over time. That is, rather than the expected smooth trends over the entire period, the graphs show sharp changes in the slope of the curve representing the estimated total number of adults in South Africa and implausible 'jumps' in short periods of time. The same phenomenon is even more evident within each age class. In particular, differences are large between the results obtained from the SADHS samples from one hand and NIDS and SANHNES samples from the other, because both the population totals and the analytical methods used for calibration differed.

Considering that population estimates of BP are strongly affected by the age, sex and race

Figure 4.3: Comparisons of estimated population totals using the original vs. the recalibrated sampling weights, **by age class**.

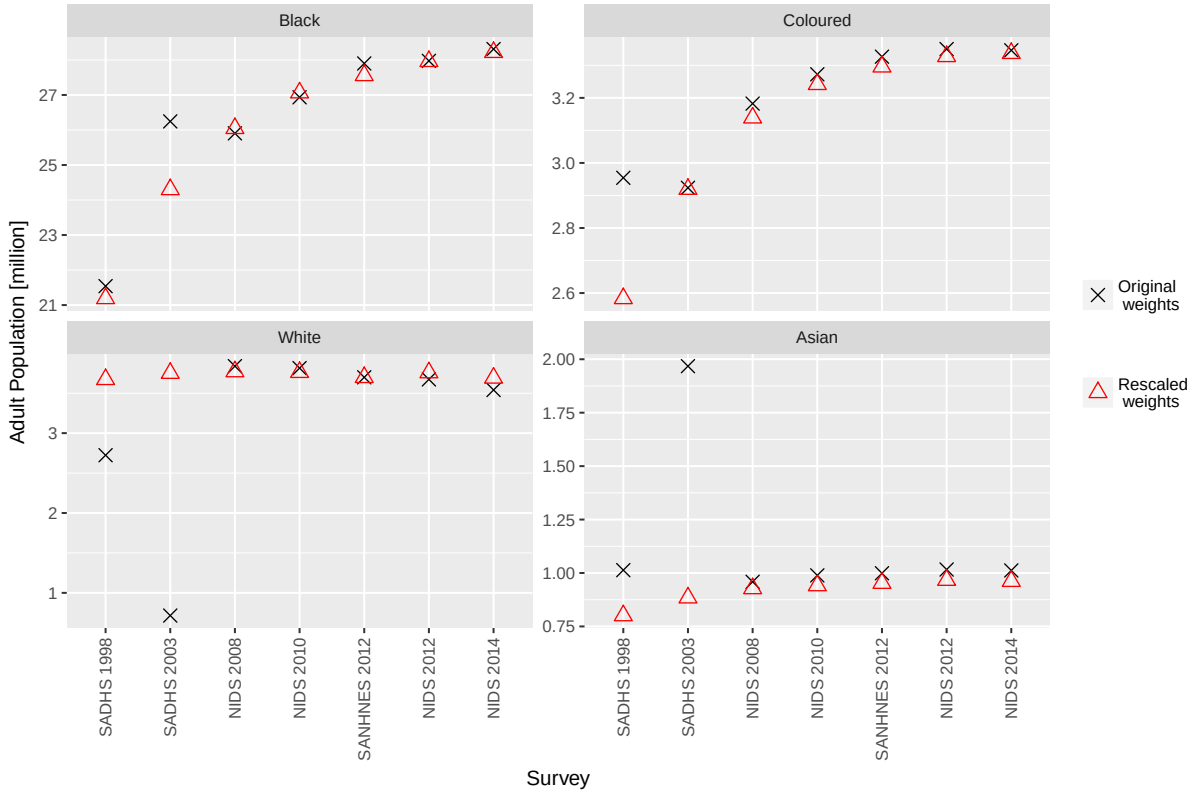


structure of the population as well as by the urban or rural place of residence, the use of the original sets of weights is likely to introduce artefactual elements in the estimation of trends. It is not possible to identify a priori which kind of bias is to be expected, because of the complex interaction between these (and other) factors in determining BP values. However, the graph by age categories suggests a substantial level of under-representation of younger age classes and over-representation of older subjects in SADHS compared to NIDS and SANHNES. Given the strong positive relationship between BP and age — and not taking into account other factors — this may introduce an artefactual reduction in mean BP in the surveys carried out in 1998 and 2003 compared to those carried out in the following period. This, in turn, may lead to the underestimation of any positive trends in BP or, conversely, an overestimation of any decreasing trend.

The population totals after recalibration constituted a much more consistent series across age, sex and race[1], with temporal trends represented by smooth curves which are a more plausible representation of the underlying demographic processes.

As expected, the recalibration did not produce appreciable relative changes in the four waves

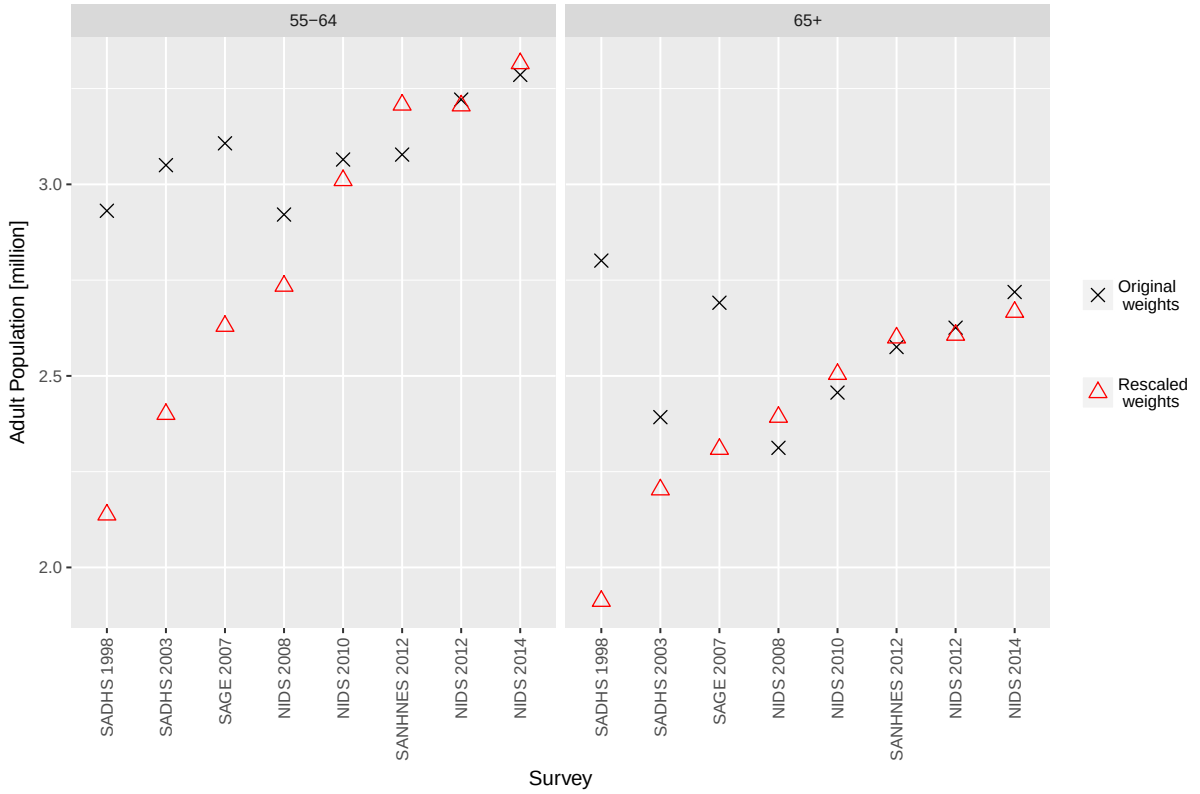
Figure 4.4: Comparisons of estimated population totals using the original vs. the recalibrated sampling weights, **by population group**.



of the NIDS and in the SANHNES, the weights of which were already calibrated using similar methods and population totals, but substantively affected the estimates from the two editions of the SADHS.

The figures above exclude the SAGE sample because of the the different age ranges involved. However, if we limit the analysis to the oldest age groups, the same considerations and conclusions apply when the SAGE data are included in the comparisons. This is illustrated, for example, in Figure 4.5 which depicts the effect of recalibration on the estimate population totals in the oldest age groups.

Figure 4.5: Comparisons of estimated population totals using the original vs. the recalibrated sampling weights, by age class. Subjects 55 years and older.



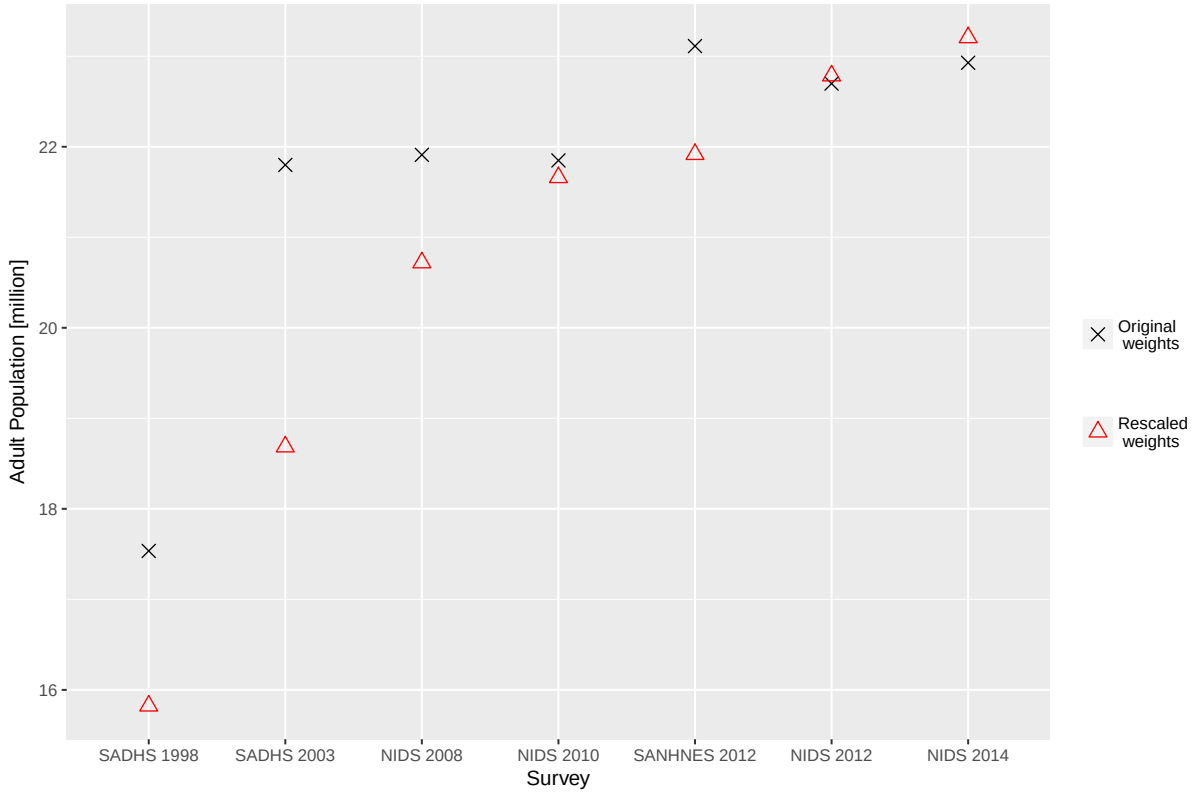
The recalibration involved the proportion of subjects living in urban areas, which is another variable known to be strongly associated with BP levels in population. The ASSA models did not provide estimates for this variable, and therefore, a consistent series of population totals were extracted from the World Development Indicators database maintained by the World Bank[380].

The result of the adjustment is shown in Figure 4.6.

Using the original sampling weights, the SADHS sample over-estimated the urban population compared to the other surveys, and this — because of the established positive relationship between urban status and BP — could lead again to the underestimation of any underlying growing trend or to the overestimation of any true decrease. As before, the recalibrated weights produced a much more consistent time series.

The population totals from the ASSA model do not represent a 'gold standard', and therefore, we cannot be sure that the recalibrated weights produce better population estimates within a specific year than the original weights included in the datasets. However, when the interest is

Figure 4.6: Comparisons of estimated urban population totals using the original vs. the recalibrated sampling weights.



in investigating changes over time, using a coherent series of weights ensures that the different datasets are representing the same population over time — at least according to basic demographic characteristics — and therefore that changes observed in the variables of interests are not the result of spurious changes in the population represented by the samples.

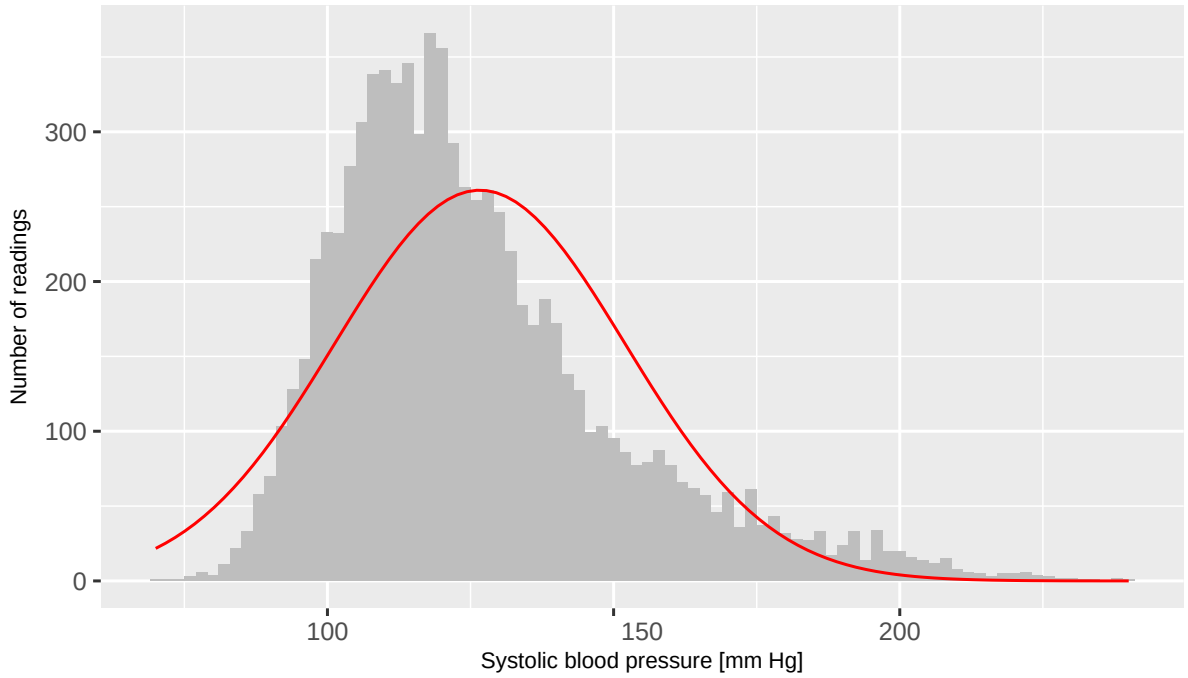
As a final consideration regarding sampling weights, it is worth noticing that the statistical consequence of the sampling unbalances described above is the presence of very large sampling weights for some subgroup of respondents (e.g. white young males), which inflates standard errors and reduces the precision of the estimates. A common solution to this problem is '*trimming*' the weights, i.e. setting an upper limit (usually at the 99^{th} percentile) and assigning this value to all weights that are larger than that. Unfortunately, the price for the gain in efficiency produced by this method is, often, the introduction of bias, especially in the estimates of means and totals, which are of special interest in this thesis.[692] Therefore, I avoided trimming and used untrimmed weights as a basis for all estimations.

4.3 Blood pressure and heart rate data

4.3.1 Univariate distributions

As commonly found in literature, the distributions of both SBP and DBP are not far from normal, and only moderately skewed to the right and with the tails that are slightly heavier than those of a normal distribution. The histogram in Figure 4.7 shows a typical example of the overall shape of the univariate distributions in out study.

Figure 4.7: Distribution of values of the first systolic reading in the female subsample of the SADHS 1998 survey: Histogram and overlapping normal distribution with the same mean and standard deviation.



The distribution in the figure is a specific example relative to the first systolic reading in the female sample of the SADHS. However, the shape of the remaining multiple readings on both systolic and diastolic BP and RHR across all surveys does not differ qualitatively from the one in figure 4.7.

A summary of the characteristics of each of these distributions is shown in Table 4.13 to 4.17. Results are presented by gender, because all the analyses in this study were carried out separately by gender, on account of the substantial evidence that many of the relationships between the variables of interest differ between males and females.

Table 4.13: Sample distribution of blood pressure and resting heart rate in the **SADHS 1998**. Summary statistics, by gender.

	Females						Males					
Variable	n	Range	Mean	SD	SK	KT	n	Range	Mean	SD	SK	KT
sys1	7 717	[71;251]	123.8	23.7	0.8	4.0	5 529	[71;243]	127.7	20.7	0.8	4.2
sys2	7 682	[71;250]	119.8	23.0	1.0	4.6	5 502	[71;248]	123.9	20.2	0.9	4.7
sys3	7 633	[71;250]	117.6	22.4	1.1	5.0	5 498	[73;232]	121.9	20.0	1.0	4.8
dia1	7 734	[35;142]	78.6	14.0	0.5	3.3	5 526	[35;150]	78.8	13.8	0.5	3.4
dia2	7 691	[34;140]	75.6	13.9	0.5	3.4	5 506	[36;135]	76.3	13.6	0.5	3.4
dia3	7 655	[30;139]	74.1	13.6	0.5	3.4	5 504	[33;136]	74.7	13.5	0.5	3.5
pul1	7 807	[40;139]	76.9	13.3	0.2	3.3	5 631	[40;172]	73.4	13.5	0.5	3.8
pul2	7 794	[40;175]	77.2	13.0	0.3	3.7	5 634	[40;130]	73.4	13.1	0.4	3.1
pul3	7 786	[40;160]	77.1	13.0	0.2	3.4	5 631	[40;128]	73.2	12.8	0.4	3.1

n = Number of nonmissing values; SD = Standard deviation; SK = Skewness; KT = Kurtosis.

Table 4.14: Sample distribution of blood pressure and resting heart rate in the **SADHS 2003**. Summary statistics, by gender.

	Females						Males					
Variable	n	Range	Mean	SD	SK	KT	n	Range	Mean	SD	SK	KT
sys1	4 619	[78;240]	126.9	22.5	1.2	5.1	3 228	[75;263]	127.7	19.0	1.3	6.5
sys2	4 581	[73;235]	124.0	21.7	1.3	5.5	3 216	[76;224]	124.9	18.2	1.3	6.2
sys3	4 587	[70;240]	122.2	21.1	1.3	5.5	3 233	[77;214]	123.3	17.8	1.2	6.0
dia1	4 616	[30;146]	79.8	13.4	0.4	3.7	3 223	[30;131]	77.3	12.9	0.3	3.8
dia2	4 584	[30;146]	78.3	13.1	0.4	3.7	3 218	[33;138]	75.6	12.7	0.4	3.9
dia3	4 587	[30;132]	77.2	12.9	0.4	3.5	3 234	[30;131]	74.9	12.8	0.4	3.9
pul1	4 660	[40;144]	78.0	12.7	0.6	4.2	3 259	[40;157]	72.9	13.5	0.6	4.2
pul2	4 648	[42;149]	77.8	12.6	0.6	4.1	3 252	[40;137]	72.7	13.1	0.5	3.6
pul3	4 644	[40;144]	77.8	12.7	0.5	3.9	3 256	[40;133]	72.9	13.0	0.5	3.6

n = Number of nonmissing values; SD = Standard deviation; SK = Skewness; KT = Kurtosis.

Table 4.15: Sample distribution of blood pressure and resting heart rate in the **NIDS**. Summary statistics, by gender.

	Females						Males					
Variable	n	Range	Mean	SD	SK	KT	n	Range	Mean	SD	SK	KT
NIDS 2008:												
sys1	8 308	[70;240]	126.6	25.4	1.1	4.3	5 484	[71;230]	128.7	21.6	1.0	4.6
sys2	8 265	[70;240]	124.3	24.8	1.1	4.5	5 467	[70;244]	126.4	21.3	1.1	4.9
dia1	8 315	[30;146]	82.4	15.1	0.4	3.4	5 495	[30;146]	80.2	14.1	0.4	3.5
dia2	8 254	[31;137]	80.9	14.7	0.4	3.4	5 459	[30;150]	79.0	13.8	0.5	3.6
pul1	8 424	[40;150]	79.2	12.8	0.3	3.7	5 578	[40;145]	72.4	13.3	0.6	3.7
pul2	8 391	[40;177]	78.6	12.8	0.3	4.8	5 574	[40;172]	72.1	13.4	0.9	5.2
NIDS 2010:												
sys1	8 732	[70;239]	124.7	23.2	1.1	5.0	6 013	[70;234]	126.4	20.6	1.1	5.0
sys2	8 666	[70;237]	122.8	22.9	1.1	4.9	5 956	[73;239]	124.2	20.0	1.1	5.4
dia1	8 722	[32;140]	81.0	14.4	0.4	3.5	6 008	[30;139]	79.5	13.7	0.3	3.6
dia2	8 670	[31;140]	79.9	14.3	0.4	3.5	5 974	[30;140]	78.4	13.5	0.3	3.5
pul1	8 881	[40;156]	79.5	12.8	0.3	3.5	6 150	[40;154]	74.0	13.4	0.5	3.6
pul2	8 841	[40;141]	78.8	12.8	0.3	3.3	6 132	[40;170]	73.5	13.2	0.5	3.9
NIDS 2012:												
sys1	10 899	[72;239]	123.9	23.4	1.1	5.1	7 419	[72;227]	126.4	20.7	1.1	5.1
sys2	10 891	[72;235]	121.8	22.8	1.2	5.0	7 415	[71;227]	124.1	20.2	1.2	5.4
dia1	10 899	[40;140]	82.2	14.4	0.6	3.6	7 421	[40;138]	81.3	13.7	0.6	3.7
dia2	10 894	[40;140]	80.8	13.9	0.6	3.6	7 414	[41;140]	80.0	13.4	0.5	3.7
pul1	10 890	[40;174]	77.3	12.7	0.5	4.3	7 414	[40;136]	71.0	13.0	0.6	3.6
pul2	10 885	[40;171]	76.7	12.6	0.5	3.8	7 403	[40;138]	70.7	12.8	0.6	3.6
NIDS 2014:												
sys1	13 114	[74;236]	119.2	22.8	1.2	4.9	9 341	[74;236]	123.8	20.1	1.1	5.2
sys2	13 110	[72;237]	117.7	22.5	1.3	5.1	9 336	[70;224]	122.0	19.6	1.1	5.1
dia1	13 122	[40;149]	79.8	14.1	0.7	3.8	9 344	[40;142]	79.0	13.5	0.6	3.8
dia2	13 115	[40;148]	78.9	13.8	0.7	3.8	9 340	[40;141]	78.2	13.2	0.6	3.6
pul1	13 120	[40;146]	78.9	12.3	0.4	3.4	9 337	[40;141]	71.8	13.2	0.6	3.6
pul2	13 113	[40;148]	78.6	12.2	0.3	3.4	9 338	[40;136]	71.8	13.0	0.6	3.5

n = Number of nonmissing values; SD = Standard deviation; SK = Skewness; KT = Kurtosis.

Table 4.16: Sample distribution of blood pressure and resting heart rate in the **SAGE**. Summary statistics, by gender.

	Females						Males					
Variable	n	Range	Mean	SD	SK	KT	n	Range	Mean	SD	SK	KT
sys1	2 304	[76;240]	148.3	27.7	0.6	3.2	1 701	[74;240]	147.0	28.0	0.6	3.3
sys2	2 305	[71;240]	146.6	26.8	0.5	3.2	1 693	[79;240]	144.7	27.1	0.6	3.2
sys3	2 303	[72;240]	145.0	26.7	0.6	3.3	1 685	[80;236]	144.0	26.3	0.6	3.3
dia1	2 268	[44;150]	97.1	18.0	0.4	3.1	1 667	[42;150]	96.6	18.6	0.5	3.0
dia2	2 281	[40;150]	95.1	17.5	0.4	3.1	1 669	[48;150]	95.6	18.0	0.5	3.0
dia3	2 289	[41;150]	94.1	17.2	0.5	3.2	1 683	[46;150]	94.7	17.9	0.6	3.3
pul1	2 347	[42;175]	78.3	14.2	1.2	7.8	1 731	[40;178]	77.1	15.6	1.7	10.8
pul2	2 347	[40;174]	77.7	14.5	1.3	7.8	1 730	[42;161]	76.9	15.0	1.3	8.0
pul3	2 345	[40;174]	77.3	13.5	1.1	8.5	1 726	[40;174]	76.4	13.9	1.2	8.7

n = Number of nonmissing values; SD = Standard deviation; SK = Skewness; KT = Kurtosis.

Table 4.17: Sample distribution of blood pressure and resting heart rate in the **SANHNES**. Summary statistics, by gender.

	Females						Males					
Variable	n	Range	Mean	SD	SK	KT	n	Range	Mean	SD	SK	KT
sys1	4494	[73;237]	136.4	25.3	1.0	4.0	2449	[75;240]	138.3	23.0	0.8	4.0
sys2	4433	[73;238]	134.3	24.8	1.0	4.0	2416	[86;240]	136.5	22.5	0.9	4.2
sys3	3742	[70;237]	132.4	24.3	1.1	4.3	2032	[85;251]	135.2	22.2	1.0	4.4
dia1	4481	[34;150]	79.2	13.7	0.5	3.6	2441	[34;142]	78.0	14.0	0.3	3.4
dia2	4422	[32;140]	78.3	13.5	0.5	3.5	2409	[33;133]	77.1	13.8	0.3	3.3
dia3	3731	[36;141]	77.7	13.7	0.6	3.7	2027	[31;135]	76.5	13.9	0.4	3.3
pul1	4488	[40;150]	80.7	13.1	0.4	3.6	2448	[41;148]	73.0	13.5	0.6	3.6
pul2	4430	[40;161]	80.3	13.6	0.6	4.5	2412	[40;151]	73.0	13.7	0.7	3.9
pul3	3731	[41;145]	80.1	12.9	0.4	3.5	2028	[40;140]	73.2	13.4	0.6	3.7

n = Number of nonmissing values; SD = Standard deviation; SK = Skewness; KT = Kurtosis.

The tables show a relative uniformity of the shape parameters of the distributions of BP (skewness and kurtosis) across surveys and replicate measurements. Skewness parameter are all positive, between 0.3 and 1.3, most of them < 1. The values of kurtosis are consistently >3, between 3.1 and 6.5. This indicates that, as in the example of Figure 4.7, all distributions are slightly skewed to the right, i.e. number of the observations falling in their tails is greater that the number expected in the normal case.

The distributions of RHR are similar but, in general, slightly more skewed and kurtotic compared to those of BP.

In any case, the values of skewness and kurtosis in the tables are well within the limits considered acceptable in the SEM literature for the application of likelihood-based estimation methods.[580, p. 63] [593]

The standard deviation also show a relative uniformity across surveys and gender, with a consistent tendency to decrease slightly across successive readings.

Mean values of both SBP and DBP (but not RHR) across replicate readings tend to decrease, as commonly found in most populations. The pattern is similar for all samples.

A graphical summary of the distributions of the different BP and RHR readings is shown in the box plots in Figures 4.8 to 4.10.

It is interestingly to note — from the values of the tables and the box plots — the large differences in the mean and median systolic values between the NIDS 2012 and the SANHNES sample, which refer both to the same population 15+ years and in approximately the same period. The statistics presented in this section are sample statistics and the weighting procedures applied to estimate population parameters could partly explain the difference. However, differences of more than 12 $mmHg$ in the average systolic values (not accompanied, moreover, by noticeable differences in diastolic and heart rate readings) are difficult to justify purely in terms of sampling design (which were similar in the two surveys) and suggest the presence of a substantial amount of (relative) selection bias.

Figure 4.8: Distribution of **systolic blood pressure** across surveys and measurements. Box plots.

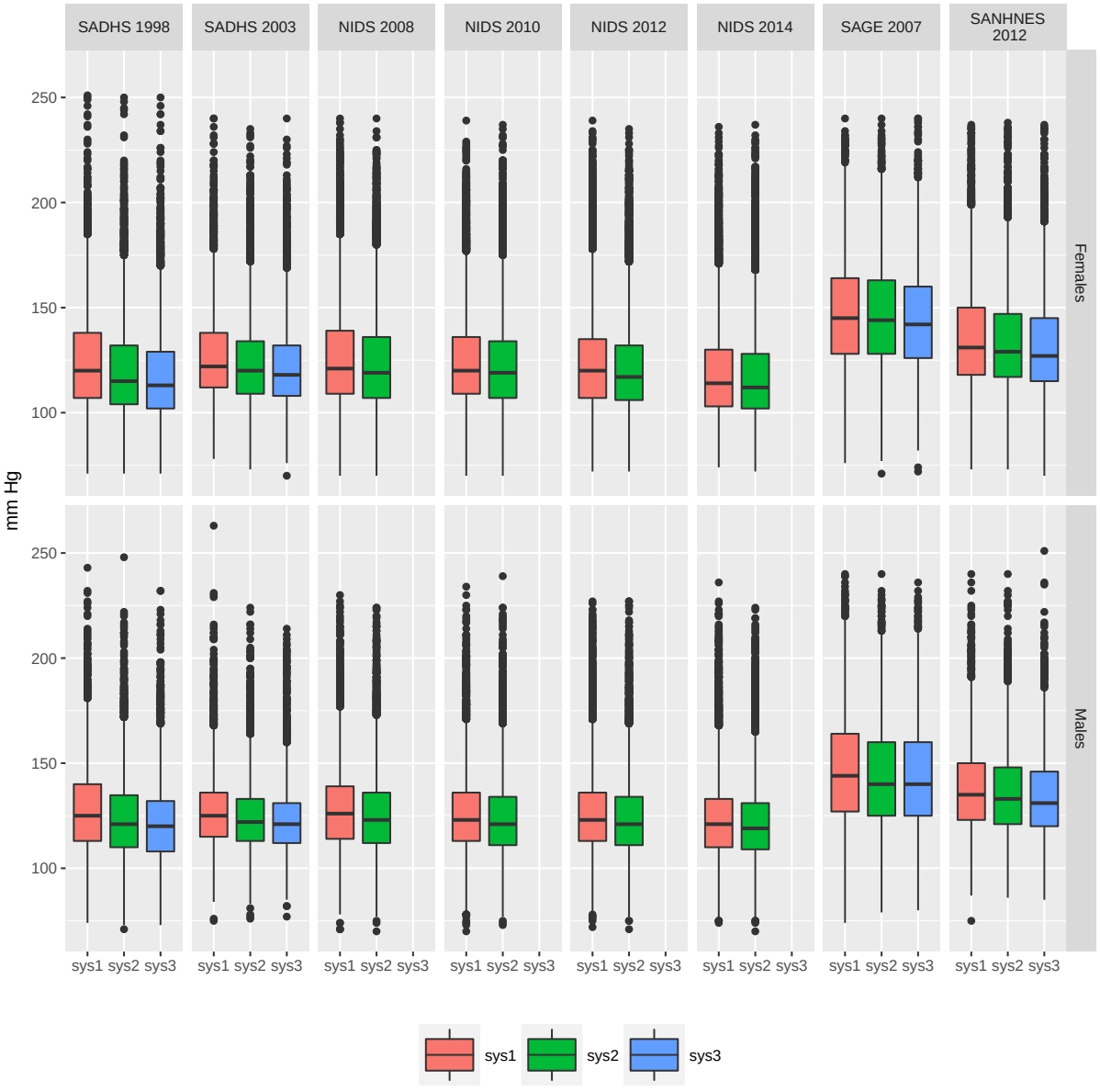


Figure 4.9: Distribution of **diastolic blood pressure** across surveys and measurements. Box plots.

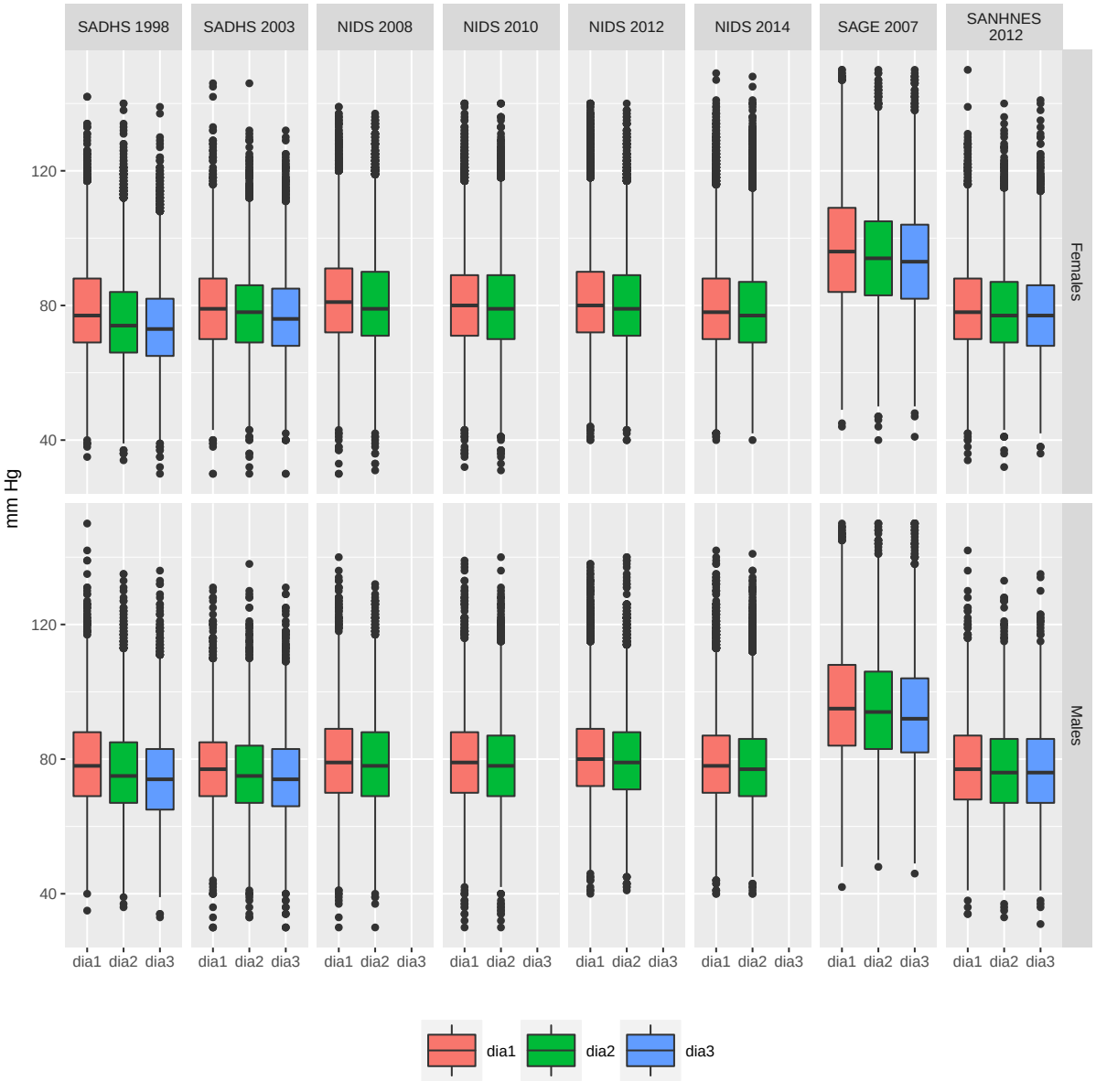
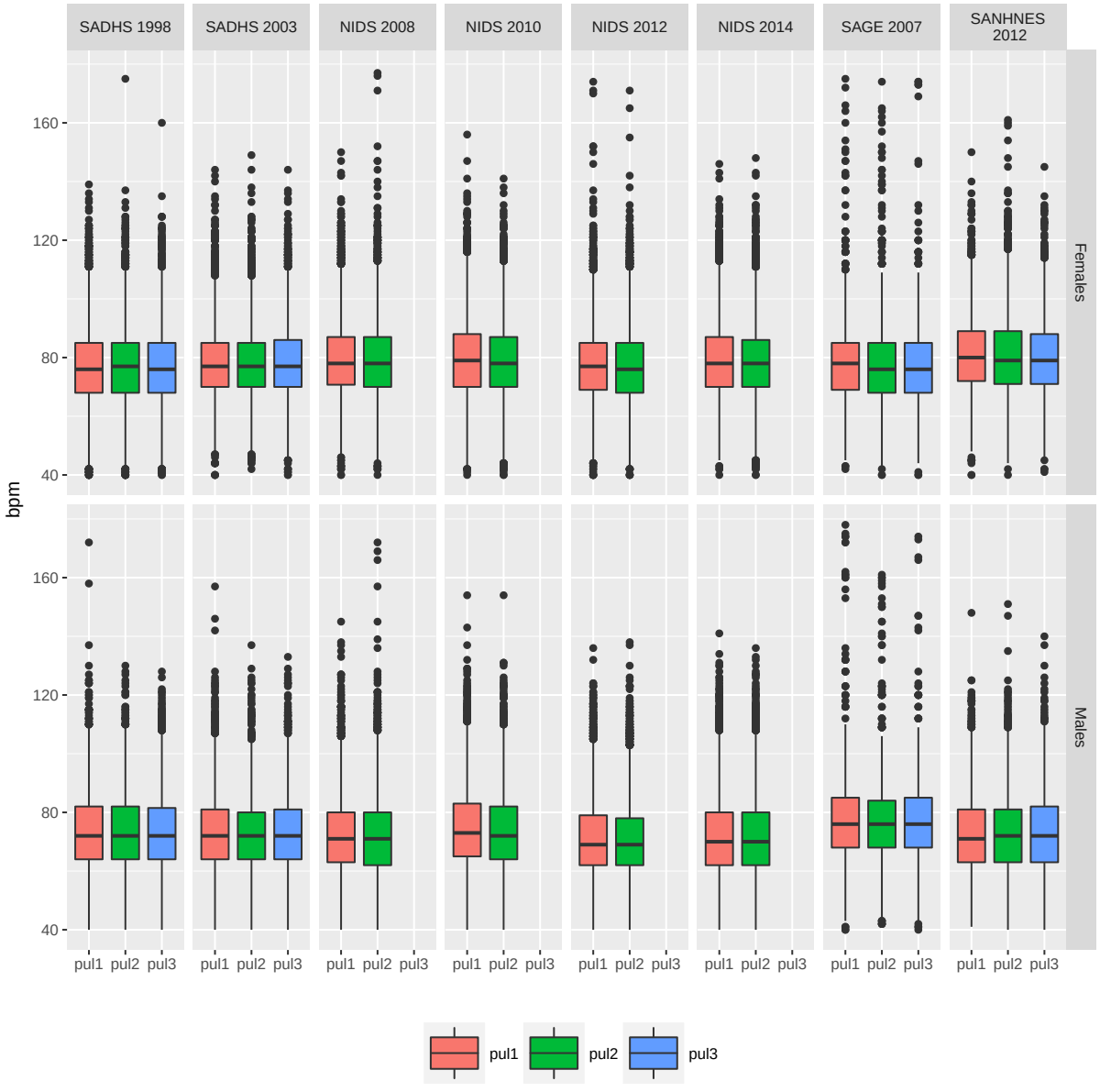


Figure 4.10: Distribution of **resting heart rate** across surveys and measurements. Box plots.



4.3.2 Multivariate distributions and outliers

Non excessive departures of the *univariate distribution* of the exogenous variables from a normal distribution (in particular unimodality and absence of evidence of floor or ceiling effects resulting in the accumulation of the observations at the extreme of the distribution) are a necessary condition for the correct application of likelihood-based estimation methods in SEM. However, this condition is only necessary because the actual sufficient requirement is that the *joint distribution* of all outcomes is not too far from multivariate normal[2]. In our analytic strategy where the multiple readings of BP and RHR are used as indicators of a set of underlying latent variables and jointly modelled, the normality requirement applies to the combined distribution of the $3 + 3 + 3 = 9$ ($2 + 2 + 2 = 6$ in the NIDS) BP/RHR readings.

Table 4.18 shows the results of the assessment of the plausibility of the hypothesis of multivariate normality by listing the values of Mardia's coefficients of multivariate skewness and (normalised) kurtosis.

Table 4.18: Values of Mardia's multivariate skewness and normalized kurtosis coefficients for the joint distributions of the multiple readings of systolic and diastolic blood pressure and resting heart rate.

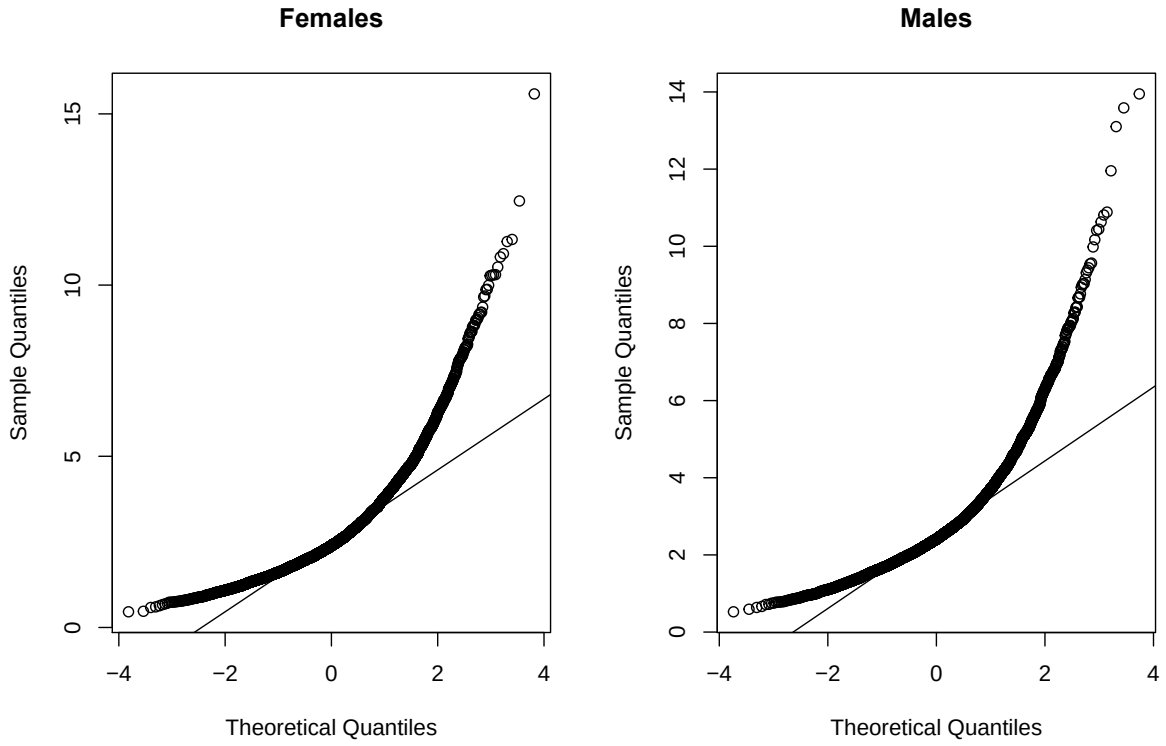
	Females			Males		
Survey	p	Skewness	Kurtosis	p	Skewness	Kurtosis
SADHS 1998	9	10.2	309.2	9	8.7	276.4
SADHS 2003	9	8.2	319.0	9	11.3	272.7
NIDS 2008	6	6.7	255.8	6	9.1	280.8
NIDS 2010	6	4.1	272.8	6	3.8	223.3
NIDS 2012	6	4.7	308.7	6	3.5	230.5
NIDS 2014	6	5.2	245.1	6	3.5	173.4
SAGE 2007	9	49.2	413.1	9	38.6	299.5
SANHNES 2012	9	8.6	226.4	9	13.2	174.9

p = Number of variables.

Considering that both the skewness and the kurtosis coefficients assume value 0 in the case of a multivariate normal distribution, the figures in the table show that, in all samples, the distributions are positively skewed and severely leptokurtic. The kurtosis and, especially, the skewness coefficient are much higher in the SAGE sample. This might be partly due to the higher age of the subjects in this sample (see considerations in Section 2.1.4.5.1), but it is unlikely that this element alone could justify values that are four- to fivefold greater that those recorded in the other surveys.

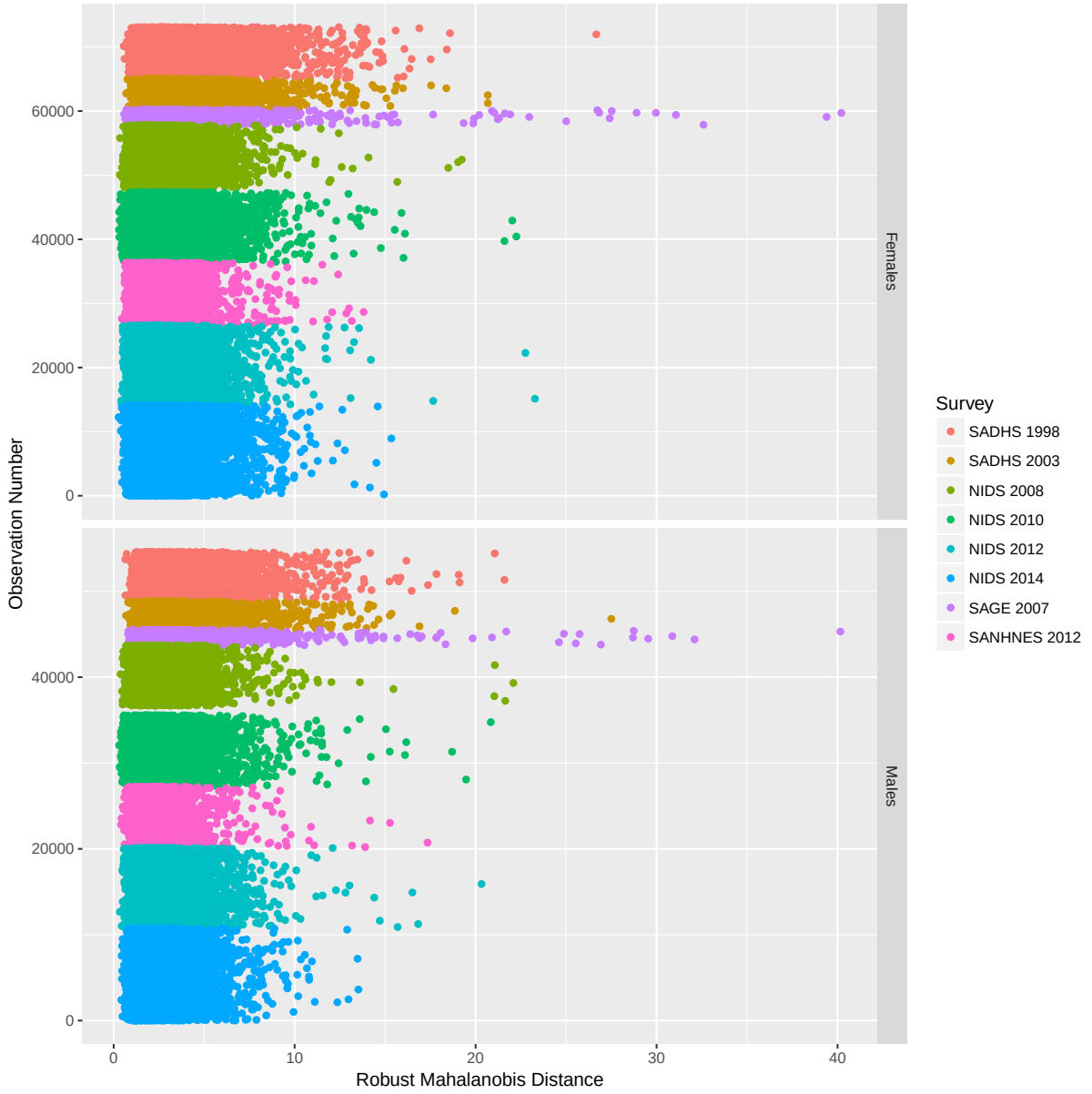
The example quantile-quantile plots shown in Figure 4.11 for the male and female subsample of the SADHS 1998 clearly indicates the presence of a very heavy tail in the multivariate distribution in correspondence of large values of the variables[3].

Figure 4.11: Quantile-Quantile plot for the multivariate distribution of blood pressure and resting heart rate readings in the SADHS 1998.



The presence of especially influential outliers in the multivariate distribution might partly explain these characteristics. To identify these outliers, Figure 4.12 shows a plot of the Mahalanobis statistics for each observation in the various datasets. From the visual inspection of the graph, a cut-off of 12 was deemed reasonable to select observations with extremely unlikely combinations of replicate readings of BP/RHR. The values of all BP/RHR readings were set to missing for these observations. A total of 334 observations were identified across all surveys, corresponding to the 0.33% of the total number of cases.

Figure 4.12: Robust Mahalanobis statistics for the multivariate distribution of blood pressure and resting heart rate readings in the eight samples.



The elimination of the outliers led to a substantial improvement of the values of Mardia's coefficients for all datasets (Table 4.19). The improved values are still clearly indicative of large departures from normality, certainly incompatible with the use of standard ML estimators. This justifies the choice, described in Chapter 3, of a robust ML estimator.

Table 4.19: Values of Mardia's multivariate skewness and normalized kurtosis coefficients for the joint distributions of the multiple readings of systolic and diastolic blood pressure and resting heart rate, after the elimination of multivariate outliers.

	Females			Males		
Survey	p	Skewness	Kurtosis	p	Skewness	Kurtosis
SADHS 1998	9	7.4	203.1	9	5.8	172.1
SADHS 2003	9	6.3	170.2	9	5.4	155.6
NIDS 2008	6	3.8	142.7	6	2.9	120.5
NIDS2010	6	3.5	149.7	6	3.0	124.2
NIDS2012	6	4.0	166.5	6	3.1	119.0
NIDS2014	6	4.8	192.4	6	3.3	149.4
SAGE 2007	9	6.5	116.5	9	7.4	97.6
SANHNES 2012	9	7.6	211.5	9	8.1	134.2

p = Number of variables.

4.3.3 Quality indices

The proportion of missing data in each variable and the proportion of complete measurements in each survey are shown in Table 4.20.

Table 4.20: Proportion of missing data in each variable and proportion of complete measurements [%].

	SADHS	SADHS	NIDS				SAGE	SANHNES
	1998	2003	2008	2010	2012	2014	2007	2012
sys1	4.2	3.3	25.9	23.6	15.9	9.7	5.2	59.0
sys2	4.6	3.9	26.2	24.2	16.0	9.7	5.3	59.1
sys3	5.0	3.6	-	-	-	-	5.6	59.1
dia1	4.1	3.4	25.7	23.6	15.9	9.6	6.8	59.6
dia2	4.6	3.9	26.4	24.1	16.0	9.7	6.5	59.7
dia3	4.8	3.6	-	-	-	-	5.9	59.7
pul1	2.8	2.4	24.7	22.1	16.0	9.7	3.4	65.9
pul2	2.9	2.6	25.0	22.4	16.1	9.7	3.5	66.0
pul3	3.0	2.6	-	-	-	-	3.6	66.0
Complete measurements	92.8	94.6	73.0	73.8	83.7	90.2	88.1	33.2

Both editions of the SADHS and SAGE showed similar low values for the proportion of missing

data and incomplete measurements, in line with best international practice.

In the NIDS the proportion of missing data on blood pressure was notably higher, especially in the first two waves of data collection where about a fourth of measurements were missing. These proportions, however, are similar to the proportion of valid blood pressure measurements in other internationally cited large scale surveys, namely the last editions of the NAHNES,[693] where response rates for physical examination of about 75% were also recorded.[694] The finding of major concern refers, clearly, to the SANHNES. As expected because of the particular organization of the survey in comparison with all other nationally representative surveys carried out in South Africa (see Chapter 3), BP readings were only available for a minority of subjects: about 40% of the sample for SBP/DBP and 36% of the subjects for RHR readings. Only about a third of subjects has a complete set of measurements taken.

Table 4.21 compares the proportion of identical readings across the repeated measurements. It shows that this proportion was low and similar across surveys. As expected, the second and third reading were more likely to be similar that the first and the second, and this is reflected by the figures.

The proportion of identical readings was notably higher in the 2010 wave of the NIDS than in the other surveys and, limited to RHR, for the SAGE. These discrepancies might indicate some deviation from the study protocol, chiefly the possibility that the fieldworkers avoided in some cases taking the successive measurements and filled the data collection sheet by repeating the values from the first (and only) measurement. However, even in those surveys, the proportion of identical readings is still well within the range considered acceptable and observed in other large scale surveys.[339]

Table 4.21: Proportion of identical readings across the repeated measurements [%].

	SADHS		SADHS		NIDS				SAGE		SANHNES	
	1998		2003		2008	2010	2012	2014	2007		2012	
Var	1-2	2-3	1-2	2-3	1-2	1-2	1-2	1-2	1-2	2-3	1-2	2-3
sys	4.3	5.7	5.6	8.1	5.6	15.8	6.0	4.9	5.4	8.8	6.4	7.3
dia	6.3	8.7	9.8	11.4	8.4	19.2	8.8	6.9	9.1	11.2	9.1	10.2
pul	9.9	10.7	13.6	14.8	11.5	22.5	14.7	10.3	21.2	25.3	11.5	12.9

1-2 = Proportion of identical first and second reading; 2-3 = Proportion of identical second and third reading.

Table 4.22 compares the digit preference scores for each reading and survey.

Table 4.22: Digit Preference Score.

	SADHS	SADHS	NIDS				SAGE	SANHNES
Variable	1998	2003	2008	2010	2012	2014	2007	2012
sys1	2.3	4.0	2.6	3.0	2.2	0.6	13.1	3.3
sys2	2.1	3.7	2.4	4.0	3.1	1.3	14.0	3.8
sys3	1.5	4.4	-	-	-	-	14.3	3.9
dia1	3.1	4.3	1.9	3.2	3.1	0.7	11.7	4.1
dia2	2.9	3.6	2.1	4.9	3.2	1.4	14.6	3.2
dia3	3.5	3.6	-	-	-	-	14.4	4.1
pul1	2.8	2.9	1.3	3.9	2.5	1.4	9.8	2.7
pul2	3.2	3.8	1.8	5.3	3.1	1.2	8.1	2.6
pul3	2.5	3.8	-	-	-	-	8.0	3.8

The DPS was very low for all surveys except the SAGE, where it assumes values three to four times higher. Values of DPS below 20 are considered acceptable and are not a compelling indication of data manipulation. However, finding such a large discrepancy between surveys carried out in the same population and with similar measurement procedures is worth some consideration.

The origin of the extreme values of DPS in the SAGE is evident from figures 4.13 to 4.15 which compare the distribution of the values of the first reading of BP and RHR in the various surveys. The tendency to round to even numbers and, especially ending by 0 (in red in the graph) is evident in all distributions, but it is striking for the SAGE. Interestingly, as an example of the discussed phenomenon of *selective recording*, the peak corresponding to the threshold for systolic hypertension (140 $mmHg$) is more than four times higher than the adjacent values. For the first DBP reading, the peak corresponding to the threshold for diastolic hypertension (90 $mmHg$) is also more than 2.5 times higher than the adjacent values, but the most evident selective recording effect can be seen in correspondence of the 100 $mmHg$ reading[4].

Figure 4.13: Distribution of first measurement of systolic blood pressure across surveys.

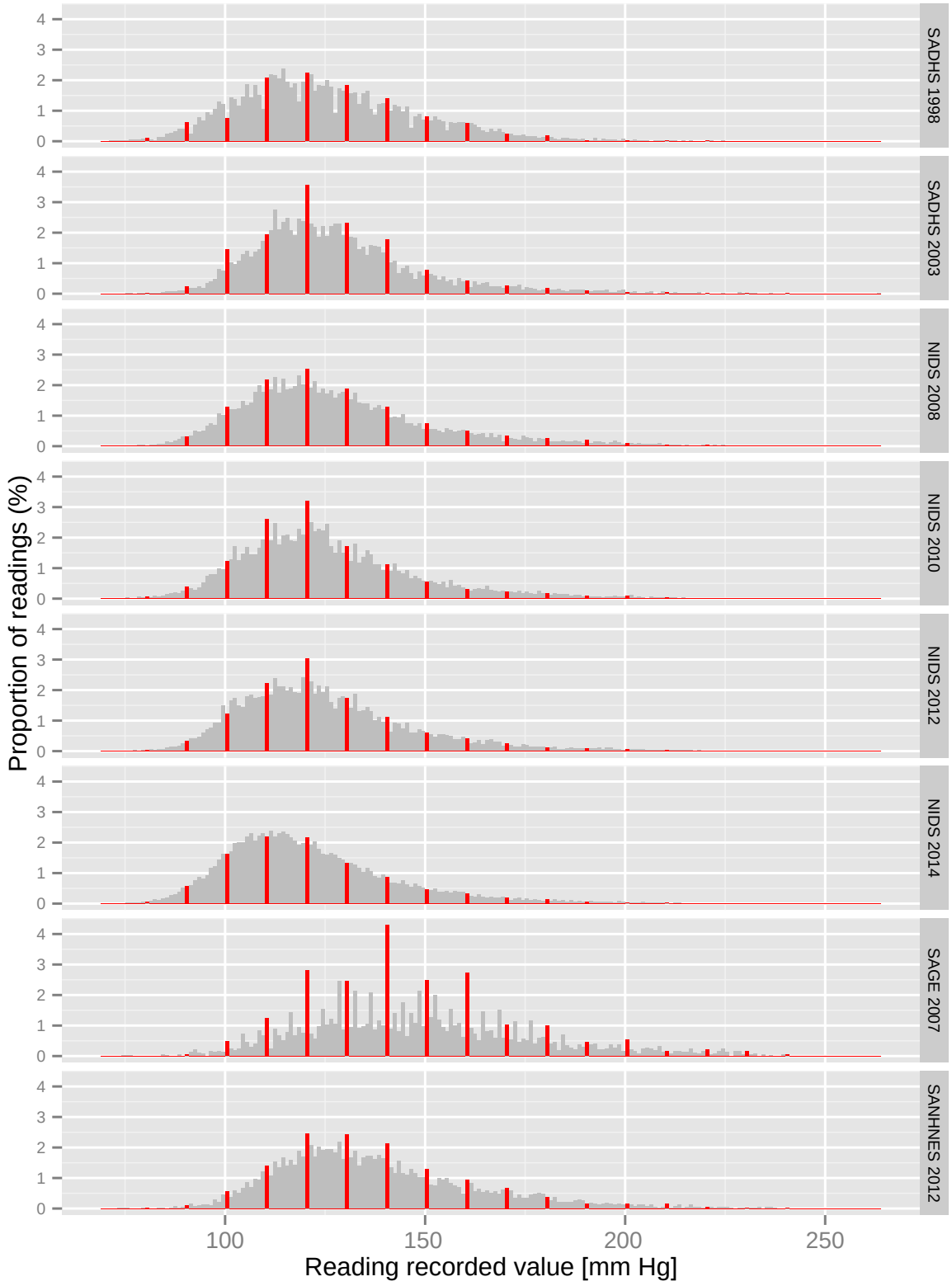


Figure 4.14: Distribution of first measurement of diastolic blood pressure across surveys.

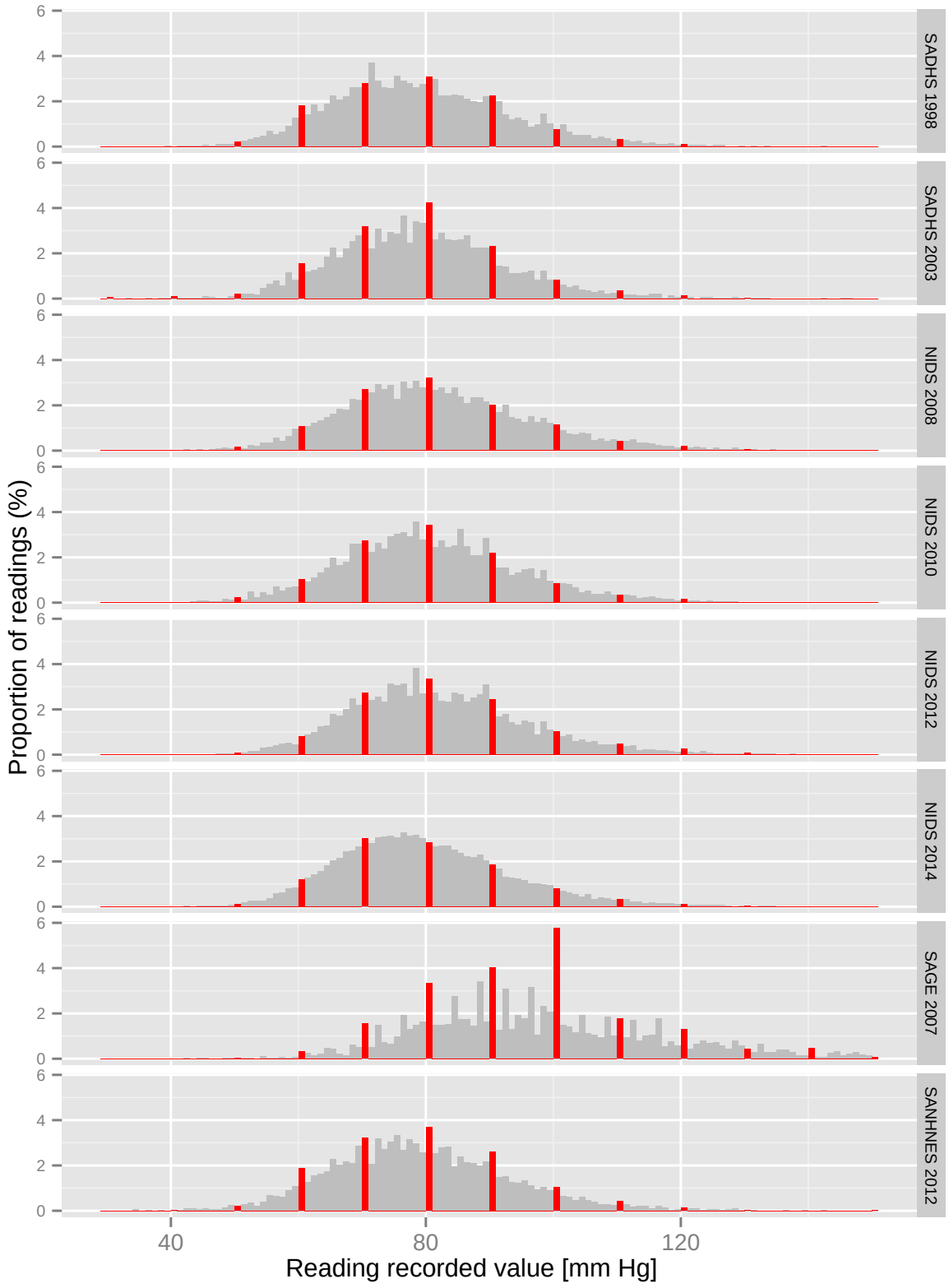
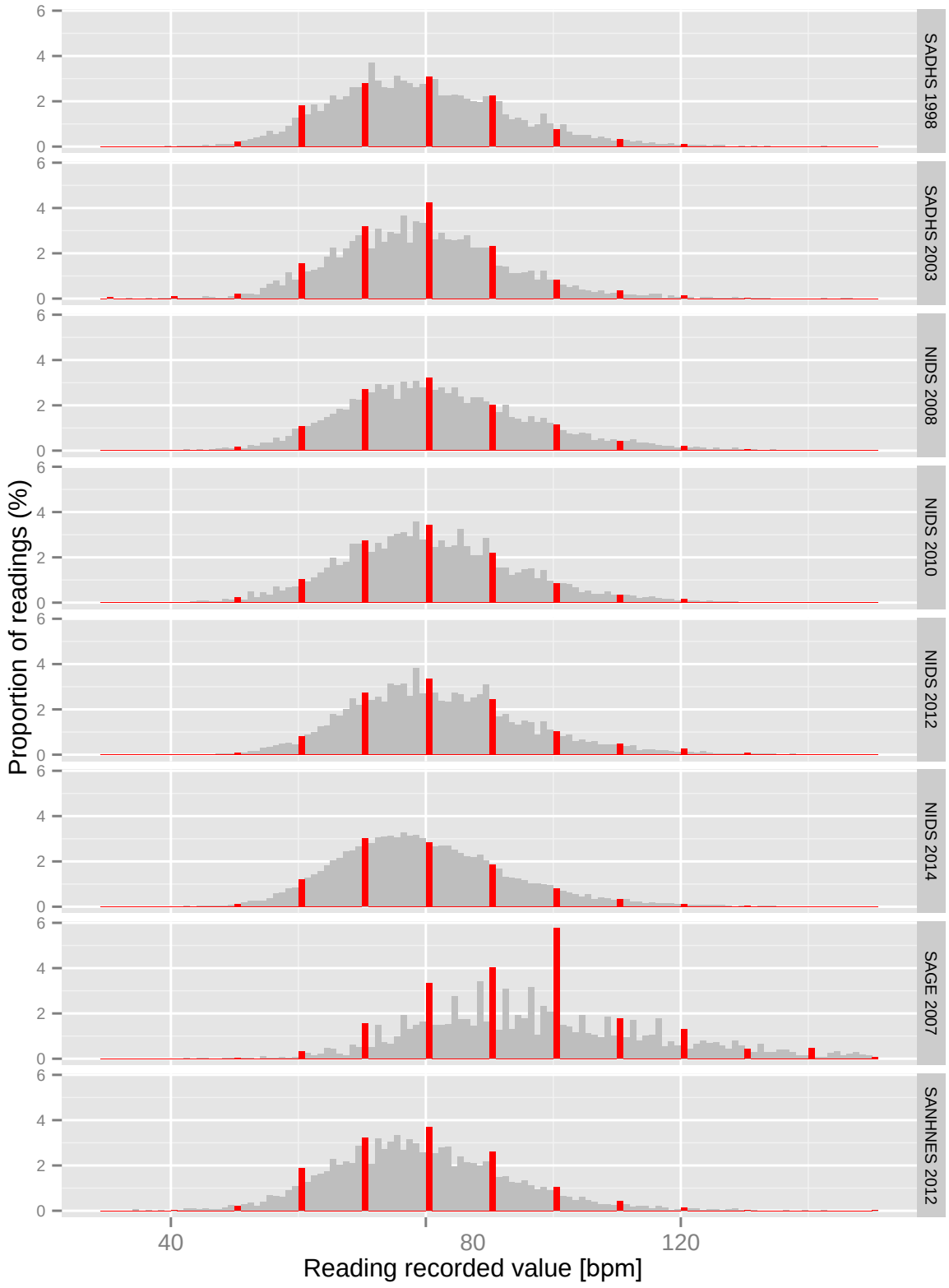
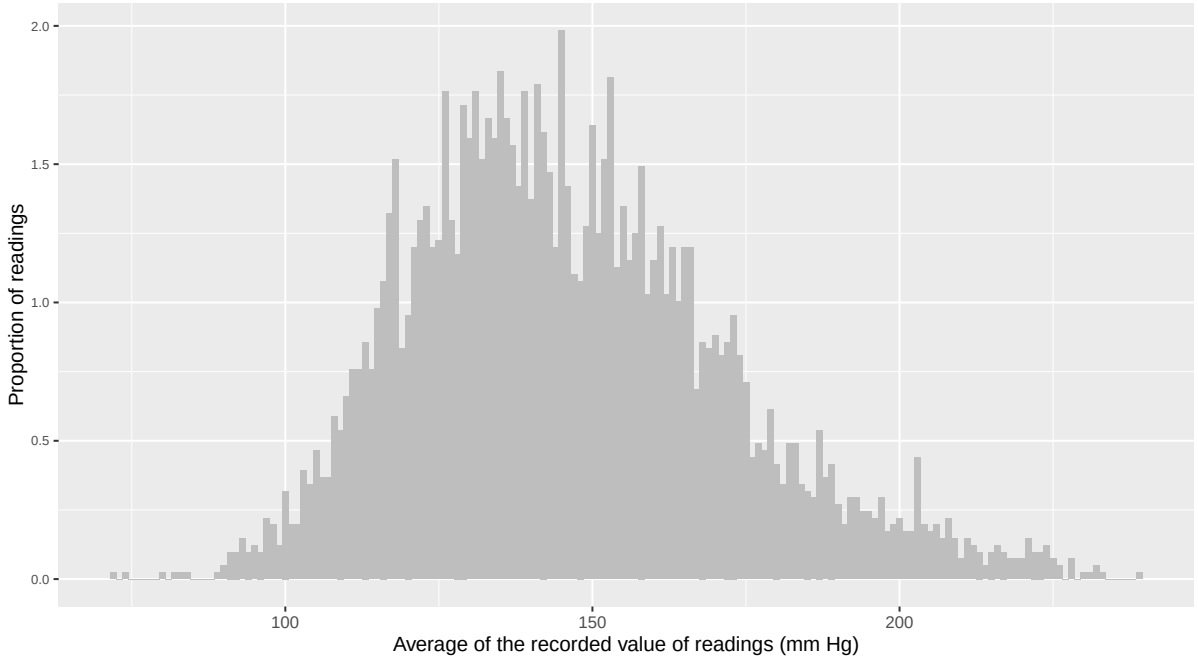


Figure 4.15: Distribution of first measurement of resting heart rate across surveys.



It is worth noticing that when the initial level of digit preference is high, averaging multiple readings reduces but does not eliminate the 'spikes' in the distribution. This is shown, for example, in Figure 4.16 for the case of SBP in the SAGE and it further supports the systematic nature of the rounding process that originated the excess of reading ending with specific digits. That is, it is a likely indication that the fieldworkers tended to apply the same unwarranted 'rounding' procedure to all successive readings.

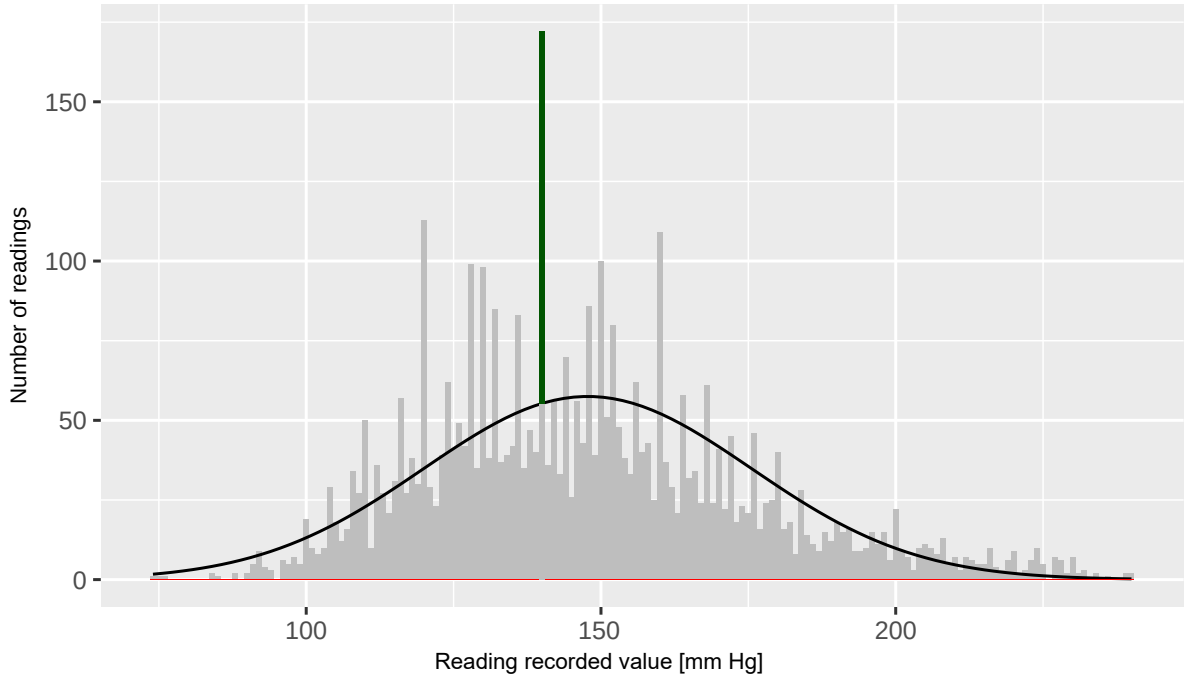
Figure 4.16: Distribution of the average of the multiple readings of systolic blood pressure in the SAGE sample.



As already pointed out in Chapter 2, even high values of digit preference are unlikely to produce significant bias *per se* in the estimates of mean values of BP/RHR. However, the 'heaping' of measurements around the diagnostic thresholds of 140/90 $mmHg$ can affect significantly the estimates of the prevalence of hypertension if made from the raw data.

For example, Figure 4.17 shows that, compared to an hypothetical underlying normal distribution of 'true' SBP values, the SAGE datasets would record about 120 *excess cases* of 140 $mmHg$ readings (dark green spike in the the histogram), corresponding to the systolic threshold for hypertension.

Figure 4.17: Distribution of the values of the first systolic reading in the SAGE sample.



The effect of this excess on the estimated prevalence of systolic hypertension depends on the mechanism of rounding, and can range from no effect (when rounding only happens '*from above*' (e.g. 142 $mmHg$ recorded as 140 $mmHg$) to a maximum when rounding happens only '*from below*' (e.g. 138 $mmHg$ recorded as 140 $mmHg$). In this latter hypothesis, all excess cases would represent normotensive individuals incorrectly classified as hypertensive. This number corresponds to an artefactual increase of the prevalence of hypertension *in the sample* by $\approx$ 2.8 percentage points[5].

More generally, and more of concern, the presence of extreme 'spikes' in the distribution of BP readings as those recorded in the SAGE) — other than challenging the widespread myth that "*Electronic devices that display the results as numbers on a screen eliminated digit preference*"[695, p. 218] — might indicate broader deficiencies in the training and supervision of the observers and in the consistent application of the measurement protocol, which could have more widespread consequences[6].

4.3.4 Further considerations of data quality and exclusion of datasets

Even though the 25% of missing BP data in the NIDS is certainly not a desirable characteristics, the overall interpretation of the quality indices described in the previous sections does not

necessarily imply the conclusion that the data from the SADHS and the NIDS are unsuitable for our analyses.

However, the same conclusion cannot be reached for the SAGE and the SANHNES. Major elements of concern regarding these two surveys are:

- The extremely high proportion of missing BP data in the SANHNES, which adds to the already low response rate at individual level. The final result is that valid data on BP and RHR are only available for about 25% of the the original random sample of the population.
- In the SAGE, (1) the use of a wrist rather than a arm BP monitor, (2) the low coverage of the originally selected sample, and (3) the finding of a high relative level of digit preference and the anomalous characteristics of the combined multivariate distribution of BP and RHR.

As already pointed out in the Methods chapter, a large proportion of missing data reduces the precision of the estimates and, more problematic, if the probability that a BP reading is missing depends on the participant characteristics and/or on the unmeasured value itself, this dependence can introduce substantial bias.

While there is no way of assessing the absence of association between probability of missingness and the missing value itself without external information, it is possible to examine the extent to which participants with missing values on BP differ from those for whom the values are available, at least in basic demographic and bio-behavioural variables. The results of this comparison are shown in Table 4.23.

The data in the table indicates that subjects without BP measurement were significantly older, more frequently men and urban, much more educated and less frequently black than those with valid BP measurements. All characteristics that, taken together, suggest a form of self-selection based on socioeconomic status, with participants in the higher socioeconomic strata more likely to have missing BP values[7].

Subjects in the two subsamples also differed regarding alcohol use and smoking, with subjects with missing measurements significantly more frequently alcohol drinkers and smokers. The magnitude of the difference was, however, modest.

Table 4.23: Descriptive statistics of subjects with missing systolic and/or diastolic blood pressure measurements compared to subjects with available measurements†. SANHNES dataset.

	Missing BP measurements		Complete BP measurements		
Variable	n	Median/ percentage	n	Median/ percentage	Difference (95% CI)
Men	9 927	47.0%	7 014	35.2%	11.8 (10.3 ; 13.2)
Age class	9 868		7 012		
25-24		29.0%		26.9%	2.1% (0.6 ; 3.3)
25-34		22.5%		16.6%	5.5% (4.5 ; 6.9)
35-44		17.0%		15.2%	1.8% (0.5 ; 2.8)
45-54		14.3%		16.0%	-1.7% (-2.9 ; -0.7)
55-64		9.8%		13.5%	-3.7% (-4.7 ; -2.7)
65+		7.4%		11.8%	-4.4% (-5.3 ; -3.5)
Race	9 882		6 859		
Black		63.3%		70.2%	-6.9% (-7.1 ; -4.2)
Coloured		18.7%		22.7%	-4% (-4.8 ; -2.3)
White		6.4%		1.9%	4.5% (3.9 ; 5.1)
Asian		11.6%		5.1%	6.5% (5.7 ; 7.4)
Education	8 430		5 890		
None		6.3%		10.4%	-4.1% (-4.2 ; -2.6)
Primary		11.2%		16.4%	-5.2% (-5.3 ; -3.3)
Secondary		69.2%		67.5%	1.7% (0.5 ; 3.6)
Tertiary		13.3%		5.7%	7.6% (5.7 ; 7.4)
Urban	9 469	70.9%	6 869	60.0%	10.9% (-12.3 ; -9.4)
Current smoking	9 015	17.9%	6 252	19.2%	-1.3% (-2.6 ; -0.0)
Current alcohol use	9 050	25.5%	6 224	23.0%	2.5% (1.1 ; 3.8)
Waist circ. [cm]	541	79.3	6 706	84.0	-4.7 (-7.0 ; -2.5)
BMI [kg/m^2]	530	24.7	6 686	25.1	-0.4 (-1.5 ; 0.4)
BMI category	530		6 686		
Underweight		8.3%		5.9%	2.4% (-0.1 ; 4.9)
Normal weight		43.4%		43.6%	-0.2% (-4.7 ; 4.3)
Overweight		24.3%		22.1%	2.2% (-1.7 ; 6.1)
Obese		24.0%		28.4%	-4.4% (-8.3 ; -0.5)
CVD history	9 927	5.4%	7 014	8.4%	-2.7% (-3.8 ; -2.2)
Diagnosis of hypertension	8 964	17.3%	6 182	24.8%	-7.5% (-8.9 ; -6.2)
Antihypertensive treatment	9 927	9.0%	7 014	21.2%	-12.2% (-13.3 ; -11.1)

† = At least one systolic and one diastolic measurement.
n = number of not missing values; CI = confidence interval.
Confidence intervals for proportions are calculated using the normal approximation, without correction for multiple comparisons when more than two categories are considered. Confidence intervals for medians are boostrapped (R package *PairwiseCI* [676]).

More important, the last three comparisons in the table indicates that subjects with valid measurements were much more likely to have a history of CVD, to have been diagnosed with hypertension and to be on antihypertensive treatment. Besides being statistically significant, the differences were large in magnitude, especially for treatment status. These differences — albeit partly explained by the higher percentage of older subjects in that subsample — strongly suggest that subjects with valid measurements are representative of a population at higher risk of hypertension compared with those with no measurements[8].

Indirect support to the hypothesis of self-selection based on biological factors directly associated with hypertension is provided by Table 4.24, which compares population estimates calculated from the SANHNES sample with those calculated from the other datasets. The risk factors considered for this comparison are self-reported history of CVD and previous diagnosis of hypertension, antihypertensive treatment, BMI and waist circumference.

Table 4.24: Comparisons of population estimates of some risk factors for hypertension.

	Females					Males				
Survey	cvd [%]	htnd [%]	treat [%]	BMI $[Kg/m^2]$	waist $[cm]$	cvd [%]	htnd [%]	treat [%]	BMI $[Kg/m^2]$	waist $[cm]$
SADHS 1998	5.8	15.8	7.3	26.8	84.3	3.3	7.2	4.3	23.2	81.9
SADHS 2003	5.2	17.5	8.0	26.4	81.2	3.9	8.7	4.3	23.2	78.7
NIDS 2008	4.4	18.1	13.7	28.0	88.7	2.4	8.1	5.6	23.7	83.0
NIDS 2010	2.8	15.6	13.2	28.5	82.8	1.2	7.0	5.5	24.3	76.5
SANHNES 2012	9.2	25.7	21.3	28.7	88.4	7.9	15.5	11.3	23.6	81
NIDS 2012	3.5	20.4	15.6	28.3	91.7	2.8	11.0	7.7	24.2	85.3
NIDS 2014	3.6	13.4	17.7	28.8	91.9	1.5	6.8	8.3	23.8	84.7

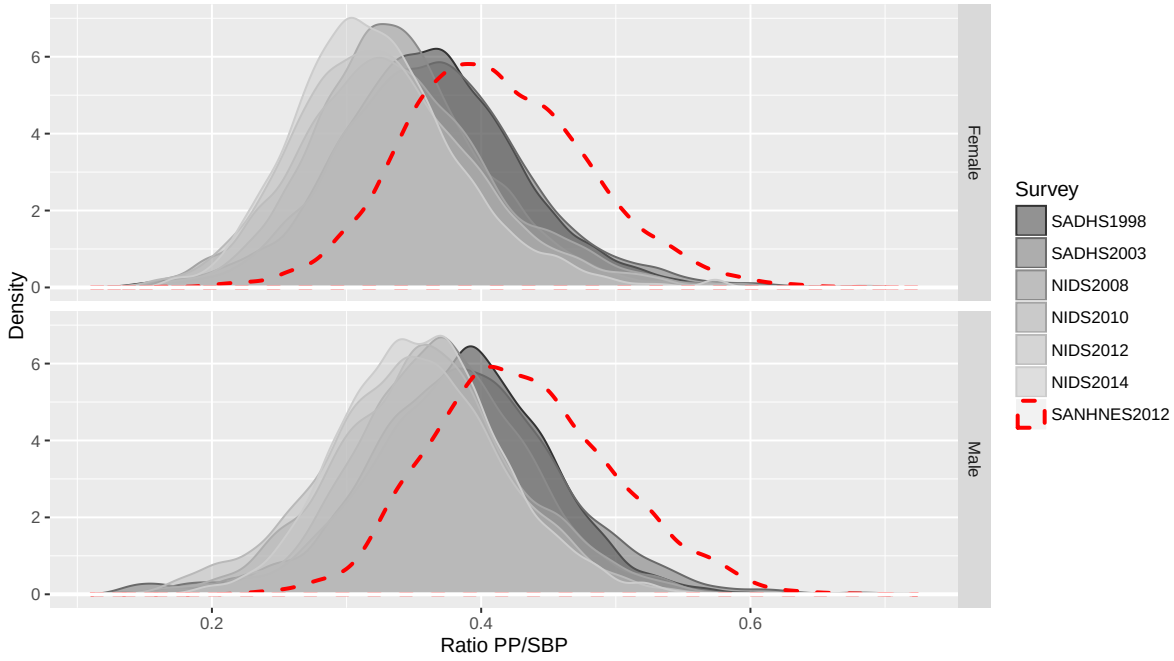
cvd = History of cardiovascular disease; htnd = Previous diagnosis of hypertension; treat = Current antihypertensive treatment; BMI = Body mass index; waist = waist circumference.
Values are weighted using the recalibrated weights from Section 4.2. The SAGE data are excluded because of the different age range.

It is quite evident that, even after the adjustment for differences in the race-age-place or residence provided by the sampling weights — the population represented by the SANHNES sample had a much higher percentage of subjects with history of CVD, previous diagnosis of hypertension and in antihypertensive treatment compared to all other surveys. The comparison is especially interesting for the SANHNES and the third wave of the NIDS, because the periods of data collection largely overlapped. These values strongly suggest the presence of selection bias in the SANHNES, and, more precisely, that the sample of subjects with valid

anthropometric measurements represents a population at higher risk of CVD compared to all other surveys.

Another indicator of CVD risk that can be easily be derived from the data available in all datasets is the PP.[696] Figure 4.18 shows the distribution of the ratio PP/SBP, that was considered rather than the original values to minimise the (possible) confounding effect of differences in the average BP.

Figure 4.18: Ratio between pulse pressure and systolic blood pressure. Smoothed distribution.



PP = Pulse pressure; SBP = Systolic blood pressure.

Again, the SANHNES dataset behaved quite differently from the others, and the comparison points towards a sampled population with higher CVD risk than those sampled in the other surveys.

The observations above, taken together, led to the exclusion of the SANHNES data from the rest of the analyses in this thesis.

For the SAGE, the reasons for exclusion were, individually, less compelling. However, taken together, they pointed towards the conclusion of an insufficient level of comparability with the other datasets, if not necessarily to the conclusion of low data quality in itself.

In particular, the use of a wrist monitor is of concern. Wrist monitors are able to provide accurate measurements (as confirmed by the results of the validation study of the specific monitor

used in the SAGE [536]), but the accuracy and repeatability in uncontrolled conditions such as those encountered in field surveys are an open question. The position of the arm during measurement (i.e. the level relative to the heart) is critical for accurate measurements, and the assumption that this critical alignment could be maintained during field measurements is still to be proven. This doubt is reinforced by the results of a preliminary validation study of the SAGE methodology on 1446 respondents. The study, which included a re-test component after 7 days, shoved very modest values reliability for the diagnosis of hypertension (kappa coefficient = 0.5, vs. 0.8, for example, for obesity).[376] These concerns regarding low reliability add to doubts about possible bias suggested by various studies (see Chapter 2) which found that wrist monitors tend to systematically overestimate both SBP and DBP. This might partly explain the exceptionally high prevalence of hypertension estimated by Lloyd-Sherlock et al. [376] from the SAGE data (74.9 % among men, and 80.3% among women 50+ years).

Considering also that the SAGE data do not cover the whole range of ages as the remaining surveys, and that data for the same period (approximately) are provided by the first wave of the NIDS, the consideration above led to the exclusion also of the SAGE dataset from the remaining analyses.

Notes

[1]Also within each province (data not shown).

[2]More precisely, this requirement applies to the joint distribution *conditional* on the observed covariates.

[3]Plots for the other samples show a very similar picture, and are not reported here.

[4]Similar results are valid for the distributions of the second reading and, when available, for the third, and are not shown here.

[5]The effect on the population estimates depends on the sampling weights attached to each individual incorrectly classified. It could be, therefore, either higher or lower than the effect on the sample statistic.

[6]For completeness, I must mention that all surveys analysed in this thesis used oscillometric measurement devices from the same manufacturer, but the SAGE survey was the only one that used a *wrist* (as opposed as *arm*) monitor. No evidence exists, in my knowledge, that the different algorithms used to estimate BP from the oscillometric waveform themselves introduce some form of asymmetric 'rounding'. However, given the proprietary nature of the algorithms, this possibility cannot be completely excluded. In any case, the hypothesis that this difference justifies more than a small part of the observed discrepancies between surveys is extremely unlikely to hold.

[7]Even though the proportion of missing data was much lower in the NIDS than in the SANHNES, the same analysis of difference in sociodemographic characteristics between subjects with and without valid BP measurements was repeated for the baseline wave of the NIDS, with a similar conclusion of a moderate overepresentation of subjects with low socioeconomic status among those without valid measurements.

[8]The same comparisons applied to the other surveys were the proportion of missing data is of concern (glsNIDS 2008, 2010 and 2012) show also higher proportions of subjects in treatment among those with valid BP measurements, but the differences are smaller than those recorded in SANHNES, and accompanied by similar proportions of other CVD risk factors. These comparisons are shown in Appendix B

Chapter 5

Measurement of blood pressure

This chapter deals with the measurement of BP and RHR, and includes three main sections.

1. **Measurement model and invariance across surveys**

   The first section analyses the characteristics of the proposed multiple group measurement model, namely its ability to adequately explain the variability in the observed replicate readings in each survey and in the overall dataset.

2. **Validity of individual and composite measures**

   The second section uses the estimated model parameters to calculate, and compare across surveys, validity coefficients of each individual reading of BP and RHR and of the composite measures obtained as weighted and unweighted averages.

3. **Relative bias and the problem of a different number of readings**

   The third section provides estimates of the relative bias of the subsequent readings of BP and RHR taken during the data collection in each survey. Based on the results of this estimation, the section discusses the problem of comparing BP estimates calculated from surveys where measurements are taken with a different number of repetitions and proposes a modelling approach that allows for unbiased comparisons while avoiding discarding part of the available information. The advantages of the approach in comparison with more common techniques are highlighted by the results of a simulation.

5.1 Measurement model and invariance across surveys

The independent estimation of the measurement model in Figure 5.1 with the identification constraints described in Chapter 3 was successful in all samples, i.e. the estimation procedure converged normally to admissible values.

Figure 5.1: Measurement model: path diagram.

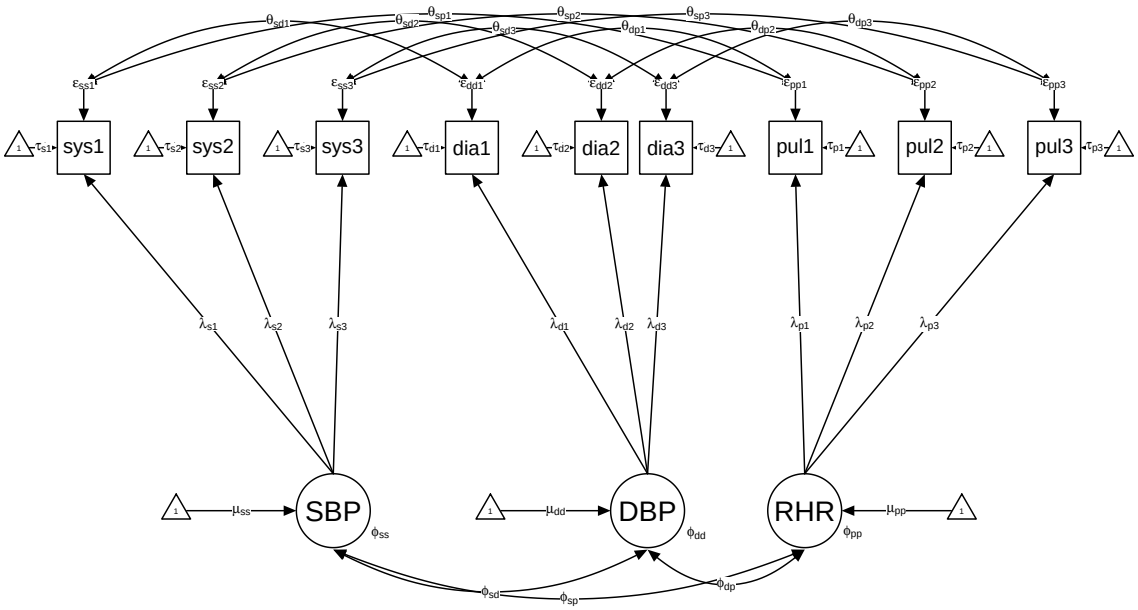


Table 5.1 summarises the values of the indices of model fit. The p-value of the χ^2 test was, as expected given the large samples, below the 0.05 threshold in many cases, but all other indices consistently indicated an excellent fit with the data. This finding supports the assumption of *configural invariance*. This means that the observed multiple readings of BP and RHR in each survey can be plausibly thought as the combined effect of an underlying unobserved 'true' value, plus an error term, specific for each repeated reading, that subsumes all other sources of variability.

Table 5.2 compares the fit of the model with different levels of between-sample constraints, corresponding to *configural invariance* (where all parameters are free to differ across groups and which therefore amounts to fitting each model individually), and metric and scalar invariance.

Table 5.1: Indices of model fit for the measurement model in each sample.

Sample	n	k	$\chi^2(df)$	p	CFI	RMSEA (90% CI)	p-close	SRMR
Females								
SADHS 1998	7794	39	67.28 (15)	<0.001	0.998	0.021 (0.016;0.026)	>0.999	0.017
SADHS 2003	4638	39	34.90 (15)	0.002	0.999	0.017 (0.010;0.024)	>0.999	0.013
NIDS 2008	8424	24	8.70 (3)	0.034	0.999	0.015 (0.004;0.027)	>0.999	0.008
NIDS 2010	8911	24	2.30 (3)	0.513	1.000	0.000 (0.000;0.016)	>0.999	0.004
NIDS 2012	10893	24	4.95 (3)	0.176	1.000	0.008 (0.000;0.019)	>0.999	0.006
NIDS 2014	13116	24	5.75 (3)	0.124	1.000	0.008 (0.000;0.019)	>0.999	0.008
Males								
SADHS 1998	5612	39	37.25 (15)	0.001	0.999	0.016 (0.010;0.023)	>0.999	0.009
SADHS 2003	3242	39	39.84 (15)	<0.001	0.999	0.023 (0.014;0.031)	>0.999	0.012
NIDS 2008	5579	24	0.90 (3)	0.826	1.000	0.000 (0.000;0.013)	>0.999	0.003
NIDS 2010	6176	24	12.88 (3)	0.005	0.999	0.023 (0.011;0.037)	>0.999	0.016
NIDS 2012	7412	24	4.23 (3)	0.237	1.000	0.007 (0.000;0.022)	>0.999	0.004
NIDS 2014	9339	24	12.29 (3)	0.006	0.999	0.018 (0.008;0.029)	>0.999	0.014

n = sample size; k= number of free parameters; $\chi^2(df)$ = Chi-squared statistics of model fit (degrees of freedom); p = p-value for the χ^2 test of model fit; RMSEA = Root mean square error of approximation; p-close = probability RMSEA < 0.05; CFI = Comparative Fit Index; SRMR = Standardized Root Mean Residual.

The results of the χ^2-difference tests were all statistically significant, with the exception of the difference test for comparing the scalar and metric invariance models among men. However, the values of the other indices of model fit clearly supported the hypothesis of both *metric* and *scalar invariance*, according to the criteria proposed by Meade et al. [621]. The assumption is further supported by the fact that the absolute fit of the most constrained models was still excellent.

In substantive terms, this means that the latent variables representing unobserved values of BP and RHR are measured with the same scale and with the same 'zero' across all surveys, and therefore, we can meaningfully compare their variances and covariances and their means between surveys. Comparisons of variances and covariances (and, as a consequence, regression coefficients in relationships involving latent variables) is allowed because metric invariance holds, and comparisons between latent means is allowed because scalar invariance also holds.

Table 5.2: Comparison of fit between configural, metric and scalar invariant models.

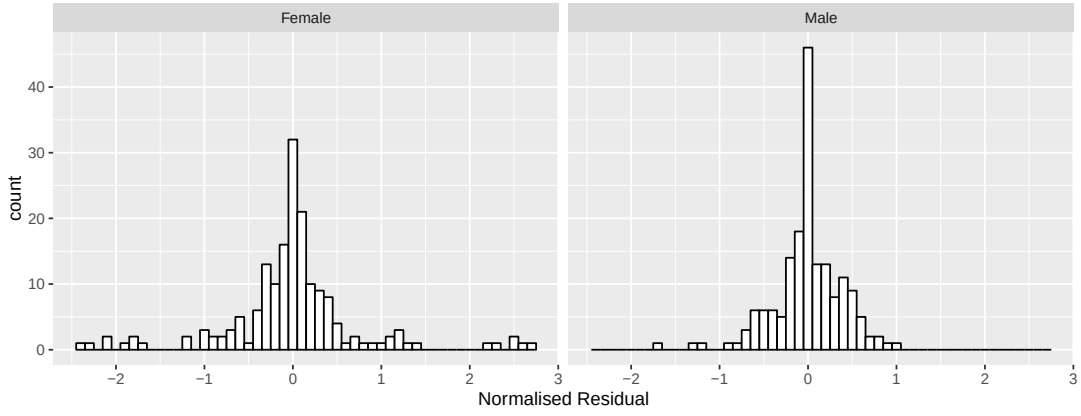
Model	n	k	$\chi^2(df)$	p	CFI	NCI	RMSEA (90% CI)	p-close	BIC
Females									
C	53776	174	91.37 (42)	<0.001	1.000	1.000	0.011 (0.008;0.015)	1.000	1294501.637
M	53776	168	125.72 (48)	<0.001	0.999	1.001	0.013 (0.011;0.016)	1.000	1294522.455
S	53776	150	474.67 (66)	<0.001	0.997	1.004	0.026 (0.024;0.029)	1.000	1295220.283
M-C			36.57 (6)	<0.001	-0.001	0.000	0.002		20.818
S-M			358.58 (18)	<0.001	-0.002	0.003	0.013		697.828
Males									
C	53776	174	83.57 (42)	<0.001	0.999	1.001	0.013 (0.009;0.017)	1.000	883818.694
M	53776	168	95.87 (48)	<0.001	0.999	1.001	0.013 (0.009;0.016)	1.000	883783.249
S	53776	150	300.31 (66)	<0.001	0.997	1.003	0.024 (0.021;0.027)	1.000	884107.210
M-C			12.35 (6)	0.055	0.000	0.002	0.003		-35.445
S-M			206.35 (18)	<0.001	-0.002	0.002	0.011		323.961

C = Configural invariant model; M = Metric invariant model; S = Scalar invariant model.
n = sample size; k = number of free parameters; $\chi^2(df)$ = Chi-squared statistics of model fit (degrees of freedom); p = p-value for the χ^2 test; RMSEA = Root mean square error of approximation; p-close = probability RMSEA $<$ 0.05; CFI = Comparative Fit index; NCI = McDonald's Noncentrality Index; BIC = Bayesian Information Criterion
Degrees of freedom and fit statistics are adjusted for the missing variables in the NIDS samples.

5.1.1 Model checking

The histogram in Figure 5.2 shows the distribution of normalised residuals for the scalar invariant models used for our analyses.

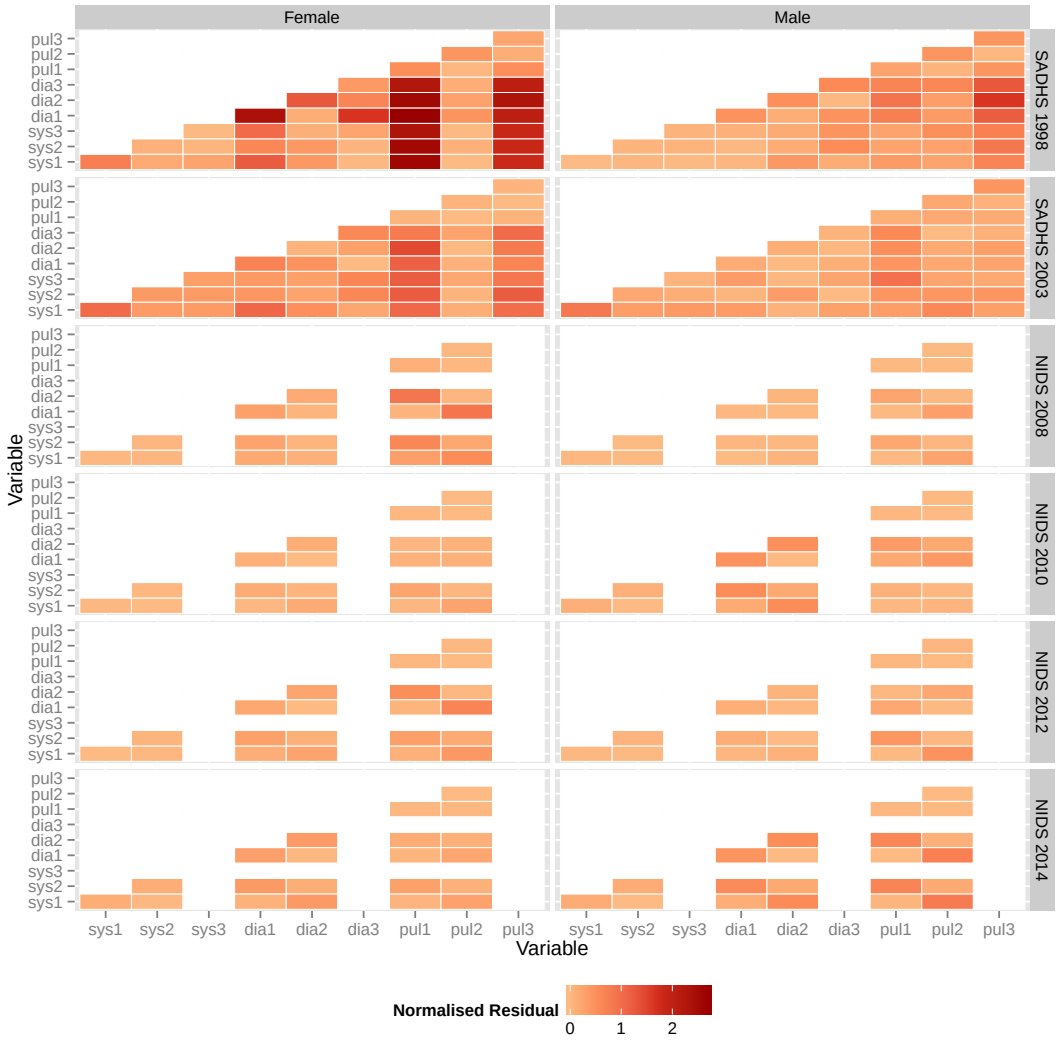
Figure 5.2: Distribution of normalised residuals for the scalar invariant models. Histogram.



Among males, the distribution was almost symmetrical around 0, and no residual exceeded 2 (in absolute value). Among women the distribution was similar in shape with most residuals very close to 0. A small number of them had absolute values between 2 and 3.

The heat map in Figure 5.3 provides an overview of the magnitude of the normalised residuals for each element of the covariance matrix between each of the observed variables (multiple readings of BP and RHR), separately for each dataset.

Figure 5.3: Normalised residuals for the scalar invariant models. Heat map.



Each coloured rectangle represents the magnitude of the normalised residual corresponding to the variance/covariance of the two variables indicated in the rows and the columns, according to the scale below. The map is incomplete in the NIDS samples, because of the absence of the third reading.

Residuals are consistently below 1 in the NIDS datasets and (with a few exceptions) in the male sample of the two SADHS datasets. Large residuals are concentrated in the female sample of the SADHS, and especially in the 1998 edition. While this fact is certainly an indication that the model better fitted the data in the NIDS samples than in the SADHS samples, the absolute values of the residuals was still low, and well below the generally accepted cut-off of 4 that might indicate serious local misspecification problems.

5.2 Validity of individual and composite measures

The complete list of the parameter estimates for the measurement model in Figure 5.1 with the scalar invariance constraints in place is reported in Appendix H.

Tables 5.3 and 5.4 show the decomposition of the observed variance of each reading into trait and error variance, and the following Table 5.5 the validity coefficients as the ratio between trait and observed variance.

Validity tended to be higher for SBP readings (where the proportion of true variance in a single reading varied from 85% to 96%), lower for DBP (77% to 92%) and lowest for RHR (71% to 95%), with no evident differences across genders. In all measurements the first reading showed the lowest validity, the second the highest and the third, when present, intermediate values. The finding that the second reading tends to be the least affected by measurement error is in agreement with the prevalent literature, and, specifically, with the results of the analyses by Kepe [556] of data from two community surveys conducted in South African populations[1].

Values were similar across surveys, with the exception of the SADHS 1998, which showed significantly lower values for the validity coefficients than the other surveys. Excluding the effect of the device (which was the same used in the 2003 edition) and considering that the values of the population variance were similar, the consistency of the finding across multiple readings of both BP and RHR might suggest a less uniform application of the measurement protocol compared to the other surveys.

Most of the covariances between readings taken during the same procedure were statistically significant, albeit small in magnitude (see Appendix H), thus supporting the hypothesis of the presence of a share of variance that is specific of the position of the reading in the sequence of repeated measurement. This is confirmed by the fact that, when the covariances θ_{ij} (with $i \neq j$) were constrained to zero in the model of Figure 5.1, the fit notably worsened in all samples, and all indices indicated that the assumption of adequate fit was untenable[2].

Table 5.3: Decomposition of the total variance for blood pressure and resting heart rate measurements in **females**. Estimates and 95% confidence intervals.

Reading	Total variance	Trait variance	Error variance
SADHS 1998			
sys1	503.7 (478.1 ; 529.2)	427.8 (403.1 ; 452.6)	75.8 (67.1 ; 84.6)
sys2	460.6 (435.1 ; 486.1)	429.5 (404.3 ; 454.7)	31.1 (26.9 ; 35.3)
sys3	453.6 (428.3 ; 478.9)	410.5 (385.9 ; 435.1)	43.1 (38.9 ; 47.3)
dia1	192.0 (184.1 ; 199.8)	147.0 (140.2 ; 153.8)	45.0 (40.3 ; 49.7)
dia2	172.9 (165.8 ; 179.9)	148.2 (141.3 ; 155.1)	24.7 (21.6 ; 27.7)
dia3	176.4 (169.1 ; 183.7)	145.1 (138.4 ; 151.8)	31.3 (27.5 ; 35.1)
pul1	175.5 (168.1 ; 182.8)	124.8 (118.8 ; 130.9)	50.6 (45.9 ; 55.3)
pul2	158.3 (151.7 ; 165.0)	129.0 (122.8 ; 135.1)	29.4 (25.7 ; 33.0)
pul3	162.7 (155.9 ; 169.6)	126.3 (120.3 ; 132.3)	36.4 (32.7 ; 40.2)
SADHS 2003			
sys1	441.3 (410.3 ; 472.3)	408.1 (377.6 ; 438.7)	33.2 (29.9 ; 36.5)
sys2	427.4 (397.4 ; 457.4)	409.7 (379.9 ; 439.5)	17.7 (14.9 ; 20.5)
sys3	422.5 (392.3 ; 452.7)	391.6 (362.7 ; 420.5)	30.9 (25.4 ; 36.4)
dia1	173.0 (163.7 ; 182.3)	147.4 (138.7 ; 156.2)	25.6 (22.5 ; 28.6)
dia2	162.3 (153.4 ; 171.2)	148.7 (139.9 ; 157.4)	13.6 (10.8 ; 16.4)
dia3	167.8 (157.8 ; 177.8)	145.5 (136.9 ; 154.1)	22.3 (18.9 ; 25.7)
pul1	154.0 (144.4 ; 163.6)	130.9 (121.7 ; 140.1)	23.1 (20.0 ; 26.3)
pul2	146.4 (137.1 ; 155.7)	135.2 (125.9 ; 144.5)	11.2 (9.2 ; 13.2)
pul3	151.7 (142.3 ; 161.1)	132.4 (123.3 ; 141.5)	19.3 (16.7 ; 21.8)
NIDS 2008			
sys1	561.0 (530.8 ; 591.1)	501.8 (471.6 ; 532.0)	59.2 (48.5 ; 70.0)
sys2	536.8 (505.9 ; 567.7)	503.7 (473.3 ; 534.1)	33.1 (21.2 ; 45.0)
dia1	215.8 (205.4 ; 226.1)	181.7 (171.8 ; 191.6)	34.1 (29.5 ; 38.6)
dia2	205.7 (195.7 ; 215.6)	183.2 (173.1 ; 193.4)	22.5 (17.9 ; 27.0)
pul1	159.6 (148.6 ; 170.7)	132.7 (121.9 ; 143.4)	27.0 (22.9 ; 31.1)
pul2	154.8 (143.9 ; 165.6)	137.1 (126.0 ; 148.1)	17.7 (12.3 ; 23.2)
NIDS 2010			
sys1	518.1 (479.5 ; 556.7)	462.3 (427.6 ; 497.1)	55.8 (42.2 ; 69.4)
sys2	492.1 (458.9 ; 525.3)	464.1 (429.0 ; 499.3)	28.0 (18.0 ; 38.0)
dia1	207.5 (194.5 ; 220.6)	178.7 (165.8 ; 191.6)	28.8 (24.4 ; 33.3)
dia2	206.5 (192.9 ; 220.1)	180.2 (166.9 ; 193.4)	26.3 (20.9 ; 31.7)
pul1	160.4 (151.9 ; 168.8)	136.9 (129.1 ; 144.7)	23.5 (20.0 ; 26.9)
pul2	156.3 (148.2 ; 164.5)	141.4 (133.4 ; 149.5)	14.9 (11.1 ; 18.6)
NIDS 2012			
sys1	500.7 (466.9 ; 534.4)	454.3 (420.2 ; 488.4)	46.4 (37.8 ; 55.0)
sys2	473.8 (437.4 ; 510.1)	456.0 (421.4 ; 490.7)	17.7 (8.7 ; 26.8)
dia1	191.7 (182.4 ; 201.0)	162.8 (154.6 ; .0171)	28.9 (25.1 ; 32.7)
dia2	178.9 (170.3 ; 187.5)	164.1 (155.8 ; 172.5)	14.7 (11.6 ; 17.8)
pul1	160.3 (151.3 ; 169.3)	141.0 (132.2 ; 149.8)	19.3 (16 ; 22.7)
pul2	158.2 (149.2 ; 167.3)	145.7 (136.4 ; 154.9)	12.6 (9.3 ; 15.9)
NIDS 2014			
sys1	460.4 (435.3 ; 485.4)	416.0 (392.2 ; 439.7)	44.4 (36.5 ; 52.3)
sys2	441.8 (417.1 ; 466.5)	417.6 (392.9 ; 442.2)	24.3 (17 ; 31.5)
dia1	185.1 (175.7 ; 194.6)	160.7 (150.9 ; 170.6)	24.4 (20.7 ; 28.1)
dia2	182.0 (171.2 ; 192.9)	162.1 (152.0 ; 172.1)	20.0 (16.1 ; 23.8)
pul1	149.2 (142.1 ; 156.4)	127.1 (120.0 ; 134.2)	22.1 (19.0 ; 25.3)
pul2	143.0 (135.2 ; 150.7)	131.3 (124.0 ; 138.6)	11.7 (8.5 ; 14.8)

Values are in $mmHg^2$ for blood pressure and in bpm^2 for heart rate readings.
Confidence intervals in brackets.

Table 5.4: Decomposition of the total variance for blood pressure and resting heart rate measurements in **males**. Estimates and 95% confidence intervals.

Reading	Total variance	Trait variance	Error variance
SADHS 1998			
sys1	401.6 (376.6 ; 426.6)	345.9 (321.1 ; 370.6)	55.7 (50.5 ; 61.0)
sys2	377.5 (352.2 ; 402.8)	355.1 (329.9 ; 380.3)	22.4 (18.7 ; 26.2)
sys3	384.9 (359.5 ; 410.3)	340.2 (315.2 ; 365.2)	44.7 (40.0 ; 49.3)
dia1	194.7 (183.8 ; 205.5)	153.0 (143.2 ; 162.8)	41.6 (36.6 ; 46.6)
dia2	176.9 (166.8 ; 187.1)	158.0 (148.0 ; 167.9)	19.0 (15.7 ; 22.3)
dia3	181.7 (172.0 ; 191.3)	153.2 (143.7 ; 162.7)	28.5 (25.3 ; 31.6)
pul1	175.1 (167.1 ; 183.2)	140.8 (133.5 ; 148.2)	34.3 (30.5 ; 38.1)
pul2	161.2 (153.6 ; 168.8)	143.3 (136.3 ; 150.4)	17.9 (15.1 ; 20.6)
pul3	163.6 (156.4 ; 170.9)	136.7 (129.8 ; 143.7)	26.9 (23.9 ; 30.0)
SADHS 2003			
sys1	319.9 (295.4 ; 344.4)	279.6 (255.4 ; 303.9)	40.3 (32.8 ; 47.8)
sys2	305.3 (280.4 ; 330.2)	287.1 (262.4 ; 311.7)	18.3 (14.5 ; 22.0)
sys3	298.7 (274.8 ; 322.6)	275.0 (251.1 ; 299.0)	23.6 (19.8 ; 27.5)
dia1	184.0 (134.2 ; 233.8)	161.9 (111.6 ; 212.3)	22.1 (19.2 ; 25.0)
dia2	182.1 (131.3 ; 233.0)	167.2 (115.8 ; 218.5)	15.0 (11.9 ; 18.1)
dia3	184.2 (133.0 ; 235.4)	162.1 (110.6 ; 213.6)	22.1 (18.5 ; 25.7)
pul1	174.8 (163.2 ; 186.4)	148.7 (137.5 ; 159.9)	26.1 (21.5 ; 30.7)
pul2	163.3 (152.1 ; 174.4)	151.3 (140.2 ; 162.5)	11.9 (9.2 ; 14.6)
pul3	162.9 (152.0 ; 173.8)	144.4 (133.6 ; 155.1)	18.5 (15.6 ; 21.4)
NIDS 2008			
sys1	407.3 (375.7 ; 438.8)	349.5 (318.6 ; 380.3)	57.8 (47.2 ; 68.4)
sys2	388.2 (356.4 ; 420.0)	358.8 (326.8 ; 390.7)	29.5 (18.6 ; 40.3)
dia1	190.0 (174.7 ; 205.4)	149.2 (138.1 ; 160.2)	40.9 (28.9 ; 52.8)
dia2	172.9 (162.7 ; 183.1)	154.0 (142.8 ; 165.1)	19.0 (14.5 ; 23.4)
pul1	163.7 (154.6 ; 172.8)	141.1 (131.9 ; 150.3)	22.6 (17.9 ; 27.3)
pul2	159.7 (150.0 ; 169.3)	143.6 (134.2 ; 153.0)	16.1 (11.3 ; 20.8)
NIDS 2010			
sys1	398.1 (367.3 ; 428.9)	345.3 (316.2 ; 374.4)	52.8 (45.0 ; 60.6)
sys2	368.9 (338.9 ; 398.8)	354.5 (324.3 ; 384.7)	14.4 (6.9 ; 21.8)
dia1	174.7 (163.6 ; 185.7)	138.0 (128.1 ; 148.0)	36.6 (30.2 ; 43.1)
dia2	162.8 (153.4 ; 172.1)	142.5 (132.3 ; 152.7)	20.3 (14.5 ; 26.2)
pul1	161.6 (150.6 ; 172.7)	139.3 (128.7 ; 150.0)	22.3 (18.2 ; 26.4)
pul2	155.3 (144.6 ; 166.1)	141.8 (131.0 ; 152.6)	13.5 (8.7 ; 18.4)
NIDS 2012			
sys1	385.8 (357.6 ; 413.9)	343.6 (316.1 ; 371.1)	42.2 (35.5 ; 48.8)
sys2	370.3 (340.9 ; 399.6)	352.8 (324.2 ; 381.3)	17.5 (9.9 ; 25.1)
dia1	182.1 (169.7 ; 194.5)	150.8 (138.8 ; 162.8)	31.3 (26 ; 36.6)
dia2	170.8 (158.3 ; 183.3)	155.6 (143.2 ; 168.1)	15.1 (10.9 ; 19.3)
pul1	165.7 (152.7 ; 178.7)	146.1 (134.4 ; 157.8)	19.6 (15.4 ; 23.7)
pul2	156.8 (145.5 ; 168.1)	148.7 (136.9 ; 160.5)	8.1 (4.4 ; 11.7)
NIDS 2014			
sys1	386.9 (356.0 ; 417.8)	334.0 (307.2 ; 360.8)	52.9 (45.0 ; 60.9)
sys2	357.4 (331.3 ; 383.4)	342.9 (314.8 ; 370.9)	14.5 (7.5 ; 21.5)
dia1	176.4 (166.1 ; 186.8)	143.7 (134.5 ; 153.0)	32.7 (28.0 ; 37.4)
dia2	166.0 (156.7 ; 175.3)	148.4 (138.4 ; 158.3)	17.7 (13.3 ; 22.0)
pul1	173.5 (162.6 ; 184.3)	151.3 (141.6 ; 161.1)	22.1 (17.6 ; 26.6)
pul2	164.7 (155.0 ; 174.5)	154.0 (144.0 ; 164.1)	10.7 (5.9 ; 15.5)

Values are in $mmHg^2$ for blood pressure and in bpm^2 for heart rate readings.
Confidence intervals in brackets.

Table 5.5: Standardised validity coefficients of individual readings of blood pressure and resting heart rate. Population estimates and standard error.

	SADHS 1998		SADHS 2003		NIDS 2008		NIDS 2010		NIDS 2012		NIDS 2014	
Reading	Q	se	Q	se	Q	se	Q	se	Q	se	Q	se
Females												
sys1	0.851	0.009	0.926	0.004	0.896	0.01	0.894	0.012	0.908	0.009	0.905	0.008
sys2	0.933	0.005	0.959	0.003	0.939	0.011	0.944	0.011	0.963	0.009	0.946	0.008
sys3	0.902	0.005	0.925	0.007	-	-	-	-	-	-	-	-
dia1	0.766	0.011	0.852	0.009	0.842	0.01	0.861	0.011	0.849	0.009	0.868	0.011
dia2	0.859	0.009	0.917	0.009	0.892	0.011	0.874	0.013	0.918	0.009	0.891	0.01
dia3	0.821	0.010	0.866	0.009	-	-	-	-	-	-	-	-
pul1	0.708	0.012	0.848	0.011	0.829	0.013	0.852	0.011	0.878	0.011	0.85	0.011
pul2	0.817	0.011	0.925	0.007	0.887	0.017	0.906	0.012	0.922	0.011	0.92	0.011
pul3	0.776	0.011	0.873	0.009	-	-	-	-	-	-	-	-
Males												
sys1	0.861	0.008	0.874	0.012	0.858	0.013	0.867	0.01	0.89	0.009	0.863	0.009
sys2	0.942	0.005	0.941	0.006	0.926	0.014	0.962	0.01	0.954	0.010	0.960	0.010
sys3	0.882	0.007	0.919	0.007	-	-	-	-	-	-	-	-
dia1	0.784	0.012	0.879	0.020	0.783	0.027	0.788	0.017	0.826	0.015	0.813	0.012
dia2	0.895	0.009	0.919	0.015	0.892	0.014	0.877	0.018	0.913	0.012	0.896	0.013
dia3	0.842	0.009	0.879	0.021	-	-	-	-	-	-	-	-
pul1	0.805	0.010	0.851	0.013	0.862	0.014	0.862	0.013	0.882	0.012	0.873	0.012
pul2	0.891	0.008	0.928	0.008	0.901	0.014	0.915	0.015	0.95	0.012	0.936	0.014
pul3	0.832	0.010	0.884	0.010	-	-	-	-	-	-	-	-

Q = Standardised validity coefficient; se = Standard Error.

Table 5.6 shows the improvement in the validity coefficients obtained by averaging the multiple readings (*composite validity*, Q_c) and by calculating a weighted average with weights given by the factor score coefficients (*optimal validity*, Q_o).

As expected, the validity coefficients of composite measures were larger than the validity coefficients of any individual reading, and the validity of the optimally weighted measure was greater than the validity of simple averages.

The composite validity in the NIDS samples was lower than in the SADHS, as the expected consequence of there being only two readings available in the NIDS. The figures show that using optimal weights in these cases is especially advantageous because the increase in validity is much greater. Substantively, this results suggests that when the validity of simple averages

is high, the advantages of calculating optimal composites are small, but when the composite validity is low, the complication of unequal weights might be worthwhile. These results explain why two similar analyses of BP data (the first by Batista-Foguet et al. [553] with a series of individual measures with low validity, and the second by Bauldry et al. [555] with a set of much more valid individual readings) reached opposite conclusions regarding the advantages of optimal averages.

Table 5.6: Standardised validity coefficient of composite measures of blood pressure and resting heart rate. Population estimates.

	SADHS 1998		SADHS 2003		NIDS 2008		NIDS 2010		NIDS 2012		NIDS 2014	
Measure	Q_c	Q_o	Q_c	Q_o	Q_c	Q_o	Q_c	Q_o	Q_c	Q_o	Q_c	Q_o
Females												
SBP	0.962	0.984	0.978	0.990	0.914	0.981	0.91	0.981	0.918	0.988	0.910	0.983
DBP	0.929	0.969	0.956	0.980	0.824	0.968	0.823	0.966	0.821	0.976	0.817	0.971
RHR	0.908	0.955	0.956	0.980	0.788	0.963	0.801	0.969	0.814	0.975	0.794	0.973
Males												
SBP	0.962	0.984	0.968	0.986	0.884	0.975	0.895	0.986	0.899	0.984	0.892	0.985
DBP	0.939	0.975	0.962	0.982	0.792	0.964	0.781	0.963	0.808	0.973	0.796	0.970
RHR	0.941	0.973	0.958	0.982	0.806	0.969	0.808	0.972	0.824	0.982	0.823	0.978

Q_c = Composite validity; Q_o = Optimal validity.

Note that the increase in precision of optimal vs. simple averages is not only due to the fact that each reading is included in the measures with a weight proportional to its validity (i.e. more valid readings are given more weight), but also because *all* readings of both BP and RHR are included in all measures and contribute to the precision. For example, the optimal composite for the calculation of SBP for a generic female i in the NIDS 2008 would be:

$$SBP_i = 0.34 \cdot sys1_i + 0.57 \cdot sys2_i - 0.02 \cdot dia1_i + 0.11 \cdot dia2_i - 0.05 \cdot pul1_i + 0.04 \cdot pul2_i \quad (5.1)$$

Even though the multiple readings of systolic BP are those with (by far) the greatest weights, the 'best guess' for SBP is also affected by the values of DBP and RHR. The coefficients in Equation 5.1 are the factor score coefficients, calculated from the model coefficients with the regression method.[663].

For comparison, calculating ordinary averages would mean substituting the coefficients of Equation 5.1 with 0.5,0.5,0,0,0,0:

$$SBP_i = 0.5 \cdot sys1_i + 0.5 \cdot sys2_i + 0 \cdot dia1_i + 0 \cdot dia2_i + 0 \cdot pul1_i + 0 \cdot pul2_i \quad (5.2)$$

The "0" coefficients for readings of diastolic BP and RHR indicate that they do no participate in the calculation of SBP. Because DBP and RHR are correlated with SBP, this means that calculating simple averages wastes part of the available information.

5.3 Relative bias and the problem of a different number of readings

Tables 5.7 and 5.8 show the estimates of the relative bias of the second and third readings in respect of the first.

The figures in the tables show how relative bias was large in magnitude across all surveys, and statistically significant in most cases. Differences were larger between the first and the second reading than between the second and the third, consistently with the literature which shows that differences between readings tend to be reduced after the second.[312]

On the contrary, the figures do not indicate meaningful bias between successive readings of RHR. The point estimates of the relative bias were, in fact, small and in most cases not statistically significant.

Table 5.7: Relative bias between individual readings of blood pressure and resting heart rate in the SADHS samples. Population estimates and standard error.

	SADHS 1998				SADHS 2003			
Variable	δ_{12}	se	δ_{13}	se	δ_{12}	se	δ_{13}	se
Females								
SBP	-2.08	0.06	-4.22	0.11	-2.06	0.07	-4.44	0.12
DBP	-0.99	0.26	-3.32	0.4	-0.94	0.3	-3.39	0.45
RHR	0.95	0.32	0.17	0.36	1.13	0.36	0.23	0.4
Males								
SBP	-2.28	0.07	-4.23	0.11	-2.23	0.07	-4.25	0.12
DBP	0.14	0.33	-2.58	0.42	0.19	0.34	-2.58	0.44
RHR	0.73	0.42	-1.55	0.47	0.76	0.43	-1.6	0.48

δ_{ij} = difference between reading i and j; se = Standard Error.
Values are in $mmHg$ for blood pressure and in bpm for heart rate readings.

Table 5.8: Relative bias between individual readings of blood pressure and resting heart rate in the NIDS samples. Population estimates and standard error.

	NIDS 2008		NIDS 2010		NIDS 2012		NIDS 2014	
Variable	δ_{12}	se	δ_{12}	se	δ_{12}	se	δ_{12}	se
Females								
SBP	-2.06	0.07	-2.06	0.06	-2.06	0.06	-2.08	0.07
DBP	-0.95	0.29	-0.96	0.29	-0.96	0.28	-1	0.25
RHR	1.1	0.35	1.08	0.35	1.06	0.34	0.9	0.31
Males								
SBP	-2.23	0.07	-2.24	0.07	-2.24	0.07	-2.3	0.07
DBP	0.2	0.34	0.18	0.34	0.18	0.34	0.11	0.33
RHR	0.76	0.43	0.75	0.42	0.75	0.43	0.71	0.41

δ_{ij} = difference between reading i and j; se = Standard Error.
Values are in $mmHg$ for blood pressure and in bpm for heart rate readings.

The expression of the relative bias between two readings i and j given by Equation 3.33 in Chapter 3 clearly shows that relative bias can be zero for all measures only if:

$$\lambda_i = \lambda_j \; and \; \tau_i = \tau_j \qquad \forall i, j \tag{5.3}$$

This hypothesis can be formally tested by imposing the constraints in Equation 5.3 and comparing the fit of the constrained models with the fit of the scalar invariant model (from Table 5.2).

The results of the comparison in both genders showed a large deterioration in all indices of fit, incompatible with the hypothesis of absence of relative bias[3].

The substantive consequences of the non equivalence of successive readings both in terms of validity and bias are important, especially for the comparability of results between surveys where a different number of readings is taken.

In fact, given a population with a true BP distribution with mean μ and variance σ^2, the observed values of both mean and variance will depend on which reading (or which combination of readings) is used for the estimation. Namely, using single readings leads to an overestimation of the true variance, compared to using averages. This overestimation can be large (over 25% in our data) if the first reading is used. An overestimation of the variance, other than being detrimental for statistical analyses involving BP,[574] can lead in itself to an overestimation of the prevalence of uncontrolled hypertension.[352]. When using composite measures, the overestimation of the variance tends to be greatly reduced. The reduction is greater when

three measures and/or optimally weighted averages are used, but the improvement is much smaller than the improvement observed when using two readings rather than one.

The population means are also affected, and those estimated using the first, second and third reading decrease in this order. Similarly means obtained by averaging three readings are systematically lower than those calculated using only the first and second reading.

These considerations pose an immediate problem for our specific case because of the different number of readings available in the different datasets. Usual methods to deal with situation are:

A Discarding the third reading in all surveys and calculating estimates from the first and second only.

B Ignoring the problem, and comparing directly estimates calculated from three readings with those recovered from two readings;

C Comparing estimates from three readings with those calculated from two readings, but excluding the first reading where it differs more than a given threshold (usually 5 $mmHg$) from the second.

   This last procedure is not explicitly used to address the problem of different number of readings, but it is a commonly applied data cleaning method for BP data (applied, for example, in all published estimated from the SADHS and the NIDS), and, therefore, it implicitly affects the comparison of estimates from population studies.

All options have significant drawbacks. Option A discards part of the available information and is likely to reduce the precision of the estimates. Option B introduces obvious bias in the estimated differences. Option C also discards part of the information and its effect on bias is difficult to judge. It would reduce the bias compared to option B if subjects with large difference between first and second reading were a random sample of the population, but this is quite an implausible assumption, because the drop between consecutive readings of BP has been shown to be associated to specific subjects' characteristics, such as the presence of white coat effect.[220]

Another possibility (method D), which is advocated in this thesis, is using the MGM approach described in Section 3.3.2.9 of Chapter 3. With this approach, in fact, all available readings are used, but the relative bias is taken into account by constraining loadings and intercepts of the first two readings to be equal across surveys, and freeing the third in the NIDS.

To explore the validity of this approach, a simple Montecarlo simulation was carried out. In the simulation, values of triplicate readings of BP and RHR were randomly generated from

two populations (**A** and **B**) with known characteristics. The underlying 'true' distributions were simulated as normal with means:

$$\mu^A_{SBP} = 120\, mmHg\ ;\ \mu^A_{DBP} = 75\, mmHg\ ;\ \mu^A_{RHR} = 75\, bpm \tag{5.4}$$

$$\mu^B_{SBP} = 122\, mmHg\ ;\ \mu^B_{DBP} = 77\, mmHg\ ;\ \mu^B_{RHR} = 75\, bpm \tag{5.5}$$

and variances:

$$\sigma^2_{SBP} = 400\, mmHg^2\ ;\ \sigma^2_{DBP} = 150\, mmHg^2\ ;\ \sigma^2_{RHR} = 150\, bpm^2 \tag{5.6}$$

Multiple readings were generated by adding relative bias and systematic and random error variances. Population values, relative bias and error variances were fixed at realistic values estimated from the SADHS 1998 survey, resulting in validity coefficients for each reading varying from 0.84 to 0.93 for SBP, from 0.77 to 0.82 for DBP, and from 0.75 to 0.85 for RHR. The full model used to generate the data is reported in Appendix I.

A series of samples of different sizes were randomly drawn from the hypothesized populations. For each pair of samples, an estimate of the difference between mean SBP and DBP in the two populations (2 $mmHg$ for both) was calculated with the different methods, hypothesising that three readings were available for population A but only two for population B.

The combinations of sample sizes were the following:

Simulation	**Sample A**	**Sample B**
I	3000	3000
II	1000	1000
III	500	500
IV	250	250
V	1000	250
VI	2000	250

The procedure was repeated 1000 times and the results used to calculate average values for the following parameters:

BIAS:
Absolute value of the difference between d (estimate difference in mean SBP and DBP between population B and A) and its true value (2 $mmHg$);

SE:
Standard error of d ;

COVERAGE:
Proportion of times where the estimated 95% confidence intervals of d included the true value;

POWER:
Proportion of times where the estimated 95% confidence interval for d did not include 0.

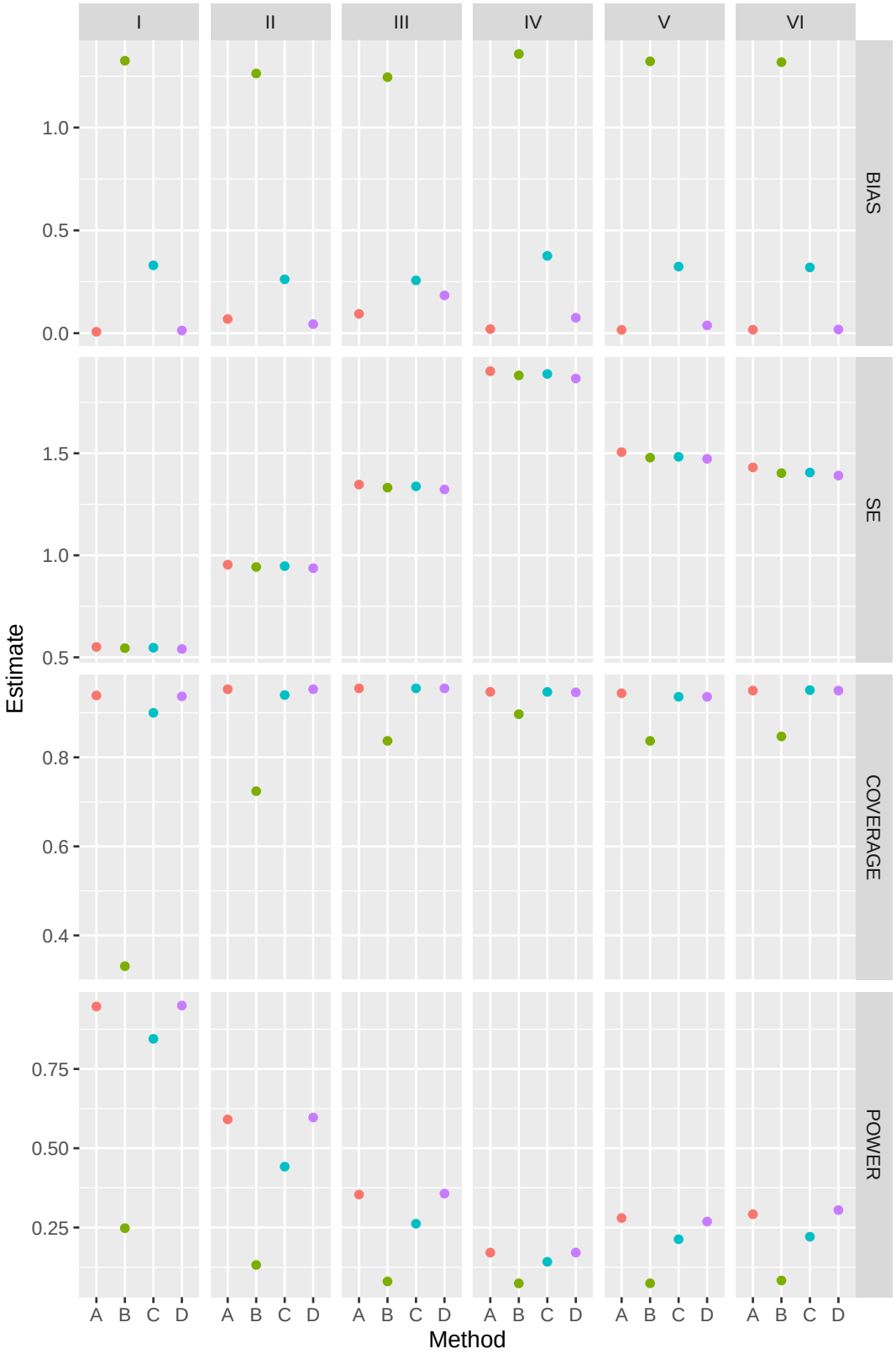
A summary of results is shown in Figures 5.4 and 5.5

Within the limitations of this example which only examined a small number of conditions, the results of the simulation supported our initial hypotheses that:

1. Using only two readings (method A, which discards the third reading in the second population), produces unbiased estimates;
2. Using all available readings (Method B) produces severely biased estimates, with very low coverage and power;
3. Using all available readings but excluding the first reading if the difference with the second is $> 5\ mmHg$ (Method C) is less biased than method B and has greater power, but still compares unfavourably with method A.
4. The MGM approach (method D) is unbiased and has similar level of power and coverage of method A, but produces more precise estimates. The reduction in standard error is more evident in small samples and when the sample size in the group with three measurement is greater. This is not unexpected, because this is the case where excluding the third reading of BP and all RHR readings corresponds to the greater loss of information.

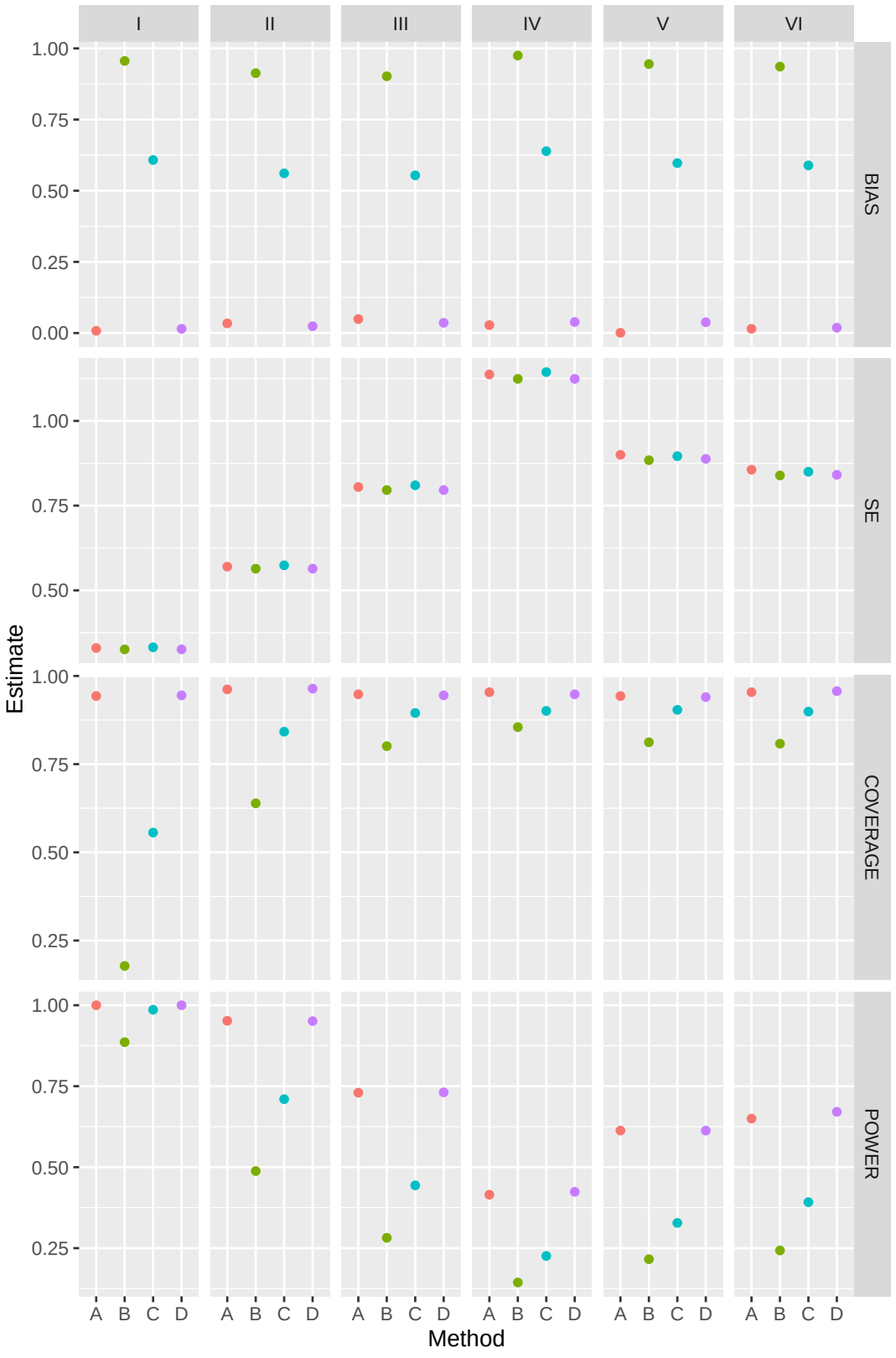
These observations supports the choice of applying the multiple group approach within the SEM framework to joint analyses of BP data when a different number of repeated measurements is available in the different datasets; in our case for the joint analysis of the SADHS and NIDS samples.

Figure 5.4: Bias, standard error, coverage and power of different methods to recover difference in population means of systolic blood pressure when different numbers of readings are available. Average results over 1000 replications.



Details on the simulation procedure are described in the text. Bias and SE (standard error) are measured in $mmHg$. A,B,C and D are defined in the text.

Figure 5.5: Bias, standard error, coverage and power of different methods to recover difference in population means of diastolic blood pressure when different numbers of readings are available. Average results over 1000 replications.



Details on the simulation procedure are described in the text. Bias and SE (standard error) are measured in $mmHg$. A,B,C and D are defined in the text.

Notes

[1]The studies were conducted in 1989 in Mamre and Mitchell Plain, two communities in the greater Cape Town area, in the Western Cape Province.

[2]These results are not shown.

[3] $\Delta\chi^2 = 1889.1$, $df = 12$, $p < 0.001$, $\Delta CFI = -0.022$, $\Delta RMSEA = 0.034$, $\Delta BIC = 5562.8$ for females and $\Delta\chi^2 = 1707.2$, $df = 12$, $p < 0.001$, $\Delta CFI = -0.025$, $\Delta RMSEA = 0.041$, $\Delta BIC = 4400.2$ for males.

Chapter 6

Trends in blood pressure in the South African adult population

This chapter analyses the changes in the distribution of BP, RHR and prevalence of uncontrolled hypertension in South African adult population during the 17-years study period. In includes three main sections.

1. **Secular trends**

   This first section presents and compares the estimated characteristics of the distribution of SBP, DBP and RHR in the population at each time point defined by the median period of data collection of the source datasets. Unadjusted estimates — calculated as simple averages of the available multiple readings — are presented together with estimates adjusted for between-surveys differences in the seasonal distribution of data collection and other discrepancies. An estimate of the prevalence of uncontrolled hypertension and the number of subjects affected in each period is also shown.

2. **Exploring potential drivers**

   The second section analyses the changing distribution of the *untreated* BP (i.e. the hypothetical values of SBP and DBP that would have been observed in the population in absence of antihypertensive treatment) and its relationship with a series of known biological, behavioural and socieoconomic factors.

   The individual contribution of each of these factors to explaining the changes in mean BP during the study period is estimated, and adjusted trends presented and discussed.

3. **Group specific trends**

   To further explore possible drivers of the changes in BP during the study period, this last section presents season- and age-adjusted trends in the observed and untreated BP,

estimated separately per sub-population defined by age class, race, education and urban vs. rural dwelling.

6.1 Secular trends

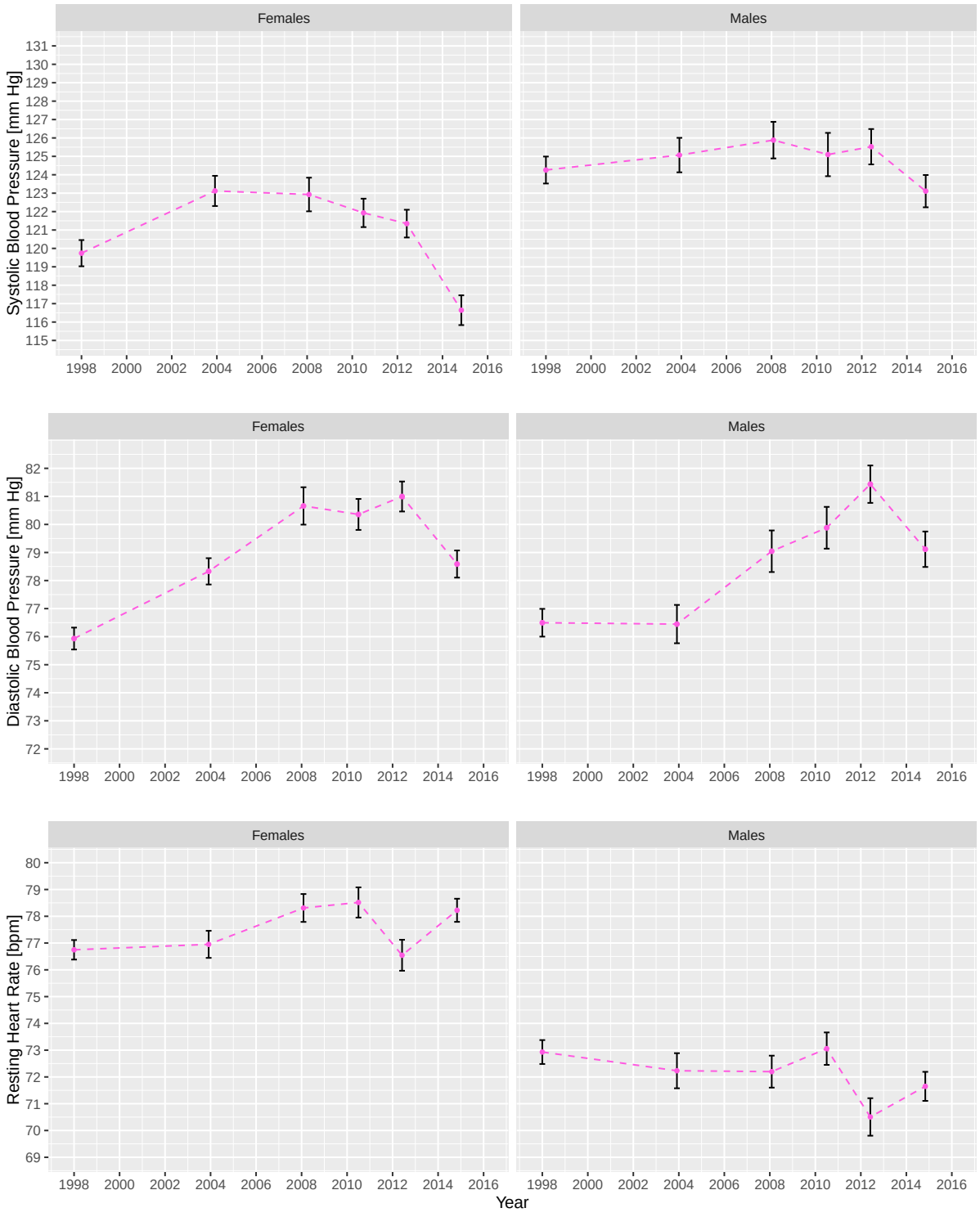
6.1.1 Unadjusted estimates

Table 6.1 and Figure 6.1 compare the population estimates of mean BP and RHR recovered from each dataset as a weighted average (using the *original* sampling weights) of the individual values calculated by taking the mean of all available readings.

Table 6.1: Mean values of blood pressure and resting heart rate in the South African adult population (15+ years). Unadjusted estimates and 95% confidence intervals.

Survey	Systolic BP (95% CI) $[mmHg]$	Diastolic BP (95% CI) $[mmHg]$	Resting heart rate (95% CI) $[bps]$
Females			
SADHS 1998	119.7 (119.0 ; 120.5)	75.9 (75.5 ; 76.3)	76.7 (76.4 ; 77.1)
SADHS 2003	123.1 (122.3 ; 123.9)	78.3 (77.9 ; 78.8)	77.0 (76.4 ; 77.5)
NIDS 2008	122.9 (122.0 ; 123.8)	80.7 (80.0 ; 81.3)	78.3 (77.8 ; 78.8)
NIDS 2010	121.9 (121.2 ; 122.7)	80.4 (79.8 ; 80.9)	78.5 (78.0 ; 79.1)
NIDS 2012	121.3 (120.6 ; 122.1)	81.0 (80.5 ; 81.5)	76.5 (76.0 ; 77.1)
NIDS 2014	116.6 (115.8 ; 117.5)	78.6 (78.1 ; 79.1)	78.2 (77.8 ; 78.7)
Males			
SADHS 1998	125.1 (124.1 ; 126.0)	76.5 (75.8 ; 77.1)	72.9 (71.6 ; 72.9)
SADHS 2003	125.9 (124.9 ; 126.9)	76.4 (78.3 ; 79.8)	72.2 (71.6 ; 72.8)
NIDS 2008	125.1 (123.9 ; 126.3)	79.0 (79.1 ; 80.6)	72.2 (72.5 ; 73.7)
NIDS 2010	125.5 (124.6 ; 126.5)	79.9 (80.8 ; 82.1)	73.1 (69.8 ; 71.2)
NIDS 2012	123.1 (122.2 ; 124.0)	81.4 (78.5 ; 79.7)	70.5 (71.1 ; 72.2)
NIDS 2014	123.1 (121.2 ; 125.1)	79.1 (77.2 ; 81.1)	71.6 (69.7 ; 73.6)

Figure 6.1: Trends in blood pressure and resting heart rate in the South African adult population (15+ years). Unadjusted estimates and 95% confidence intervals.



The overall trends are far from linear for both SBP and DBP, and rather reverse-U shaped with a period of increase followed by a more recent phase of decline. The trend reversal seems to have happened earlier among women than among men and for SBP the magnitude of the variations was much greater among women.

Considering the whole period, estimates of mean SBP from the last survey were *lower* than the estimates in the first assessment in 1998, by 3.1 $mmHg$ (95% CI: 2.1 to 4.1) among women and by 2 $mmHg$ (0.9 to 3.2) among men. Conversely, estimates of DBP were *higher* in 2014-2015 than in 1998, by 2.7 $mmHg$ (95% CI: 2.1 to 3.3) among women and by 2.6 $mmHg$ (1.8 to 3.4) among men.

Differences between RHR estimates across the various surveys were small in magnitude. The average RHR in the population was higher in 2014-2015 than in 1998 for women (+1.5 bpm, 95% CI: 0.9 to 2.1) and lower for men (-1.3 bpm, 95% CI: -2.0 to -0.6).

Estimates calculated separately for subjects with or without previous diagnosis of hypertension and for those with or without antihypertensive treatment (see Figure B.1, Appendix B) showed a similar reverse-U shaped trend.

6.1.2 Taking into account artefactual differences

The population estimates of BP and RHR shown in the previous section do not take into account methodological dissimilarities between surveys that might have introduced artefactual differences.

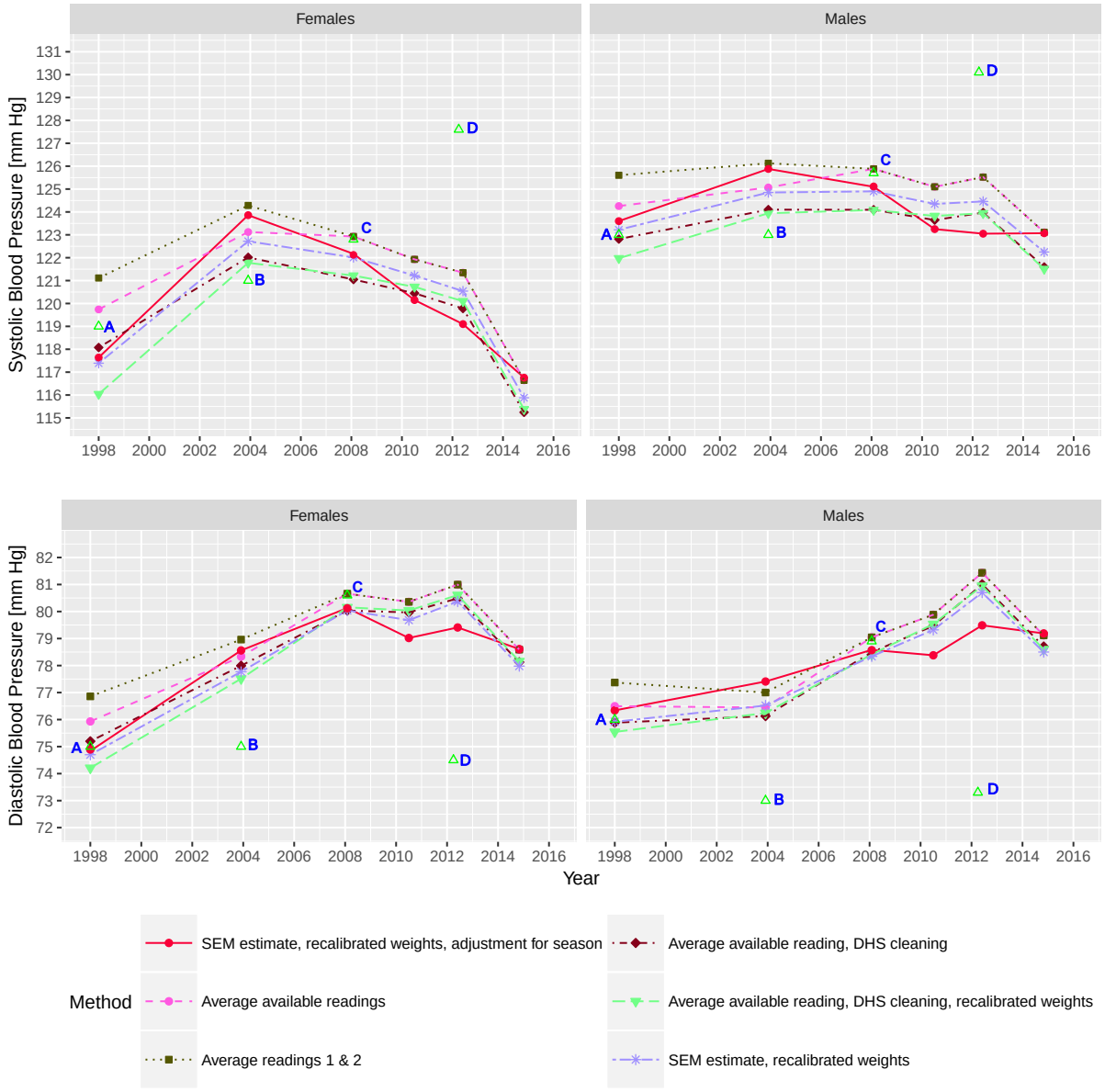
In particular, according to the considerations of sources of error summarised in Chapter 2, the methodological differences between surveys described in Chapter 3 and the results of the exploratory data analysis, part of the observed changes in BP over time may be the artifactual consequence of: (1) the varying number of readings used for the calculation of averages, (2) the inconsistent methods and population totals used to calibrate the sampling weights and (3) the different seasonal distribution of data collection across surveys.

The estimated effects of these plausible sources of artefactual differences are shown in Figure 6.2, which compares the unadjusted estimates from the previous section (short-dashed line, - - -) with those calculated after introducing various forms of adjustment.

As expected, taking into account methodological differences and seasonal effects produced non negligible changes in the estimates. The differences were as large as 3.5 $mmHg$ in some cases.

On its own, the recalibration of weights — i.e. without taking into account the other adjustments — reduced the differences between estimates from the SADHS and the NIDS datasets.

Figure 6.2: Trends in systolic and diastolic blood pressure in the South African adult population (15+ years). Adjustment for methodological differences between surveys and period of data collection.



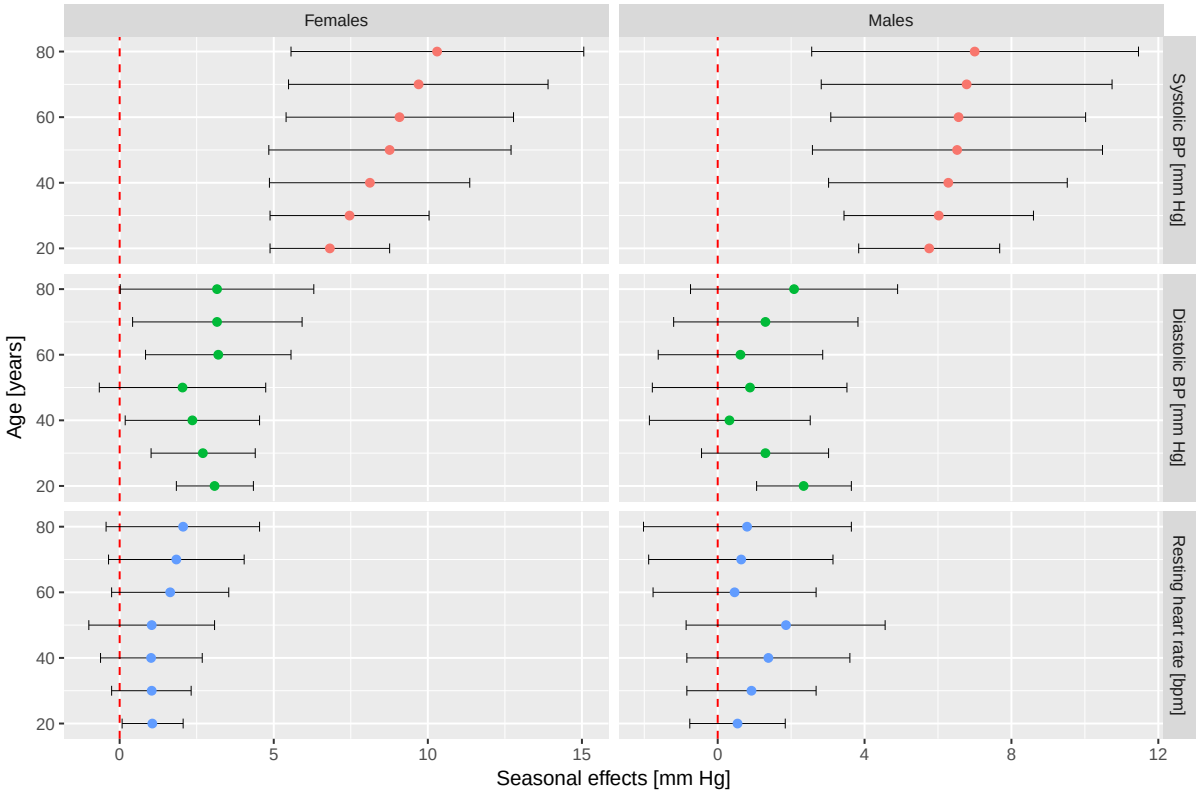
△= published estimates from the SADHS 1998 (A, [372]), SADHS 2003 (B, [373]), NIDS 2008 (C, [377]) and SANHNES 2012 (D, [374]).

Excluding the third reading produced an overestimation of BP compared to using all readings.

Seasonal adjustment had a remarkable effect on the estimates, especially evident in those from the SADHS 2003, which showed a large increase. This was expected, given the restriction of data collection to summer-early autumn (period of lower average BP) in that survey.

Figure 6.3 shows the size of the seasonal effect on BP and RHR — defined as the difference between the maximum and minimum values reached during the annual cycle — for subjects of different ages. The overall pattern of effects on BP is consistent with the literature, and characterised by: (1) large effects on SBP, with magnitude between 5 $mmHg$ among young males to more than 10 $mmHg$ among elderly females, all statistically significant; and (2) more modest effects on DBP, mostly non statistically significant for males.

Figure 6.3: Seasonal effects on blood pressure and resting heart rate in the South African adult population (15+ years). Estimates and 95% confidence intervals.



The magnitude of these effects confirms that the period of data collection plays an important role in the comparisons of estimates between different surveys, and may explain some observed differences between population strata. Because of this potentially large impact, seasonal effects in the different strata of the South African population are studied in greater detail in Chapter 7, where the NIDS data are re-analysed with a longitudinal approach, in principle able to reduce confounding due to time-invariant factors.

Contrary to those for BP, the results of the estimation did not provide evidence of any sizeable seasonal effect on RHR, with all estimates small in magnitude and not statistically significant.

This result, together with the absence of relative bias between subsequent measurements, accords with the finding that point estimates of RHR were only marginally affected by the different forms of adjustment, as shown in Figure 6.4[1].

Figure 6.4: Trends in resting heart rate in the South African adult population (15+ years). Adjustment for methodological differences between surveys and period of data collection.

Based on the methodological and substantive considerations from the previous chapters, I consider the estimates of BP and RHR recovered with the structural equation modelling method taking into account seasonality (solid line — in the Figures) to be more accurate than those recovered with the other methods and best able to describe secular trends during the study period.

The numerical values of the estimates calculated with this method ('base' estimates hereafter) are shown in Table 6.2 together with their 95% confidence intervals.

Table 6.2: Mean values of systolic and diastolic blood pressure and resting heart rate in the South African adult population (15+ years). Base estimates and 95% confidence intervals.

Survey	Systolic BP (95% CI) $[mmHg]$	Diastolic BP (95% CI) $[mmHg]$	Resting heart rate (95% CI) $[bps]$
Females			
SADHS 1998	117.6 (117.0 ; 118.3)	74.8 (74.4 ; 75.3)	76.6 (76.2 ; 77.0)
SADHS 2003	123.9 (123.1 ; 124.6)	78.6 (78.0 ; 79.2)	77.1 (76.6 ; 77.7)
NIDS 2008	122.2 (121.4 ; 123.0)	80.1 (79.5 ; 80.8)	78.0 (77.5 ; 78.6)
NIDS 2010	120.2 (119.3 ; 121.0)	79.0 (78.4 ; 79.6)	78.7 (78.2 ; 79.3)
NIDS 2012	119.1 (118.4 ; 119.8)	79.4 (78.9 ; 79.9)	76.8 (76.3 ; 77.4)
NIDS 2014	116.8 (116.1 ; 117.4)	78.6 (78.2 ; 79.1)	78.2 (77.8 ; 78.6)
Males			
SADHS 1998	123.6 (122.9 ; 124.3)	76.3 (75.8 ; 76.9)	73.1 (72.6 ; 73.6)
SADHS 2003	125.9 (124.8 ; 126.9)	77.4 (76.0 ; 78.8)	72.6 (71.8 ; 73.3)
NIDS 2008	125.1 (124.3 ; 125.9)	78.6 (78.0 ; 79.2)	72.4 (71.8 ; 73.0)
NIDS 2010	123.3 (122.3 ; 124.2)	78.4 (77.8 ; 79.0)	72.9 (72.3 ; 73.6)
NIDS 2012	123.1 (122.2 ; 123.9)	79.5 (78.9 ; 80.1)	70.4 (69.8 ; 71.1)
NIDS 2014	123.1 (122.4 ; 123.8)	79.2 (78.7 ; 79.7)	71.7 (71.2 ; 72.2)

Analysing the base estimates, we can make the following observations:

1. Compared to the raw estimates in Figure 6.1, the base estimates of SBP reinforce the conclusion of the existence of an inverse U-shaped trend, with a large increase between 1998 and 2003 followed by a consistent decline in the subsequent period, both among females and males. The reversal seems to have happened earlier than suggested by the unadjusted estimates.

   Between 1998 and 2003-2004 SBP increased by 6.3 $mmHg$ among females and by 2.3 $mmHg$ among males, corresponding to a rate of 1.26 $mmHg/year$ (95% CI: 1.04 to 1.44) and 0.46 $mmHg/year$ (0.20 to 0.72), respectively. In the following 11 years SBP decreased by an average 0.64 $mmHg/year$ (95% CI: 0.56 to 0.73) among females, and by 0.29 $mmHg/year$ (0.18 to 0.40) among males[2].

2. Among females, DBP also showed a similar trend, with a large increase in the first part of the observation period (until 2008), followed by a slower decline. The average rate of change was +0.53 $mmHg/year$ (95% CI: 0.46 to 0.61) in the first period, and -0.20 $mmHg/year$ (-0.31 to -0.08) afterwards.

For men, the trend was almost linear over the whole observation period, with an average increase by 0.18 $mmHg/year$ (95% CI: 0.14 to 0.23).

3. The overall trend in RHR was increasing for females (average +0.08 $bpm/year$, 95% CI: 0.05 to 0.11) and decreasing for males (-0.10 $bpm/year$, -0.14 to -0.07). Similarly to the unadjusted trends, the magnitude of the change was, however, small.

Figure 6.2 also shows some published estimates of average BP from the same datasets (marked as △). The discrepancies of those values from not only our season-adjusted base estimates, but also from most of those calculated as simple averages with different data-cleaning procedures are worth some comment.

The first observation is that the estimates from the SANHNES show much higher values of SBP (about +11 $mmHg$) and much lower values of DBP (about -5 $mmHg$). The difference might be partly due to: (1) the relative bias of the devices used for measurement (see Table 3.7 in Chapter 3, and (2) a possible greater white coat effect in the SANHNES than in the NIDS because of the clinical rather than domestic environment in what the measurements took place[3]. However, the magnitude of the differences is so large that it is difficult to explain them only on these considerations. Therefore, this finding is another element which supports our previous hypothesis of selection bias in the SANHNES sample toward high-risk individuals, which led us to the exclusion of the sample from our analyses.

The second observation refers to the low values of the published estimates of DBP from the SADHS 2003 data, especially for men. Doubts about the accuracy of these values are reported in the official report of the survey and attributed — in the absence of other plausible explanation — to the fact that "*it is likely that the measurements were not taken correctly by the field-workers*"[373, p. 238]. Without excluding this possibility, our relatively consistent estimates (much higher than the published data) obtained from the same data by different procedures suggest an alternative explanation. That is, they suggest that the low estimates are at least partly the result of the data cleaning and/or the estimation procedure used to produce the values published in the report. In any case, the data in our possession do not suggest any particularly anomalous pattern in DBP readings in the second edition of the SADHS.

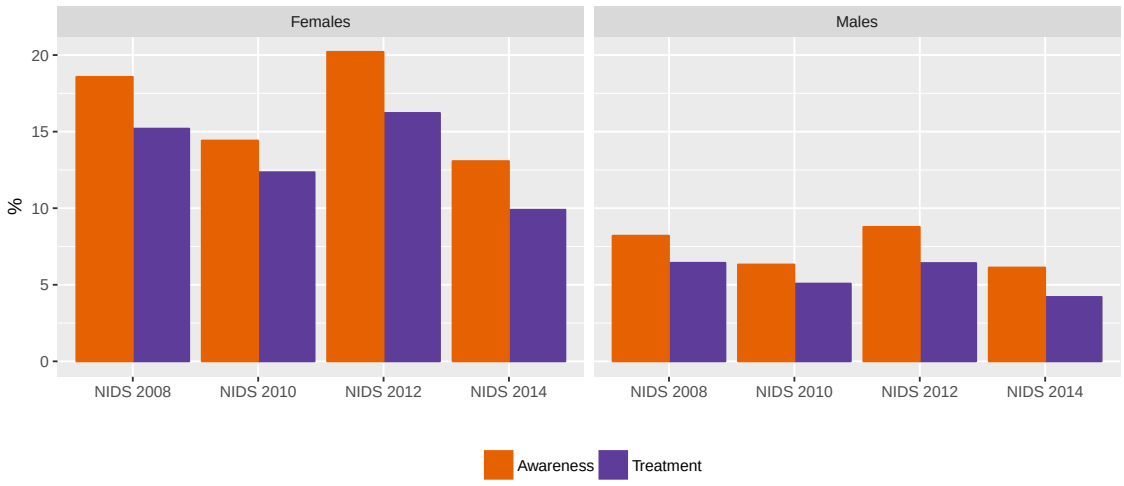
Given that the finding of a consistent decline in BP in the last decade is mostly based on the estimates from the four waves of the NIDS *panel* survey, another possible source of artifactual differences must be considered. The protocol of this survey prescribed (for evident ethical reasons) that individuals whose BP measurements exceeded some thresholds were invited to go for a doctor or a hospital visit within a certain time depending on the severity of the readings[4]. This procedure — together with the the longitudinal nature of the NIDS that implies that the same individuals are repeatedly interviewed — might have artificially inflated the level of awareness (and possibly the proportion of hypertensive subjects initiated

on treatment) recorded in the following waves. This practice might have made the sample less representative of the general population of South Africa regarding blood pressure. Therefore, part of the rapid decline in SBP values observed after 2008 might have been present only in the sample, and not in the population.

We cannot completely exclude that this has been the case, but I have reasons to think that this phenomenon, if present, could have produced no more than a marginal overestimation of the recent downward trend. The two reasons are:

1. The trend in the proportion of subjects in the NIDS sample aware of their condition (i.e. that self-reported having being diagnosed with hypertension any time in the past) and/or in antihypertensive treatment does not show any consistent increase from wave to wave supporting the hypothesis of an appreciable effect of the referral protocol. The proportions seem rather to fluctuate between waves with an overall *decreasing* trend (Figure 6.5).

Figure 6.5: Proportion of subjects who reported previous diagnosis of hypertension and proportion of subjects on antihypertensive treatment in the NIDS samples. Unweighted sample statistics.



Awareness = previous diagnosis of hypertension; Treatment = current use of antihypertensive drugs. Both self-reported.

This apparent irrelevance of the referral protocol on increasing hypertension awareness and prevalence of treatment in the sample may be the consequence of different phenomena. Besides the hypothesis of a poor compliance of respondents with raised BP to the suggestion by the fieldworkers to report to a clinic for assessment, a possible reason is that the samples in the various waves only partly overlapped (see Chapter 3 for a description of the sampling strategy of the survey) and, therefore, any artifactual

increase of awareness/treatment in the participants to the previous waves would have been 'diluted' by the new first-time respondents.

In any case, the trend in awareness and treatment among the sampled subjects do not support the hypothesis of any major effect of the referral protocol on our estimates.

2. As shown in the following Section 6.2.1, the decline in BP is evident also in the youngest age class (15 to 25 years), unlikely to include an appreciable proportion of hypertensive subjects who might have been made aware of their condition by the NIDS fieldworkers.

Generally, the hypothesis of a decline in the average BP in the South African adult population during the last decade finds some support in the results of an independent study with different data sources and approach. Namely, it is consistent with the results of the recent study by Nojilana et al. [697] who analysed cause-specific age-standardised death rates in South Africa between 1997 and 2010. Of relevance for our study is their finding that death rates for CVD increased until 2003 but then started a consistent and almost linear decline, both among males and females. In particular, the authors found that *stroke* mortality rates reached a peak in 2003 (at 133 per 100 000 population) and then declined constantly to about 114 per 100 000 population in 2010. The result is interesting from our perspective, because of the large literature that supports a direct association between SBP and risk of stroke, with a dose-response relationships which starts well below the 140 $mmHg$ cut-off usually considered for hypertension.[698] A meta analysis of 61 studies found that each incremental rise by 20 $mmHg$ in SBP was associated with a twofold increase in death rates from stroke.[512] This association underlies the finding of many epidemiological studies of a decline in mortality rates for stroke that follows quite closely, and with short time lags, reductions in mean values of BP in the population.[512, 699] This is consistent with our observations and supports the hypothesis that the reduction in SBP in the South African population is a real phenomenon and not an artifact of measurement and/or representation error.

6.1.3 The changing shape of the blood pressure distribution

The tables and figures in this section show the results of the analysis of temporal trends in some of the parameters that defines the overall *shape* of the BP distribution, beyond its mean value. All estimates are obtained by relaxing the hypothesis of normal distribution in the population and allowing for moderate levels of skewness through the estimation method described in Section 3.3.2.8 in Chapter 3.

Table 6.3 reports, for each period, the estimated standard deviation and skewness and kurtosis coefficients.

Table 6.3: Standard deviation, skewness and kurtosis of the distribution of blood pressure in the South African adult population (15+ years).

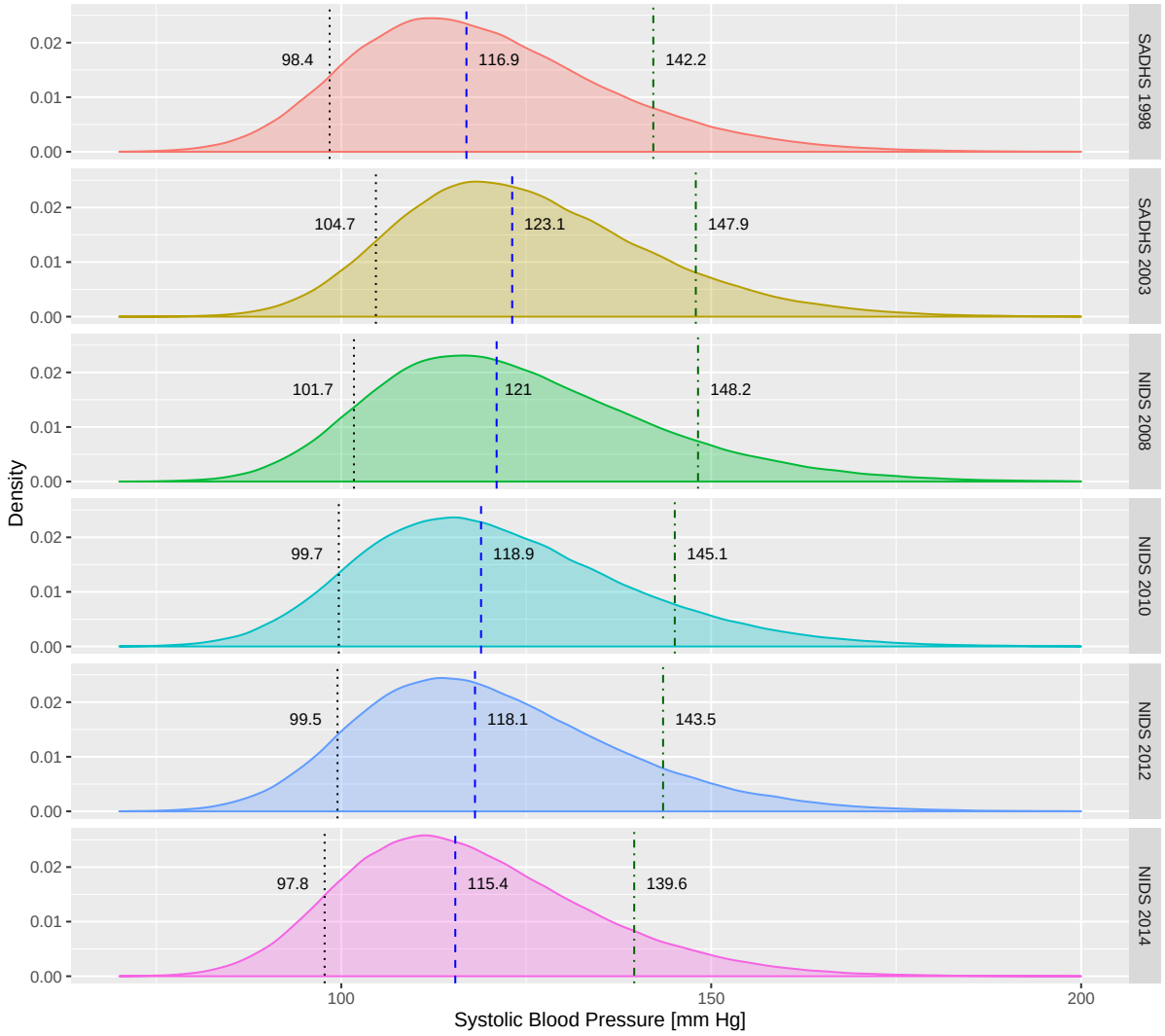
	Systolic BP			Diastolic BP		
Survey	SD $[mmHg]$	SK	KT	SD $[mmHg]$	SK	KT
Females						
SADHS 1998	17.3	0.6	0.3	10.8	0.1	0.3
SADHS 2003	17.1	0.6	0.3	11.3	0.0	0.3
NIDS 2008	18.4	0.6	0.3	12.1	0.1	0.3
NIDS 2010	17.9	0.6	0.3	12.1	0.0	0.3
NIDS 2012	17.4	0.6	0.3	11.5	0.1	0.3
NIDS 2014	16.5	0.6	0.3	11.4	0.1	0.3
Males						
SADHS 1998	15.1	0.5	0.3	11.1	0.2	0.3
SADHS 2003	15.5	0.6	0.3	12.3	0.1	0.3
NIDS 2008	16.6	0.6	0.3	11.0	0.1	0.3
NIDS 2010	16.7	0.6	0.3	10.9	0.1	0.3
NIDS 2012	16.5	0.6	0.3	11.4	0.3	0.3
NIDS 2014	16.4	0.6	0.3	11.0	0.1	0.3

SD = Standard deviation; SK = Skewness; KT = Kurtosis.

The statistics in the Table indicate that the distribution are all moderately right-skewed and slightly leptocurtic with no appreciable changes over time of the skewness and kurtosis coefficients[5]. The values of the standard deviation, however, suggest that the 'spread' of the distribution of both SBP and DBP has been moderately but consistently decreasing since 2008 (by 20% the former and by 11% the latter). The same effect, with smaller magnitude, seems to be present among men only for SBP (3% reduction since 2008).

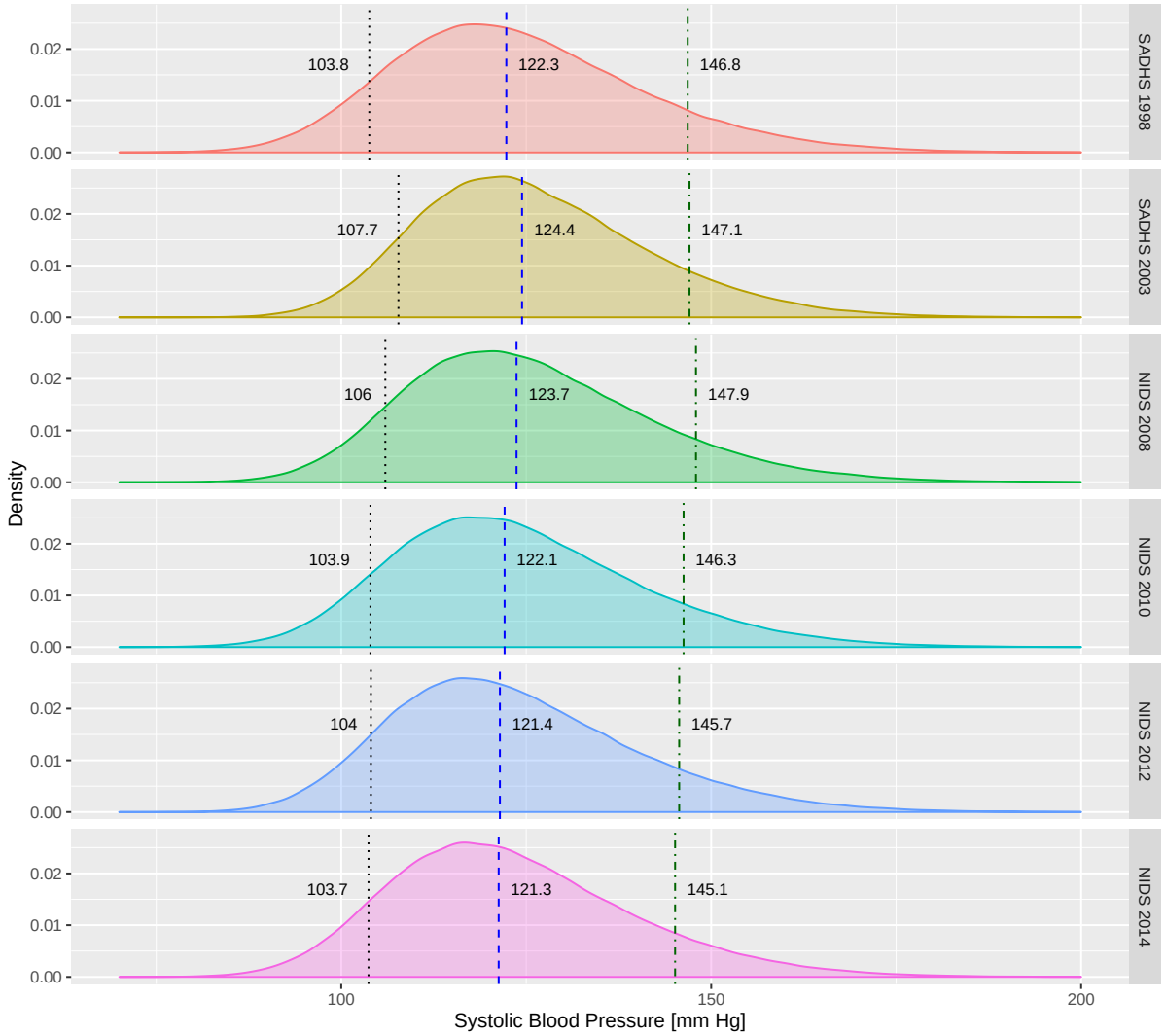
The inspection of the graphs in Figures 6.6 to 6.9 offers some indication of the origin of these changes. In particular the relative changes over time of the 10^{th}, 50^{th} and 90^{th} percentiles suggest that the reduction observed after 2003-2004 in both SBP and DBP for women is due mostly to changes in the the 'high risk' section of population. Between-surveys changes in the 90^{th} percentile are, in fact, almost ever larger than the corresponding changes in other percentiles, especially among women.

Figure 6.6: Estimated distribution of systolic blood pressure in the South African adult female population (15+ years). Quantiles.



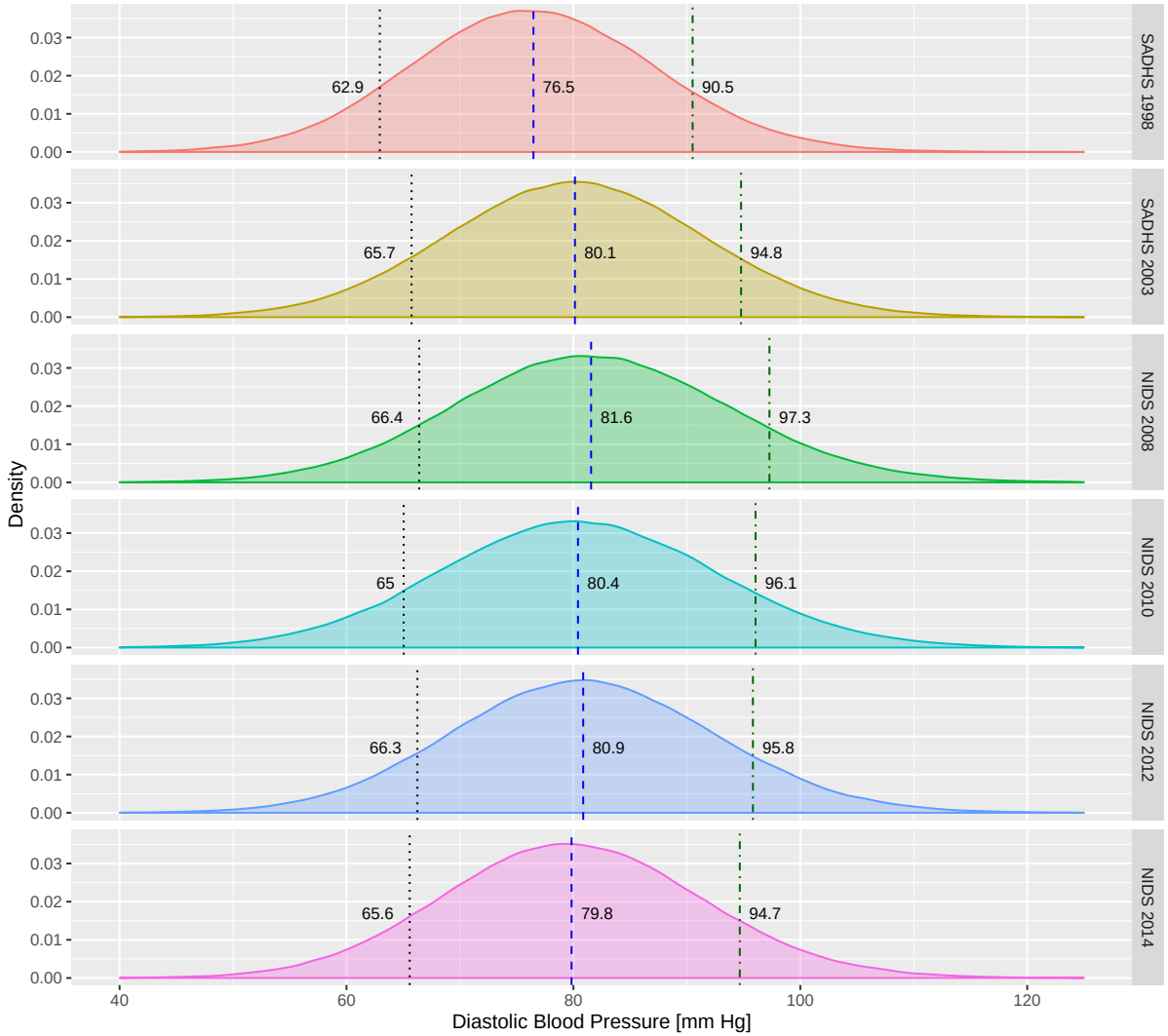
⋯⋯ = 10^{th} percentile; — — — = median; — · — · = 90^{th} percentile

Figure 6.7: Estimated distribution of systolic blood pressure in the South African adult male population (15+ years). Quantiles.



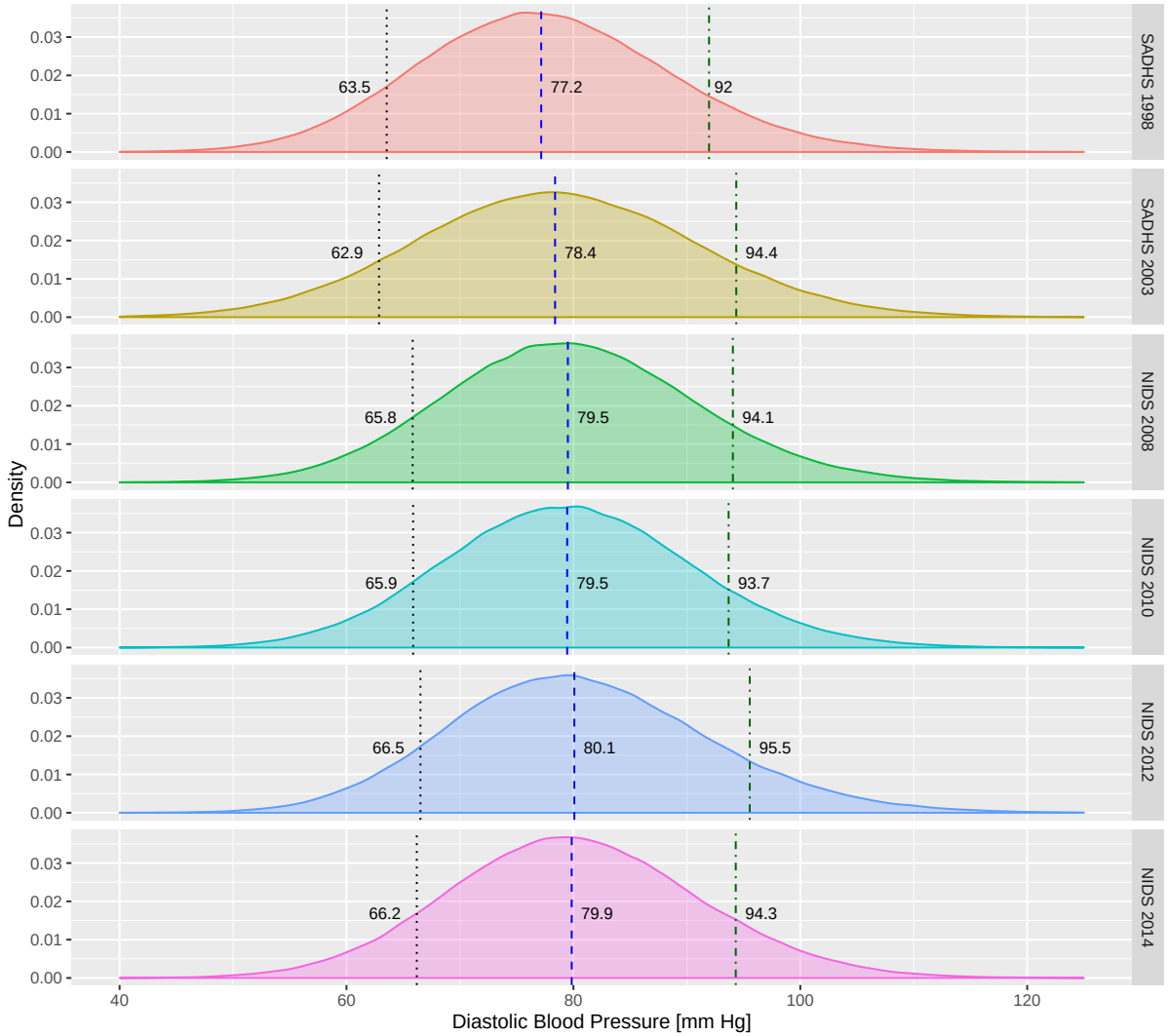
⋯⋯ = 10^{th} percentile; – – – = median; —·—· = 90^{th} percentile

Figure 6.8: Estimated distribution of diastolic blood pressure in the South African adult female population (15+ years). Quantiles.



····· = 10^{th} percentile; – – – = median; — · —· = 90^{th} percentile

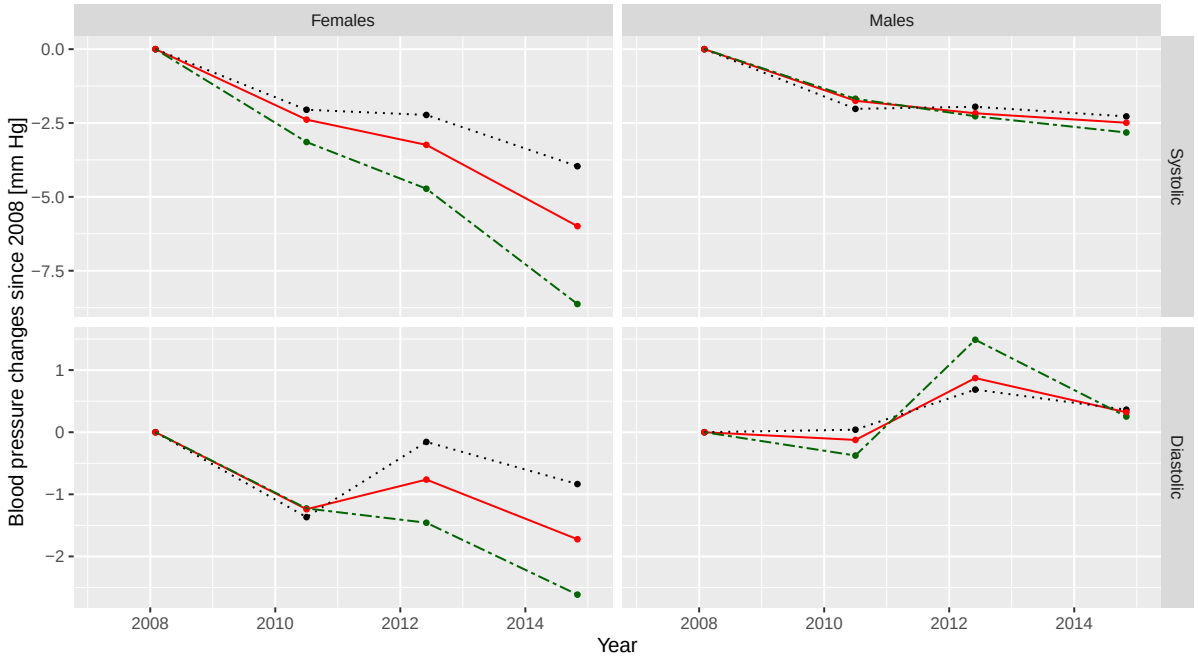
Figure 6.9: Estimated distribution of diastolic blood pressure in the South African adult male population (15+ years). Quantiles.



····· = 10^{th} percentile; – – – = median; — · —· = 90^{th} percentile

This phenomenon better illustrated in Figure 6.10, which compares trends in the mean and the 10^{th} and 90^{th} percentile for the period from 2008 to 2014-15.

Figure 6.10: Estimated distribution of diastolic blood pressure in the South African adult male and female populations (15+ years). Quantiles and mean.



· · · = 10^{th} percentile; — — — = mean; —· = 90^{th} percentile

Among females, the decrease of the BP value corresponding to the 90^{th} percentile is notably steeper than the decrease in the mean and in the 10^{th} percentile. The phenomenon is less evident among males because of the smaller variations observed, but the pattern of relative changes between quantiles points to the same conclusion that variations in the mean BP (in either direction) are mainly driven by changes in the right tail rather than due to a uniform shift of the whole distribution.

These observations — which are consistent with the decreasing standard deviation in recent periods — might be a first indication that part of the mean reduction is attributable to the diffusion of antihypertensive treatment which, obviously, does not affect the left tail of the distribution.[699]

We will find more direct support for this hypothesis in the next Section 6.2.1, where the characteristics of the estimated distribution on the hypothesis of no-treatment will be presented.

6.1.4 Prevalence of uncontrolled hypertension and number of subjects affected

Based on the distributions from the previous section, Table 6.4 show the estimated prevalence of uncontrolled hypertension and the number of subjects affected[6].

Table 6.4: Prevalence of uncontrolled hypertension and number of subjects affected in the South African adult population (15+ years). Estimates and 95% confidence intervals.

Survey	Prevalence [%]	Number affected [millions]
Females		
SADHS 1998	17.1 (16.0 ; 17.9)	2.5 (2.4 ; 2.7)
SADHS 2003	30.4 (28.2 ; 32.1)	5.1 (4.7 ; 5.4)
NIDS 2008	31.5 (29.3 ; 33.4)	5.6 (5.2 ; 5.9)
NIDS 2010	29.7 (27.7 ; 31.4)	5.5 (5.1 ; 5.8)
NIDS 2012	28.2 (26.2 ; 29.8)	5.3 (5.0 ; 5.6)
NIDS 2014	22.4 (21.0 ; 23.5)	4.3 (4.0 ; 4.5)
Males		
SADHS 1998	21.3 (19.8 ; 22.4)	2.9 (2.7 ; 3.0)
SADHS 2003	28.0 (24.1 ; 33.3)	4.3 (3.7 ; 5.1)
NIDS 2008	25.7 (23.7 ; 27.3)	4.1 (3.8 ; 4.4)
NIDS 2010	24.7 (22.6 ; 26.4)	4.1 (3.8 ; 4.4)
NIDS 2012	24.6 (22.7 ; 26.0)	4.2 (3.9 ; 4.4)
NIDS 2014	23.5 (21.7 ; 25.0)	4.1 (3.8 ; 4.4))

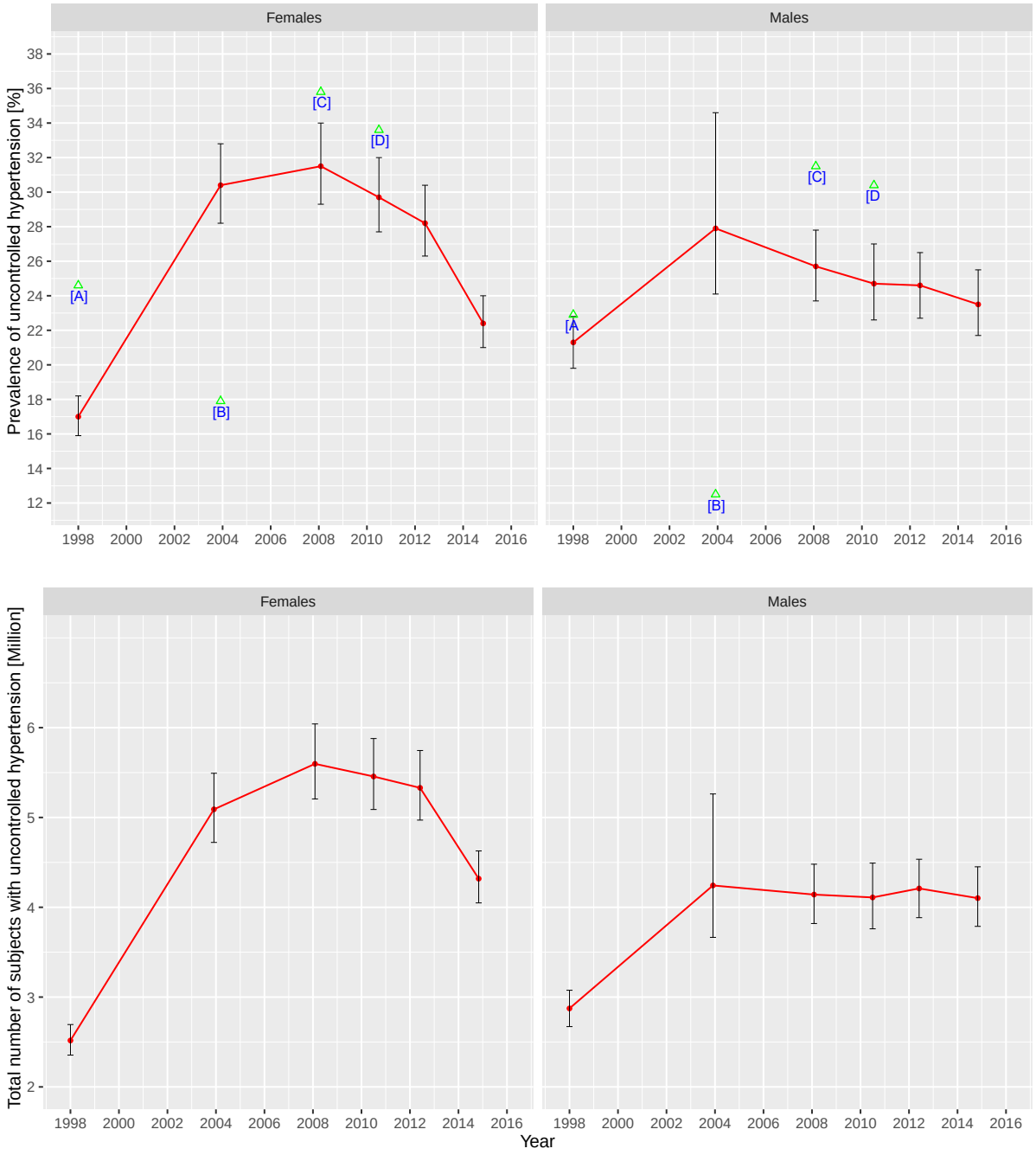
Uncontrolled hypertension defined as SBP $\geq$ 140 $mmHg$ and/or DBP $\geq$ 90 $mmHg$.

The same data are graphically depicted in Figure 6.11 for ease of interpretation.

The estimates in Table 6.4 and Figure 6.11 are not directly comparable with the published estimates reported in Section 2.2.1. Our estimates, in fact, refer to *uncontrolled* hypertension while those in Section 2.2.1 consider all subjects on antihypertensive treatment as hypertensive, regardless of their actual BP values.

The choice of reporting estimates of uncontrolled hypertension is motivated by the fact that the cardiovascular risk is related to the actual values of BP, and therefore the proportion of subjects with BP above the hypertensive thresholds is a more direct indicator of the total population risk than the prevalence of hypertension which excludes the beneficial effect of antihypertensive treatment. The impact of treatment is analysed separately in this thesis,

Figure 6.11: Prevalence of uncontrolled hypertension and number of hypertensive subjects in the South African adult population (15+ years). Estimates and 95% confidence intervals.



△= published estimates from the SADHS 1998 (A, [372]), SADHS 2003 (B, [373]), NIDS 2008 (C, [377]) and SANHNES 2012 (D, [374]).

by modelling the counterfactual distribution of BP that would have observed in absence of treatment (see Section 6.2.1), and it contributes to the interpretation of the primary trends.

Because they exclude the contribution represented by subjects in treatment but with normal BP, the estimates in Table 6.4 and Figure 6.11 are always lower than published estimates, with the exception of those from the SADHS 2003, for the reasons discussed above.

Moreover, our estimates: (1) are calculated with an analytical method that deals with random measurement error more efficiently that simple averages of multiple readings, (2) are based on BP values adjusted for seasonality, and (3) are plausibly unaffected by digit preference because of the 'smoothing' implicit in the latent variable representation. Because of this, and differently from unadjusted simple averages, our estimates of the variance of the BP distribution do not include the 'extraneous' variance components due to measurement error, seasonality and digit preference. They are therefore *lower* than the simple averages and, hopefully, a closer representation to the true prevalence of uncontrolled hypertension in the population. Keeping the mean constant, the proportion of subjects in the right tail of a distribution decreases if the variance decreases and this phenomenon makes further contributes to explain the differences with the published estimates.

The reduction in the blood pressure observed in the last period from its maximum reached in 2003-2004 translates into an estimated reduction by about one million in the number of women with uncontrolled hypertension. Among men, however, the smaller reduction in the last decade was balanced by the increase in the population, and as a result the total number of uncontrolled hypertensive men has not appreciably changed and it is stable at around 4.1 million.

6.2 Exploring potential drivers

To explore possible drivers of these notable changes in mean values of BP and prevalence of uncontrolled hypertension in the South African population, the following three sections examine how the 'base' secular trends in Figure 6.2 are modified when the estimates are adjusted to take into account:

1. The effect of the diffusion of antihypertensive treatment;
2. The varying distribution of a series of biological (age, body mass index), behavioural (smoking and alcohol use) and socioeconomic (urban vs. rural living and education) risk factors;
3. Possible differences among subjects belonging to different birth cohorts.

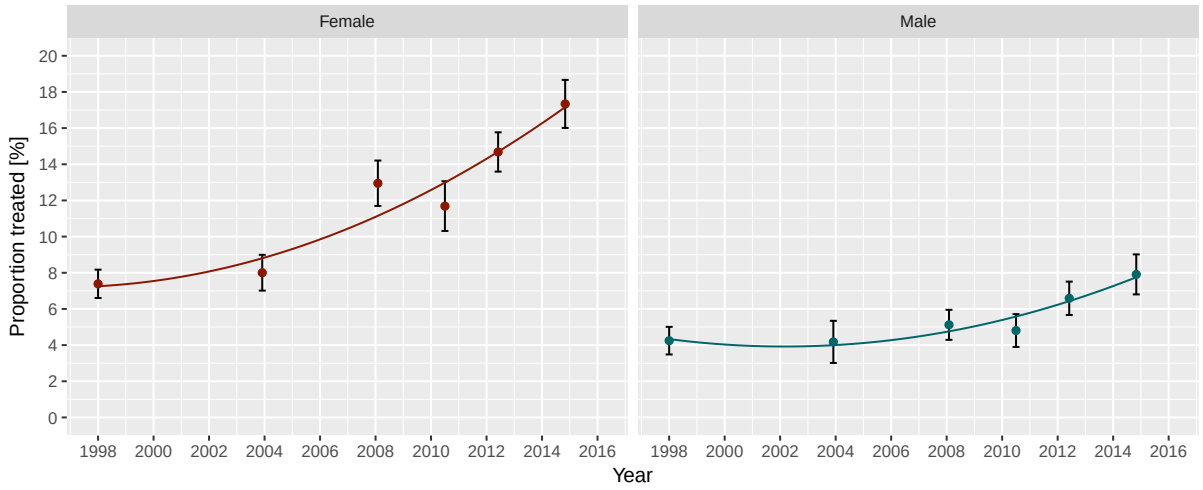
The discrepancies between base and adjusted trends provide a visual indication of the ability of the various candidates to explain the observed trends. An adjusted trend which is 'flatter' than the base trend indicates that changes over time in the distribution of the relevant variable are able to partly[7] explain the variations in the mean values of BP observed in the population. On the contrary, adjusted trends which are 'steeper' that the base trends are an indication that changes over time in the distribution of the relevant variable are partly or totally 'masking' the variations in the mean values of BP in the population due to other reasons.

6.2.1 Antihypertensive treatment

Changes in antihypertensive treatment is an obvious candidate to explain changes in the mean value of BP in the population.

As shown in Figure 6.12, during the study period the proportion of South Africans on medication for high BP rose substantially. The prevalence of men in treatment increased from 4.2% in 1998 to 7.9% in 2014-2105, and the growth was even greater for women, from 7.4% to 17.3% during the same period.

Figure 6.12: Proportion of subjects on antihypertensive treatment in the South African adult population between 1998 and 2015. Cross-sectional estimates and quadratic trend, by gender.



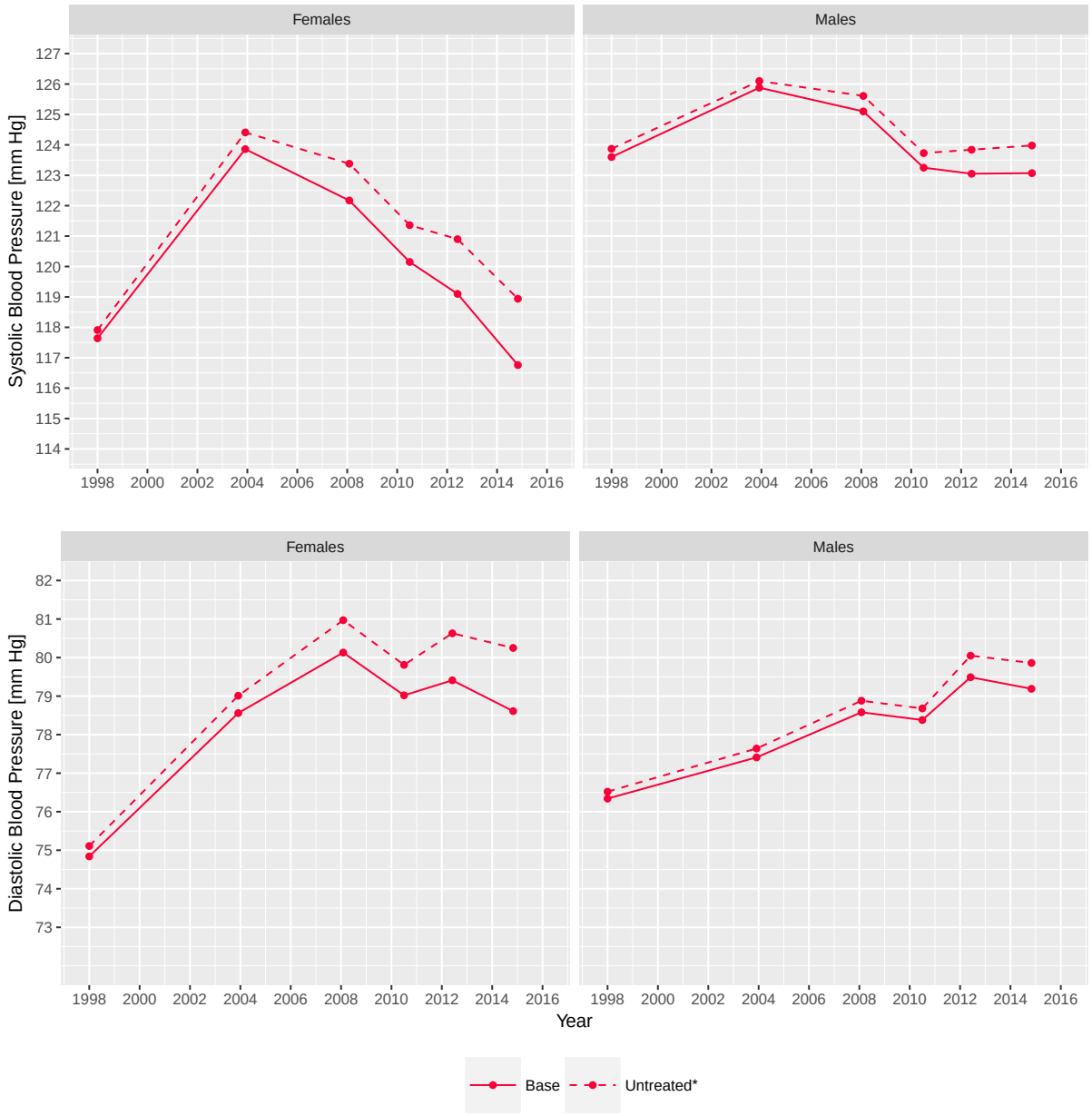
Antihypertensive drugs are prescribed to lower BP, making it plausible that the growing prevalence of treatment could partly explain the decrease observed in the last decade in both SBP and DBP among women and in SBP only among men.

The results illustrated in Figure 6.13, where the base trends are compared with those that would have been observed in absence of treatment (*untreated* trends, estimated as described in section 3.3.2.11 of Chapter 3), support this hypothesis. They show how in the absence of treatment, in the last decade we would have observed a smaller reduction in SBP in both genders, and a steeper increase in DBP among males. The increasing trend between 1998 and 2003 would have been practically unmodified, coherently with the low absolute prevalence of treatment and minimal changes during that period.

The difference between untreated and treated values — constrained to be ≥ 0 by the structure of the model, coherently with the assumption that antihypertensive drugs do not increase BP — increased from period to period, as an expected consequence of the growing proportion of subjects in treatment.

An estimate of the mean values of SBP and DBP that we would have observed in the South African adult population at the different time points in *the absence of antihypertensive treatment* is shown in Table 6.5.

Figure 6.13: Trends in systolic and diastolic blood pressure in the South African adult population (15+ years). Estimates in absence of antihypertensive treatment.



* See pp. 176-178 for the analytic procedure used for the estimation of the untreated values.

Table 6.5: Mean values of systolic and diastolic blood pressure in the South African adult population (15+ years) that would have been observed in the absence of antihypertensive treatment. Estimates and 95% confidence intervals.†

Survey	Systolic BP (95% CI) $[mmHg]$	Diastolic BP (95% CI) $[mmHg]$
Females		
SADHS 1998	117.9 (117.3 ; 118.6)	75.1 (74.7 ; 75.5)
SADHS 2003	124.4 (123.6 ; 125.2)	79.0 (78.4 ; 79.6)
NIDS 2008	123.4 (122.6 ; 124.2)	81.0 (80.4 ; 81.6)
NIDS 2010	121.4 (120.6 ; 122.2)	79.8 (79.3 ; 80.4)
NIDS 2012	120.9 (120.2 ; 121.6)	80.6 (80.1 ; 81.2)
NIDS 2014	118.9 (118.3 ; 119.6)	80.3 (79.8 ; 80.7)
Males		
SADHS 1998	123.9 (123.2 ; 124.6)	76.5 (76.0 ; 77.0)
SADHS 2003	126.1 (125.0 ; 127.2)	77.6 (76.2 ; 79.1)
NIDS 2008	125.6 (124.8 ; 126.4)	78.9 (78.3 ; 79.5)
NIDS 2010	123.7 (122.8 ; 124.7)	78.7 (78.1 ; 79.3)
NIDS 2012	123.8 (123.0 ; 124.7)	80.1 (79.5 ; 80.6)
NIDS 2014	124.0 (123.3 ; 124.7)	79.9 (79.4 ; 80.3)

† Confidence intervals do not take into account the uncertainty in the estimation of the censored values of the readings according to the procedure described in Chapter 3.
Estimates are adjusted for seasonality.

Table 6.6 shows the estimated values for the average treatment effect on the population (ATE) and the average treatment effect on the treated (ATT), averaged across the available readings in each survey. The average effect of the treatment on the SBP of the treated subjects was a reduction between 8.38 $mmHg$ and 12.83 $mmHg$ among women, and similarly, between 7.59 $mmHg$ and 12.32 $mmHg$ among men. The effect on DBP, as usually found, was consistently smaller that the effect of SBP, but of the same order of magnitude (between 6.32 $mmHg$ and 9.39 $mmHg$ among women and between 5.01 $mmHg$ and 8.39 $mmHg$ among men).[230]

It is worth noticing that the ATT seems to increase over time. More investigation is needed, but this fact might indicate better compliance with treatment or, more in general, better management of hypertension in the affected subjects.

Table 6.6: Average treatment effects (reduction) on systolic and diastolic blood pressure. Estimates and 95% confidence intervals.

	Systolic blood pressure		Diastolic blood pressure	
Survey	ATE (95% CI) $[mmHg]$	ATT (95% CI) $[mmHg]$	ATE (95% CI) $[mmHg]$	ATT(95% CI) $[mmHg]$
Females				
SADHS1998	0.53 (0.44 ; 0.63)	8.38 (7.29 ; 9.47)	0.40 (0.32 ; 0.47)	6.23 (5.41 ; 7.05)
SADHS2003	0.62 (0.45 ; 0.80)	8.33 (6.46 ; 10.2)	0.47 (0.35 ; 0.59)	7.76 (5.84 ; 9.67)
NIDS2008	1.43 (1.21 ; 1.65)	11.15 (9.76 ; 12.54)	0.87 (0.74 ; 1.00)	6.83 (6.01 ; 7.65)
NIDS2010	1.27 (1.05 ; 1.50)	9.77 (8.3 ; 11.25)	0.86 (0.70 ; 1.02)	6.84 (5.83 ; 7.85)
NIDS2012	1.86 (1.6 ; 2.11)	12.22 (10.83 ; 13.61)	1.31 (1.14 ; 1.47)	8.59 (7.80 ; 9.39)
NIDS2014	2.32 (2.05 ; 2.58)	12.83 (11.54 ; 14.12)	1.67 (1.41 ; 1.92)	9.39 (8.32 ; 10.47)
Males				
SADHS1998	0.31 (0.21 ; 0.40)	7.59 (5.24 ; 9.93)	0.20 (0.12 ; 0.28)	5.01 (2.92 ; 7.10)
SADHS2003	0.28 (0.18 ; 0.37)	6.70 (4.90 ; 8.50)	0.26 (0.15 ; 0.37)	6.2 (4.65 ; 7.75)
NIDS2008	0.59 (0.37 ; 0.81)	11.14 (8.29 ; 13.98)	0.34 (0.21 ; 0.47)	6.68 (5.03 ; 8.33)
NIDS2010	0.45 (0.29 ; 0.60)	8.59 (6.52 ; 10.67)	0.30 (0.21 ; 0.38)	5.68 (4.36 ; 7.00)
NIDS2012	0.76 (0.58 ; 0.95)	10.43 (8.42 ; 12.43)	0.55 (0.41 ; 0.68)	7.46 (6.16 ; 8.76)
NIDS2014	1.00 (0.76 ; 1.25)	12.32 (10.35 ; 14.28)	0.71 (0.55 ; 0.86)	8.39 (7.22 ; 9.57)

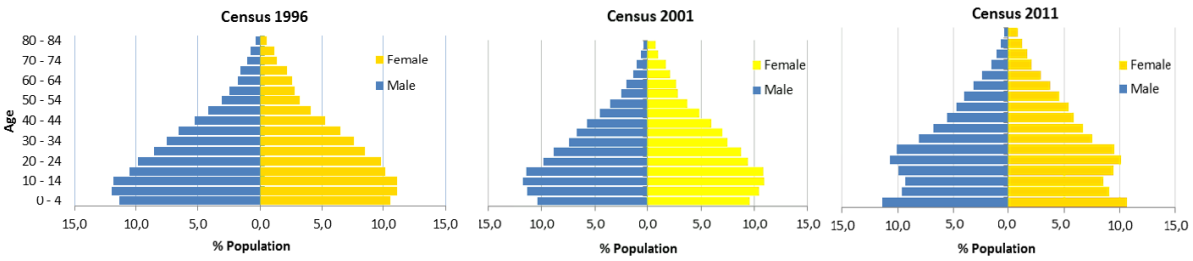
ATE = Average treatment effect in the population; ATT = Average treatment effect in the treated.
See pp. 176-178 for method of estimation.

6.2.2 Age effects

A second factor to consider as possible driver of the observed changes in BP is the changing age structure of the population.

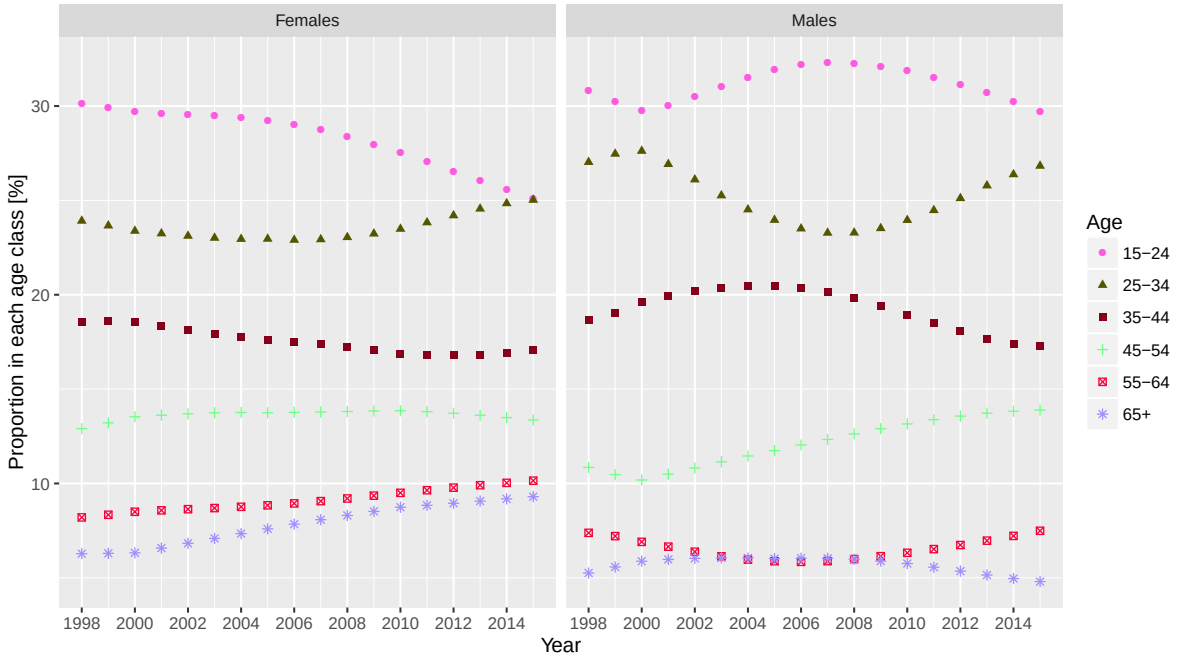
As shown in Figure 6.14, the age distribution of the South African population has undergone profound changes during the study period. While the most evident modifications have happened at the bottom of the population pyramids and affected the youngest age categories which are not considered in our study, the figure shows remarkable changes also in the relative proportion of subjects in the remaining classes. This is made more evident in Figure 6.15, which focuses only on the adult population. Interesting for our study is the fact that the variations in the proportions of individuals in each age class do not have a consistent trend, especially among males. Assuming a consistent relationship between age and BP, this fact could explain part of the reversal of the BP trends described above.

Figure 6.14: South African population age and sex structure, 1996, 2001 and 2011.



Source: Statistics South Africa [700]

Figure 6.15: Age distribution of the adult population of South Africa between 1998 and 2015.



Data: World Bank [380]

The cross-sectional relationships of the *untreated* BP and RHR with age estimated from our models are shown in Table 6.7, and agree with the findings of the great majority of population studies. Untreated values were used for the analyses of the relationship of BP with age and the other risk factors because of the endogenous nature of the antihypertensive treatment variable. As explained in greater detail in Section 2.1.4.1.11 and Section 3.3.2.11, failure to properly take

into account the fact that treatment is initiated based on the pre-treatment values of BP and either introducing treatment status as a covariate or ignoring it produces biased estimates of the relationships between BP and risk factors[8].[240]

The estimates presented in Table 6.7 and the subsequent Tables 6.8 to 6.12 are derived from the *same model* including all predictors and also adjusted for seasonality (*fully adjusted* model), and thus represent independent effects. They are presented separately only for descriptive purposes.

Table 6.7: Effect of age on untreated blood pressure and resting heart rate in the South African adult population (15+ years). Estimates and 95% confidence intervals.†

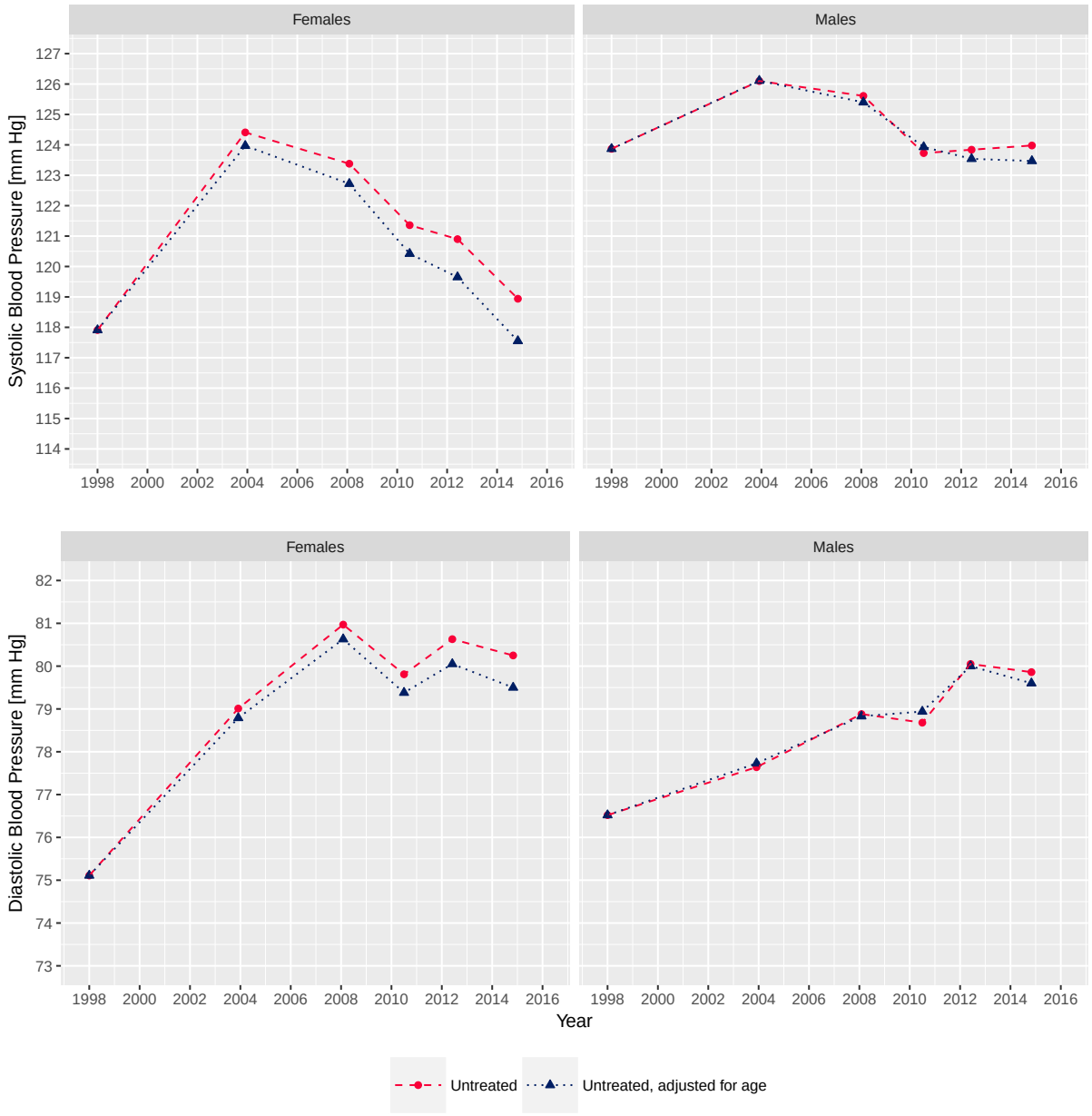
Factor	Difference in systolic BP (95% CI) $[mmHg]$	Difference in diastolic BP (95% CI) $[mmHg]$	Difference in resting heart rate (95% CI) $[bps]$
Females			
Age (< 55 years)	0.51 (0.45 ; 0.57)	0.34 (0.30 ; 0.39)	-0.01 (-0.05 ; 0.03)
Age (≥ 55 years)	0.60 (0.54 ; 0.66)	0.33 (0.29 ; 0.38)	0.00 (-0.04 ; 0.04)
1 year increase			
Males			
Age (< 55 years)	0.46 (0.39 ; 0.53)	0.39 (0.34 ; 0.44)	0.07 (0.02 ; 0.12)
Age (≥ 55 years)	0.54 (0.47 ; 0.60)	0.35 (0.30 ; 0.39)	0.06 (0.02 ; 0.11)
1 year increase			

Fully adjusted estimates.
† The models are adjusted for seasonality and and include interaction terms. Because of this, the effect of age is not constant, and the coefficients in the table refer to the main effects (i.e. the effect for the mean month of data collection).

Both SBP and DBP increase with age, but while for SBP the increase continues into old age with the same (or slightly higher) pace, the rate of increase in DBP tends to fall slightly after 55 years. Rates of change in RHR are clinically irrelevant in magnitude, and only significantly different from 0 in males.

The combined effect on the population trends of the increase of BP with age and the varying age structure of the population is illustrated in Figure 6.16.

Figure 6.16: Trends in untreated systolic and diastolic blood pressure in the South African adult population (15+ years). Adjustment for age.



Among women, coherently with the increase of the mean age between 2003-2004 and 2014-2016 (from 36.3 to 38.1 years, estimated from the sample), adjusting for age[9] produced a *steeper* decrease in BP (mainly SBP) than the unadjusted estimates, rather than explaining the reasons of the decline. Among men (whose mean age changed less, from 34.8 to 35.8 years) differences

were smaller, but showed the same pattern.

As expected given the much smaller effect of age on RHR, adjustment for age produced even smaller changes in the RHR trend, not graphically appreciable (not shown).

6.2.3 Changing prevalence of biological and behavioural risk factors

Population trends in BMI, alcohol consumption and smoking during the study period are depicted in Figure 6.17, which shows, for each variable the population averages calculated from each cross-section (● markers and vertical line representing the 95% CI) and the estimated linear trend between 1998 and 2015 (black lines and grey areas representing the 95% confidence band[10]).

The figure shows that — in substantial agreement with the findings of the literature, including the local one[701–703] — the South African adult population has seen:

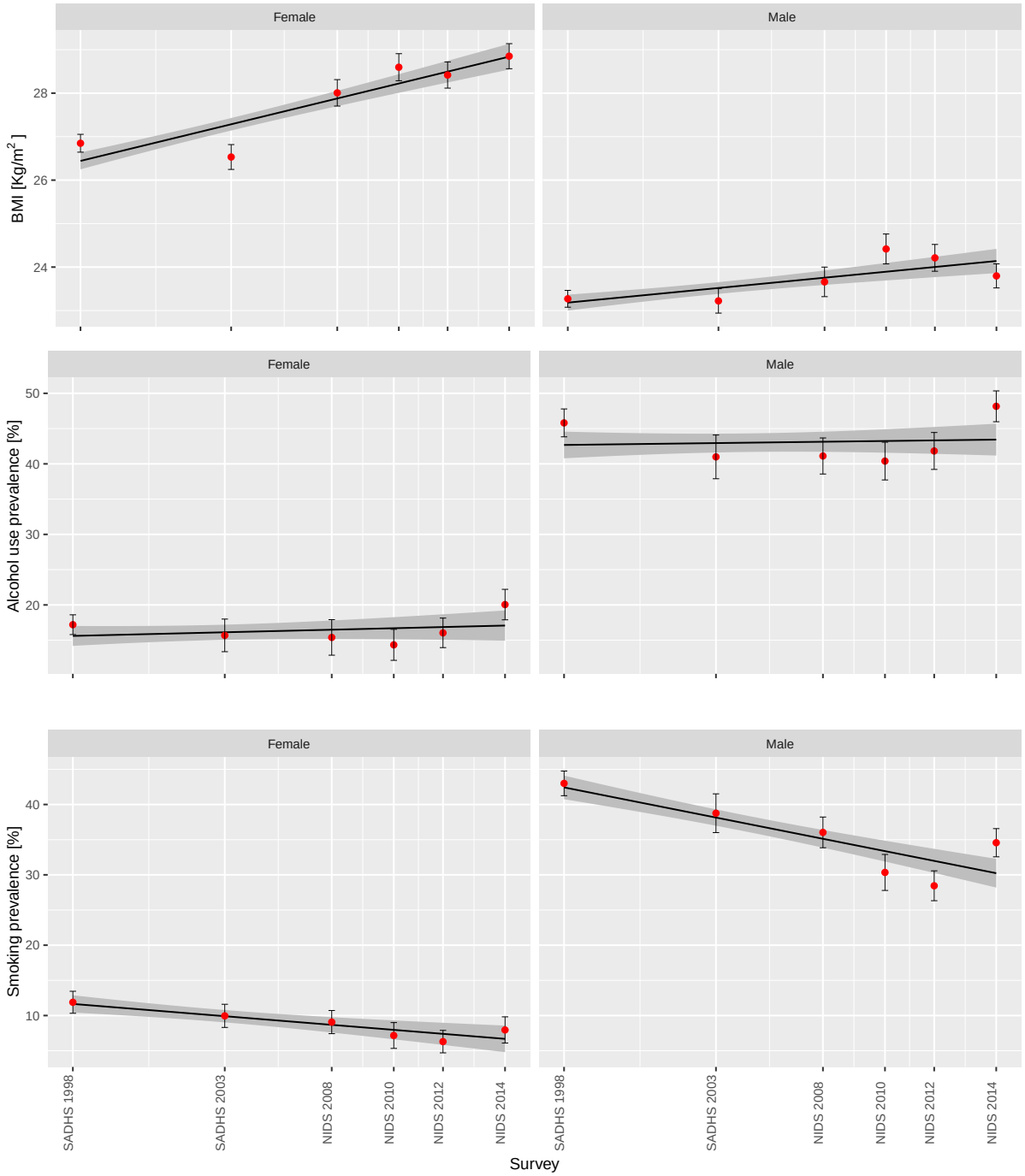
1. A clear increasing trend in BMI, both among women and men but more pronounced among women;
2. A stable prevalence of alcohol use;
3. A steady decrease in the prevalence of smokers, more evident among men.

The numerical values of the slope coefficients of the estimated linear trends are listed in Table 6.8 together with their 95% CIs.

Table 6.8: Estimated linear trends for bio-behavioural risk factors in the South African adult population (15+ years) between 1998 and 2015. Regression coefficients and 95% confidence intervals.

		Females		Males	
Variable	Unit	Slope coefficient	95% CI	Slope coefficient	95% CI
BMI	$kg/m^2/decade$	1.42	(1.19 ; 1.66)	0.57	(0.35 ; 0.79)
Alcohol use	$\%/decade$	0.87	(-0.77 ; 2.51)	0.45	(-1.45 ; 2.35)
Smoking	$\%/decade$	-2.95	(-4.46 ; -1.45)	-7.25	(-8.98 ; -5.51)

Figure 6.17: Mean BMI and prevalence of alcohol use and smoking in the South African adult population between 1998 and 2015. Cross-sectional estimates and linear trend, by gender.



The estimated cross-sectional effects of smoking, alcohol consumption and BMI on the untreated BP and RHR are summarised in Table 6.9, and are largely coherent with the literature

reviewed in Chapter 2.

Table 6.9: Effect of smoking, alcohol consumption and BMI on untreated blood pressure and resting heart rate in the South African adult population (15+ years). Estimates and 95% confidence intervals.

Factor	Difference in systolic BP (95% CI) $[mmHg]$	Difference in diastolic BP (95% CI) $[mmHg]$	Difference in resting heart rate (95% CI) $[bps]$
Females			
Smoking *Yes vs. no*	3.63 (2.32 ; 4.94)	2.54 (1.69 ; 3.38)	2.27 (1.47 ; 3.07)
Alcohol use *Yes vs. no*	-0.46 (-1.25 ; 0.33)	0.65 (0.06 ; 1.25)	0.03 (-0.55 ; 0.61)
BMI *1 kg/m^2 increase*	0.49 (0.44 ; 0.54)	0.43 (0.39 ; 0.46)	0.07 (0.04 ; 0.10)
Males			
Smoking *Yes vs. no*	0.19 (-0.55 ; 0.93)	-0.31 (-0.81 ; 0.18)	1.06 (0.57 ; 1.55)
Alcohol use *Yes vs. no*	2.02 (1.35 ; 2.69)	1.70 (1.19 ; 2.20)	1.11 (0.63 ; 1.58)
BMI *1 kg/m^2 increase*	0.58 (0.50 ; 0.66)	0.41 (0.36 ; 0.47)	0.13 (0.08 ; 0.17)

Fully adjusted estimates.

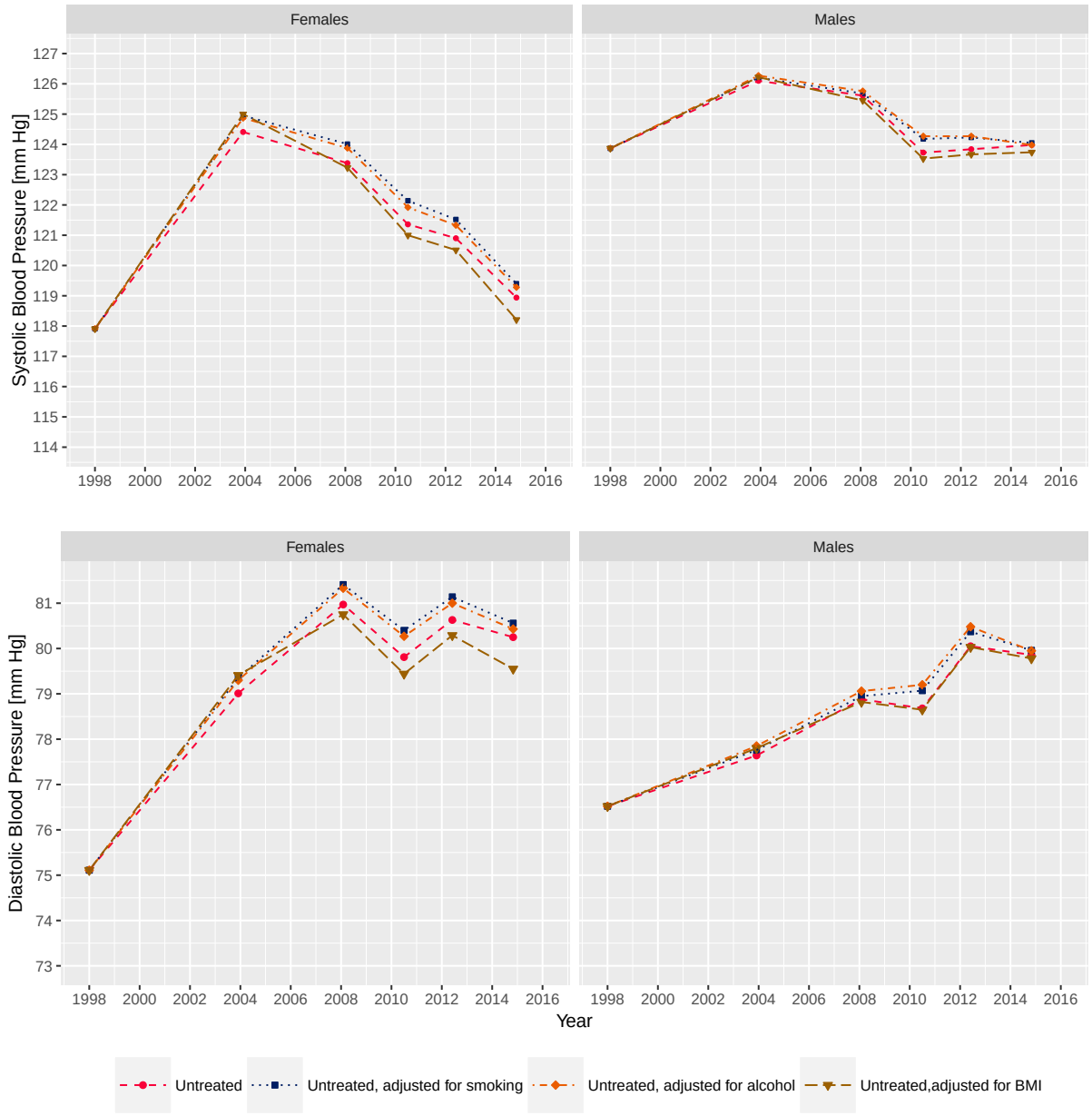
Among females, smoking and larger BMI were significantly associated with higher values of BP and RHR. Alcohol consumption predicted only higher DBP.

Among males, BMI and alcohol consumption were associated with higher values of both BP and RHR, while smoking predicted only higher RHR.

Considering these relationships together with the trends in their population distribution, I expected that adjusting for these risk factors would have produced more gradual increases in BP during the first part of the study period and a steeper decrease in the last decades. I also expected almost no contribution by the adjustment for alcohol consumption, given its relatively stable level across the whole period.

These hypotheses were confirmed, as shown in Figure 6.18.

Figure 6.18: Trends in untreated systolic and diastolic blood pressure in the South African adult population (15+ years). Adjustment for bio-behavioural risk factors.



Among women, both smoking and BMI produced appreciable changes in the trend line and, as expected, in opposite directions. In 2014-2015, adjusting for smoking produced an *increase* of the estimates by 0.66/0.45 $mmHg$ (SBP/DBP) compared to the untreated values. On the contrary, adjustment for BMI produced a *decrease* of the estimates by 1.09/1.01 $mmHg$[11].

Among men, the pattern of changes introduced by adjustment for BMI and smoking was similar, but smaller in magnitude.

In both genders, adjustment for alcohol consumption did not produce appreciable effects.

6.2.4 Urbanization and changes in education

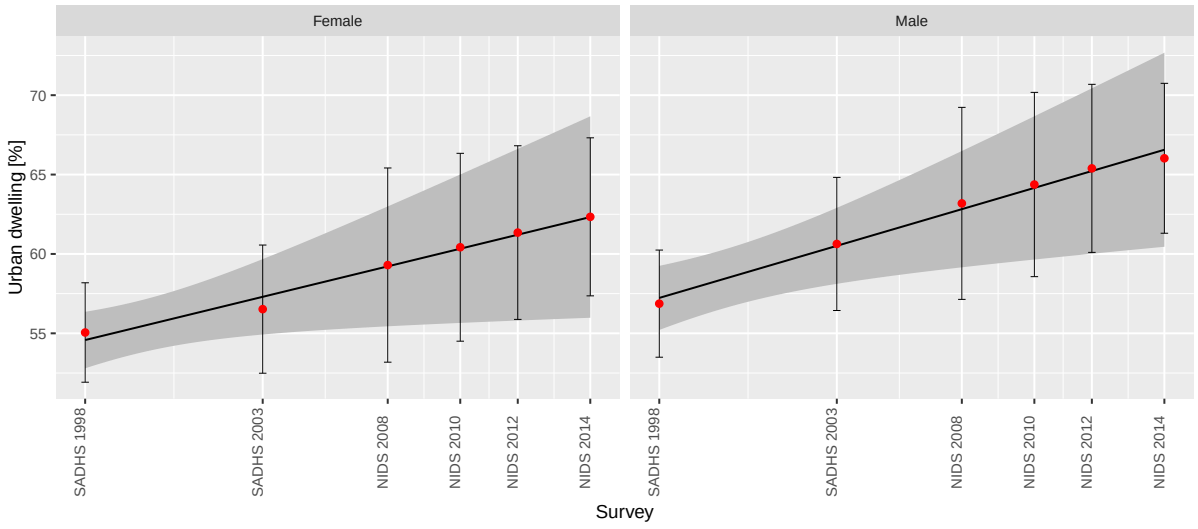
Urbanization and level of education are two further risk factors known to be associated with BP.

Population trends in urbanization and education are illustrated in Figures 6.19 and 6.20 and Table 6.10, and clearly indicate:

1. A rapid increase in the proportion of subjects living in urban rather than rural areas[12];
2. A consistent increase in the educational level of the population of both sexes, especially in the proportion of people with some tertiary education, which rose from a few percentage point is 1998 to about 20% in 2014-2015[13].

   The substantial improvement in formal education attainment and the reduction of the gender gap since 1994 (especially evident, in the latter, for tertiary education) is confirmed by the results of the 2001 census elaborated by Statistics South Africa.[704]

Figure 6.19: Prevalence of subjects living in urban areas in the South African adult population between 1998 and 2015. Cross-sectional estimates and linear trend, by gender.



The numerical values of the slope coefficients of the estimated linear trends are listed in Table 6.10.

Figure 6.20: Proportion of subjects per educational attainement class in the South African adult population between 1998 and 2015. Cross-sectional estimates and linear trend, by gender.

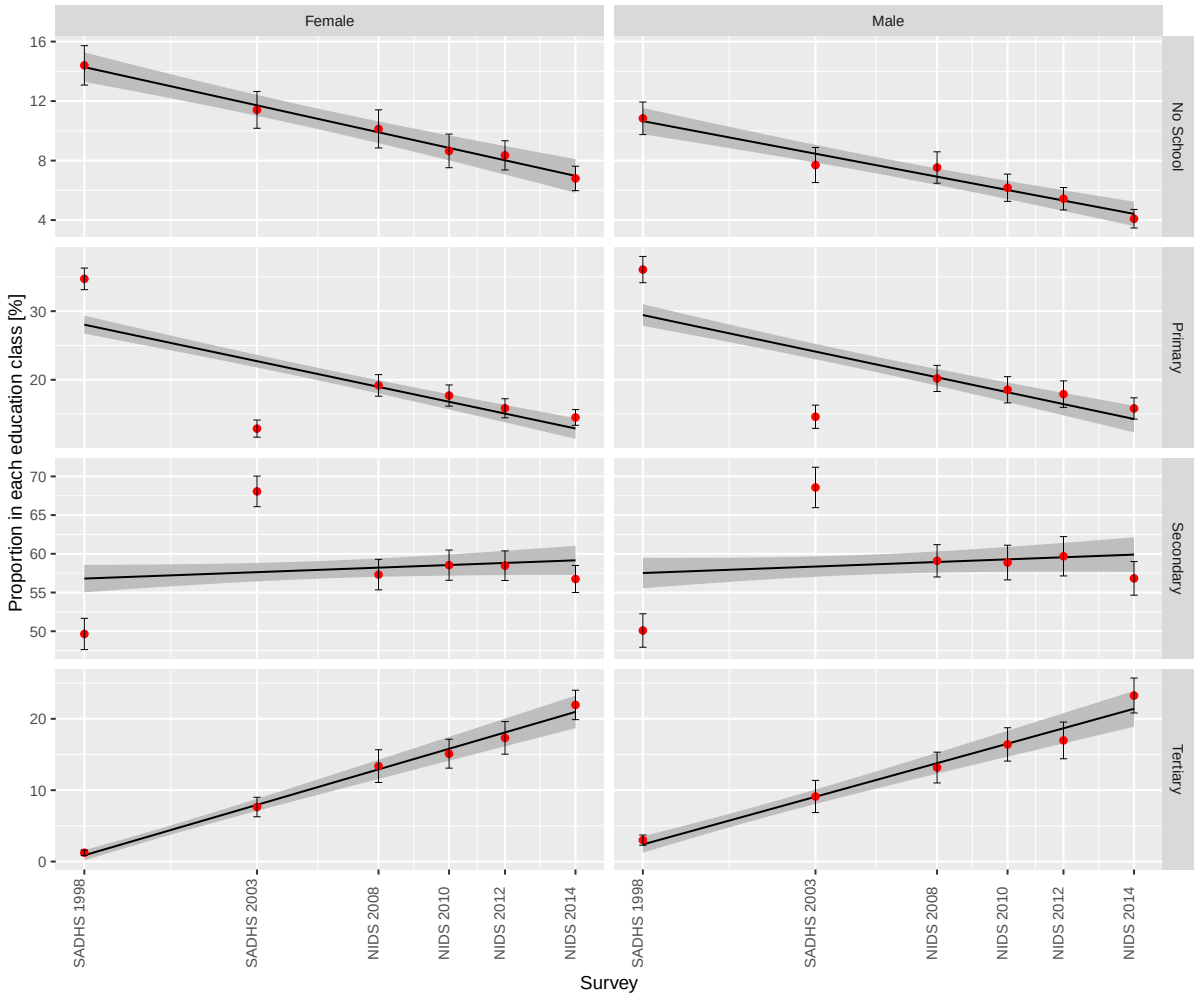


Table 6.10: Estimated linear trends in the proportion of urban dwellers and in each educational attainment class in the South African adult population (15+ years) between 1998 and 2015. Regression coefficients and 95% confidence intervals.

		Females		Males	
Variable	Unit	Slope coefficient	95% CI	Slope coefficient	95% CI
Urban dwelling	$\%/decade$	4.60	(0.56 ; 8.64)	5.54	(1.6 ; 9.49)
No school	$\%/decade$	-4.35	(-5.3 ; -3.39)	-3.70	(-4.48 ; -2.93)
Primary education	$\%/decade$	-8.99	(-10.27 ; -7.71)	-9.00	(-10.62 ; -7.38)
Secondary education	$\%/decade$	1.40	(-0.28 ; 3.08)	1.41	(-0.56 ; 3.38)
Tertiary education	$\%/decade$	11.93	(10.44 ; 13.42)	11.29	(9.52 ; 13.07)

The association between urban dwelling and educational attainment with blood pressure is illustrated by the regression coefficients in Table 6.11.

Table 6.11: Effect of urban vs. rural living and level of educational attainment on untreated blood pressure and resting heart rate in the South African adult population (15+ years). Estimates and 95% confidence intervals.

Factor	Difference in systolic BP (95% CI) $[mmHg]$	Difference in diastolic BP (95% CI) $[mmHg]$	Difference in resting heart rate (95% CI) $[bps]$
Females			
Urban *Yes vs. no*	0.93 (0.28 ; 1.58)	1.13 (0.72 ; 1.54)	-0.09 (-0.51 ; 0.34)
Primary	0.38 (-1.08 ; 1.84)	0.11 (-0.63 ; 0.85)	-0.69 (-1.22 ; -0.15)
Secondary	-3.27 (-4.88 ; -1.66)	-2.17 (-3.00 ; -1.33)	-2.03 (-2.59 ; -1.47)
Tertiary *vs. no education*	-7.12 (-8.83 ; -5.41)	-4.30 (-5.22 ; -3.38)	-3.66 (-4.47 ; -2.86)
Males			
Urban *Yes vs. no*	1.14 (0.42 ; 1.86)	1.00 (0.47 ; 1.53)	0.23 (-0.29 ; 0.75)
Primary	0.04 (-1.35 ; 1.43)	0.16 (-0.65 ; 0.98)	-0.62 (-1.40 ; 0.17)
Secondary	0.11 (-1.30 ; 1.52)	0.00 (-0.85 ; 0.85)	-1.57 (-2.32 ; -0.81)
Tertiary *vs. no education*	-0.71 (-2.54 ; 1.11)	0.07 (-1.09 ; 1.23)	-2.27 (-3.33 ; -1.21)

Fully adjusted estimates.

The results are again consistent with previous findings. Male urban dwellers had significantly higher BP (but not RHR) than people in rural areas, while among women the positive association was significant only for DBP.

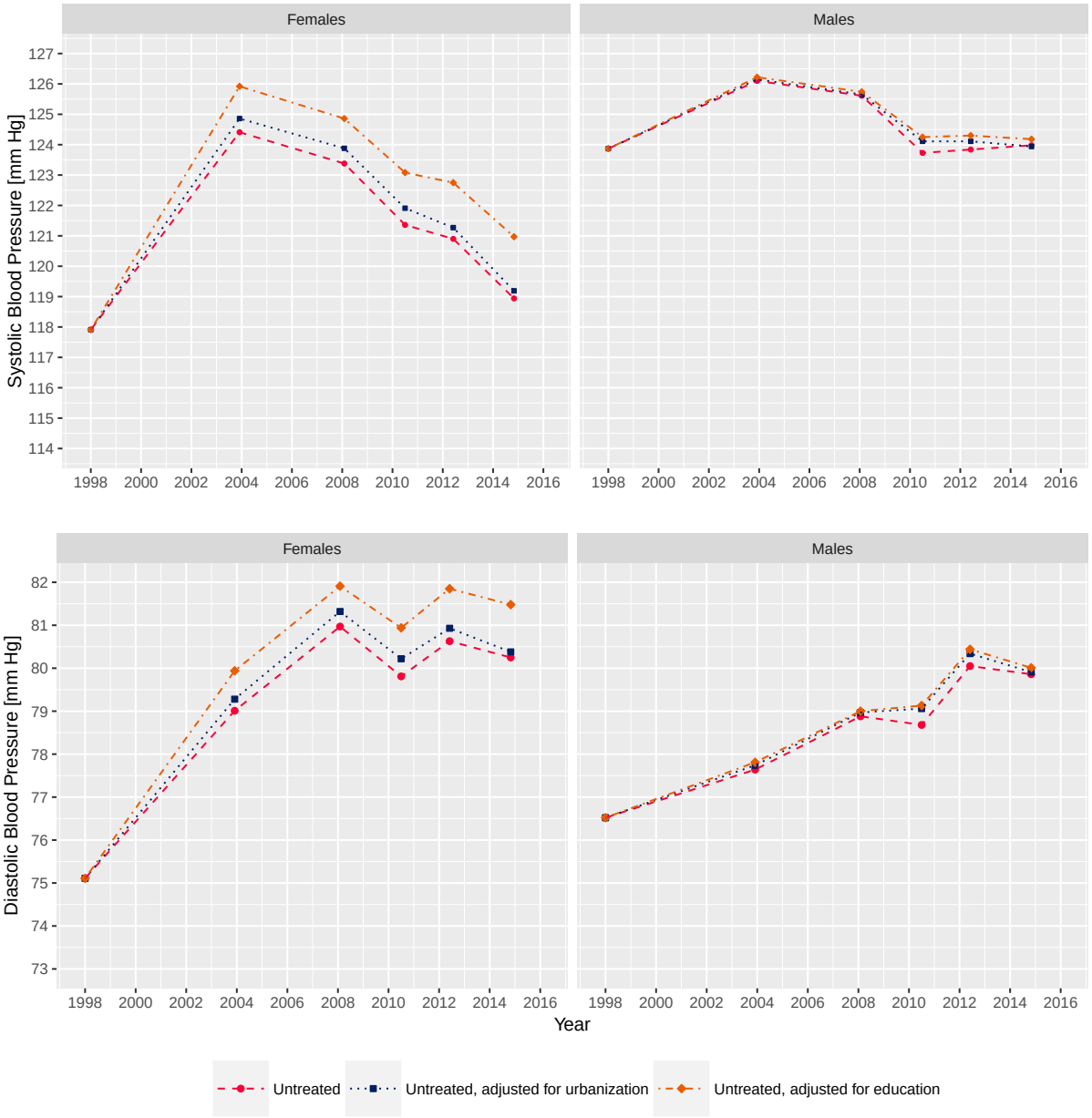
Higher levels of education were associated with *lower* levels of both SBP and DBP in women, while among men the association was in the opposite direction. In both genders, higher levels of education were associated with lower RHR.

It is worth noticing that the estimates in Table 6.11 refer to multivariate models which include adjustment for all other risk factors considered in our analyses. This means that the protective effect of education on elevated blood pressure present among women must be considered the *net* effect of education on BP after adjustment for smoking, alcohol and BMI, which a vast literature has identified as the main bio-behavioural mediators of the association between SES and BP (see Chapter 2). A recent cross-sectional analysis of the first wave of the NIDS — which included also a measure of physical exercise among the possible mediators of the

effect of education on BP — reached the same conclusion that the observed protective effect of education on elevated BP cannot be explained by differences in the distribution by education of the most commonly considered biological and behavioural risk factors.[19]

The effect of the inclusion of education and urban vs. rural living on the trends of untreated BP is shown Figure 6.21.

Figure 6.21: Trends in untreated systolic and diastolic blood pressure in the South African adult population (15+ years). Adjustment for urbanization and educational attainment.



Adjustment for urbanization produced negligible changes in both genders. Adjustment for

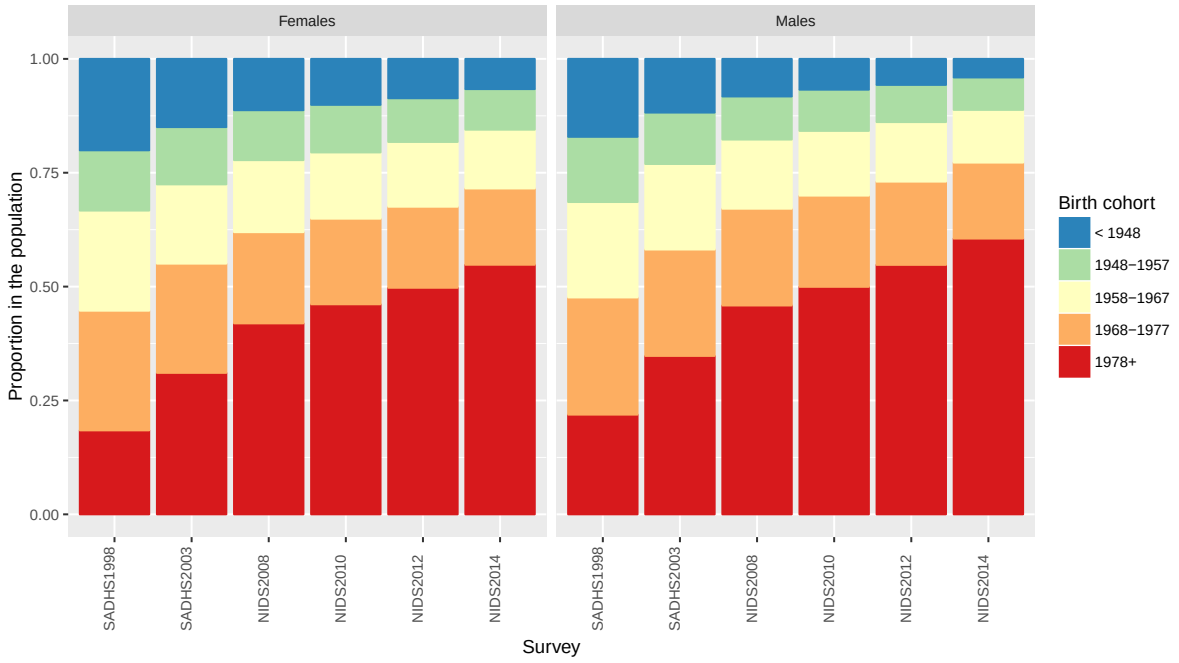
education produced relatively large changes among women, in the expected direction„ with the adjusted values consistently higher than the base estimates.

Effects among men were very small in magnitude.

6.2.5 Cohort effects

Due to the natural population dynamics, the birth cohort composition of the population changed largely during the study period, as shown in Figure 6.22.

Figure 6.22: Estimated birth cohort composition of the South African adult population (15+ years) between 1998 and 2015.



The estimated effects of belonging to each of these different birth cohorts — potentially representative of prenatal and lifecourse cumulative effects — on the average BP and RHR are shown in Table 6.12.

Table 6.12: Cohort effects on untreated blood pressure and resting heart rate in the South African adult population (15+ years). Estimates and 95% confidence intervals.

Factor	Difference in systolic BP (95% CI) $[mmHg]$	Difference in diastolic BP (95% CI) $[mmHg]$	Difference in resting heart rate (95% CI) $[bps]$
Females			
< 1948	4.09 (0.76 ; 7.42)	-1.54 (-3.74 ; 0.65)	-1.46 (-3.34 ; 0.42)
1948 - 1957	4.26 (2.05 ; 6.47)	0.73 (-0.81 ; 2.27)	-1.62 (-3.01 ; -0.23)
1958 -1967	2.84 (1.18 ; 4.50)	0.79 (-0.44 ; 2.02)	-1.70 (-2.83 ; -0.56)
1968 - 1977	0.44 (-0.68 ; 1.56)	0.34 (-0.47 ; 1.16)	-1.02 (-1.79 ; -0.26)
vs. 1977+			
Males			
< 1948	2.48 (-6.35 ; 1.38)	-3.39 (-5.87 ; -0.90)	0.24 (-2.07 ; 2.54)
1948 - 1957	1.23 (-3.89 ; 1.43)	-0.91 (-2.82 ; 0.99)	1.00 (-0.86 ; 2.85)
1958 -1967	1.78 (-3.68 ; 0.11)	-1.58 (-2.94 ; -0.22)	0.37 (-0.98 ; 1.73)
1968 - 1977	1.24 (-2.67 ; 0.18)	-0.45 (-1.51 ; 0.60)	0.07 (-0.88 ; 1.03)
vs. 1977+			

Fully adjusted estimates.

In both genders there was no evidence of cohort effects on RHR, with all regression coefficients small in magnitude and non statistically significant.

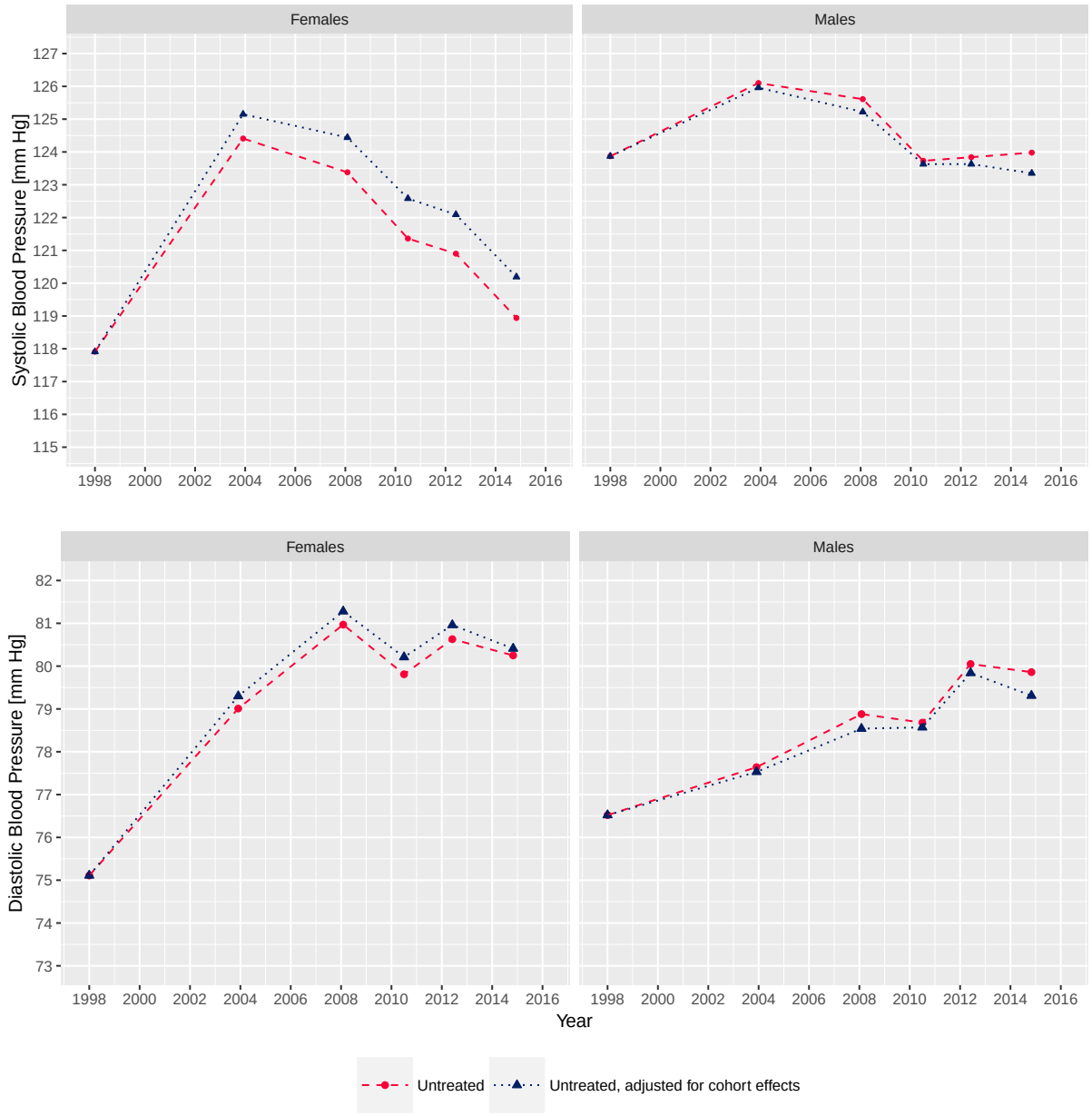
Conversely, cohort effects on BP were statistically significant for both men and women, in opposite directions. Generally, women in the earlier birth cohorts had higher BP values than in later cohorts. Among men, there was no difference in systolic BP but lower mean diastolic BP among the earlier birth cohorts.

Adjusting BP trends to take into account these effects produced the results shown in Figure 6.23.

Among women, adjusting for cohort effects produced a steeper increase of BP in the first part of the study period and a more gradual decrease after 2003. In substantive terms, this suggest that part of the observed decrease in the last decade is due to the decreasing prevalence of individuals in the earlier birth cohorts, who had higher mean BP compared to the later ones.

Given the different cohort effects among men, the diminishing presence of the earlier birth cohort could partly explain the increase in DBP, but not the decrease in SBP.

Figure 6.23: Trends in systolic and diastolic blood pressure in the South African adult population (15+ years). Adjustment for cohort effects.



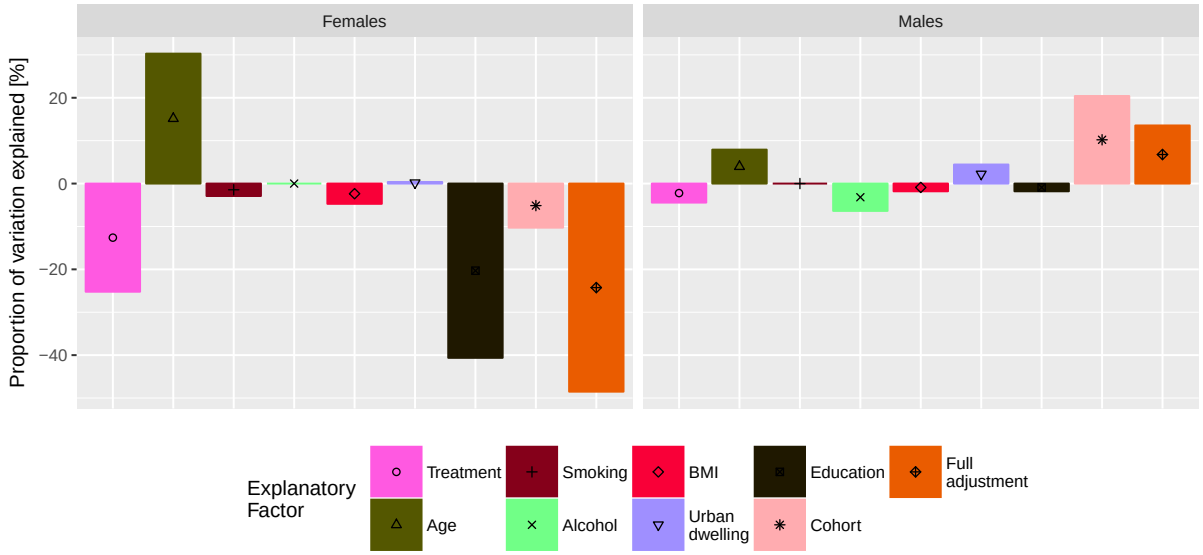
6.2.6 Relative contribution of different factors and unexplained changes

Figures 6.24 to 6.28 summarise the results of the analyses presented in the previous sections, and compare graphically the individual contribution of each risk factor to the observed vari-

ation in mean SBP and DBP during the study period. Because of the likely different determinants, periods of increase and decrease in the observed mean SBP/DBP are analysed separately[14].

The bars in the figures represent the proportion of variation of SBP/DBP during the period of interest which is explained by the relevant risk factor, calculated as one minus the ratio between the variance of the trend adjusted for the risk factor and the variance of the base trend[15]. Positive values indicate that the variance of the adjusted trend is smaller than the variance of the base trend, and the risk factor is thus 'explaining' part of the observed variations. Negative values, on the contrary, indicate that the variance of the adjusted trend is larger than the variance of the base trend, and the risk factor is thus 'masking' larger variations that would have been observed if no changes in its distribution had happened during the period.

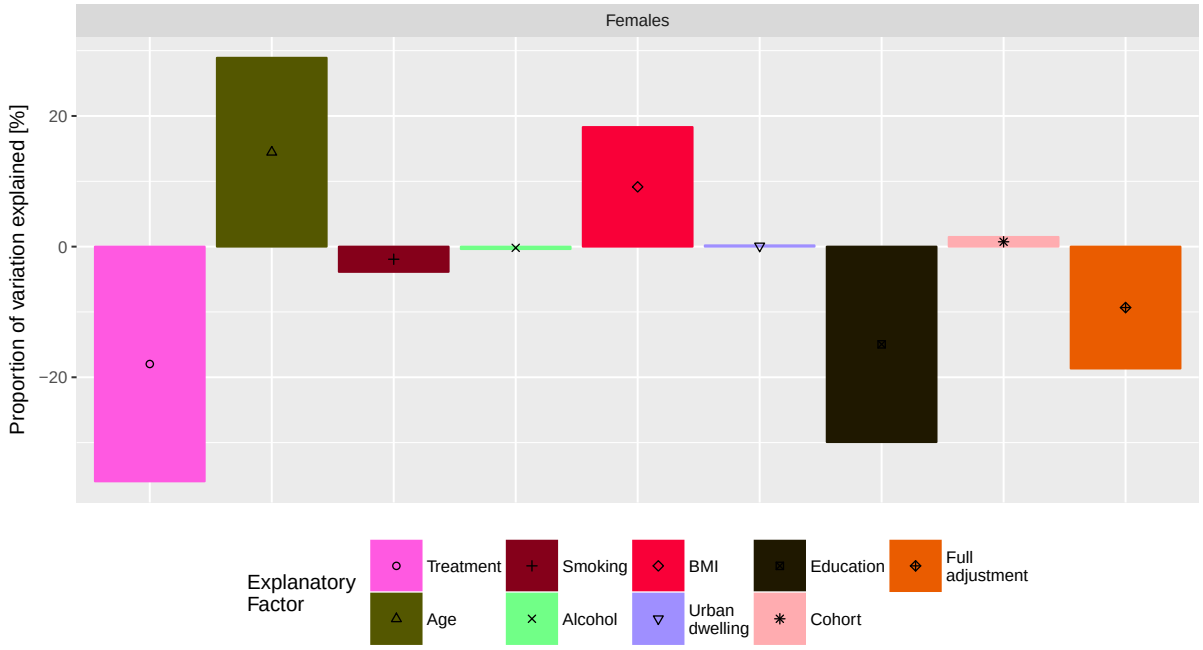
Figure 6.24: Estimated contributions of explanatory variables to changes in mean blood pressure in the South African adult population (15+ years). **SBP increase between 1998 and 2003/2004, both genders.**



Details on calculation of the proportion of variation explained are provided in the text.

The increased diffusion of antihypertensive treatment was, overall, the largest and consistent contributor to the observed decreases of BP, in both genders, as shown in Figures 6.27 and 6.28. The figures also suggest that the increase in educational attainment and, to a lesser extent, cohort effects also played an explanatory role, but only among women. On the contrary, adjustment for the ageing of the population and, especially, for the rapid increase in the average BMI produced further deviations of the trend line form the ideal horizontal line representative of no variation.

Figure 6.25: Estimated contributions of explanatory variables to changes in mean blood pressure in the South African adult population (15+ years). **DBP increase between 1998 and 2008, females**.



Details on calculation of the proportion of variation explained are provided in the text.

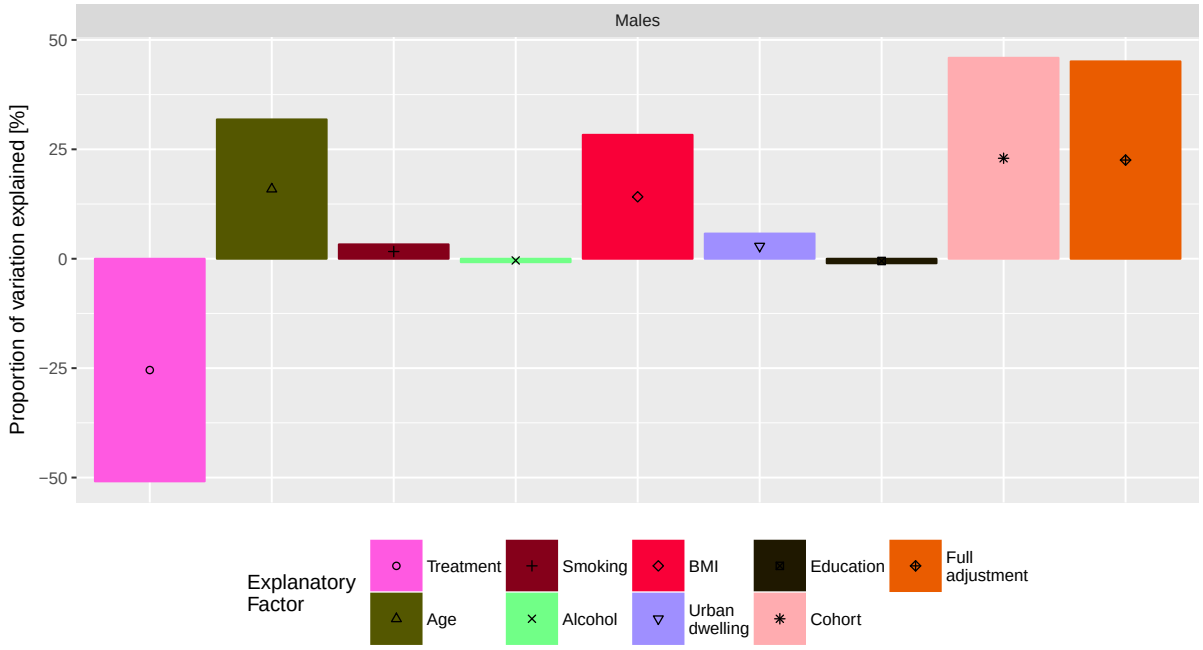
The major explanatory factors for the increasing part of the observed trends in the mean BP of the South African population (6.24, 6.25 and 6.26) were age, BMI and (only for men) cohort effects. Treatment effects — as expected, given the consistent increase in their diffusion over the whole study period — played an opposite role, and adjustment for them produced an increase in BP variations.

The effect of the simultaneous adjustment for all considered risk factors on the observed variability of BP is also shown in Figures 6.24 to 6.28 (*Full adjustment*). With the exception of the increase in DBP among males, where the combined effect of all risk factors accounted for about 50% of the observed variation, in all other cases the proportion of variation explained was either modest or even negative, meaning that changes in the distribution of the risk factors considered in our analyses was 'masking' variation for other reasons.

The combined effect of the simultaneous adjustment for all considered risk factors on the BP trends is shown by Figure 6.29.

Among women, beyond the already discussed effect of antihypertensive treatment, further adjustment for the combination of all other factors produced slightly steeper increases of the untreated BP in the last part of the study period and slightly steeper decreases after 2003.

Figure 6.26: Estimated contributions of explanatory variables to changes in mean blood pressure in the South African adult population (15+ years). **DBP increase between 1998 and 2014/15, males**.

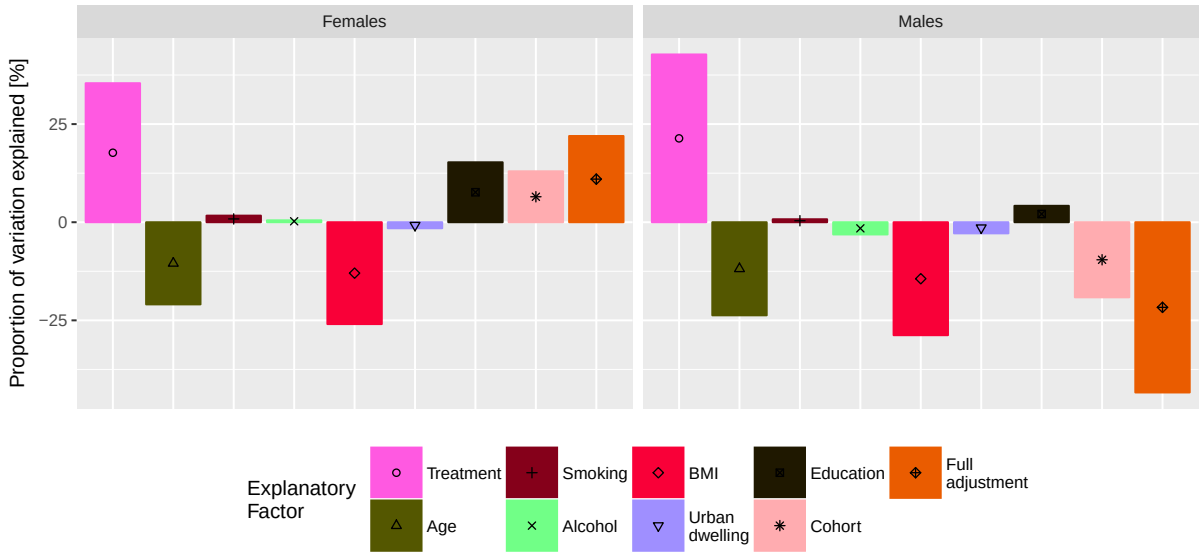


Details on calculation of the proportion of variation explained are provided in the text.

Substantively, this means that the trends in the untreated BP are not explained by the combined changes in the distribution of the risk factors. On the contrary, keeping constant the distribution of the risk factors during the study period would have produced more pronounced changes in BP over time.

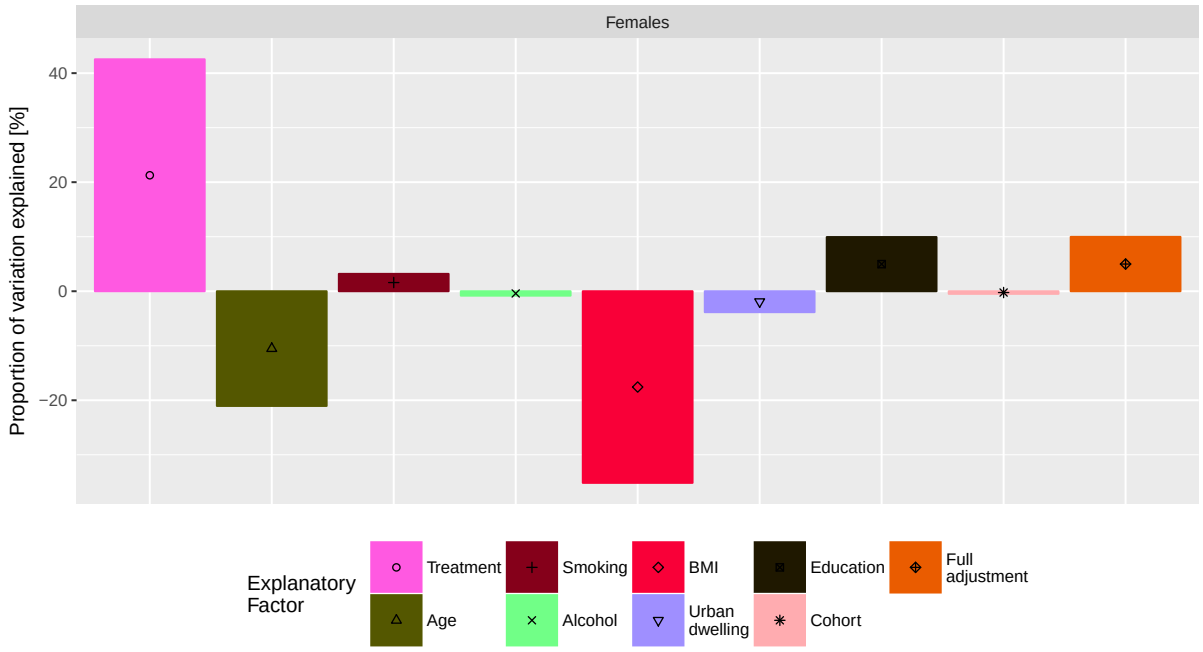
Among men, the same observation applies for SBP, while the more gradual increase in DBP shown in the figure suggests that its rising trend is partly due of changes in the distribution of the risk factors above.

Figure 6.27: Estimated contributions of explanatory variables to changes in mean blood pressure in the South African adult population (15+ years). **SBP decrease between 2003/2004 and 2014/2015, both genders**.



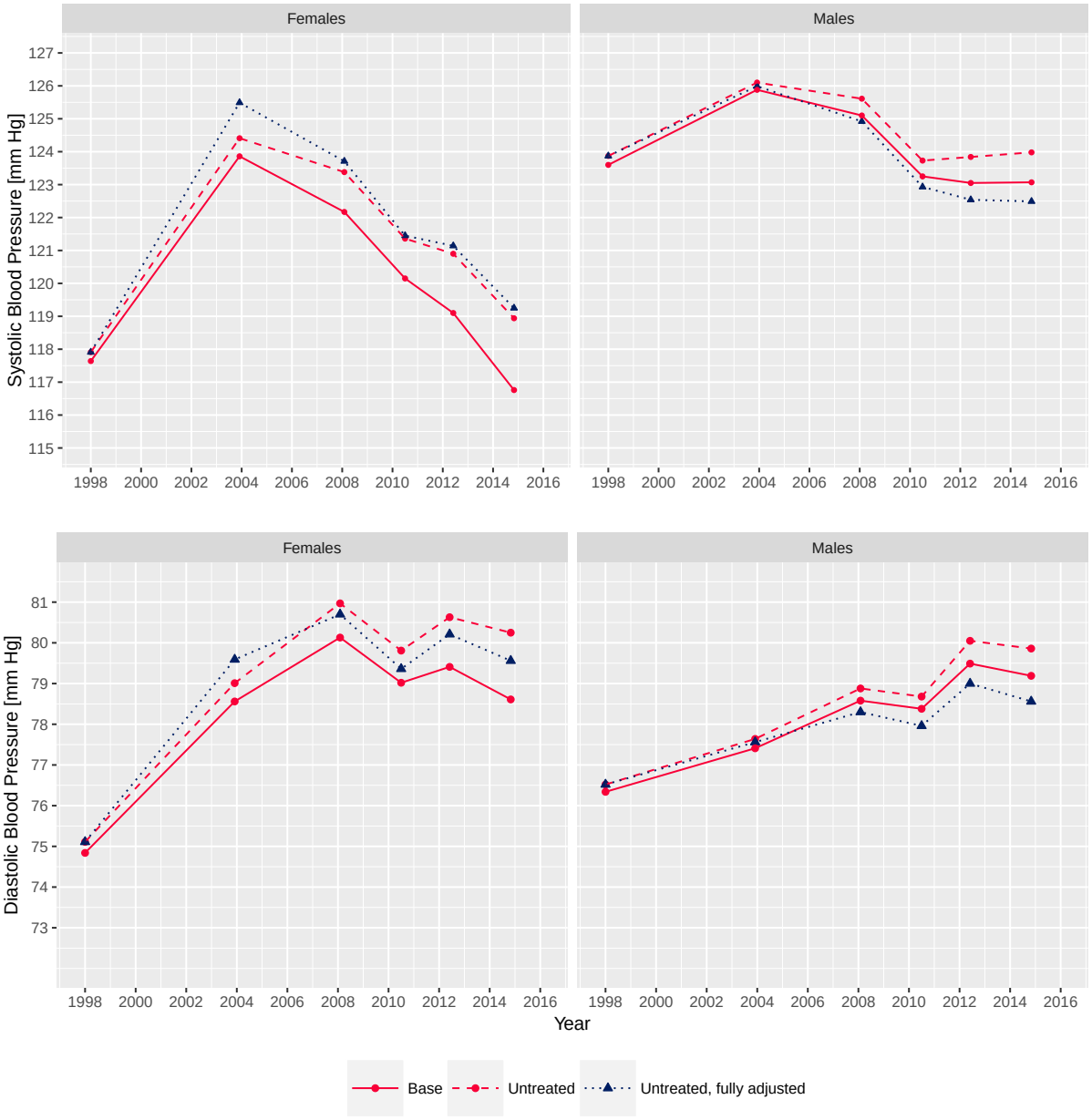
Details on calculation of the proportion of variation explained are provided in the text.

Figure 6.28: Estimated contributions of explanatory variables to changes in mean blood pressure in the South African adult population (15+ years). **DBP decrease between 2008 and 2014/2015, females**.



Details on calculation of the proportion of variation explained are provided in the text.

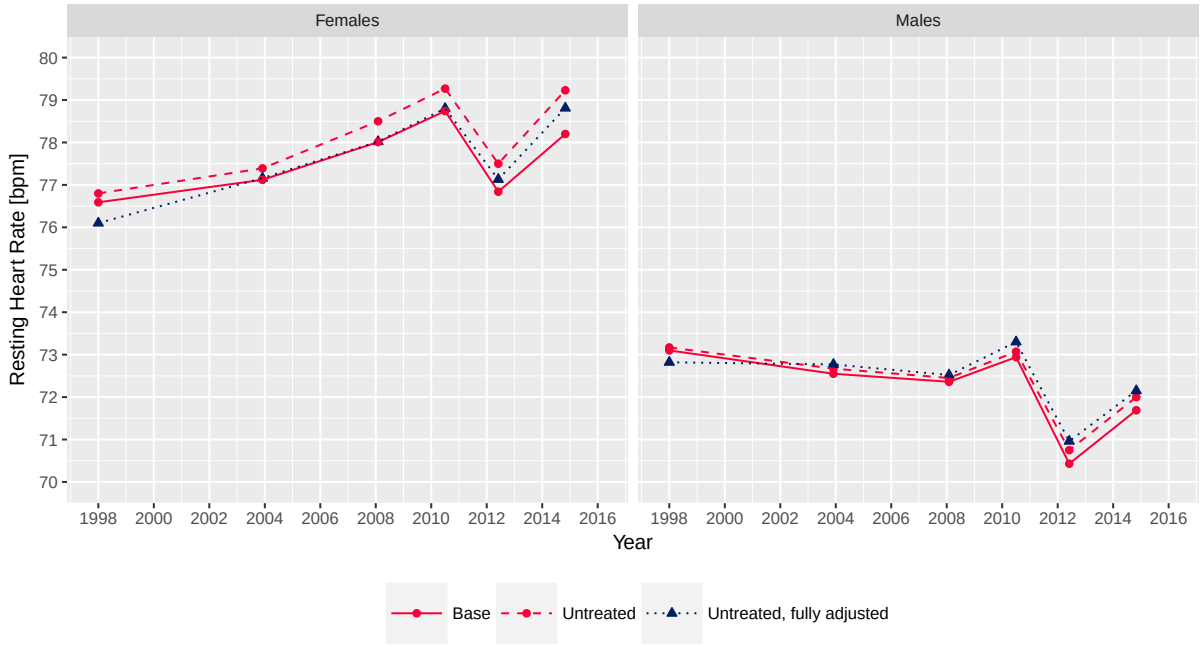
Figure 6.29: Trends in systolic and diastolic blood pressure in the South African adult population (15+ years). Full adjustment.



6.2.7 A note on heart rate and its variations

Figure 6.30 compares the base RHR trends with those adjusted for treatments effects that the joint effect of all other risk factors above.

Figure 6.30: Trends in resting heart rate in the South African adult population (15+ years). Full adjustment.



Excluding the effect of treatment produced a slight increase of the mean RHR in all periods, and further adjustment produced an opposite effect. The resulting fully-adjusted trends that would have been observed in absence of treatment and in the hypothesis of no change of the distribution of all risk factors since 1998 do not differ appreciably from the observed one.

Among women, both unadjusted and adjusted trends were upward for most of the study period, with some evidence of reversal in the last years. Among men, conversely, the trends were decreasing. In all periods, mean RHR was higher in women than in men. The result is consistent with the epidemiological literature (see for example the analyses by [25] on a large representative sample of the US population) and partly explained with differences in the mean heart size, which is typically smaller in females than males of the same age[16].

In both genders, changes were modest and difficult to associate with the much more evident changes in BP trends. The most relevant finding, other than the opposed trend among men and women, is the relative insensitivity to adjustment for the various risk factors.

6.3 Group-specific trends

Figures 6.31 to 6.34 compare age- and season-adjusted BP trends in sub-populations defined by age category, race[17], education and urban vs. rural place of residence. Each graph shows both the actual trends and the hypothetical trend that would have been observed in the absence of treatment.

Besides the obvious observation of an increasing overall level of BP with increasing age, Figure 6.31 shows how the effect of treatment in explaining the observed trends, negligible in the youngest age groups, became substantial among subjects 55 years and older. In particular, the graphs suggest that, in the absence of treatment, almost no decrease in SBP would have been observed in that group. Considerations are similar for DBP.

Comparisons between racial groups across genders and SBP/DBP suggest that Whites have seen a much steeper decrease of SBP in the last decade than the other groups, and also a decrease in DBP opposite to the increase observed in the other groups. The greater discrepancies between observed and untreated BP despite lower untreated values might suggest a greater access to pharmacological treatment by members of this group. This is coherent with the fact that the average SES of the White population group is much higher that the SES of Black and Coloured groups.

These observations must be viewed cautiously, because of the relatively small size of the White sample, the low response rates, and also because the mean age of the White group is higher and statistical adjustment for age might not have completely offset the discrepancies. However, the consideration found some support in Figure 6.33, which shows BP trends disaggregated by level of education, another important indicator of SES. The graphs, in fact, suggest again that the group with the highest SES (highest level of education here) is the group that is showing a more rapid decrease in its mean SBP and, in countertendency to the average increasing trend, members of this group are also experiencing a reduction in their DBP.

Figure 6.34 confirms the common finding in most population studies in sSA that BP is higher among urban dwellers. More interestingly, it also suggests that the discrepancies between the two settings are decreasing. This result matches similar findings regarding BMI, where the rural population of South Africa (which has still an average BMI lower that its urban counterpart) is quickly 'catching up', plausibly because the rapid diffusion of 'urban' risk factors in rural areas.[482, 705]

Figure 6.31: Trends in systolic and diastolic blood pressure in the South African adult population (15+ years), per **age group**.

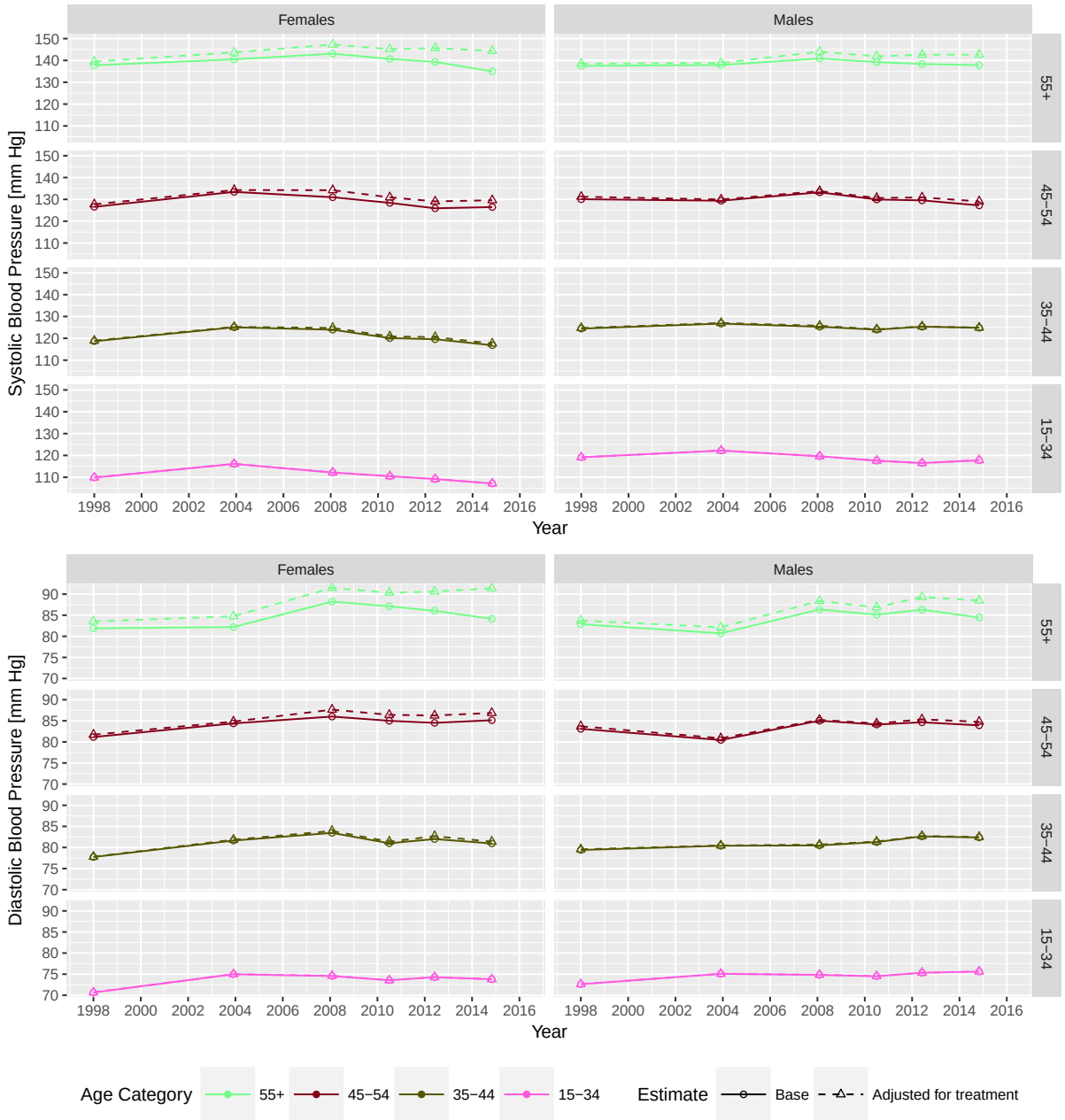


Figure 6.32: Age-adjusted trends in systolic and diastolic blood pressure in the South African adult population (15+ years), by **race**.

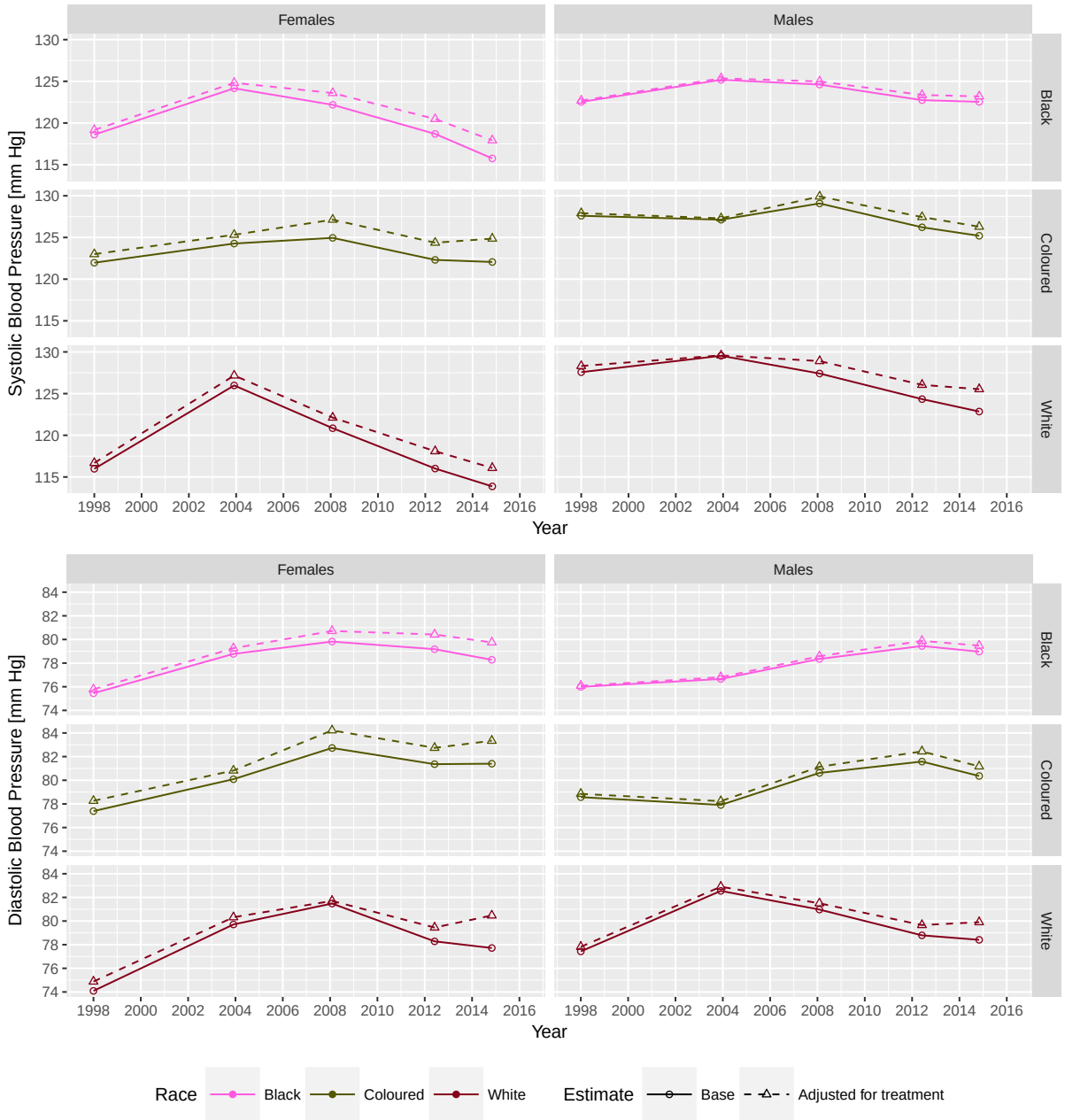


Figure 6.33: Age-adjusted trends in systolic and diastolic blood pressure in the South African adult population (15+ years), per **level of education**.

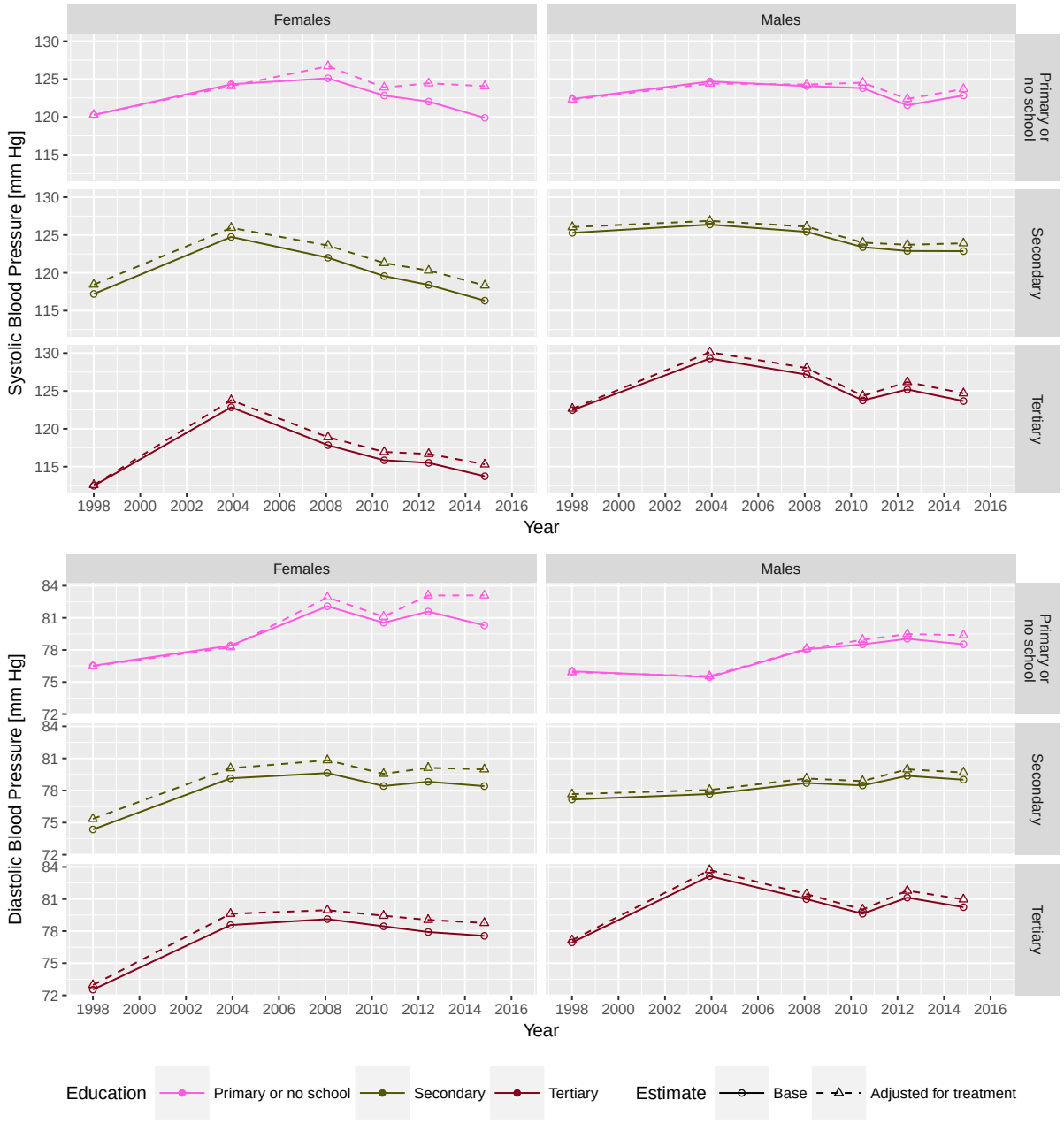
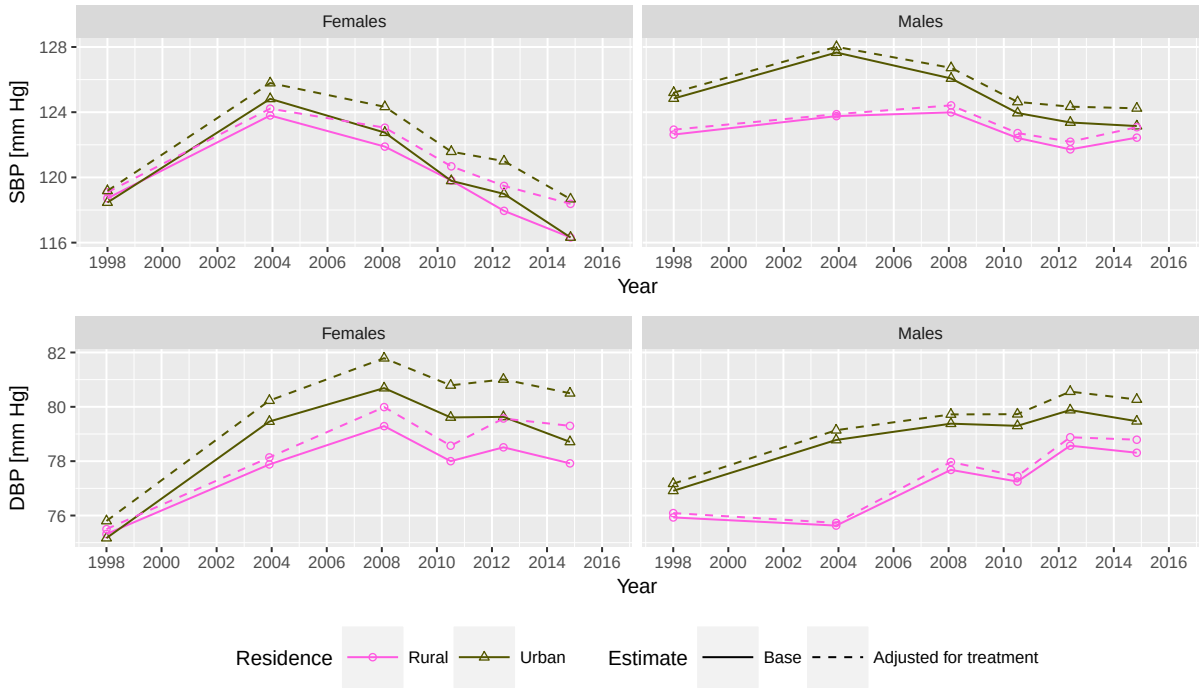


Figure 6.34: Trends in systolic and diastolic blood pressure in the South African adult population (15+ years), per **urban vs. rural residence**.



Overall, the results presented above suggest that the decreasing trend observed in the mean SBP of the South African adult population after 2003/2004 is the result of a generalised decrease in all groups defined by age, racial ascription, education and place of residence. The figures certainly indicate differences in the rate of decrease — and the comparison between the actual trends and the trends that would have been observed in the absence of treatment might suggest partly different determinants — but some decrease seems to have happened in all groups.

On the contrary, the bottom parts of Figures 6.31 to 6.34 show that trends in DBP are less consistent across the sub-populations defined by the characteristics listed above, especially among males. In particular, they suggest that males of higher socioeconomic status (as indicated by tertiary education and white racial ascription[18]) experienced a reduction in the mean DBP in the last decade, opposite to the increases experienced by the other groups. However, these considerations should be taken cautiously, because of the severe under-representation of Whites and subjects of high SES in the NIDS sample (see Section 4.1 in Chapter 4).

Notes

[1]This is not true for the precision of the estimates, which differed depending on the number of readings and the estimation methods, albeit only moderately.

[2]Mean rates of change were calculated as the slope of the regression line with point estimates of BP in each survey as outcome and the median period of data collection as predictor. The confidence intervals represent the uncertainty in the value of the slope due to the uncertainty of the outcomes. They were calculate by simulation. That is, the estimation of the regression slope was repeated 1000 times, with the outcome (mean BP) randomly chosen on each iteration from a normal distribution with mean and standard deviation given by the point estimates and their standard errors in each survey. The point estimates and 95% CI were then calculated as quantiles of the empirical distribution of the slope across replications.

[3]This possibility is also supported by the unusual magnitude of the PP in the SANHNES sample, because PP is known to be directly associated with the magnitude of the white coat effect.[225]

[4]Michael Brown, Director of Operation of the NIDS. Personal communication, 5 May, 2015.

[5]Relaxing the normality assumption produced a significant decrease in the information indices (BIC and AIC) compared to the normal models, and estimates of the skewness parameters different from zero at the 5% significance level. These facts indicate that the distribution of both SBP and DBP are different from a normal distribution beyond sampling variability. However, the small magnitude of the departures supports the use, in the remaining parts of this thesis, of estimates obtained assuming a normal distribution of the latent variables coupled with a robust estimator. The estimated coefficients of the skewed-normal model are shown in Appendix J.

[6]The number of subjects affected is obtained by multiplying the prevalence for the total population 15+ years in the same period from the ASSA 2008 model, assumed to be correct.

[7]Or totally, in the extreme case of an adjusted trend approximately horizontal

[8]In simple regression models, the coefficients are biased downwards, but this is not ensured in multivariate analyses.

[9]For this risk factor and for the others examined in the following sections, the relevant predictors were centred at their value in 1998. Therefore, the estimates can be interpreted as the trends that would have been observed on the hypothesis of no change of the relevant factor from the 1998 distribution. All other factors were centred at their mean in each cross-section.

[10]Linear trends were estimated by pooling data from all surveys, taking into account the complex sampling scheme of each of them and using the sampling weights recalibrated as per Section 3.3.2.13 in Chapter 3. The estimation of the confidence bands neglects the non-independence of the four cross-sections extracted from the NIDS due to the partial overlap of the samples, which might have resulted in a slight underestimation of their width. Given the exploratory nature of these estimates and the fact that the point estimates are not affected, the consequences of this omission are not relevant for our aims. Calculations were done using the function *svyglm* from the R package *Survey* [675].

[11]Trends in waist circumference over the study period and their effect on the estimates of BP were also estimated. Waist Circumference increased by an average 5.17 $cm/decade$ (95% CI: 4.55 to 5.79) among women and by 2.05 $cm/decade$ (1.23 to 2.88) among males. The effects on BP were very similar to those of increasing BMI and and are not reported. Including both variables in the fully-adjusted models created some problem of collinearity

given the strict correlation, and was thus avoided.

[12] The almost perfect linear growth is partly artefactual. The proportion of population living in urban areas was among the reference data used for the re-calibration of the sampling weights, and the benchmark data were the population totals published by the World Bank.[380] Not all totals were actually observed, and some of them were estimated, plausibly with linear approximation, and this could explain the almost perfect fit of the trend line. A consistent growing trend was, however, present even when the estimation was carried out with the original sampling weights, as shown in Figure 4.6 in Chapter 4.

[13] Some minor discrepancies in the point estimates for the education categories are likely to be the result of differences in the classification scheme used by the different surveys to record educational achievements. This might have led to some inaccurate attributions of the educational status of some subjects.

[14]For SBP the reversal in the slope of the observed trend adjusted for artifactual differences (base trend) occurred in 2003/2004 in both genders. For DBP the reversal occurred in 2008 for females and never for males. See Figure 6.29.

[15] If :

BP_i^b = mean blood pressure (either SBP or DBP) at time point i from the base estimates;

BP_i^a = mean blood pressure at time point i from the estimates adjusted for factor x;

$\bar{BP}^b$ = mean blood pressure over the period, calculated from the base estimates;

$\bar{BP}^a$ = mean blood pressure over the period, calculated from the estimates adjusted for factor x;

the proportion p_x of variance explained by factor x is calculated as:

$$p_x = 1 - \frac{\sum_i (BP_i^a - \bar{BP}^a)^2/n}{\sum_i (BP_i^b - \bar{BP}^b)^2/n}$$

where the sums are extended to the n time points in the relevant period.

[16]The female heart, being on average smaller than that of males and pumping less blood with each beat, needs to beat on average at a faster rate to match the larger male heart's output.

[17]Trends per race were only estimated in the Black, Coloured and White groups, because the small sample size did not make it possible to obtain reliable estimates for the Asian group

[18]See p. 95 for considerations regarding racial ascription as indicator of socioeconomic status.

Chapter 7

Season, blood pressure and socioeconomic status

This sections present the results of a sub-study that examined in greater detail than in the previous sections seasonal variations in BP in the South African population[1].

In particular, the study examined differences not only across sub-populations defined by age, but also by indicators of socioeconomic status, namely education, household income per capita and residence in formal vs. informal settlements. It also analysed some implications of seasonal effects for cardiovascular risk and levels of control of blood pressure among hypertensive subjects in treatment.

The analyses in this chapter are based on a subset of the data used for the analyses presented in the previous chapter, namely the first three waves of the NIDS[2]. The exclusion of the SADHS datasets is motivated by (1) The availability in the NIDS (but not in the SADHS) of reliable data on household income, which allowed for a more detailed analysis of the interaction between season and SES in determining BP; and (2) by the longitudinal nature of the NIDS, which allowed for a better control of time-invariant confounders.

7.1 Introduction

A large number of studies have consistently observed winter peaks and summer troughs in BP values, in clinical,[171–174] general[175–177] and special populations such as children[178] and pregnant women[179, 180].

The study of seasonal variation of BP in various settings is of substantial clinical and public health interest, not least because such variation mirrors seasonal variations in cardiovascular morbidity and mortality. The evidence of this relationship is especially strong for some pathologies directly associated with hypertension, such as haemorrhagic stroke, whose incidence is higher in winter than in summer.[176, 706] The size or amplitude of the seasonal effect (measured as the difference between the winter peak and summer trough of the population averaged annual cycle) varies across populations and studies. Average effects across 24 adult population surveys in 15 countries have been calculated in a recent meta-analysis by Marti-Soler et al. [181]. The results confirm the existence of a clear seasonal pattern in BP, with higher values consistently recorded in winter and lower values in summer.

In the northern hemisphere, the magnitude of the pooled effect was 2.93 $mmHg$ and 1.32 $mmHg$ respectively for SBP and DBP. In the southern hemisphere, the values were 3.44 $mmHg$ and 0.86 $mmHg$. A previous joint analysis of the SBP data collected in 25 populations during the MONICA Project, found a slight lower pooled effect of 2.01 $mmHg$ (95% Bayesian posterior interval: 1.05 to 3.08 $mmHg$).[167] Studies which reported separate estimates for age categories have also shown consistently that the seasonal effect tends to increase with age.[171, 174, 177, 182, 183] Gender differences have also been repeatedly observed, with varying patterns by population, clinical status and age, but generally showing a slightly higher seasonal effect in men.[174, 176, 177]

The causal mechanisms underlying these variations remain unclear, but substantial evidence points to the seasonal variation of outdoor temperature as the main driver of the seasonal variability of BP, possibly accompanied by an independent effect of the varying number of daylight hours.[185, 186, 707]

However, while the overall evidence of seasonal variations in BP and the major causative role of temperature is strong and widely acknowledged, substantial uncertainty remains about the size of the effect in different parts of the world, especially in low and middle-income countries. In particular, data from sub-Saharan Africa are lacking. Neither of the cited reviews includes studies from this large region with a population of 960 million and covering 47 countries. To our knowledge, only a few small-scale cross-sectional studies of this region have addressed the subject of seasonal variation in BP[708, 709], while others have addressed it only indirectly, through its effects on hypertension related morbidity and mortality[710–713].

Also poorly understood are the factors that, beyond climatic differences, explain the large differences observed in seasonal effect across and within populations. Among other biological, environmental and behavioural factors, various authors have suggested that individual socioeconomic status may play a sizeable role as an effect modifier of the relationship between season and blood pressure. In particular, it has been suggested that individuals with low socioeconomic status may have both restricted access to adequate means of protection from low temperatures (e.g. sufficient heating at home and adequate clothing) and working conditions which require more time outdoors than subjects with higher socioeconomic status. This would translate into a higher exposure to winter-summer temperature differences and, consequently, higher variations in blood pressure.[177, 187] Despite the plausibility of this hypothesis and some evidence that the availability of indoor temperature control attenuates the difference between winter and summer blood pressure[182, 714], to our knowledge a direct estimation of the modifying effect of individual socioeconomic status on the magnitude of the seasonal effect on blood pressure is lacking.

This study aimed to narrow these knowledge gaps by estimating the magnitude of the seasonal variation in blood pressure in the adult population of South Africa — a middle-income country characterized by high level of socioeconomic inequality — and by testing the hypothesis of an inverse relationship between seasonal effect and socioeconomic status as measured by education and household income. The study used data from the first three waves of the National Income Dynamics Study (NIDS), a panel survey of individuals randomly selected in 2008 and successively re-contacted in 2010-11 and 2012.

7.2 Methods

7.2.1 Participants

The NIDS is a nationally representative panel survey of 28 255 South Africa's residents.[80] The first wave of the survey was conducted in 2008 and the target population was private households and residents in workers' hostels, convents and monasteries. A two-stage cluster sample design was used to randomly select about 7 300 households across 400 primary sampling units (areas), stratified by district council (a second level administrative division of South Africa's territory into 53 areas). Trained fieldworkers were instructed to interview and collect anthropometric data on all available subjects belonging to the selected households. The same individuals were re-contacted in the two subsequent waves, in 2010-2011 and 2012, and administered the same questionnaire. The household level response rate for the first wave was 69% and the individual response rate within households was 93%. The individual attrition rate was 19% between wave 1 and wave 2, and 16% between wave 2 and wave 3.

The NIDS has been granted ethical approval by the Commerce Faculty Ethics Committee at the University of Cape Town, and its datasets are publicly available for research purposes.[715] All participants received an information sheet with their blood pressure readings, and those with elevated readings were advised of the risks and of the need to seek medical attention. Out of the 18 526 participating individuals who were 15 years old or over at the time of the first interview, this study considers the 11 440 individuals successfully re-interviewed both in the second and the third wave. Sampling weights were adjusted to take into account unequal response rates across population strata.[528] Wave 1 dataset version 5.2, Wave 2 version 2.2, and Wave 3 version 1.2 were used in the analyses.

7.2.2 Measures

Sociodemographic variables

Age in years was categorised into 6 groups. Education was measured in years of completed schooling and categorized as Primary, Secondary, Tertiary and None. Place of residence was categorised as urban/rural according to Statistics South Africa's Census 2001.[716] Urban areas were further classified as formal or informal[3]. Household monthly income per capita was calculated as the summation of a wide array of sources, as detailed by Argent [717].

Blood pressure

Sitting blood pressure was measured twice by trained fieldworkers in the left arm after a 5

minute rest period, using an automated blood pressure monitor (Omron M7 BP, multi-size cuff, factory calibrated). Measurements were retained if SBP was between 80 and 240 $mmHg$, DBP $\geq$ 30 $mmHg$, and their difference $\geq$ 15 $mmHg$.

Time

Year, date and month of blood pressure measurement were recorded, and used to create a new variable, day of measurement, representing the number of days since the first of January regardless of the year.

Other measurements

Duplicate measures of weight and height were recorded, with a third measure taken if their difference was greater than 0.5 kg or 0.5 cm respectively. Excluding measures with implausible values (height $<$ 60 cm or $>$ 230 cm, weight $<$ 30 kg or $>$ 250 kg), the average of the available readings was used to calculate BMI in kg/m^2. BMI was then categorised in four classes according to the World Health Organization's cut-off points.

Current smoking, use of antihypertensives and past diagnosis of hypertension by a health professional were self-reported by subjects in response to direct questions.

Controlled hypertension was defined as having a past diagnosis of hypertension but readings of blood pressure within the normal range (SBP $<$ 140 $mmHg$ and DBP $<$ 90 $mmHg$).

7.2.3 Statistical analyses

Sample characteristics were described as the median and interquartile range for continuous variables and frequency for categorical measures.

The association between SBP and DBP with day of measurement were estimated simultaneously using a multilevel linear structural equation model, with measurements at each wave nested within subjects. Considering that the relationships between many of the variables involved in the model have been shown to differ among males and females, models were fit separately by gender.

To minimise bias due to measurement error, systolic and diastolic blood pressure were introduced in the models as latent variables, with the observed multiple readings as indicators.[582, 718]

Seasonal effect for individual i at wave j was modelled using a trigonometric spline[664] in

the form:

$$S_{i,j} = \sum_{k=1}^{6}(\alpha_k \cdot age_{i,j,k} \cdot \sin\frac{2\pi \cdot day_{i,j}}{365}) + (\beta_k \cdot age_{i,j,k} \cdot \cos\frac{2\pi \cdot day_{i,j}}{365})$$

Where α_k and β_k are coefficients estimated in the model, $age_{i,j,k}$ are the dummy variables used to code the six age classes, and $day_{i,j}$ represents the day of measurement for individual i at wave j, relative to the first of January.

Trigonometric splines are frequently used in epidemiological studies to model seasonal patterns, and they have been previously applied in the study of seasonal variations in blood pressure.[167, 175, 181] Our specific implementation, including interaction terms for each age category, allowed for the estimation of the magnitude of the seasonal effect independently for each age category. Overall effects were obtained as weighted averages of the age-specific estimates, with weights reproducing the age structure of the South African population in 2011.

Categorical age, urban or rural place of residence, categorical BMI and smoking status were introduced in the model as occasion-dependent covariates.

Adjustment for effect of antihypertensive treatment was done adding a constant (10 $mmHg$ for SBP and 5 $mmHg$ for DBP) to the observed readings of treated individuals.[240] The sensitivity of the estimates to the exact values of the constants was assessed by replicating the model estimation with different values for the constants. The estimation was also replicated excluding treated individuals from the dataset.

Random intercepts were used to take into account differences in average blood pressure values across individuals, while the coefficients α_k and β_k, which defined the seasonal effects and all other coefficients were considered as fixed.

Missing data in the outcome variables were addressed by estimating model coefficients by full-information maximum likelihood, which provides asymptotically unbiased estimates under the hypothesis that data are missed at random, conditional on the observed covariates.

Effect modification by socioeconomic status was assessed by repeating the analyses in the subpopulations defined by level of education, tertile of household monthly income per capita, and formal vs. informal housing type (restricted to urban settlements). The existence of a statistically significant monotonic trend in the seasonal effect across increasing levels of education and income was tested by simulation, adapting the procedure proposed by Soderberg and Hennet [719].

For illustrative purposes, a simulated effect attributable to seasonal variations in blood pressure was modelled by calculating the absolute difference of 10-year risk of developing any major atherosclerotic cardiovascular disease when the values of blood pressure vary according

to the estimated seasonal effect. The simulations were conducted for different subpopulations using the Framingham's study general cardiovascular risk equations.[720] Significance level for hypothesis testing was set at $\alpha = 0.05$. Statistical calculations were carried out using R Statistical Environment v. 3.0.2 (R core Team, Vienna) and Mplus v. 7.3 (Muthén & Muthén, Los Angeles).

Further details on modelling assumptions are provided in Appendix K.

7.3 Results

Unweighted sample characteristics at wave 1 are described in Table 7.1.

Table 7.1: Sample descriptive statistics at baseline.

Variable	n	Median/percentage	IQR/frequency	Range
Men	11 440	39.12%	4 475	
Age [$years$]	11 439	35	[22 ; 50]	[15 ; 101]
Education	11 431			
None		13.86%	1 584	
Primary (1 - 7 years)		25.35%	2 898	
Secondary (8 - 13 years)		53.57%	6 124	
Tertiary ($>$ 13 years)		7.22%	825	
Place of residence	11 440			
Urban formal		6.5%	738	
Urban informal		12.9%	1 780	
Rural formal		10.1%	1 152	
Rural informal		44.9%	5 140	
Household monthly income p.c. [ZAR]	11 440	499	[277 ; 987]	[0 ; 62343]
Household monthly income p.c. tertile	11 440			
I ($\leq$ 302 ZAR)		27.9%	3 189	
II ($>$ 302 ZAR; $\leq$ 626 ZAR)		32.0%	3 658	
II ($>$ 626 ZAR)		40.1%	4 593	
Current smoking	10 391	18.2%	1 896	
BMI category	9 474			
Underweight		6.71%	631	
Normal weight		46.75%	4 395	
Overweight		21.98%	2 066	
Obese		24.56%	2 309	
Systolic Blood Pressure [$mmHg$]	9 445	121.5	[110 ; 137]	[80 ; 240]
Diastolic Blood Pressure [$mmHg$]	9 566	79.5	[71 ; 89.5]	[40 ; 136.5]
Blood pressure classification†	8 225			
Normal		42.32%	3 481	
Pre-hypertension		33.00%	2 714	
Stage I hypertension		15.34%	1 262	
Stage II hypertension		9.34%	768	
Antihypertensive treatment	11 137	12.00%	1 336	

n = number of non-missing values; IQR= interquartile range; ZAR = South African Rands; p.c = per capita.
† According to the *Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*[2], excluding subjects in treatment.

Population strata of higher socioeconomic status were under-represented relative to the South

African population, owing to their low response rate in the first wave and their higher attrition than the other population groups.

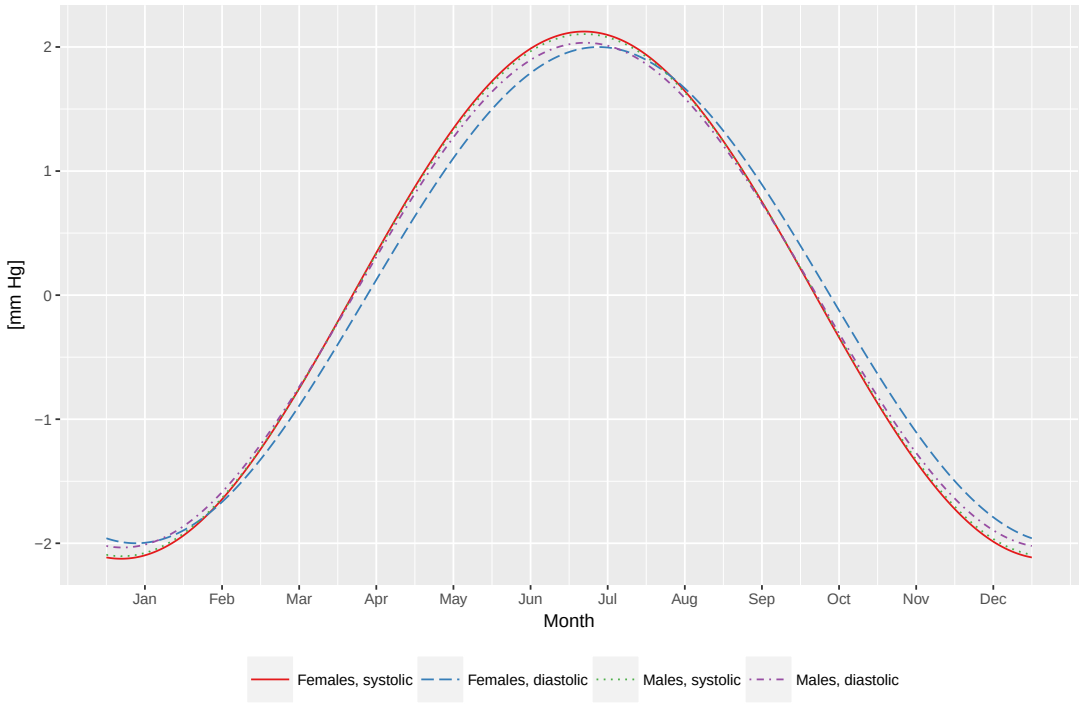
Current use of antihypertensives was reported by 6% of men and 16% of women. Using SBP $\geq$ 140 $mmHg$ and/or DBP $\geq$ 90 $mmHg$ as cut-offs, 20.0% of untreated male participants and 21.7% of untreated female participants would be classified as hypertensive. Additional Tables in Appendix K provide sample descriptive statistics at wave 2 and 3 and distribution of subjects by month of data collection.

7.3.1 Seasonal effects

In both genders, season had a statistically significant effect on SBP and DBP.

The magnitude of the overall seasonal effect on SBP was 4.25 $mmHg$ (95% CI: 3.18 to 5.31 $mmHg$) among females and 4.21 $mmHg$ (95% CI: 2.98 to 5.44 $mmHg$) among males. The effect of season on DBP was slightly lower in both genders: 4.00 $mmHg$ (95% CI: 3.21 to 4.78 $mmHg$) among females vs. 4.01 $mmHg$ (95% CI: 3.17 to 4.96 $mmHg$) among males.

Figure 7.1: Estimated seasonal variation of blood pressure in the South African population, by gender.

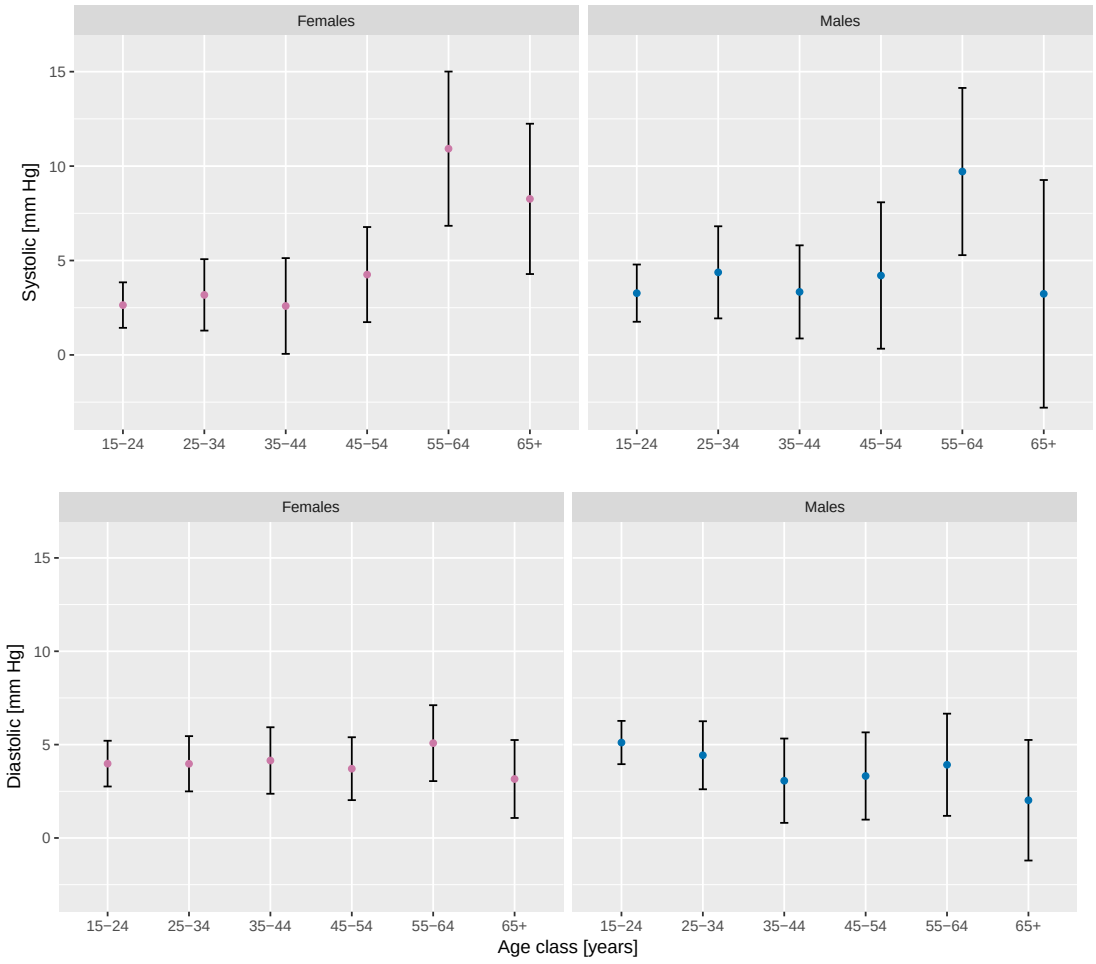


Values represents variations over the annual mean. Estimates are adjusted for age, urban or rural place of residence, BMI and smoking status.

As shown in Figure 7.1, the position of the overall seasonal peak (and, consequently, the position of the trough, constrained to be 6 months apart by the analytical form of the trigonometric spline) showed little variation between systolic and diastolic values and across genders. All peaks occurred in a 6 days range in the Southern hemisphere winter, during the second week of July, in most parts of South Africa the coldest period in the year [4]. The differences in the position of the peak were not statistically significant.

Age-specific magnitudes of seasonal effects are depicted in Figure 7.2. In both genders, seasonal effects on systolic blood pressure increased with age, reached a maximum in the 55-64 years age category, and then fell among the oldest participants (65 years and above). Age related differences in seasonal effect on diastolic blood pressure were much smaller, and none of them reached statistical significance.

Figure 7.2: Age-specific magnitude of seasonal effect on blood pressure, by gender. Estimates and 95% confidence intervals.

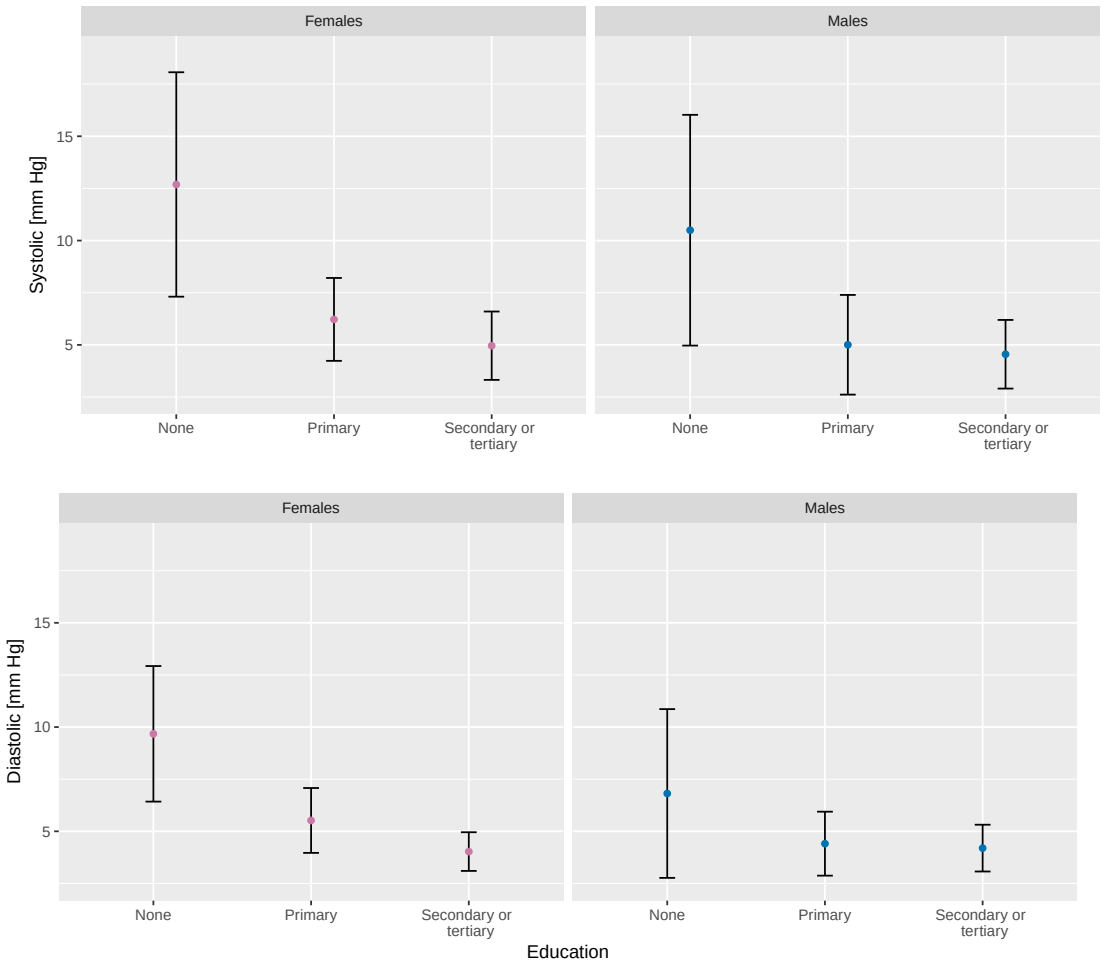


Estimates are adjusted for age, urban or rural place of residence, BMI and smoking status.

7.3.2 Seasonal effects and socioeconomic status

The magnitude of the age-standardised seasonal effect by socioeconomic status in selected subpopulations is depicted in Figures 7.3 and 7.4.

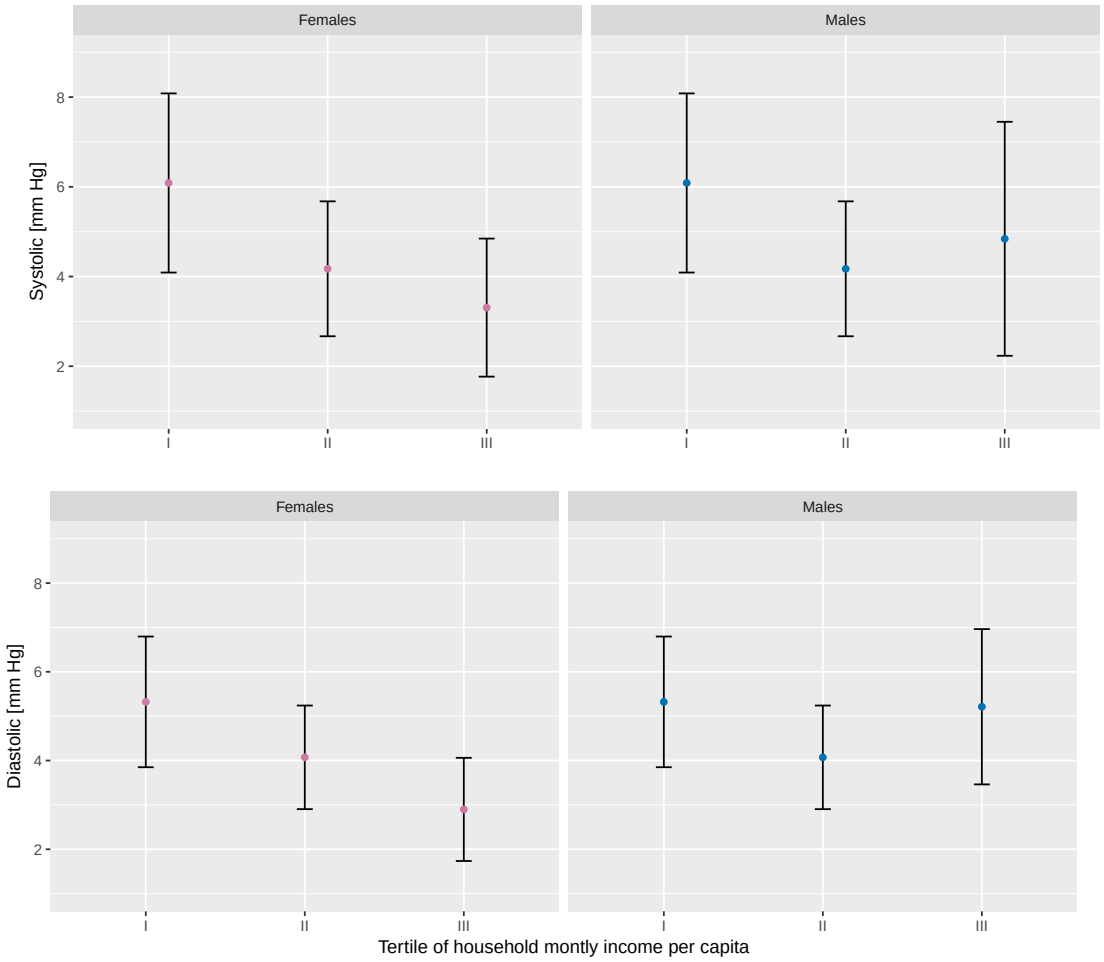
Figure 7.3: Magnitude of seasonal effect on blood pressure by education and gender. Estimates and 95% confidence intervals.



Estimates are adjusted for age, urban or rural place of residence, BMI and smoking status.

Among females, increasing education and household monthly income per capita were associated with a decreasing seasonal effect on both SBP and DBP. The average seasonal effect on SBP decreased by 7.7 $mmHg$ (from 12.7 $mmHg$ to 5.0 $mmHg$) going from no education to secondary education or above, while the effect on DBP decreased by 5.7 $mmHg$ (from 9.7 $mmHg$ to 4.0 $mmHg$). Differences in seasonal effects between the first and last income tertile were smaller than those for education, viz. 2.8 $mmHg$ (from 6.1 $mmHg$ to 3.3 $mmHg$) in SBP and 2.4 $mmHg$ (from 5.3 $mmHg$ to 2.9 $mmHg$) in DBP.

Figure 7.4: Magnitude of seasonal effect on blood pressure by household income per capita and gender. Estimates and 95% confidence intervals.



Estimates are adjusted for age, urban or rural place of residence, BMI and smoking status

Among males, the overall pattern of association between socioeconomic status indicators and seasonal effects was similar to that among females. Increasing education was associated with decreasing seasonal effect, with a reduction by 5.9 $mmHg$ (from 10.5 $mmHg$ to 4.6 $mmHg$) and 2.6 $mmHg$ (from 6.8 $mmHg$ to 4.2 $mmHg$) moving from the lowest to the highest education class, respectively for SBP and DBP. The lowest income tertile was also associated with a higher seasonal effect than higher income tertiles, but the relationship was not monotonic.

Table 7.2 shows the estimated values for the Kendall's correlation coefficients (and associated 95% confidence intervals) between seasonal effect and socioeconomic status indicators.

Among women, all estimates for the Kendall's correlation coefficients were negative and none of their 95% confidence intervals included 0, thus supporting the existence of a statistically

significant monotonic decreasing trend between socioeconomic status and seasonal effects on BP. Among men, the test for trend showed a statistically significant result only for the relationship between education and SBP.

Table 7.2: Kendall's tau correlation coefficients between seasonal effects and socioeconomic status indicators. Estimates and 95% confidence intervals.

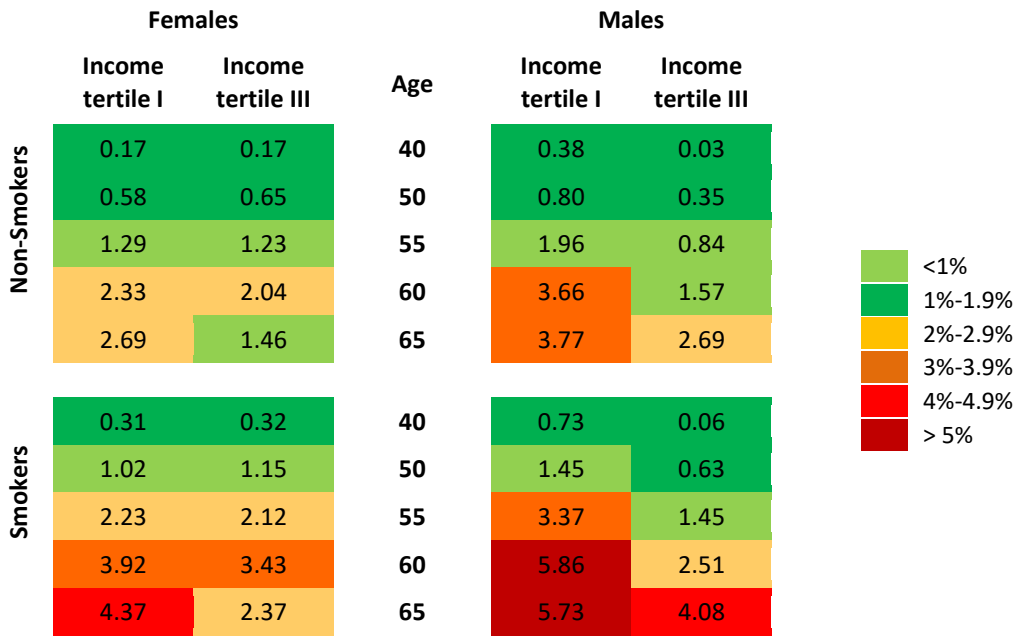
	Education class	Household income tertile
Females		
Systolic	**-1.00** (-1.00 ; -0.33)	**-1.00** (-1.00 ; -0.33)
Diastolic	**-1.00** (-1.00 ; -0.33)	**-1.00** (-1.00 ; -0.33)
Males		
Systolic	**-1.00** (-1.00 ; -0.33)	-0.33 (-1.00 ; 1.00)
Diastolic	-0.33 (-1.00 ; 1.00)	-0.33 (-1.00 ; 1.00)

Seasonal effects were higher among urban dwellers living in informal than formal settlements, both for SBP and DBP, and for men and women (see Appendix K). None of the differences reached statistical significance.

7.3.3 Projected impact on cardiovascular risk

The projected absolute difference in 10-year cumulative risk percent of developing any major atherosclerotic cardiovascular disease when the systolic blood pressure varies according to the estimated seasonal effect is summarised in Figure 7.5, for different subpopulations. The projected excess risk between winter and summer increased with age, and was higher among males, smokers, and subjects with low socioeconomic status (as indicated by low household income). Overall, the excess risk was negligible in the younger age groups, but became evident among elderly subjects, especially those with low socioeconomic status.

Figure 7.5: Simulated effect of seasonal variation in blood pressure on 10-year cumulative risk of developing any major atherosclerotic cardiovascular event.



The chart shows the absolute difference on 10-year risk of developing any major atherosclerotic cardiovascular event when the values of blood pressure vary according to the estimated seasonal effect, by gender, age, smoking status and income tertile.
Absolute risks are calculated as in D'Agostino et al. [720] BMI is kept constant at the population average, by gender and age category. Other risk factors not explicitly shown in the chart (diabetes and antihypertensive treatment) are considered to be absent.

7.3.4 Model fit and sensitivity analysis

All models used for the analyses had an excellent fit the data.

On repeating the analyses using different combinations of constants to adjust for antihypertensive treatment, none of the population estimates of seasonal effects changed more than 4.5%, thus supporting a relative insensitivity to the exact value of the constants. Constants were allowed to vary in the range 5 $mmHg$ to 15 $mmHg$ for DBP and 10 $mmHg$ to 20 $mmHg$ for SBP. These ranges approximately correspond to the 95% confidence intervals of the average effects of antihypertensive treatment estimated by Wu et al. [230] in their meta analysis of 165 clinical trials. As expected, omitting the correction produced a decrease of the estimated seasonal effect,[240] by 0.12/0.19 $mmHg$ (SBP/DBP) among females, and by 0.11/<0.01 $mmHg$ among males.

Excluding subjects on hypertensive treatment produced modest changes in the values of the

estimates, and did not affect the conclusions of the study.

Fit indices for the models estimated in the different subpopulations, and numerical results of the sensitivity analyses are available in Appendix K.

7.4 Discussion

In line with the literature referring to other geographical areas, the results of this study showed a clear seasonal pattern in the values of blood pressure in the South African adult population, with higher values recorded in winter months and lower values in summer. The magnitude of the seasonal effect on both systolic and diastolic blood pressure was almost identical across genders. In agreement with most of the studies, the seasonal effect was more pronounced for SBP.

The commonly observed positive relationship between magnitude of the seasonal effect and age has been confirmed in our study, as well as the finding of a greater age effect on systolic blood pressure than on diastolic blood pressure.[176, 183] In our population, the positive trend seems to be reversed in the eldest age category ($>$ 64 years). This result replicates the findings of a large cross-sectional study in China, which found that the average difference between winter and summer blood pressure increased with age up to about 70 years, and then showed a relative decrease.[182] In another study, a more detailed analysis of the seasonal effect among older individuals (hypertensive subjects 69 to 91 years old, divided into 5-year age groups), found a peak in the magnitude among the 70-75 years old, and a progressive downward trend in the subsequent age classes, suggesting that the relative reduction of the seasonal effect continues in older ages.[172]

The causal mechanism underlying this complex relationship between age and seasonal effect on blood pressure is unclear, and it is likely to reflect a combination of factors both biological and behavioural. Previous studies have shown a decrease of autonomic response to cold,[176] a lower ability to control deep body temperature,[721] and a reduction of the baroreflex sensitivity[722] with increasing age. These phenomena point to a reduced ability of older subjects to compensate for the increase in blood pressure caused by cold-induced peripheral vasoconstriction (an effect which itself does not seem to be impaired by age[723]). This physiological 'mismatch' may thus produce the positive relationship between age and seasonal effect. Increased arterial wall rigidity — which has been shown to be correlated with winter-summer differences in SBP and is strongly associated with age — could also be an important causal mediator of this relationship.[724] A tentative explanation of the relative decrease of winter-summer differences in the oldest age groups could be related to lower exposure to outdoor temperature by the oldest subjects because of reduced working activity and deteriorating health.

In our study, the magnitude of the seasonal effect in the population as a whole, was only slightly lower for diastolic than for systolic blood pressure. This result is in contrast with the findings of the systematic review by Marti-Soler and other large studies, which generally indicated an average seasonal effects on DBP substantially lower than the corresponding effect on SBP.[167, 176, 177] This discrepancy is not unexpected, given that the populations considered

in those studies were, on average, much older that the population analysed here. As previously observed, seasonal effects on SBP increase rapidly with age, while the same trend is less evident for DBP. Therefore, in older populations the differences between diastolic and systolic effects tend to be larger than those observed in younger samples. To test the validity of this hypothesis, seasonal effects were re-calculated modifying the age structure to approximately match the population studied by Su et al. [177][5]. As expected, the ratio between seasonal effects on systolic and diastolic blood pressure increased from 1.1:1 to 1.6:1, closer to the 2.5:1 ratio in their study and the 2:1 in the review by Marti-Soler et al.

Previous studies have observed that the negative relationship between outdoor temperature and blood pressure is mitigated in populations with good access to central heating at work and at home, thus suggesting socioeconomic status as a plausible effect modifier of the relationship between season and blood pressure.[182, 714] Our results support this hypothesis, providing evidence of an inverse relationship between magnitude of seasonal effect and education and household income, both commonly used indicators of socioeconomic status. The finding that seasonal effect is lower among urban dwellers living in formal settlements than those in informal settlements, lends some support to the hypothesis that housing conditions contribute to this effect.

The effect modification appears to be stronger in women than in men, and the reasons of this discrepancy warrant further investigation.

The findings of this study have implications for epidemiological, clinical and public health practice.

For epidemiological investigation, the magnitude of the seasonal effect strongly suggests that — in South Africa as in the rest of the world — studies involving the estimation of blood pressure and prevalence of hypertension should routinely take into account the period of data collection, especially when comparison with other studies is involved. Ignoring this phenomenon could bias the results, particularly if the period of data collection is restricted to a single season, as was the case of the third wave of the NIDS, where almost 50% of subjects were interviewed in winter between June and August, and none between January and March. In this case, for example, adjustment for seasonality produced a reduction of the prevalence of hypertension measured in this way among South African adults by 2 percentage points (30.9% to 28.9%) in males and 1.3 percentage points (36% to 34.7%) in females[6]. In absolute numbers, the restriction of the data collection to the winter season produced an overestimation of the number of hypertensive adults by almost 600 000, relative to the projected result were data collection spread across the seasons[7].

Taking the seasonal variation of blood pressure into account during routine clinical practice may improve the management of hypertensive (and pre-hypertensive) patients. The preva-

lence of controlled hypertension has been previously found to have a clear seasonal pattern, deteriorating in winter, which not surprisingly mirrors the fluctuations in blood pressure.[177] Overall, our data support the existence of this seasonal pattern, i.e. poorer control in winter than summer (see appendix K), suggesting that average current clinical practices are not sufficiently responsive to the seasonal modification of the patient's blood pressure levels. The last edition of the South African hypertension guidelines acknowledges the effects of temperature on blood pressure measurement, but makes no provision for modification of diagnostic criteria and treatment in relation to season.[232] The large seasonal variations observed especially in the older age groups suggest the need for seasonal modification of diagnostic and therapeutic clinical practice — not least because of the cited evidence of a direct correlation between winter increase of blood pressure and cardiovascular morbidity.

Finally, the seasonal variations in blood pressure translated into non-negligible differences by season in the projected 10-year risk of cardiovascular disease, especially in elderly subjects with low socioeconomic status where the excess risk (cumulative incidence) in winter compared to summer ranges from 2.6% (females, non-smokers) to 5.7% (males, smokers).

The simulations were performed mainly for illustrative purposes, and the winter increase in blood pressure may not have the same predictive meaning as long-term or chronic elevation. However, at population level the projection is consistent with the substantial evidence of higher number of deaths for cardiovascular diseases in colder months,[725] that recent studies suggest exceeds what can be explained by the phenomenon known as 'harvesting' or 'mortality displacement'[8].[726]

In our study, the pattern of association between estimated cardiovascular risk, age and socioeconomic status mimics previously observed pattern in mortality for cardiovascular diseases, where the winter-summer differences increased with age and with decreasing education.[727] These results further suggest that seasonal variations in blood pressure could contribute to the explanation of seasonal variations in cardiovascular mortality.

The greater seasonal effect observed among subjects with low socioeconomic status and living in informal settlements — which translates directly in increased winter-summer excess in cardiovascular risk — has public health implications. It suggest that improving people's housing conditions and ability to protect themselves from low winter temperatures may have a positive effect on hypertension prevalence and cardiovascular morbidity and mortality. This is especially true for older subjects, where seasonal effects and excess risk appear to be amplified.

7.4.1 Strengths

Strengths of the present study include the large sample with a broad age distribution, and the repeated measures design which allowed each subject to serve as his or her own control in the estimation of the differences in blood pressure due to seasonal effect. The latter aspect is likely to have produced less biased estimates than those obtained from cross-sectional studies, where the seasonal effect is estimated comparing measurements of blood pressure between different individuals, creating room for the confounding effect of inter-individual differences.

From the analytical point of view, the use of a random intercept model within the framework of structural equation modelling allowed for (1) a better control of the potential bias due to unrealistic assumptions of homogeneity across individuals; (2) a reduction of the effect of measurement error in blood pressure; and (3) an efficient treatment of missing data under the relatively weak assumption that they are missing at random conditional on the observed covariates. The use of a validated method of adjustment for antihypertensive treatment should also have contributed to bias reduction.

7.4.2 Limitations

Among possible confounding factors, this study did not take into account the variability of blood pressure measurement due to its circadian rhythm.[192] In absence of any specific reason suggesting a relationship between time of day of measurement and season, it is plausible that the omission of this factor produced a bias towards the null of the estimated seasonal effect, thus reinforcing our finding of a strong and statistically significant seasonal effect.

Indoor temperature during measurement has also been shown to affect blood pressure,[707] and was not recorded during the NIDS study. However, in a large scale population study where blood pressure measurements were taken at the respondents' homes and not in a controlled environment, it is plausible to assume a causal correlation between indoor temperature and season. In this case, indoor temperature acts more as a (partial) mediator of the observed seasonal effect than a confounder, and statistical adjustment for its effect would be questionable. Adjustment for indoor temperature in the MONICA datasets produced only a marginal change (towards the null, as expected) in the estimated seasonal effects.[167]

The analytical form chosen for the seasonal effect assumes a symmetric peak and trough 6 months apart, and does not allow for other possible seasonal patterns (e.g., a sharp increase in autumn and steady decline in spring and summer). However, the plausibility of this shape is well supported by the results of large studies which recovered the seasonal effect non-parametrically.[176, 177] Further, the irregular number of measurements in the different months, and especially the low number in December and January, made it inadvisable to use

excessively flexible forms for the seasonal effect.

Finally, while suboptimal response and greater attrition rates were observed in some social strata in the NIDS survey, this phenomenon does not automatically create selection bias, especially in analytical studies and when differences in observed characteristics between respondents and non-respondents are taken into account through appropriate adjustment of sampling weights.[728] However, we cannot exclude the possibility that unobserved differences between respondents and non-respondents might have biased the results of our study in an unpredictable way.

7.5 Conclusion

The present analysis found clear evidence of substantial seasonal variation in blood pressure. In both genders, seasonal variation was slightly larger for systolic than diastolic blood pressure. Seasonal effects in systolic (but not in diastolic) blood pressure were significantly greater among older participants. Seasonal effects were highest among subjects with low education, income or living in informal areas.

Our results indicate that seasonal variations in blood pressure have concrete implications and should be routinely taken into account both in epidemiological research and in clinical practice. From a public health perspective, our findings suggests that interventions to reduce older subjects' exposure to low temperatures may contribute to reduction of the winter peak in blood pressure observed in the South African population, and the associated increase in cardiovascular risk.

Notes

[1] The study has been published as a peer-reviewed article in the journal *Medicine®*: Cois, A., Ehrlich, R. (2015). Socioeconomic Status Modifies the Seasonal Effect on Blood Pressure: Findings From a National Panel Study. Medicine, 94(35), e1389.

[2]The data for the fourth wave of the NIDS were not available when this section was written. The dataset was made available only in May 2016.

[3]According to Statistics South Africa, an informal settlement is "*An unplanned settlement on land which has not been surveyed or proclaimed as residential, consisting mainly of informal dwellings (shacks)*".

[4]South Africa is situated between 22 °S and 35 °S, in the Southern Hemisphere's subtropical zone. Temperature excursions between summer and winter are moderated by the presence of the ocean on three sides of the country and the altitude of the interior plateau. Maximum temperatures in summer (mid-October to mid-February) are usually below 30 °C, and minimum temperatures in winter (May to July) above 5-6 degrees.[729]

[5]The study by Su et al. used different cut-offs to define age classes. To recreate a distribution compatible with the age categories used in our study, I hypothesised that the ages of the individual were distributed uniformly within each of the Su's classes.

[6]Adjustment for seasonality was done by randomly redistributing the period of data collection across the year, adjusting the individual values of blood pressure according to the average seasonal effect and recalculating the proportion of hypertensive subjects with the modified values of systolic and diastolic blood pressure.

[7]The estimation is based on the South African adult population as per Census 2011.[730]

[8]'Harvesting' is the phenomenon for which some factor (in this case cold weather) causes death among very frail people who are approaching the end of their life and would have died in any case in a short time.

Chapter 8

Discussion

From a *substantive* perspective, the main results of this study are:

1. The average SBP and DBP of the South African adult women have progressively decreased since 2003-2004, reversing the previous rising trend. Among men, the reversal only happened in average SBP, while average DBP continued rising, although at a lower pace than previously.

   In both genders, this pattern resulted in a reduction of the prevalence of uncontrolled hypertension between 2003-2004 and 2014-2015, by 8 percentage points among women, and by 4.5 percentage points among men.

2. This consistent and rapid decrease cannot be explained by changes in the age structure of the population, smoking or alcohol consumption habits, distribution of BMI or urbanization.

   The diffusion of antihypertensive treatment and, among women, the rapidly increasing education partly explain the recent trend. However, a substantial part of the observed decrease remains unexplained by the factors considered in our analyses.

3. Large seasonal variations on both SBP and DBP are present in the South African population, and their magnitude is greater among low-SES population strata.

4. Trends and their likely determinants differ across genders.

   For most of the study period women had a higher prevalence of uncontrolled hypertension than men, but the relationship has been reversed in the most recent estimates, owing to the faster rate of decrease of SBP in women, accompanied by a similar reduction in DBP not present among men. The pattern of association between bio-behavioural risk factors and BP are similar across genders, but cohort and education effects are present only in women.

From a *methodological* point of view, two further results are:

5. Estimates of BP and related quantities from the eight nationally representative population surveys carried out in South Africa between 1998 and 2015 are not directly comparable, because of large differences across surveys in the realisation of the sample, data management, calibration of sampling weights, measurement protocols, seasonal distribution of data collection and overall data quality.

6. A series of techniques within the general framework of latent variable modelling (namely multiple group modelling, normal-censored regression, mixture analysis with skew-normal distributions and the use of additional parameters and phantom variables) represent a viable and advantageous alternative to current methods of comparative analysis of blood pressure data.

In the following sections these results are interpreted on the light of previous findings in the literature, and their epidemiological and public health implications discussed. The last two sections highlight strengths and limitations of the present study and its overall conclusions.

8.1 The declining blood pressure in the South African population

The most unexpected finding of this study is the presence of a consistent decline in the prevalence of uncontrolled hypertension in the south African adult population during the last decade.

Decreasing trends in age-specific averages of BP and prevalence of (controlled or uncontrolled) hypertension — accompanied by declines in mortality for cardiovascular diseases — are not a new phenomenon, and have been repeatedly observed since the 1980s in many populations, especially in high-income countries. However, observing such large decreases in the prevalence of uncontrolled hypertension and — at least among women — in the number of subjects affected as those observed in our study is surprising in a middle-income country in full demographic and epidemiological transition with a rapidly growing and ageing population. In my knowledge, a decline in absolute — and not only relative — measures of burden of disease related to hypertension has been previously observed only in high-income countries, and, more precisely only in the European WHO macro-region.[6]

The reasons of this decline cannot be fully explained by the data available for this analysis. However, the findings (1) of an appreciably smaller decline of the estimated untreated BP than the observed BP, (2) of larger changes in the right than in the left tail of the distribution of

BP during the study period, and (3) of a concurrent substantial increase of BMI that would justify an increase rather than a decrease in BP suggest that the reduction in the prevalence of uncontrolled hypertension is more likely due to improvements in BP control among high-risk individuals rather than to widespread improvements in lifestyle factors.

Our data did not allow for the analysis of underlying trends in those factors that are usually acknowledged as the three major lifestyle-related risk factors for hypertension beyond BMI/waist circumference, smoking and alcohol consumption, namely nutritional habits, physical exercise and salt consumption. However, the current literature is quite consistent in indicating that, similarly to BMI[1], the distribution of these factors in the South African population during the study period has *worsened*, and not improved, from the perspective of cardiometabolic risk.[374, 482, 731–735] On the specific of salt consumption, the South Africa government has approved a series of pioneering measures in salt limiting legislation, but these have stated their implementation phase only in the second part of 2016, after the 1998-2015 period to which the analyses in this thesis refer. While it is possible that some of the discussions in the media related to the approval of the measures might have had some influence in raising awareness regarding the negative effects of excessive salt consumption in some population strata, it quite unlikely that this could have produces any appreciable change in salt consumption at the population level. These considerations make the changing distribution of these lifestyle factors an unlikely explanation for a decrease in the average BP of the population.

On the contrary, not only has the proportion of subjects on antihypertensive treatment consistently grown since 2003, but our study offers some evidence that the effectiveness of the treatment in reducing the BP of the treated has also increased. The latter is not an implausible finding considering (1) the repeated changes of the guidelines for the treatment of hypertension which have progressively introduced more effective therapeutic algorithms, specifically targeted at the South African population, and (2) the improvement in the socioeconomic conditions of some segments of the population, given that adherence to medication has been shown to increase dramatically with SES.[362, 411]

More investigation is needed to reach strong conclusions, but these elements suggest that a non- negligible share of the observed decrease in BP is attributable to improved access to adequate antihypertensive treatment. These observations match similar conclusions regarding plausible explanations of the reduction in the incidence of strokes and heart attacks in the US in the period between 1972 and 2012. Even though studies have provided evidence that stroke mortality rates started falling in high-income countries at least since 1930s — well before any effective antihypertensive treatments were available —-[736], the literature is quite consistent in acknowledging that a major driver of the dramatic reduction observed in that period (70% to 80%) has been the National High Blood Pressure Programme, which achieved this remarkable success through better BP control by more effective use of antihypertensive drugs. This is

despite the concurrent and substantial increase in the prevalence of diabetes and obesity, a clear indication that the concurrent efforts to persuade the population to adopt more healthy lifestyles in the US have not been similarly effective.[737]

This is not to say that nothing has happened in the left tail of the BP distribution, which includes health individuals with BP well below the hypertension diagnostic threshold. On the contrary, the analyses of the distribution shape show that the 10^{th} percentile has also shifted to the left, albeit less than has the 90^{th} percentile. The same conclusion is also backed by the results of group-specific analyses, which show that a downward shift in mean SBP has happened in almost all subpopulations defined by age, race, education and place of residence. Notably, it has also happened among the subjects in the youngest age group, where the prevalence of treatment is negligible. All these observations clearly point towards the conclusion that the declining trend in BP cannot be attributed solely to treatment effects, but is also the results of some population-wide influences on naturally occurring BP levels.

What these influences are is not fully evident from our data, especially considering the adverse trends in BMI/waist circumference and other bio-behavioural risk factors in recent periods.

Among women, part of the decline is explained by increasing average educational attainment, a strong indicator of SES which has already been found to be independently associated with lower BP in women (but not in men) in the South African population.[19, 407] Other than increased awareness of hypertension, factors such as accessibility of and adherence to antihypertensive treatment, less chronic stress and more favourable neighbourhood characteristics have been indicated in the literature as possible mediators of this protective effect of higher SES on raised BP. Such factors may contribute to the persistence of a significant protective effect of higher SES on elevated BP after adjustment for treatment. The reason why the same relationship between SES and BP is not observed in men might be their lower sensitivity to the adverse effect of unfavourable neighbourhood characteristics on BP that recent studies suggest.[10, 373, 404, 433, 738, 739]

Another intriguing possibility is that part of the decline reflects the cumulative effect of lifestyle and environmental conditions over long periods of time and/or lifecourse effects.

Cohort effects on BP and prevalence of hypertension have been repeatedly reported in the literature.[740–744] The majority of studies found that, after adjusting for period-specific factors, more recent cohorts tends to have lower BP values. These results are consistent with our findings regarding the female subsample.

The hypothesis that in utero and early-life growth and nutrition processes may play a role in explaining these effects is coherent with the literature briefly reviewed in Section 2.3.11.

Inter-generational changes in nutritional habits and food availability might be involved in

explaining the declining BP in the more recent cohorts, despite the likely opposite effect of the recent shift towards diets rich in fat and sodium. A similar hypothesis has been advanced among the possible reasons for the share of decrease in BP in the US not explained by improvement in treatment.[744] The cited association between early-life undernutrition — which has been decreasing in South Africa since 1995[745] — and risk of hypertension later in life is a possible contributing factor, together with the reduction of the sodium content of formula feeds observed across the last century.[466]

In our analyses, changes in *current* smoking habits explain very little of the observed decrease. However, the effects of smoking on cardiovascular risk and BP^2 are known to last for long periods after quitting[447], and this might contribute to explain differences between earlier cohorts (where non-smokers at the time of assessment include a fair share of ex-smokers) and later cohorts (where the proportion of subjects who never smoked is higher).

Finally, in our speculation of possible drivers on declining trends in BP, we should mention the possible contribution of decreasing exposure to low environmental temperatures, both because of the secular rising trends in the average annual temperature in South Africa (approximately + 1 ^oC between 2000 and 2012) and because of reduced individual low temperature exposure due to better living conditions. This according with our finding discussed in the next section of (a) strong seasonal variations in BP in the South African population, plausibly related to temperature changes, and (b) a substantial effect modification by SES and housing conditions.

The epidemiological and public health implications of the findings discussed above are manifold:

- First, and on the positive side, we should probably stop considering age-specific prevalence of elevated BP as an indicator which is bound to increase or, at best, to stay stable. This widespread conception — supported neither by our findings nor by the literature on the whole — is reflected in the common habit of defining estimates of future prevalence of hypertension and/or number of individuals affected as "conservative" when based on stable age-specific prevalences (see for example the comments by Ogah and Rayner [362, p. 3]). Age-specific prevalences have been actually decreasing in high-income countries since the 1970s, and the same trends seems to be occurring in developing countries. This is not to say that the burden of disease related to hypertension is going to disappear any time soon, but to highlight that reducing risk is possible in relatively short periods.
- Second, despite the fact that most of the drivers of observed changes in BP distributions in the South African population (and, similarly, in other populations) are still unknown, the results of this and other studies provide evidence that antihypertensive treatment is among the reasons of the recent decline and that improving accessibility and quality of it can have a substantial effect in further reducing the burden related to elevated blood

pressure.

As the preliminary results of the Newer versus Older Antihypertensive Agents in African Hypertensive patients (NOAAH) trial show, effective treatment with cheap generic fixed drug combinations can substantially improve adherence and BP control among hypertensive patients with modest rates of undesirable side-effects.[746] Extending to the management of hypertension the same approach that has been proven effective in curbing the epidemic of AIDS, i.e. widespread access to screening and diagnosis, timely inception of treatment through simplified protocols applicable by nurses, availability of single-pill combination drugs[3] that can improve adherence, may produce important positive effects in a relatively short period of time.

- Our data show that without the steady increase of mean BMI during the study period, the decline in BP would have been appreciably greater.

  Interventions tailored to curb the obesity epidemic are, therefore, likely to produce beneficial effects on the prevalence of hypertension as well, and, more importantly, will contribute to shift the whole distribution of BP to the left, differently from treatment that only acts on the right tail including high-risk individuals. Given that the risk of disease associated with elevated BP (such as stroke or renal failures) is a continuous function of BP that starts well below the diagnostic cut-offs for hypertension, the potential benefits of this reduction can be substantial.

  While changing behavioural habits (in particular nutrition and level of physical exercise) is known to be more difficult than improving treatment accessibility, the current Strategic Plan for the Prevention of Non-communicable Diseases 2013-17, launched in September 2013 by the South African National Department of Health and currently being implemented identifies a series of legislative and regulatory interventions (including educational campaigns and increased taxation of sugary drinks) that are likely to have a positive effect on BMI and, therefore, on the future distribution of BP.[747]

- Finally, the considerations above regarding early-life influences on adult BP strongly suggest that improving maternal and child health — a field in which, unfortunately, South Africa has achieved less than optimal results — is another suitable target for public health intervention likely to produce long-term beneficial effects on the prevalence of hypertension.

8.2 Seasonal effects and socioeconomic factors

The magnitude of the seasonal effects is large in the South African population and the immediate consequence of this finding for the epidemiological investigation is that studies involving

the estimation of blood pressure and prevalence of hypertension should routinely take into account the period of data collection, especially when comparison with other studies is involved.

From a clinical perspective, these variations — and the related variations in hypertension detection and control rates — suggest that taking them into account in clinical practice might improve the management of the hypertensive disease in the affected patients and the consequent clinical outcomes.

The greater seasonal effect observed among subjects with low SES has public health implications, in that it suggests that improving people's housing conditions and ability to protect themselves from low winter temperatures may have a positive effect on hypertension prevalence and cardiovascular morbidity and mortality, especially among older subjects.

8.3 Gender differences

Confirming our preliminary hypothesis that justified the choice of conducting separate analyses for the male and female subsample, our findings show large gender differences in absolute values, trends and likely determinants of BP.

The most relevant finding from an epidemiological perspective is certainly the much bigger rate of decrease in SBP and prevalence of uncontrolled hypertension among women.

From a public health point of view, understanding the reasons of the relatively large decreases in BP associated with education in women[4], not visible in men, might offer opportunities to increase the efficacy of educational interventions, but more investigation is needed at this regard.

8.4 Methodological contributions

The methodological contributions of this study have implications for the analysis and comparisons of BP data collected in population surveys, and for future epidemiological investigations.

First, they indicate that 'raw' comparisons between results of independent surveys without prior assessment of the possible effects of methodological differences in design, sampling, measurement protocols and data management procedures are to be avoided because of the risk of including large amount of bias. Seasonal effects, incongruence in weighting and different number of repeated measurements are all examples of differences able to introduce substantial bias in inter-survey comparisons, of the same order of magnitude as the actual differences of

epidemiological interest.

Second, they show that analytical methods easily implementable with currently available statistical software allow for reasonable adjustments for some — though not all — of the inter-survey methodological differences. As with all statistical methods, the latent variable techniques advocated in this thesis rely on assumptions that are statistically unverifiable, and it is responsibility of the researcher to ensure the plausibility of these assumptions with substantive considerations. The explicit way in which substantive assumptions are embedded in SEMs is one of the main reasons to support this approach, without claim that other approaches can be applied with similar results.

Third, the results of this study, including the review of the literature that informed the choice of the analytical methods, strongly suggest that improvements in study and measurement protocols for BP are needed in future epidemiological investigations involving BP. Among these, for example:

a Collection of auxiliary information (such as room and outdoor temperature, time of the day, *effective* temporal distance between repeated measurements, recent intake of food, liquids and other substances). These data could allow for a direct statistical adjustment for some of the known sources of variation of BP, rather than relying on the hope that in large samples individual biases are averaged to 0.

b Automation of the procedure of recording of BP readings, without human intervention. This would avoid end digit preference, suspicious multiple readings with identical values, and other potential data entry errors.

c Calibration studies for the measurement protocols and *devices* in the specific study population, to avoid reliance on the results of device validation studies carried out in samples and with settings far from those of interest.

None of these suggestions requires excessive investments. Points **a** and **b** are easily implementable with low-cost devices, and, for example, many commercially available BP monitors can be already directly connected to a computer and other devices(including smartphones) for data transfer, with no need of manual intervention. Point **c** certainly requires extra effort and cost, but the modern survey literature shows that validation studies, if properly designed and analysed, do not require large samples, and their results can be applied to multiple wave of data collection.[748]

Finally, it is worth mentioning in this discussion on the methodological contributions of this thesis the proposed method to deal with sample dependency in multiple group modelling through bootstrapping of the between-sample covariance matrices. Even though in the specific case of our datasets the correction for sample dependency produced negligible changes

in the estimates (of no interest from a practical point of view) and was thus dropped from the analyses, the proposed bootstrapping technique is of general applicability, and might represents an useful tool for the joint analyses of non-independent datasets, especially when the structure of the correlation is difficult to formalise. More investigation is certainly needed for the assessment of the performances of the method beyond the results of the limited simulation study presented here, and this will be object of future studies.

8.5 Strengths and limitations of the study

Strengths of the present study — which support the validity of its substantive results — include (1) the large sample; (2) the application of analytical methods to reduce the biasing effects of measurement error and of inter-survey differences in the joint analysis of data collected in independent surveys; (3) the consistent justification of the different modelling assumption based on substantive considerations and evidence from the literature, and the exploration of the possible consequences of their violation by means of simulations and epidemiological reasoning; (4) the efficient treatment of missing data under the relatively weak assumption that they are missing at random conditional to the observed covariates.

Several limitations must be also acknowledged.

First, despite the fact that our modelling approach would have allowed in principle for the adjustment for a large number of possible confounders that might affect the estimates of absolute values of BP and their temporal trends — as, for example, circadian rhythm; room temperature and other environmental conditions; differences in measurement devices and protocols; participants' arm size and shape — lack of available data limited this possibility. While for many of these factors (such as circadian rhythm) the large samples and the relative homogeneity of the data collection plans make any major effect on the estimates quite unlikely, for others I cannot exclude a non negligible effect. Especially of concern are differences in devices, measurement protocols and (possibly) training of observers. Fortunately, the major finding of this study of a substantial decline in BP in the last decade is based on data collected with an uniform protocol and the same device, and therefore unlikely to be affected by this problem. I cannot, however, exclude the possibility that this problem might have affected the comparisons between the SADHS and the NIDS data. In particular, the use of a cuff inadequate for larger arm circumferences could have produced an overestimation of the average BP of the South African population in 1998 and 2003 and thus of the magnitude of the decline observed in the following period.

Secondly, suboptimal response rates — albeit comparable with those recorded in international good quality studies — have been observed in some population strata. It is known that this

phenomenon does not automatically create selection bias, especially in analytical studies and when differences in observed characteristics between respondents and non-respondents are taken into account through appropriate adjustment of sampling weights.[728]. However, we cannot exclude the possibility that unobserved differences between respondents and non-respondents might have biased the results of our study in an unpredictable way.

Third, low reliability of self-report data and the coarse measures used to assess smoking and alcohol use, and the absence of measurement of some important risk factors, including early life determinants, have certainly limited our ability of identify the possible drivers of the observed changes in BP and prevalence of uncontrolled hypertension. More precise measurements and the availability of data on the omitted variables could allow to explain a further share of the temporal changes unexplained by our models. It is however unlikely that the consideration of further risk factors could change the substantive conclusions regarding the large explanatory role of treatment and (in the opposite direction) BMI.

Finally, as already pointed out, the separation of the intrinsically linked age, period and cohort effects relies on quite arbitrary modelling assumptions, and I cannot exclude that different choices, especially regarding the definition of birth cohorts, would have produces different results.

8.6 Conclusions

Encouraging signs regarding the future development of the burden of diseases related to elevated BP in the South African population emerge from this study. Age-specific prevalence of uncontrolled hypertension seems to be decreasing, especially among women, and this decrease is accompanied by declining mortality for cardiovascular disease, especially for stroke.

The reasons of this decrease are largely unexplained and warrant further investigation. However, among the possible drivers analysed in this study, increased accessibility and efficacy of antihypertensive treatment are likely to be playing an important role in explaining the observed decrease in BP. On the other hand, in our analyses — and coherently with the prevalent literature — adjustment for the rising mean BMI *sharpens* BP decline, thus suggesting that the growing obesity epidemic is limiting the benefits achievable with the diffusion of treatment. Both of these factors can be targeted to maintain and improve the current decline in population values of BP and prevalence of uncontrolled hypertension. The large seasonal variations of blood pressure and their unequal distribution across socioeconomic strata also suggest that interventions to reduce exposure to low temperatures might have public health benefit.

From the point of view of the epidemiological investigation, the results of this study suggest that the current methods for the analysis of survey data on BP and the measurement proto-

cols for future data collections should be improved to increase between-survey comparability, gather more reliable information on temporal changes in BP and gain better understanding of their drivers. Specifically, analytical methods should take explicitly into account known sources of measurement and representation error which affect estimates of BP in population surveys to reduce their biasing effects, especially when inter-survey comparisons are involved. Protocols for future studies should routinely include collection of auxiliary information and/or explicit validation of devices and procedures in the specific population.

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Appendices

Non-essential material has been included in these appendices as electronic attachments stored in an online repository. Individual content is described in the following sections, and a direct link is provided within the text.

The URL of the repository — from which the whole set of attachments can be downloaded as a single compressed archive — is the following:

`http://tinyurl.com/AnnibaleCoisApp`

Stata (*.do*), R (*.R*) and Mplus (*.inp*) script files and Mplus output (*.out*) files are all in text format and can be opened with any text editor.

A Ethical approval and data use agreements

The study only involves secondary analyses of previously collected data. The original collection, treatment and analysis of the individual-level data utilised in the present study has been granted ethical approval by the Commerce Faculty Ethics Committee at the University of Cape Town (for the NIDS datasets), by the Ethical Committee of the South African Medical Research Council (for the SADHS datasets) and by the Human Sciences Research Council (for the SAGE and SANHNES datasets).

The NIDS and SAGE datasets are in the public domain for research purposes. The SADHS and SANHNES datasets have been obtained from the South African Department of Health and from the Human Sciences Research Council, respectively. Links to copies of the data user agreements are the following:

- SADHS Data user agreement [*pdf*]
- SANHNES Data user agreement [*pdf*]

All datasets have been provided by the maintainers in anonymized format, cleaned of all direct or indirect identifying information, so that records cannot be linked back to the subjects from whom data were originally collected.

The present secondary analysis has been approved by the Human Research Ethical Committee, Faculty of Health Sciences, University of Cape Town. Links to copies of the approval letter and extensions for the whole duration of the study are the following:

- Ethical approval [*pdf*]
- Extension 1 [*pdf*]
- Extension 2 [*pdf*]

B Extra tables and Figures

The following tables compare the characteristics of subjects with missing systolic and/or diastolic blood pressure measurements with the characteristics of subjects with available measurements for the first three waves of the NIDS.

- TABLE B.1: NIDS 2008 [*.pdf file*]
- TABLE B.2: NIDS 2010 [*.pdf file*]
- TABLE B.3: NIDS 2012 [*.pdf file*]

The following figure shows BP trends calculated separately for subjects with or without previous diagnosis of hypertension and for subjects with or without antihypertensive pharmacological treatment.

- FIGURE B.1: SUBGROUP TRENDS [*.pdf file*]

C Data cleaning and recoding: code

The following Stata® scripts have been used to import data from the datasets provided by the maintainers and consolidate them in a single file with uniform structure and variable coding:

- IMPORT SADHS: import SADHS datasets [*.do file*]

- IMPORT NIDS: import NIDS datasets [*.do file*]
- IMPORT SAGE: import the SAGE dataset [*.do file*]
- IMPORT SANHNES: import the SANHNES dataset [*.do file*]
- CROSSEC: Basic cleaning and uniform coding [*.do file*]
- MERGE: Utility for merging the NIDS files (called by CROSSEC) [*.do file*]

The following script has been used to convert the data to the .R format, and to clean anthropometric data according to the rules explained in the text:

- IMPORT & CLEANING: import from Stata and clean anthropometric data [*.R file*]

D Exploratory data analysis, outliers and auxiliary variables: code

The following R code has been used for the exploratory data analysis, the identification and exclusion of outliers, the calculation of quality indices, the generation of auxiliary variables including the predicted values of the untreated BP and for accessory data management tasks:

- EDA: Exploratory data analysis [*.R file*]
- WEIGHTS: Graphs for comparing sampling weights [*.R file*]
- QUALITY: Calculate quality indices [*.R file*]
- OUTLIERS: Outlier identification [*.R file*]
- TOBIT: Censored regression for prediction of untreated BP values [*.R file*]
- COHORT: Create birth cohort [*.R file*]
- IMPUTE: Impute third measurements in the NIDS [*.R file*]

E Auxiliary functions: code

The different scripts call a set of custom functions to perform repetitive tasks, listed below:

- FUNCTIONS_EDA: auxiliary functions for EDA [*.R file*]

- FUNCTIONS_FIT: fit indices for MGMs with incomplete covariance structure [*.R file*]
- FUNCTIONS_MPLUSAUTO: extract SEs for the latent covariance matrix from the Mplus output [*.R file*]
- FUNCTIONS_SKEW: auxiliary functions for skewed distributions [*.R file*]

F Recalibration of weights: code

The following Stata script and associated data files have been used to recalibrate the sampling weights using a consistent series of population totals:

- REWEIGHT: cross-entropy calibration of sampling weights [*.do file*]
- CONSTRAINTS_A: population proportions for the SAGE sample [*.dta file*]
- CONSTRAINTS_B: population proportions for the remaining samples [*.dta file*]

G Sensitivity analysis for sample correlation

The bootstrap estimation of the covariances between population parameters (means, variances and covariances of the observed variables) in different samples were done by replicating 4000 times the process, and averaging the results across all replications.

The convergence of the estimation to stable values was checked by plotting the averages across different number of replicates. All averages converged well beyond the 4000 iterations. An example of the stabilization of the bootstrapped estimates is shown in Figure G.1 for the variance of the first systolic reading (top pane) and its covariance with the first diastolic reading (bottom pane), between the first and second wave of the NIDS.

The results of the sensitivity analysis are summarised in Table G.1. For each combination of samples, the table shows the average and maximum percentage changes in the standard error of the model parameters estimates and adjusted and unadjusted values of some indices of model fit.

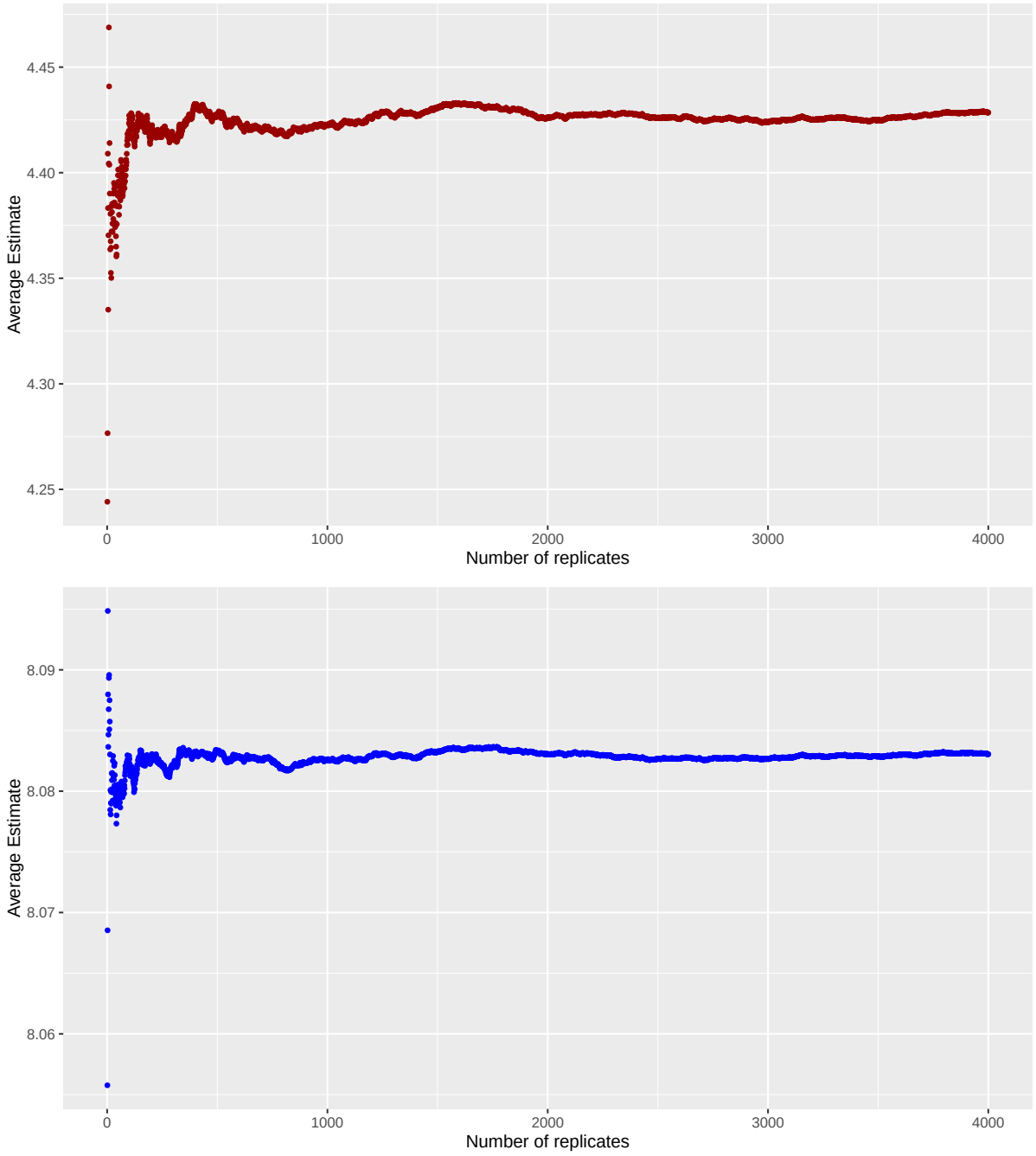
Table G.1: Results of the sensitivity analysis for sample dependence. Differences in standard errors and indices of model fit.

	SE Differences		Indices of fit					
Samples	$\overline{\Delta SE}$[%]	ΔSE_m[%]	χ^2_u	χ^2_a	CFI_u	CFI_a	$RMSEA_u$	$RMSEA_a$
NIDS 2008, NIDS 2010	0.065	0.546	18.450	18.462	1.000	1.000	0.009	0.009
NIDS 2010, NIDS 2012	0.028	0.453	24.343	24.356	0.999	0.999	0.011	0.011
NIDS 2012, NIDS 2014	-0.170	0.698	24.499	24.476	0.999	0.999	0.010	0.010
NIDS 2008, NIDS 2012	-0.009	0.162	21.649	21.649	1.000	1.000	0.010	0.010
SADHS 1998, NIDS 2014	-0.002	0.015	145.331	145.328	0.994	0.994	0.034	0.034

$\overline{\Delta SE}$, ΔSE_m = Average and maximum difference between adjusted and unadjusted estimates of standard errors; χ^2_u, χ^2_a, CFI_u, CFI_a, $RMSEA_u$, $RMSEA_a$ = Unadjusted and adjusted values of indices of model fit.

In most cases, ignoring sample dependence when the multiple group model was fitted to consecutive waves of the NIDS produced a slight underestimation of standard errors and of the χ^2 statistics. The differences between adjusted and unadjusted values were extremely small, and never greater than 0.7% of the unadjusted value. The differences practically disappeared when the models were fitted the two NIDS waves more distant in time (when the correlation was plausibly lower) and when the two samples were really independent, such at the SADHS 1998 and the NIDS 2014.

Figure G.1: Convergence of the bootstrapped replicates. Example.



The lines show the covariance of the estimates of each variable calculated in the two samples. Variance/covariances are measured in $mmHg^2$.

No differences were observed (within the numerical precision of the calculation) between the other indices of model fit.

The R code used for the analyses is the following:

- SENSITIVITY ANALYSIS [*.R file*]
- FUNCTIONS_SENSITIVITY: auxiliary functions [*.R file*]

H Measurement model: Mplus output

The Mplus estimates of all parameters for the multigroup models with the scalar invariance constraints in place are the following:

- MEASUREMENT_FEMALES [*.out file*]
- MEASUREMENT_MALES [*.out file*]

The correspondence of group names with each of the surveys is as follows:

1	SADHS 1998
2	SADHS 2003
4	NIDS 2008
5	NIDS 2010
7	NIDS 2012
8	NIDS 2014

Groups 3 and 6 (excluded from the estimation) correspond to the SAGE and SANHANES samples.

The degrees of freedom and the values of the indices of model fit do not match the values reported in the text, because they do not take into account the post-estimation adjustment for the presence of the 'imaginary' variables introduced to deal with the incomplete covariance structure in the NIDS samples.

I Montecarlo simulation: Mplus code

The Mplus code below implements the population model for the simulation study to compare the performances of various estimation methods in recovering the difference in SBP and DBP

from surveys carried out with different numbers of readings. The values of the BP population parameters are divided by 10 (means, intercepts) and by 100 (variances and covariances) in the model for numerical stability, but reported in the correct unit ($mmHg/mmHg^2$) in the text.

SAMPLE1 and SAMPLE2 represent the size of the random samples drawn in the different hypotheses (see Section 5.3 in Chapter 5).

```
TITLE: RANDOM GENERATION OF SAMPLES - MISSING THIRD READING IN GROUP 1

MONTECARLO:
NAMES =  sys1 sys2 sys3 dia1 dia2 dia3 pul1 pul2 pul3;
NOBSERVATIONS = SAMPLE1 SAMPLE2;
NGROUPS = 2;

NREPS = 1000;
SEED = 27091962;

REPSAVE = ALL;
SAVE = ../Data/M2*.DAT;

MODEL POPULATION:

  SBP BY sys1@1.002 sys2@1.023 sys3@0.975; DBP BY dia1@0.971 dia2@1.038 dia3@0.991;
  RHR BY pul1@0.978 pul2@1.029 pul3@0.993;
  SBP@4.00; DBP@1.50; RHR@1.50;
  SBP WITH DBP@2.02; SBP WITH RHR@0.09; DBP WITH RHR@0.12;

  sys1 WITH dia1@0.24; sys1 WITH pul1@0.05; dia1 WITH pul1@0.04;
  sys2 WITH dia2@0.04; sys2 WITH pul2@0.00; dia2 WITH pul2@0.02;
  sys3 WITH dia3@0.13; sys3 WITH pul3@0.04; dia3 WITH pul3@0.03;

  SYS1@0.74; SYS2@0.30; SYS3@0.44;
  DIA1@0.44; DIA2@0.23; DIA3@0.32;
  PUL1@0.50; PUL2@0.28; PUL3@0.37;

  [SYS1@0.29]; [SYS2@-0.33]; [SYS3@0.03];
  [DIA1@0.46]; [DIA2@-0.34]; [DIA3@-0.12];
  [PUL1@0.14]; [PUL2@-0.20]; [PUL3@0.06];

  [SBP@12.00 DBP@7.50 RHR@7.70];


MODEL POPULATION-g1:

  SBP BY sys1@1.002 sys2@1.023 sys3@0;
  DBP BY dia1@0.971 dia2@1.038 dia3@0;
  RHR BY pul1@0.978 pul2@1.029 pul3@0;
  SBP@4.00; DBP@1.50; RHR@1.50;
  SBP WITH DBP@2.02; SBP WITH RHR@0.09; DBP WITH RHR@0.12;

  sys1 WITH dia1@0.24; sys1 WITH pul1@0.05; dia1 WITH pul1@0.04;
  sys2 WITH dia2@0.04; sys2 WITH pul2@0.00; dia2 WITH pul2@0.02;
  sys3 WITH dia3@0; sys3 WITH pul3@0; dia3 WITH pul3@0;

  SYS1@0.74; SYS2@0.30; SYS3@0.44;
  DIA1@0.44; DIA2@0.23; DIA3@0.32;
  PUL1@1; PUL2@1; PUL3@1;
```

```
  [SYS1@0.29]; [SYS2@-0.33]; [SYS3@0];
  [DIA1@0.46]; [DIA2@-0.34]; [DIA3@0];
  [PUL1@0.14]; [PUL2@-0.20]; [PUL3@0];

  [SBP@12.00 DBP@7.50 RHR@7.50];

MODEL POPULATION-g2:

  SBP BY sys1@1.002 sys2@1.023 sys3@0.975; DBP BY dia1@0.971 dia2@1.038 dia3@0.991;
  RHR BY pul1@0.978 pul2@1.029 pul3@0.993;
  SBP@4.00; DBP@1.50; RHR@1.50;
  SBP WITH DBP@2.02; SBP WITH RHR@0.09; DBP WITH RHR@0.12;

  sys1 WITH dia1@0.24; sys1 WITH pul1@0.05; dia1 WITH pul1@0.04;
  sys2 WITH dia2@0.04; sys2 WITH pul2@0.00; dia2 WITH pul2@0.02;
  sys3 WITH dia3@0.13; sys3 WITH pul3@0.04; dia3 WITH pul3@0.03;

  SYS1@0.74; SYS2@0.30; SYS3@0.44;
  DIA1@0.44; DIA2@0.23; DIA3@0.32;
  PUL1@0.50; PUL2@0.28; PUL3@0.37;

  [SYS1@0.29]; [SYS2@-0.33]; [SYS3@0.03];
  [DIA1@0.46]; [DIA2@-0.34]; [DIA3@-0.12];
  [PUL1@0.14]; [PUL2@-0.20]; [PUL3@0.06];

  [SBP@12.20 DBP@7.70 RHR@7.50];

  ANALYSIS:
  TYPE = BASIC;
```

The models used to recover the different estimates are available here:

- MONTECARLO_A: Method A (means 2+2) [*.inp file*]
- MONTECARLO_B: Method B (means 2+3) [*.inp file*]
- MONTECARLO_C: Method C (means 2+3, adjusted) [*.inp file*]
- MONTECARLO_D: Method D (SEM 2+3) [*.inp file*]

J Skewed distributions: Mplus output

The values of the indices of model fit and the estimates of the skewness parameters for the measurement models (adjusted for seasonal effect) with skew-normal distribution of the latent variables are reported below:

Female sample:

```
MODEL FIT INFORMATION

Number of Free Parameters                       197

Loglikelihood

          H0 Value                    -721117.382
          H0 Scaling Correction Factor      4.8690
            for MLR

Information Criteria

          Akaike (AIC)                1442628.764
          Bayesian (BIC)              1444380.504
          Sample-Size Adjusted BIC    1443754.434
            (n* = (n + 2) / 24)

Skew and Df Parameters

Latent Class 1 (1)

    SBP                2.412      0.063     38.196      0.000
    DBP                0.774      0.070     10.987      0.000
    RHR                0.052      0.054      0.962      0.336

Latent Class 2 (2)

    SBP                2.354      0.080     29.529      0.000
    DBP                0.643      0.100      6.436      0.000
    RHR                0.201      0.077      2.625      0.009

Latent Class 3 (4)

    SBP                2.638      0.079     33.211      0.000
    DBP                0.880      0.091      9.671      0.000
    RHR                0.059      0.052      1.134      0.257

Latent Class 4 (5)

    SBP                2.497      0.096     26.050      0.000
    DBP                0.702      0.118      5.947      0.000
    RHR               -0.102      0.053     -1.917      0.055

Latent Class 5 (7)

    SBP                2.430      0.062     39.132      0.000
    DBP                0.728      0.076      9.535      0.000
    RHR               -0.100      0.055     -1.811      0.070

Latent Class 6 (8)

    SBP                2.312      0.101     22.982      0.000
    DBP                0.842      0.141      5.990      0.000
    RHR               -0.016      0.045     -0.357      0.721
```

Male sample:

```
MODEL FIT INFORMATION

Number of Free Parameters                       197

Loglikelihood

          H0 Value                       -494498.506
          H0 Scaling Correction Factor      5.4996
            for MLR

Information Criteria

          Akaike (AIC)                    989391.012
          Bayesian (BIC)                  991070.998
          Sample-Size Adjusted BIC        990444.932
            (n* = (n + 2) / 24)


Skew and Df Parameters

Latent Class 1 (1)

    SBP                2.303      0.069     33.460      0.000
    DBP                1.052      0.087     12.034      0.000
    RHR                0.230      0.098      2.344      0.019

Latent Class 2 (2)

    SBP                2.153      0.157     13.721      0.000
    DBP                0.830      0.458      1.813      0.070
    RHR                0.152      0.250      0.610      0.542

Latent Class 3 (4)

    SBP                2.318      0.085     27.377      0.000
    DBP                0.949      0.126      7.541      0.000
    RHR                0.371      0.097      3.813      0.000

Latent Class 4 (5)

    SBP                2.282      0.083     27.542      0.000
    DBP                0.857      0.120      7.115      0.000
    RHR                0.059      0.110      0.536      0.592

Latent Class 5 (7)

    SBP                2.333      0.074     31.448      0.000
    DBP                1.240      0.108     11.453      0.000
    RHR                0.296      0.135      2.195      0.028

Latent Class 6 (8)

    SBP                2.269      0.082     27.655      0.000
    DBP                0.924      0.122      7.552      0.000
    RHR                0.239      0.103      2.312      0.021
```

The estimates of the remaining model parameters are available here:

- SKEW_FEMALES: Parameters estimates, female sample [*.out file*]
- SKEW_MALES: Parameters estimates, male sample [*.out file*]

K Seasonality and socieconomic status: Additional material

K.1 Additional descriptive statistics

Table K.1 shows the distribution of subjects by month of data measurement, separately for each wave. Table K.2 shows the characteristics of the sample at wave 2 and wave 3.

Table K.1: Distribution of subjects by month of data collection

	Wave 1	Wave 2	Wave 3
Month	n	n	n
January	10	548	-
February	1333	321	-
March	3051	193	-
April	2795	89	477
May	1022	125	1629
June	2443	667	1685
July	34	1352	1660
August	16	2522	1986
September	263	2603	1802
October	317	2214	1835
November	134	673	342
December	22	133	24
Total	11440	11440	11440

n = number of subjects.

Table K.2: Sample descriptive statistics at wave 1 and wave 2

	Wave 1			Wave 1		
Variable	n	Median/ percentage	IQR/ frequency	n	Median/ percentage	IQR/ frequency
Age $[years]$	11 439	37	[24 ; 52]	11 439	39	[26 ; 54]
Education	11 438			11 428		
None		13.42%	1 535		13.37%	1 528
Primary (1 - 7 years)		23.12%	2 644		22.71%	2 595
Secondary (8 - 13 years)		53.94%	6 170		50.91%	5 818
Tertiary ($>$ 13 years)		9.52%	1 089		13.01%	1 487
Place of residence	11 379			11 415		
Urban formal		39.08%	4 447		40.40%	4 612
Urban informal		6.47%	736		6.96%	794
Rural formal		10.31%	1 173		10.26%	1 171
Rural informal		44.14%	5 023		42.38%	4 838
Household monthly income p.c. [ZAR]	11 426	575	[308 ; 1200]		785	[437 ; 1600]
Current smoking	10 400	15.81%	1 644	10 133	18.23%	1 847
BMI category	9 324			9 879		
Underweight		4.86%	453		2.75%	272
Normal weight		40.80%	3 804		40.95%	4 045
Overweight		24.96%	2 327		26.97%	2 664
Obese		29.39%	2 740		29.33%	2 898
Systolic BP [$mmHg$]	9 268	122.5	[111.5 ; 137.0]	9 940	123.0	[111.0 ; 137.5]
Diastolic BP [$mmHg$]	9 946	81.5	[73.5 ; 90.5]	9 946	81.5	[73.5 ; 90.5]
BP classification†	8 114			8 154		
Normal		36.33%	2 948		38.05%	3 103
Pre-hypertension		37.45%	3 039		37.55%	2 917
Stage I hypertension		16.77%	1 361		16.15%	1 317
Stage II hypertension		9.44%	766		10.02%	817
Antihypertensive treatment	11 224	11.56%	1 297	11 230	16.43%	1 845

n = number of non-missing values; IQR= interquartile range; ZAR = South African Rands; p.c = per capita.
† According to the *Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*[2], excluding subjects in treatment.

K.2 Notes on statistical analyses

Model Estimation: A full-information maximum likelihood estimator was used to estimate models coefficients. The complex sampling scheme of the NIDS was taken into account through weighting of the likelihood function and using of a sandwich estimator.[598] Standard errors and confidence intervals of the combination of model coefficients representing age-specific and population averaged seasonal effects were calculated using the delta method.

Model Fit: Model fit was assessed using multiple indices, as per common practice in the literature.[612] Table K.3 shows the values of these indices for the various models estimated in the whole sample and within each subpopulation defined by different levels of education, tertile of household monthly income per capita and (limited to the urban dwellers) residence in informal vs. formal settlements. Column 2 in the table shows the actual sample size (i.e. the total number of measurements, varying from 1 to 3 for each subject) used for the estimation in each subsample.

Table K.3: Fit indices for the structural equation models

Sunpopulation	*Sample size*	χ^2	χ^2/df	*RMSEA*	*CFI*	*TLI*	*SRMR*
Females							
Whole sample	19046	56.48, df=43, p=0.08	1.31	0.004	1.000	1.000	0.001
No education	2765	39.47, df=43, p=0.63	0.92	<0.001	1.000	1.000	0.002
Primary education	5816	29.69, df=43, p=0.06	0.69	<0.001	1.000	1.000	0.002
Secondary/Tertiary education	10453	58.11, df=43, p=0.63	1.35	0.006	1.000	0.999	0.001
Income tertile I	6076	40.05, df=43, p=0.60	0.93	<0.001	1.000	1.000	0.001
Income tertile II	6488	33.19, df=43, p=0.86	0.77	<0.001	1.000	1.000	0.001
Income tertile III	6482	35.32, df=43, p=0.79	0.82	0.000	1.000	1.000	0.001
Informal settlement	9881	46.74, df=43, p=0.32	1.08	0.003	1.000	1.000	0.001
Formal settlement	8174	49.69, df=43, p=0.22	1.15	0.004	1.000	1.000	0.001
Males							
Whole sample	11969	71.05, df=43, p=0.005	1.65	0.007	1.000	1.000	0.001
No education	1104	48.60,df=43, p=0.26	1.13	0.011	0.999	0.997	0.003
Primary education	4054	56.51, df=43, p=0.08	1.31	0.009	0.999	0.998	0.002
Secondary/Tertiary education	6080	48.97, df=43, p=0.25	1.14	0.005	1.000	0.999	0.002
Income tertile I	3261	48.58, df=43, p=0.26	1.13	0.006	0.999	0.999	0.002
Income tertile II	3558	44.61, df=43, p=0.40	1.04	0.003	1.000	1.000	0.002
Income tertile III	5150	68.05, df=43, p=0.01	1.58	0.011	0.999	0.998	0.002
Informal settlement	6329	50.21, df=43, p=0.21	1.17	0.005	1.000	0.999	0.002
Formal settlement	6403	73.21,df=43, $p < 0.01$	1.70	0.010	0.998	0.997	0.002

χ^2 = Chi-squared test of model fit; df= degrees of freedom; $RMSEA$ = Root Mean Square Error of Approximation; CFI=Comparative Fit Index; TLI= Tucker Lewis Index; $SRMR$ = Standardized Root Mean Square Residual.

Test for monotonic trends: The existence of a statistically significant monotonic trend in the seasonal effect across increasing levels of education and income was tested by simulation, adapting the procedure proposed by Soderberg and Hennet [719]. To this end, I ran a number of iterative calculations of the Kendall's tau correlation coefficient between the estimated magnitude of seasonal effects in each sub-population and the ordinal variable representing increasing levels of socioeconomic status (either education class or income tertile). To take into account the uncertainty of the estimated seasonal effects, at each iteration the value of the seasonal effects was randomly selected from a normal distribution with mean and standard deviation given by the point estimate and standard deviation of the estimated seasonal effect, per group. The procedure was repeated 50000 times, and the empirical distribution of Kendall's tau across the repetitions was used to calculate the point estimate (the distribution median) and lower and upper bound of the 95% confidence interval (the 0.025^{th} and 0.975^{th} quantiles).

Impact on cardiovascular risk: To estimate the differences in cardiovascular risk due to the winter-summer variation in blood pressure, I used the following procedure, separately for each subpopulation of interest:

A. I estimated the weighted annual average of systolic blood pressure and BMI in the subpopulation.

B. I calculated the minimum and maximum seasonal value of systolic blood pressure respectively by subtracting and adding half of the seasonal effect (age specific) to the annual average.

C. I used the Framingham equations to calculate the 10-year absolute cardiovascular risk, once with the maximum values of blood pressure, and again with the minimum values. In both cases the values of the other risk factors were kept constant at the specific values shown in Figure 5. BMI was set at the average annual value, and history of diabetes and antihypertensive treatment assumed absent.

D. The difference between the values calculated above was reported in Figure 5.

K.3 Additional results

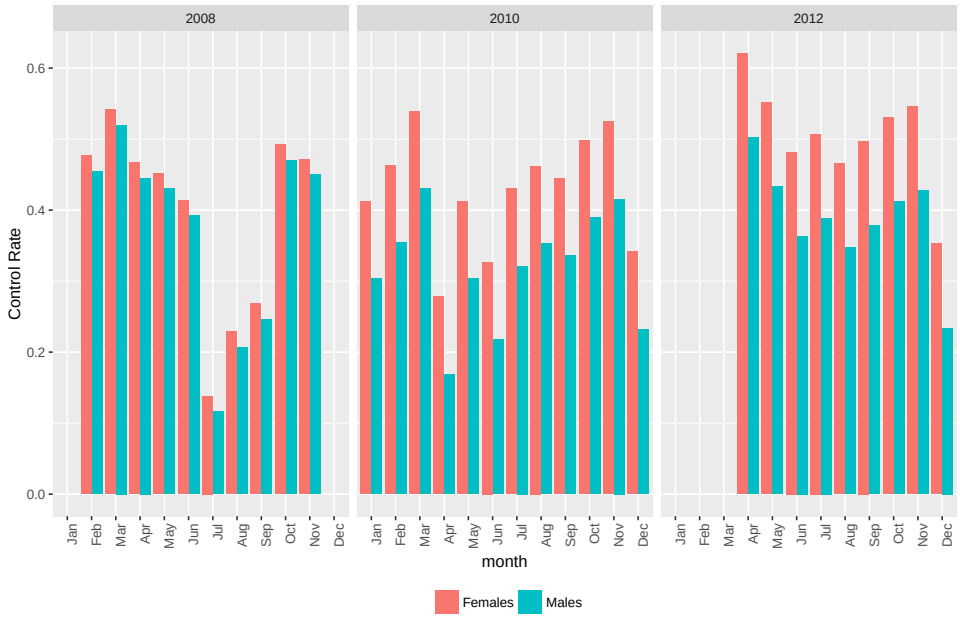
Seasonal effects in formal vs. informal dwellers: The differences in seasonal effect between urban dwellers living in formal and informal settlements are shown in Table K.4. All differences were in the expected direction, i.e. higher effects in those dwelling informal settlements, but none reached statistical significance.

Table K.4: Magnitude of seasonal effect on blood pressure among urban dwellers, by place of residence and gender. Estimates and 95% confidence intervals.

	Formal settlement $[mmHg]$	Informal settlement $[mmHg]$	Difference $[mmHg]$
Females			
Systolic	3.39 (1.59 ; 5.20)	5.35 (1.94 ; 8.76)	-1.96 (-5.82 ; 1.9)
Diastolic	3.09 (1.88 ; 4.30)	3.23 (1.45 ; 5.01)	-0.14 (-2.29 ; 2.01)
Males			
Systolic	3.60 (1.76 ; 5.55)	4.81 (0.49 ; 9.13)	-1.21 (-5.93 ; 3.51)
Diastolic	4.35 (2.91 ; 5.79)	4.53 (2.15 ; 6.92)	-0.18 (-2.97 ; 2.61)

Hypertension control: Figure K.1 shows the estimated proportion of subjects with controlled hypertension in the NIDS sample, by month, sex and year of measurement.

Figure K.1: Control of hypertension in the NIDS study, by month, sex and year of measurement.



Control prevalence is calculated as the proportion of subjects with lifetime diagnosis of hypertension who have systolic blood pressure lower than 140 $mmHg$ and diastolic blood pressure lower than 90 $mmHg$ at the time of measurement.
Estimates are adjusted for age, education and urban/rural environment, and take into account the NIDS sampling scheme. Shown values refer to the average individual in the 35-45 years age category with secondary education, as the largest strata for those variables.

Values for the month on December in two of the three years seem to be in contrast with the general pattern in which colder months record lower control rates than warmer months. However, the interpretation of this finding must take into account the low reliability of the December estimates owing to the small number of subjects interviewed in that month, as well as a possible confounding effect of the holiday season such as changes in routine behaviour, and lesser availability of medical services.

Sensitivity Analyses: Additional table K.5 shows the seasonal effect for the whole population and within each of the subpopulation defined by education and income level, estimated excluding subjects on antihypertensive treatment.

Table K.5: Magnitude of seasonal effect on blood pressure among untreated subjects, by subpopulation and gender. Estimates and 95% confidence intervals.

	Seasonal effect (95% CI), $[mmHg]$	
Subpopulation	Systolic BP	Diastolic BP
Females		
Whole sample	4.2 (3.2 ; 5.2)	3.8 (2.9 ; 4.6)
No education	12.7 (7.3 ; 18.1)	9.7 (6.4 ; 12.9)
Primary Education	6.0 (3.9 ; 8.1)	5.1 (3.5 ; 6.7)
Secondary/tertiary education	3.8 (2.2 ; 5.4)	3.5 (2.4 ; 4.6)
Income tertile I (lowest)	5.2 (3.3 ; 7.0)	4.9 (3.4 ; 6.4)
Income tertile II	4.9 (3.3 ; 6.5)	3.9 (2.8 ; 5.1)
Income tertile III	3.5 (1.9 ; 5.1)	3.1 (1.9 ; 4.2)
Males		
Whole sample	4.1 (2.9 ; 5.2)	3.9 (3.0 ; 4.8)
No education	10.2 (4.9 ; 15.6)	6.8 (2.9 ; 10.8)
Primary Education	4.5 (2.1 ; 6.8)	4.0 (2.5 ; 5.5)
Secondary/tertiary education	4.5 (2.7 ; 6.3)	3.9 (2.5 ; 5.2)
Income tertile I (lowest)	5.2 (2.7 ; 7.7)	5.0 (3.4 ; 6.7)
Income tertile II	5.0 (2.8 ; 7.1)	3.7 (2.3 ; 5.2)
Income tertile III	3.9 (2.3 ; 5.4)	3.9 (2.7 ; 5.2)