Blood pressure variation and its association with outdoor temperature among adults with hypertension in a primary care setting in South Africa

by

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To the memory of my late grandmother Ntacocera Theresa and
the love and support of my parents, Leonard Bugaye and
Jennifer Inangorore and Aunt, Ndihokubwayo Beatrice,
My inspiration

Declaration

I, Enock Havyarimana (HVYENO001), hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: Signed by candidate

Date: **15 December 2017**

Dissertation Abstract

Several observational studies have recently showed that variation in seasonal and daytime measurements of clinic, home, office and ambulatory blood pressure (BP) are inversely associated with changes in outdoor temperature. More specifically, lower outdoor temperatures recorded in cold seasons have particularly been shown to be associated with increases in systolic and diastolic blood pressure. This association may partly explain the excess prevalence of hypertension and incidence of morbidity and mortality due to a cardiovascular disease (CVD) in winter.

To date, the evidence reporting on the relationship between blood pressure, (clinic-based BP), and its association with outdoor temperature are still limited in Sub-Sahara Africa. Data from studies in high income countries and some low-middle income countries, with clinical settings similar to South Africa, have indicated that blood pressure variation driven by changes in outdoor temperature may be higher in clinical settings with limited control of indoor climate conditions. We hypothesized that blood pressure measures in these settings, and in particular primary care clinics in Sub-Sahara Africa (SSA), are strongly associated with outdoor temperature, because of the limited and mostly no access to indoor temperature control instruments in public clinics and hospitals.

The dissertation assesses the relationship between outdoor temperature and blood pressure of individuals with high blood pressure who were cared for in a primary setting with limited control to indoor climate, in South Africa. Moreover, the study addresses the gap in evidence about Sub-Sahara Africa and may explain recently published evidence showing an increase incidence of winter mortality due CVD in South Africa.

In achieving the aim of the study, we used baseline data from 2494 adults assessed for eligibility and entry in a randomised controlled clinical trial (SMS-text Adherence Support

trial, StAR study) in Cape Town, South Africa. The StAR study is a randomised three-arm open parallel group trial evaluating the effects a structured programme of hypertension treatment adherence support delivered through either informational or interactive SMS-text messages on blood pressure at 12 months as compared to usual care. Data from the trial were merged with the weather data from the South African Weather Services (SAWS), using the nearest hour of blood pressure measurement. In addition, given the potential confounding effect of air pollution on temperature and blood pressure, data from the nearest Cape Town air quality monitoring station was included in the analysis and was adjusted for as a potential confounder.

The dissertation consist of three parts:

Part A (Study protocol) provides a summary of the study aim and objectives, background on the SMS-text Adherence Support trial study (StAR), details of the present study design, data collection and methods used for data analysis.

Part B (Literature review) summarises and critically appraises literature on blood pressure variation and the influence of outdoor temperature and seasonality. Furthermore, it assesses evidence of potential confounders and effect modifiers on the association between temperature and measured blood pressure. Empirical evidence from studies with people living with cardiovascular disease were also assessed including those assessing potential clinical and public health implication of seasonal and outdoor temperature on blood pressure control and management.

Part C (Manuscript) presents and discusses the study rationale, setting, method, and results including interpretation of key study findings as it relates to evidence from elsewhere.

Main findings – 72% of study participants assessed for eligibility and entry in the trial were female and the overall mean systolic blood pressure was 137mmHg (SD: ±19, 79). Mean outdoor temperature during the trial enrolment period was 16, 73°C (SD: ±3, 88) with low mean temperatures recorded in winter (14°C) compared to spring (18°C).

Participants enrolled during winter (June-July) and in the morning (07h-10h00), when temperatures were generally low, had a higher mean blood pressure compared to those enrolled in spring-summer and afternoon (≥13h00), when temperatures were increased. On a given day, the overall mean change in outdoor temperature was 4°C (min 1.4 °C - 14.6 °C max), with highest mean temperature variation seen in July (winter).

Key results from this study shows that a 10°C increase in outdoor temperature is associated with 7.5mmHg (95% CI – 3,8; 11,2) decrease in systolic blood pressure, after adjusting for important confounders like air pollution and humidity.

These results reiterate evidence from studies in other settings that show similar inverse associations between outdoor temperature and blood pressure. More importantly, together with findings from studies in low-middle income countries, these study calls for re-assessment of policies and clinical guidelines of blood pressure monitoring and management in care settings with limited control to indoor climate and temperature.

Acknowledgment

I would first like to thank my supervisors, Dr Kirsten Bobrow and Prof Naomi Levitt for their mentorship and commitment to help me finish. Their support has been pivotal to my growth and has helped me become a better researcher. To my family, your love and support and belief in me has carried me to this point; I am who I am because of your love. To Gimenne Zwama, I am most grateful for your love and support throughout, pushing me to finish and assisting me with proof-reading. To my aunt, thank you for your investment in me early on, you have been a great inspiration and motivation to me.

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Thesis Contents

PART A
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STUDY PROTOCOL

Date: April 2015

Study title: Variation in blood pressure and its association with outdoor temperature among adults with hypertension in a primary care setting in South Africa

Protocol: A Research protocol in partial fulfilment of a degree in Master of Public Health

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STUDY PROTOCOL

1. Synopsis

Background – Outdoor temperature and seasonal variation have shown to be associated with cardiovascular and respiratory mortality globally. This association may in part be due to the effects of seasonal and temperature variation on blood pressure. Several population-based studies have shown an inverse association between temperature variation and blood pressure large enough to be clinically important. For example, a 10°C decrease in temperature may be associated with as much as a 5 mmHg increase in systolic blood pressure measurements. Implication of this association for people living with high blood pressure includes increased risk of hospitalization due to cardiovascular event in winter. To our knowledge there are no published studies reporting the relationship between outdoor temperature and blood pressure from South Africa. The proposed study serves to address this gap by investigating the association between outdoor temperature and blood pressure among adults with hypertension attending a primary care facility in South Africa, taking into account the effects of potential confounding factors

Objectives – Describe the association between outdoor temperature and blood pressure in a South African setting as well as assess the strength of the association and its clinical relevance.

Design – Cross-sectional analysis of the relationship between outdoor temperature and mean systolic and diastolic blood pressures in adults

Setting – Clinical service set-up in a single, large primary care facility to screen adult patients with hypertension for eligibility to participate in a randomised trial study (SMS-text Adherence support trial, StAR)

Participants – 2558 adults screened for eligibility to the StAR trial study and who at point of recruitment were being treated for hypertension, had at least three blood pressure readings and anthropometry measured, and who reported basic personal and demographic factors.

Outcomes of interest – Mean systolic and diastolic blood pressures at recruitment in relation to outdoor temperature, adjusted for important potential confounders.

Discussion – To our knowledge, this is the first study to describe the association between outdoor temperature and blood pressure in a primary care setting in South Africa. The resulting evidence will provide important information on the relevance and clinical importance of temperature variation in the ongoing management of people with hypertension.

2. Background

2.1 Evidence for seasonality and temperature effects on health outcomes

Seasonality, defined by interquartile periods in which weather and climatic pattern follows a continuous and predictable trend throughout a year, has long been associated with disease risk particularly for infectious diseases (1). The relationship between non-communicable diseases and seasonality is less well described. Evidence for climate change has helped raise researchers and policy makers' attention about the role of environment and climate variation on risks and outcomes associated with health (2–4). According to the World Health Organisation (WHO), climate change is estimated to contribute to 154 000 deaths/year and 5.5 million disability-adjusted life years (DALYs) worldwide; with the developing countries being the most affected (5–7). Furthermore, the recent WHO report have shown that seasonal variation in mortality rates, ranges from 10% to 25% between cold and warm seasons, in many temperate countries (8). These findings are is further supported by several observational studies showing higher cardiovascular and respiratory mortality in the winter season compared to all the other seasons (9–26). Similarly, outdoor temperature has shown an association between morbidity and mortality due to cardiovascular events, with temperature extremes in both cold and warm seasons. At particular risk are older people (>65years), those with diagnosed cardiovascular disease and those living at very low latitudes (20,21).

To date, there are no studies reporting on mechanism associated with this phenomenon. Several studies have indicated that climate markers of seasonality and weather (e.g.: outdoor temperature and air pollution) may partly explain the risk in cardiovascular outcome through their association blood pressure. (14,23,27–29).

2.2 Evidence of the effect of seasonality on blood pressure variation

Several studies have reported an association between seasonality and blood pressure. Data from both small and large population studies have shown a seasonal variation in blood pressure with highest mean systolic and diastolic blood pressures recorded in winter. Seasonal variation in weather may account for as much as a 19 mmHg difference in systolic blood pressure between warm and cold seasons (30). This variation in blood pressure is attributed to number of climate variables such as temperature (31), daylight hours (32), humidity (33) and air pollution (9). Various biological markers such as hormones and serum cholesterol (29) have also been reported to have seasonal variation between warmest and coldest months among the general population. However, for most of the variables highlighted there are few and in most cases no other studies reporting the extent of effect on blood pressure in other populations and settings. Nonetheless, temperature has consistently shown to have an association with blood pressure in various populations, mostly in regions located above the equator (Table 1).

2.3 The association between ambient temperature and blood pressure

Results from several observational studies have shown an inverse association between blood pressure and outdoor temperature (31,33–56). Although this pattern is present in younger and older people and those with and without high blood pressure (irrespective of their use of blood pressure lowering medication), the strength of the association can vary per region and by season (Table 1). For example results from some studies in Europe have shown a change of about 3 mmHg in systolic blood pressure per 10 °C in temperature change (34). In contrast, researchers from a recent large population based study in China reported a much larger effect of temperature on blood pressure (5 mmHg/10 °C change) (28). This study has also produced some evidence that the association between blood pressure and temperature can be stronger during winter than during summer (28).

3. Problem statement and rationale

To date, evidence on the association between blood pressure and temperature is largely arisen from studies in the northern temperate hemispheric countries (30-54), where temperature patterns and clinical conditions are different from South Africa. There exists a considerable gap in evidence on the strength of the association between temperature and blood pressure from the African continent and, more specifically, South Africa.

Located in the southernmost part of Africa, South Africa is a subtropical region surrounded by two oceans which have a moderating influence on its climate. For example, South Africa experiences lower temperatures as compared to other regions at a similar latitude (57). Temperature in South Africa can vary between just below zero degrees (-2°C) in winter to about thirty degrees Celsius and above (36°C) in summer (57). In addition, although results from several studies have shown an association between seasonality and temperature and blood pressure at a population level, the clinical relevance of these findings remains uncertain. Some evidence suggest poor quality of housing and increased exposure to cold climate is associated with a 25% (OR 1.25, 95% CI: 1.01-1.53) and 45% (OR 1.45, 95% CI: 1.18-1.7) increased risk at systolic and diastolic hypertension respectively (58). If outdoor temperature is strongly associated with blood pressure this may have particular relevance in settings like South Africa where primary care outpatient facilities do not provide a climate controlled environment (generally no air conditioners, heaters, central heating or similar available) (59). It is possible that temperature associated fluctuations in blood pressure may be inappropriately influencing diagnosis and measures of blood pressure control, thereby risking either under- or over diagnosis and treatment.

STUDY PROTOCOL

3.1 Study Aims

- To assess the association between outdoor temperature and blood pressure in a typical primary care setting in South Africa.
- To assess the role of important confounders and the influence of effect modifiers on this association.
- To explore the potential clinical implications of temperature-associated misclassification of blood pressure control measurements.

4. Methodology

4.1 Study design

This proposed study aims to describe the relationship between outdoor temperatures and mean systolic and diastolic blood pressure in adults using a cross-sectional analysis method. The study will use data from the SMS text Adherence Support (StAR) trial study, the South African Weather Service (SAWS) and the City of Cape Town's Department of Environmental Health. In summary, the StAR study is a randomised three-arm open parallel group trial evaluating the effects a structured programme of hypertension treatment adherence support delivered through either informational or interactive SMS-text messages on blood pressure at 12 months as compared to usual care. Full details of the study design and methods are described elsewhere (60). In brief, all patients who were being treated for high blood pressure at the clinic were offered referral to the trial. As part of the trial-eligibility screening assessment, patients were asked to report basic demographic information, and had their height, weight, and waist circumference measured. Their blood pressure was measured using a research validated apparatus (IEM Stabil-o-graph ©) and according to a standardised trial protocol (61,62). The trial screened 2558 patients to achieve its target sample size of 1320 participants, allowing for 20% loss to follow-up, (at least 440 in each group) was estimated to detect an absolute mean difference in systolic blood pressure of 5mmHg at 12 months from baseline, with 90% power and 0.05 (two-sided) level of significance (60).

The study received ethics approval from the Human Research Ethics Committee of the University of Cape Town (HREC UCT 418/211), the Oxford Tropical Research Ethics Committee (OXTREC 03–12), and a research governance approval from the Metro District Health Services, Western Cape. The trial conduct was overseen by a trial steering committee and all participants provided a written informed consent (60).

Data from the South African Weather Services consists of temperature and humidity measurements taken in the period of trial screening. Temperature and humidity are recorded within a 10 km radius of the weather station using an internationally standardized method (63). Average hourly temperature readings were recorded and used in the calculation of mean, maximum and minimum of daily temperature (61). Data on other environmental factors such as particulate matter, carbon dioxide and nitrogen dioxide will be requested from the City of Cape Town.

4.2 Population

The study populations consisted of patients attending any of the outpatient services during the trial recruitment period who had been offered referral for assessment and blood pressure measurement.

4.3 Setting

A single large primary care facility serving two diverse communities in Cape Town, South Africa.

4.4 Sample size and sampling procedure

All participants screened for participation into the StAR trial study (n=2558) were recruited as follows. Potential eligible participants for the trial were identified and invited for screening.

Information about the study was made available to potential participants through verbal and written material in an appropriate language (either English, isiXhosa or Afrikaans). Interested individuals were invited to ask a trained research staff questions about the study and their participation. Individuals interested in participating were asked a series of screening questions to assess their eligibility for inclusion in the study and had their blood pressure measured, using a research validated apparatus, according to a standardised protocol (60–62)

4.5 Measurement instruments

4.5.1 Questionnaire

A standardised questionnaire was used to capture basic demographic information such as age, gender, ethnicity, etc. (See Appendix A)

4.5.2 Blood pressure measurements

Blood pressure was measured using a research validated apparatus (IEM Stabil-o-graph ©) and according to the standardised trial protocol (61,62). Briefly, three to six sequential blood pressure measurements were recorded at 3-minute intervals in a sitting position on the right arm supported and elevated at the heart level, by a trained field worker (60,61,64). The mean blood pressure was calculated by discarding the initial reading and taking the mean of the remaining measures (60).

4.5.3 List of study variables

	Variables	**Unit**
Outcome	Blood pressure	mmHg
Exposure	Outdoor temperature	°C
Potential confounders	Humidity	%
	Particulate Matter (PM2.5/10)*	µg/m3

	Carbon dioxide (CO_2)*	Parts per million (ppm)
	Nitrogen dioxide (NO_2)*	μgm^{-3}
	Ozone (O_3)*	μgm^{-3}
	Sulphur dioxide (NO_2)*	µg/m3
	Carbon monoxide (CO)*	Parts per million (ppm)
Other	Age	Years
	BMI	Weight/height square
	Gender	Male or female

*This data will be requested from the City of Cape Town (City Health: Division of Environmental Health)

5. Data Management and Analysis

The management and analysis of the data will be conducted and stored in STATA 12 format (65). The data will be cleaned using a range of logic checks such as checking for double entry data, odd or extreme numbers that may have arisen from a technical error or data capturing error. Dates and other punctuation marks will be converted appropriately into STATA 12. An exploratory analysis will be conducted to determine the population's distribution. A univariate and bivariate analysis will be generated and summary statistics of each variable and outcome will be used to characterise our population of interest.

The association between outdoor temperature and blood pressure will be determined using multiple linear regression analysis. The study uses a hypothesised model with particular variables of interest. Therefore, all the variables to be included in the model will be tested for any violation of assumptions for a multivariate linear regression. Once the assumptions are met, a fitted model with and without potential confounders will be produced and discussed.

6. Reporting and Communication

This study will be performed in partial fulfilment of the Master of Public Health degree at the University of Cape Town. The literature review, study proposal and resulting findings will be written up in the required academic mini-dissertation format and will be held at the University of Cape Town online open access libraries. Furthermore, the research findings will be submitted as a written report to the Chronic Diseases Initiative for Africa (CDIA) of the Department of Medicine at the University of Cape Town and disseminated at its discretion. Lastly, a journal manuscript will be submitted for peer-reviewed publication.

7. Ethics

The study will use anonymised data from the StAR trial study. Access to these data is governed by signed data sharing agreements between Mr Havyarimana and the Clinical Trials Unit, University of Oxford and the CDIA, University of Cape Town. Additionally, approval from the SAWS and the City of Cape Town Department of Environmental Health will be requested for the use of their data for the here proposed study.

8. Timeline

The data analyses and subsequent write up of findings will start as soon as the additional data sourced from the South African Weather Station and the City of Cape Town has been received.

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PART B
Literature Review

Table of Contents

Acronyms

CVD	Cardiovascular disease
LMICs	Low-middle income countries
HICs	High income countries
WMO	World Meteorology Organization
BP	Blood pressure
BPV	Blood pressure variation
MI	Myocardial infarction
95%CI	95% confidence interval
SE	Standard error
NO2	Nitrogen dioxide
SO2	Sulphur dioxide
PM2.5	Particulate matter with 2.5µm diameter aerodynamic
PM10	Particulate matter with 10µm diameter aerodynamic

Glossary of key terms and concepts

i. Outdoor temperature

Outdoor temperature, also known as ambient temperature, is defined as the surface level thermo-measure and indicator of the condition of free air surrounding the weather station (1). According to the World Meteorological Organization (WMO), it is the "temperature indicated by the thermometer exposed to the air in a place sheltered from direct solar radiation"(2). Outdoor temperature is determined by climate, in particular seasonal, atmospheric pressure and ocean circulation. Changes in these climate variables drive both short and long-term variation in outdoor temperature (3). Given this influence, ambient temperature is therefore measured in real-time mainly for purposes of monitoring changes in the climate. Other purposes include monitoring critical warning signs in the atmosphere, such as upcoming storms and tide levels, and research (2).

ii. Seasonal variation

Seasonal variation, also referred to as seasonality, can be described as a cycle of insolation that is a result of the earth's rotation around the sun. The cycles are quantified in time, months and years and are associated with temperature and precipitation variation (4). Precipitation and temperature variation can mostly be observed between winter and summer, and between day and night and they account for the majority of variation in seasonal climate (4). Changes in season, particularly between summer and winter have shown to have several health implications and have been associated with morbidity and mortality. To date, the majority of evidence linking seasonality and health have been in the context of infectious diseases (5). However, there is growing evidence in support of the role that seasonal variation may play in driving seasonal differences in the outcomes and markers associated with cardiovascular disease.

iii. Blood pressure variation

Blood pressure variation is a term used to describe a continuous change in blood pressure for a given period. It is characterised by short and long-term change in blood pressure and can be assessed in beat to beat, minutes and hourly blood pressure measurements (6,7). In addition, blood pressure variation can extend to weeks, months, season and yearly variation. For example, In healthy normotensive individuals, systolic blood pressure can vary by a standard deviation (SD) of 9.5mmHg in 24 hour repeated measurements and 12mmHg SD in fortnightly measurements (8). The standard deviation is the most commonly reported measure of blood pressure variation. It is measured together with other parameters such as the mean difference and coefficient of variance. There is increasing evidence that the coefficient of variance may actually provide a better prognostic and predictive indication of blood pressure change and may provide insight into the short and long term risk associated with cardiovascular disease (5,6).

1. Introduction

There is growing evidence to show that seasonal variation in blood pressure, as seen in the general and cardiovascular disease (CVD) populations, may in part be explained by changes in outdoor temperature (9–16). This association has been shown to be true for clinic, home, office and ambulatory blood pressure measurements, particularly in western and Asian countries (10,17,18).

Moreover, mortality due to CVD have also been shown to follow a seasonal pattern, with higher death rates being seen during cold temperature extremes. Similarly, the risk of hospitalisation due to a coronary event has shown to be two-fold higher in winter compared to summer (19–31).

The cause and mechanism to explain this risk in vascular morbidity and mortality is not yet clear. Several studies have suggest that the effect outdoor temperature has on blood pressure may be large enough to explain some of the outcomes due CVD. However, more evidence is needed to affirm this hypothesis and importantly to validate these findings in vulnerable populations and settings where data is still limited.

Through an extensive search of the literature by this review, it can be seen that majority of studies reporting on the relationship between outdoor temperature/seasonality and blood pressure are predominantly from high income countries (HICs). The reported effects have shown to be trivial and may not have clinical relevance nor be generalizable to low-middle income settings where exposure to extreme climate and temperature may be increased. Few studies from LMICs have shown effects of temperature on blood pressure, is large enough to be clinically important and may even affect management decision of blood pressure care in these settings(12,15,32,33).

LITERATURE REVIEW

1.1.Aim

The review aims to summarise and critically appraise studies reporting the association between seasonality or temperature variation and blood pressure. It also examines the clinical implications of this association for patients living with a cardiovascular disease.

1.2. Objective

To review and discuss:

1. The relationship between outdoor temperature and blood pressure
2. The relationship between seasonality and blood pressure
3. The confounding factors and modifiers of temperature and blood pressure association

1.3. Search strategy

General (strategy 1)

A review was conducted of empirical studies, books and book chapters describing seasonality, outdoor temperature and basic clinical function of blood pressure and variation. Included for assessment was literature reporting on drivers or mediators of blood pressure variation and the clinical implications of such factors on the diagnosis, prognosis and management of blood pressure. The search, not intended to be exhaustive, was conducted in EBSCO, google scholar and by searching through reference list of relevant peer-reviewed journal articles.

Seasonality, outdoor temperature and blood pressure (strategy 2)

Empirical studies reporting on the association between outdoor temperature or seasonality and blood pressure were searched for irrespective of study population. Database searches included Scopus, Google scholar and EBSCO (AfriMed and Medline), of publications from 1960 to 2016. Outdoor temperature, seasonal variation and blood pressure were used as key search terms and all data extraction was done by the author.

In summary, 725 potential articles were identified (from EBSCO in June 2016), of which abstracts both in English were reviewed. Studies with outdoor (including ambient and air) temperature as (main or one of the) exposure(s) of interest AND blood pressure as an outcome were included. In addition, studies demonstrating a relationship between seasonal variation and blood pressure were assessed separately. Excluded, were studies whose population of interest were pregnant women, children and adolescents (<18 years) and studies with a low sample size (<100 for cross sectional and <50 for cohort studies). Lastly, critical reviews, laboratory and animal studies, studies reporting the effect of temperature on the prevalence and incidence of high blood pressure were also excluded. The quality of studies were assessed using the Cochrane handbook on the Preferred Reporting Items for Systematic review and Meta-Analysis method (PRISMA)(34,35) and other related literature (28). This included examining the quality of measured exposure (e.g.: distance of weather station from the clinic, confounders adjusted for) and of the statistical method used (Appendix A).

2. Blood pressure variation and its association with outdoor temperature and seasonality

2.1 Context matters: Assessing the impact of temperature and seasonal variation on blood pressure in high and low-middle income countries.

Several observational studies have indicated that the relationship between outdoor temperature/seasonality and blood pressure may differ across socio-economic groups (36,37), areas (rural vs urban) and access to indoor heating conditions(15). However, it is unclear whether similar differences exists in health care settings between high and low-middle income countries. In most European countries, indoor heating is the single leading source of energy consumption in hospitals across the public sector (38). This is unlikely in low resourced settings where provision of indoor temperature control apparatuses (e.g.: heater or air conditioning) are often limited in care settings. Moreover, at the household level, it is known that several governments in Europe provide large subsidies for energy consumption, particularly for indoor heating, to households with low to middle income (39,40). To our knowledge, no such provision exists for households in LMICs, and more specifically in Sub-Saharan Africa. This difference in access to indoor temperature control may drive differences in the impact of outdoor temperature on blood pressure between HICs and LMICs.

Our reviewing hypothesis is that the relationship between outdoor temperature and blood pressure is of stronger influence in LMICs, as exposure to extreme climate and outdoor temperature is potentially higher due to limited access to household, clinical and work place temperature controlled conditions. The studies have been stratified by the countries' income status as defined by the World Bank (41). Moreover, key findings from this comparison are provided in **Table 1 and 2** and will be discussed in the paragraphs below.

2.1.1 Seasonal variation and blood pressure

2.1.1.1 Findings from low-middle income countries

Previous evidence have already proven that blood pressure variation is strongly associated with seasonal changes in weather pattern. Most studies reporting on this association have predominantly been from HICs. More recently, from 2007 to 2015, studies have been emerging from LMICs and have further supported similar seasonal patterns in blood pressure irrespective of climate and geography (15,37,42–46). Several studies, mostly from Asia, have shown higher effects of seasonality on blood pressure in countries like China and India (15,46). An example of this can be seen from the findings by Lewington et al., 2012 and Sinha et al. 2011 (15,47). The study by Lewington et al., 2012 assessed the seasonal variation of blood pressure across 10 of China's provinces. Its observations were that the mean difference in systolic blood pressure (SBP) between winter and summer was as much as 10mmHg, with rural provinces with primarily no access to indoor heating, recording as much as 20mmHg change in SBP (15) . Similarly, Sinha et al., 2011 observed that among adult women from a peri-urban setting in India, who enrolled for the study at different times of the year, had a mean difference in SBP of 11mmHg ($p<0.001$) between winter and summer. Additionally, in a population of elderly people living with hypertension in South Korea, Youn, et al., 2007 showed a 9mmHg ($p<0,001$) mean difference in SBP between winter and summer(45).

Furthermore, fewer studies showing an association between seasonality and blood pressure have been published from Sub-Sahara Africa (SSA). The studies identified from our search (Search strategy 2) shows that, for instance, in South Africa, Cois and Ehrlich, 2015, observed a 4.25mmHg (95%CI: 3.18 – 5.31) and 4.21 mmHg (95% CI: 2.98 – 5.44) mean difference in SBP between winter and summer, in men and women respectively. Similarly, Hightower et al., 2009 observed similar differences (2.7mmHg (SD ±2.6)) in a small sample size study in Kinshasa, Congo. Furthermore, Cois and Ehrlich R., 2015 observed seasonal differences in blood pressure between individuals from high and low-middle income households. This difference ranged from 2.4mmHg to 7.7mmHg in blood pressure depending on gender and socio-economic indicator. These findings further shed light on important factors that may modify the relationship between seasonality and blood pressure at country or regional level.

2.1.1.2 Findings from high income countries

Given that there are no studies comparing LMIC-settings with HIC-settings, there exists a gap in understanding on whether or not the strength of this association is greater in LMICs than HICs and to what extent this might be. According to findings from studies identified from HICs (Table 1), it can be seen that the strength of the association between seasonality and blood pressure may be moderate in these settings compared to findings from LMICs. For instance, it can be seen in nearly 70% (8 out of 12) of studies identified from HICs, that the difference in mean SBP between winter and summer was ≤ 3.5mmHg. This in contrary to findings from LMICs, where this seasonal difference in mean SBP was on average higher (≥ 5mmHg) in 60% of studies (48–56). A meta-analysis of population-level data from 16 HICs (13 European, 1 North American and 2 from Oceania) shows a seasonal variation in blood pressure. After adjusting for variations in individual monthly measurements of blood pressure, the difference in mean SBP between summer and winter was 2.06mmHg (95% CI: 1.05; 3.08) (48). Similarly, Ulmer et al., 2004, analysed blood pressure data from 149,650 people who took part in a health monitoring survey in Austria. They showed that seasonal variation accounted for 2.25mmHg and 2.03mmHg mean SBP differences between winter and summer for men and women respectively (52).

Moreover, similar patterns have been seen in people living with hypertension and studies show that the effect seasonality on blood pressure could impact the treatment of high blood pressure especially in vulnerable groups like the (56–58). Findings from Fedeconstante et al., 2012, a study of people living with hypertension, showed that those on treatment and with controlled blood pressure during the course of medication, although not significant, had 0.9mmHg ($p>0.05$) higher SBP levels in winter compared to summer (56). With a value of 2.7 mmHg ($p<0.009$), this increase was evidently higher and significant for individuals on treatment but without controlled blood pressure levels.

While mechanisms explaining this effect of seasonality on blood pressure needs further investigated, several studies have proposed that outdoor temperature, a leading marker of seasonality and climate variation, may explain a large proportion of this variation in blood pressure. In the next chapter, data from studies in HICs and LMICs will be assessed and compared to illuminate on the impact of temperature in these two different types of settings.

Table 1: Studies reporting the association between seasonal variation and blood pressure

Author	Population / data source	Setting & period examined	Sample Size	Study design & analysis	Seasons compared	Key results (Summer – Winter)
Low-middle income countries						
Hightower et al., 2009 (42)	Rural residents of Kassena-Nankana, Ghana	Kinshasa, Congo (DRC)	232	Cross sectional time series Not mentioned	End of Winter vs end of summer	2.7mmHg SBP (SD ±2.6)
Lewington et al., 2012 (15)	General population from 10 provinces in China	10 cities, China 2004 - 2008	506673	Cross sectional, Multivariate linear regression	Winter vs summer	10 mmHg SBP (p<0.0001)
Cois A & Ehrlich R., 2015(37)	General population in South Africa	South Africa 2010 & 2012	11440	Cross-sectional, multilevel linear structural equation model	All seasons	**Women:** 4, 25mmHg SBP (95%CI: 3.18 – 5.31). **Men:** 4.21mmHg SBP (95% CI: 2.98 – 5.44)
Tu et al., 2013 (43)	General population from 4 major cities in Taiwan	4 cities in Taiwan 1996 – 2006	68045	Prospective repeated & single measures cohort GEE	All seasons	5.3mmHg SBP (SE=0.07)
Askari et al.,2014 (44)	Urban Population from Tehran Iran (>20 years)	Tehran, Iran 1998 - 2001	29777	Prospective cohort ANOVA & post-hoc pairwise Turkey test	All seasons	3mmHg SP (P<0.01)
Youn et al., 2007 (45)	Elderly people living with hypertension (≥ 55 years) patients	Yonsei, South Korea 2002 - 2005	85	Prospective cohort Multivariate linear regression	All seasons	9mmHg SBP (p<0,001)

Sinha et al., 2010 (46)	Adult females (>18years old) residing in a Peri-urban area of Gokulpiri, New Dheli, India	India 2 years	132	Prospective cohort & Paired t-test	Winter vs summer	11mmHg SBP (p<0.001)

High Income countries

Barnett et al., 2007(48)	25 populations from 16 countries in Europe & Oceania	Europe & Oceania 1979 - 1997	115234	Prospective cross-sectional GLMM[1]	Mid-winter vs mid-summer	2.06 mmHg (95% PI: 1, 05; 3, 08).
Kristal-Boneh et al.,1996 (59)	Factory workers, machining departments	Israeli Not reported	101	Cross sectional ANOVA	Winter vs summer	3.4mmHg SBP (p0.01)
Minami et al., 1998 (50)	Outpatients with essential hypertension	Japan	315	Prospective cohort, ANOVA	Winter vs summer	1.5mmHg (SD:±1.3)
Prasad GV, Nash M, Zaltzam S., 2001 (60)	Stable renal transplant recipients	Canada Not reported	163	Cross sectional	Winter vs summer	2.3mmHg (p<0.01)
Ulmer et al., 2004 (52)	Generla population in Austria	Austria 1985 - 1999	149650	Cross-sectional time series GEE[2]	Winter vs summer	**Men:** 2.25 (p<0.001) **Women:** 2.03 (p<0.001)
Madsen and Nafstad., 2006 (53)	General population in Oslo, Norway	Oslo, Norway 2000 - 2001	18770	Cross sectional time series GLM	Winter vs summer	**Men:** 0.53 (95%CI:-2.20; 1.13) **Women:** 1.08 (95%CI: 0.52 – 2.69)

[1] Generalized linear mixed effect model (GLMM)
[2] Generalized estimating equation (GEE)

Hopstock et al., 2013 (54)	Gneral population from Tromso, Norway	Tromso, Norway 1979 -2008	38037	Cohort & cross-section time series Multivariate & mixed effect linear regression	All seasons	2mmHg SBP (p<0.001).
Modesti PA et al., 2013 (55)	Outpatients referred for ABP monitoring in Florence, Italy	Florence, Italy 2005 - 2007	1897	Cross sectional Multivariate linear analysis	All seasons	2.7mmHg, (p<0.001).
Fedeconstante M et al., 2012	Adults (≥ 18 years) with hypertension (75%) & normal BP (25%) in Marche, Italy	Marche, Italy 2002 - 2011	1395	Cross sectional Logistic regression	Winter vs summer	**People wt normal BP** 2.4 mmHg (p<0.001) **People wt high BP** 2.7mmHg (p=0.017) **People wt Controlled high BP on treatment** 0.9mmHg SBP (p>0.05) **People wt Uncontrolled high BP on treatment** 2.7 mmHg (p<0.009)
Seguro et al.,1992 (61)	People with hypertension on treatment in Cagliari	Cagliari, Italy 1981 – 1990	145	Prospective cohort Paired t-test	All season	5.0mmHg (P<0.05)
Alperovitch et.al 2009 (62)	Elderly popultion (≥ 65 years) from Bordeaux, Dijon and Montpellier in France	3 Cities, France 1999 – 2002	9294	Prospective cohort & Bartlett- Kolmogorov-Smirnov test	All seasons	5.0mmHg (p<0.001)
Sega et al., 1996 (63)	Population of Monza area in Italy (25 – 64 years)	Monza, Italy 1989 – 1993	2051	Cross sectional Unpaired T-test	All seasons	**Clinic BP** 4.5mmHg (p<0.05) **Home SBP** 6mmHg (P<0.01) **24hr SBP** 4.1mmHg (p<0.001)

2.1.2 Outdoor temperature and blood pressure.

2.1.2.1 Findings from Low middle income countries.

Similar to data on seasonality and blood pressure, outdoor temperature has been shown to be associated with changes in blood pressure. The majority of studies reporting this association have predominantly been from Europe. However, as more studies emerge from countries in low-middle income settings, it is important to assess the effect of temperature in these settings in order to achieve better blood pressure management decisions and care.

As such, findings from studies in LMICs and HICs were collated and summarised in **Table 2**. In summary, based on findings from the majority of studies in LMICs, a 10°C increase or decrease in outdoor temperature was associated with a more than 5mmHg change in SBP. This pattern of effect was observed in four (12,15,33,46) of the five studies identified from our search (**search strategy 2**) . The highest effect of temperature on blood pressure was seen in adult women from India who were recruited at different times of the year. Irrespective of seasonal change, the authors observed a 1°C (OR 10°C) decrease in outdoor temperature was associated with 0.88mmHg increase in SBP (OR 8.8mmHg) (95% CI: -1.73; -0.36) (46).

Similarly, in a study by Su et al., 2014, in a rural population located in the eastern-coastal region (Zhejiang province) in China, it was observed that a 10°C decrease in outdoor temperature was associated with 6.9mmHg increase in SBP after adjusting for important confounders. Additionally, a large population study also from China, with more than a half a million participants from both rural and urban areas, showed that at 10°C decrease in outdoor temperature was associated with 5.7mmHg (SE=0.04) increase in SBP after adjusting for important environmental and cardiovascular risk factors (15). Conversely, findings from Chen et al., 2012, a cohort study of participants from Shanghai area, one of the most affluent cities in China, showed however one of the weakest effects of outdoor temperature on blood pressure, both at baseline (2.66mmHg/10°C) and follow up (2.14mmHg/10°C) (64). This within-country variation could be a result of difference in socio-economic status between cities and provinces, therefore leading to better access to indoor temperature control in some parts over others.

Overall, it can be observed that there are subtle differences in effects of temperature on blood pressure of urban (15,64) versus rural (12,33) populations and households which have access to indoor heating versus those without (15). One notable limitation across the majority of studies was that they did not take into account nor report adjusting for important cardiovascular or environmental confounders like air pollution, humidity, smoking, diet and socio-economic status (12,15,33,46). These factors (e.g.: air pollution and humidity) have shown to be independently associated with blood pressure and both air pollution and humidity can very well vary by season and may therefore be associated with temperature changes across the year (37,45,65,66). Hence, these factors should be taken into account for future studies and for studies assessing the impact of temperature and seasonality on blood pressure and cardiovascular health

2.1.2.2 Findings from High income countries

Key findings from studies identified from HICs show that the effect of outdoor temperature on blood pressure may be moderate in northern hemispheric countries and has been related to a generally better access to indoor temperature control compared to LMICs. For instance, results from a meta-analysis of temperature and blood pressure data from 25 cities in 16 European and North American countries, show that a 10° C increase in mean outdoor temperature was associated with 1.9mmHg (95% CI: -2.6; -1.1) decrease in SBP after adjusting for seasonality (48). Furthermore, similar observations were seen in other individual studies from Europe and North America. In a study by Andersen et al., 2002 which assessed the impact of temperature on blood pressure in urban populations from Copenhagen, Denmark, it was observed that at a 10°C decrease in outdoor temperature was associated with 1.6mmHg decrease in systolic blood pressure (14). In the neighbouring country, Norway, Madsen and Nafstad., 2006, showed

1.5mmHg (95% CI: 0.6; 2.3) and 2.4mmHg (95% CI: 1.6; 3.2) increase in SBP among men and women for every 10°C decrease in outdoor temperature, respectively (53).

Moreover, for studies that had access only to daily minimum and maximum temperature, it was observed by Bruce et al., 1991, that exposure to daily minimum temperature, typically observed in the mornings, was associated with 0.38mmHg ($p= <0.001$) decrease in SBP per 1°C increase in temperature (67). Kent et al., 2011 also observed a 0.7 mmHg (95% CI 3.0; 1.0) increase in SBP per 1°C change in outdoor temperature in a cohort of American men and women from 48 conterminous states in America (68).

Overall, for majority of studies found in HICs, it was unclear whether blood pressure reported was measured in temperature regulated areas/room. This was mostly common in studies using secondary data from survey studies which measured BP from home and in clinical settings, although this is under reported and is not clear. Furthermore while most of the studies adjusted for important cardiovascular risk factors such as smoking, diet and exercise, nearly 90% of all of the studies did not include environmental confounders like sulphur dioxide, nitrogen dioxide and particulate matter in the adjustment.

These factors have shown to be independently associated with blood pressure and seasonality and may potentially mask the observed effects in majority of these studies. For the next section, the role of different potential confounders in driving changes in

Table 2: Studies reporting on the association between outdoor temperature and blood pressure

Author	Population / data source	Sample Size	Setting & period examined	Study design & analysis	Temperature meas. used & distance from BP meas.	Variables adjusted for	Key results
Low-middle income countries							
Kunutsor and Powles, 2010 (33)	Rural residents of Kassena-Nankana, Ghana	574	Kassena-Nankana, Ghana N/A	Cross-sectional Multivariate linear regression	Outdoor Not reported	Age, gender, BMI, waist, time of BP measurement	5mmHg SBP/ 10°C (P=0.047) Mean daytime temperature
Lewington et al., 2012 (15)	General population from 10 provinces in China	506673	10 provinces, China 2004 - 2008	Cross-sectional Multivariate linear regression	Outdoor 15km	Age, sex, BMI, study area, humidity	5.7mmHg) SBP / 10°C (SE:0.04) (Mean daytime temperature >5°C)
Su et al., 2014 (12)	Rural residents of, Zhejiang province in China	57375	Zhejiang, China 2004 - 2008	Cross-sectional Multivariate linear regression	Outdoor	Age, sex, education, season (month), physical activity, diet and BMI	6.9mmHg SBP/10°C (no P-value or 95%CI reported) Mean daytime temperature
Sinha et al., 2010 (46)	Adult females (>18years old) residing in a Peri-urban area of Gokulpiri, New Dheli, India	132	New Dheli, India 2004 - 2005	Cross-sectional Multivariate linear regression	Outdoor Not reported	Age, BMI, day length	8.8mmHg/ 10°C (95% CI: -10.73; -3.06) Mean daytime temperature

Chen et al., 2013 (64)	People with hypertension residing in an urban area in Shanghai	1831	Shanghai, China 1997 – 2001	Prospective cohort Multilevel model	Outdoor Not reported	Age, sex, BMI, drinking & smoking, urine, medication duration, urine, baseline BP	**Baseline** - 2.66/10°C SBP (95% CI: -3.52; -0.181). Mean daytime temperature **3 year follow up** -2.14mmHg SBP/10°C (95% CI: -2.22; -2.06). Mean daytime temperature

High Income Countries

Bruce et al., 1991 (67)	Men from 24 towns in Britain	7735	24 Towns England 1978 - 1980	Cross sectional Multivariate linear regression	Outdoor Not reported	Age sex, BMI, smoking, diet	3.8mmHg SBP/ +10°C (p= <0.001) daily maximum daytime temperature
Andersen et al., 2002 (14)	General population of Copenhagen, Denmark	19698	Copenhagen Denmark 1976 - 1994	Cross sectional time series Multivariate linear regression	Outdoor Not reported	Not reported	1.6mmHg SBP/ 10°C . Mean daytime temperature
Madsen and Nafstad., 2006 (53)	Residents of Oslo, Norway	18770	Oslo, Norway 2000 - 2001	Cross sectional & General linear regression (GLM)	Outdoor Not reported	Age, sex, BMI, education, alcohol, day, month, year & TSM	**Men** 1.5mmHg SBP/-10℃ (95% CI: 0.6–2.3 and 0.1-1.8mmHg) **Women** 2.4 mmHg SBP/10℃ (95% CI – 1.6; 3.2) Mean daytime temperature

Barnett et al., 2007 (48)	25 populations from 16 countries in Europe & Oceania	115434	16 countries (Europe & US)	cross-sectional time-series Bayesian hierarchal model	Outdoor Not reported	Age, sex, type of sphygmomanometer.	3.1mmHg SBP/10° C (95% CI: -4.4; -1.9) Mean daytime temperature
Kent et al., 2011 (36)	General population (>45 years old) from 48 states in the USA	20623	48 contermino us USA 2003-2006	Cross-sectional Multivariate linear regression	Outdoor Not reported	Demographic (age, sex...etc.) Socio-economic (income & education), behavioural (alcohol & smoking), season (months)	0.7 mmHg SBP/1°C (95% CI 3.0; 1.0) (Daily min. daytime temperature ≤ 6.7°C) 1.4 mmHg SBP/1°C (95% CI 1.0; 1.9) (Daily max. daytime temperature ≤ 6.7°C)
Modesti et al., 2013 (55)	Outpatients referred for ambulatory BP monitoring to Hypertension clinic	1897	Florence, Italy 2005 - 2007	Cross-sectional Multivariate linear regression	Personal level environment (PET) & outdoor	Daylight hrs, age, BMI, HR, office BP, atm. Pressure, humidity, sex, geographical location	1.4mmHg/ 10°C (95% CI: -2.5; -0.20) SBP. Mean daytime temperature
Saeki et al.,2014 (69)	Residents of Nara, Kensai - Japan	868	Kensai, Japan 2010 - 2013	Cross-sectional Two-level Multivariate linear regression	Indoor & Outdoor Not reported	Individual level: Age, sex, smoking, alcohol, ATH meds Measurement day-level: Temperature & physical activity at BP measurements	2.9mmHg SBP /-10°C (95% CI 0.9-4.9) Mean daytime temperature
Hoffmann et al., 2012 (70)	Subjects with Type 2 Diabetes Mellitus (T2D)	70	Boston USA	Prospective cohort	Outdoor 12 km	Age, sex, BMI, HbAc1, season, air	An increase in 5 day mean daytime temperature by 11.5°C (IQR), was

			2006 - 2010	Linear mixed effect model		quality (PM2.5, SO4, BC, EC, OC, PNC)	associated with 2.5% decrease (95% CI -5.1%-0.2) in relative SBP and 3.2mmHg decrease (95% CI -6.6 - 0.3mmHg) in absolute SBP
Hozawa et al., 2011 (13)	Rural Residents of Nishiazu, Japan	79	Nishiazu, Japan 2000 - 2003	Prospective cohort Generalized mixed linear model (GLM)	Outdoor Not reported	Adjusted for different levels/category of temperature	4.0mmHg SBP/10°C. (Mean daytime temperature ≥10°C) 0.6mmHg SBP/1°C. (Mean daytime temperature ≤10°C)
Brook et al., 2011 (71)	Participants residing in Detroit, Michigan, USA	51	Michigan, USA 2005 - 2007	Cross-sectional Multivariate linear mixed regression	Outdoor (4 – 28 km) PET	Age, sex, gender, race, BMI, Time	**Morning BP** 1.44mmHg/1°C with 10 - 15 hours-long of PET measurement **Late night BP** 0.81/mmHg/1°C PET with 10 - 15 hours-long of PET measurement.
Kunes et al., 1991 (72)	People with hypertension residing in Montreal, Canada	2000	Montreal Canada 1990	Cross-sectional Parametric test & correlation	Outdoor Not reported	Not reported	The effect temperature was observed between range of 24°C to 27°C which was associated with the greatest BP difference of 7mmHg
Jehn et al., 2002 (18)	People with mild hypertension residing in CA,MA &NC[3]	333	3 cities, USA 1995 - 1996	Cross sectional Multivariate linear regression	Outdoor Not reported	Age, sex, BMI, clinic centre	Outdoor temperature ranging between 3°C - 10°C was associated 12.7/11.2 mmHg BP 24hr variability.

[3] CA: California, MA: Massachusetts, NC: North Carolina

Alperovitch et.al 2009 (62)	General population in Bordeaux, Dijon, Montpellier in France	8081	3 cities France 1999 - 2002	Retrospective cohort ANOVA	Outdoor Not reported	Not reported	**80 years and older vs 65-74 years** 5.1mmHg C SBP /-15° .Mean daytime temperature
Halonen et al., 2011 (73)	Elderly men (53-100 years old) residing in Boston area, USA	2280	Boston, America 1990 - 2009	Retrospective cohort Mixed effect model	Outdoor Not reported	Demographic (age, sex, BMI…etc.) behavioural (smoking & alcohol) treatment (hypertension, diabetes) education, season and black carbon	**5 days' lag** 0.68%/-5°C (95%CI: 0.04; 1.33%) increase in DBP. **7-day cumulative** 2.13%/-5°C SBP (95% CI 0.66% - 3.63%) Mean daytime temperature
Brennan et al.,1982 (16)	General population in England, Scotland and Wales and	17282	UK (England Scotland and Wales) 1977 – 1981	Retrospective cohort Linear regression	Outdoor Not reported	Not reported	**≥ 65 years placebo group** 6.1mmHg /20°C change in max. air temperature (i.e.: the difference between a hot summer day and cold day) **Bendrofluazide group** 6.4 mmHg/20°C change **propranolol group** 7.3/3.5 mmHg20°C change. Mean daytime temperature

3. Important confounding factors independently associated with blood pressure, seasonality and outdoor temperature

3.1. Air pollution

According to the World Health Organization (WHO, 2008), urban outdoor air pollution accounts for 1.34 million deaths globally, with LMICs being subjected to the majority of this burden (74). At particular risk are individuals living with a cardiovascular disease and those 65 years and older (75–80). A number of studies have indicated that the impact of air pollution on cardiovascular health and outcome may be through its association with blood pressure. For this section, studies reporting on the relationship between outdoor air pollution and blood pressure were evaluated and are summarised below. In addition, an assessment is made of the trends in air pollution across different seasons and implications of these trends for the modelling and reporting of temperature effects on blood pressure are discussed.

3.1.1. Nitrogen dioxide and Sulphur dioxide

Nitrogen dioxide (NO_2) and sulphur dioxide (SO_2), the two main by-products of fuel, coal and gas consumption (81,82), are considered to be one of the leading sources of air pollution in LMICs. Studies from countries with high levels of air pollution (e.g.: China and South Korea) have showed that both NO_2 and SO_2 are associated with increases in blood pressure, although the overall evidence is still mixed. (81,82). For example, Kim et al., 2016, when studying a population of elderly people living in an urban area in Seoul, South Korea, found an incremental increase of 16.8 ppb (parts per billion of air volume) for NO_2 and 2.4 ppb for SO_2, was respectively associated with an 0.96mmHg (95% CI: 0.18; 1.74) and 1.60mmHg (95%CI: 0.79; 2.42) increase in SBP after adjusting for age, BMI, sex, smoking, drinking, hypertension medication and temperature (83). Similarly, Dong et al., 2013 highlighted using population level data (n=24,845) from three urban areas in China, that short-term exposure (from 1 to 24 hours) to SO_2 (IQR 20µg/m^3 increase) and NO_2 (IQR 9µg/m^3 increase) was associated with 0.80mmHg (95%CI: 0.46; 1.14) and 0.21mmHg (95%CI: 0.21; 0.68) increase in mean arterial blood pressure after adjusting for important CVD risk factors. Similarly, Foraster et al.,2014, showed a positive association between long-term exposure to NO_2 and blood pressure increase in a in cohort of adults in Spain (n=3,700). Here, a 10µg/m^3 increase in NO_2 was reported to drive a 1.34mmHg (95%CI: 0.14; 2.55) increase in SBP among healthy, non-smoking adults (84).

Conversely, Choi et al., 2006, reported an inverse association between air pollution and blood pressure that was related to seasonality. In this study, the authors found that both NO_2 and SO_2 levels followed a seasonal pattern, with high NO_2 and SO_2 levels in winter (29.2ppb and 6.9 ppb) compared to summer (22.5ppb and 5.1 ppb) (85). More studies have indicated that air pollution follows a diurnal and seasonal pattern (86). Given the seasonal variation of air pollution and its association with blood pressure, the seasonality of air pollution should be taken into account when modelling the relationship between temperature and blood pressure.

3.1.2. Particulate matter

Particulate matter (PM) is characterised by small aero particles consisting of carbonates, silica or silicates and iron bio-waste found mostly in urban settings. PM is measured and reported as the daily or annual concentration of particles (2,5 or 10 microns in size) per cubic meter of air volume (87). The most harmful particles are those with a diameter of 10 microns, these have been shown to be associated with outcomes related to respiratory and cardiovascular disease (88–91). A systematic review by Mustafic et al, 2012, shows that at each incremental increase of 10µg/m3 in PM of 2.5µM and 10µM was associated with 0.6% (1.006 - 95% CI: 1.002; 1.009) and 2.5% (1.025 - 95% CI: 1.015; 1.036) increased risk for hospitalisation due to a myocardial infarction, respectively (90). Similarly, several studies have indicated that increases in PM2.5 and 10 levels are associated with higher systolic blood pressure, although some studies have indicated inverse effects. For example, in a study by Ibald-Mulli et al., 2013, reported that a 90µg/m^3 increase in total suspended particulate matter (PM of 2.5 and 10 µM) was associated with a 1.79mmHg increase in SBP of Augsburg's urban population in Germany. Conversely indings by by Liu et al., 2013, showed that a short-term exposure (1-24 hrs) to PM 2.5, at an inter-qaurtile range increase of 9.6µg/m^3 was associated with 0.36mmHg (95% CI: -1.24; -0.53) lower SBP in Canadian population leaving near a steel plant. Given, this evidence about PM role in driving changes in BP, it may be important to adjust for it in the assessment of temperature and seasonal effect on blood pressure.

3.2. Relative Humidity

Relative humidity, defined as the amount of water vapour in the atmosphere at a given temperature and pressure level, is an important climate predictor of weather and seasonal forecast (2,92). Given the relative dependence of humidity on temperature, variation in outdoor temperature therefore determines changes in relative humidity at a given period. For example, decreases in outdoor temperature, during winter for instance, are associated with increases in relative humidity and vice versa for humidity in summer (92). Similar patterns can be seen diurnally, with lower temperatures during the early hours of the day (morning) being associated with higher relative humidity compare to afternoons. Overall, the relationship between relative humidity and outdoor temperature is inverse with some studies reporting a seasonal variation (92,93). Studies that have reported on the relationship between relative humidity and CVD outcome show that it's effect are trivial and is generally not strongly correlated with any markers of cardiovascular health (94). Misailidou et al., 2006, assessment of blood pressure data from 5 rural cities in Greece, a Mediterranean region with wet and mild winters; showed that a 1% increase in mean relative humidity was associated with a 0.07% (95%CI: 0.032 0.011) increased risk for hospital admission due to acute myocardial infarction (95).. Similar minimal effects have been reported in relation to blood pressure. Modesti et al., 2013, observed that in an adult population seen at a hypertension clinic in Italy, a 1% increase in outdoor relative humidity was associated with 0.02mmHg increase in mean SBP after adjusting for temperature and important CVD risk factors (55).

4. Populations at particular risk for temperature and season-associated changes in blood pressure

4.1. Age

It has been shown that the risk associated with CVD and cardiovascular outcome follows a seasonal pattern (96). At particular risk are elderly who have shown to have higher blood pressure during winter than summer. This effect was first observed in a clinical trial by Brennan and colleagues, 1982, which assessed the impact of seasonality and temperature on arterial blood pressure of individuals living with hypertension in the United Kingdom. In this study, it was observed that, those participants who were 65 years and older had a 4.4mmHg higher arterial blood pressure attributable to a 20°C change in maximum ambient temperature, compared to those 40 years and younger (16). This trend has been observed in more recent studies in other populations, including Taiwan, China, Korea, Germany and Italy (15,17,55,97). For instance, Lewington and colleagues' study in China showed that, among those 60 years and older, the transition in climate from winter to summer was associated with a 11.2mmHg higher SBP compared to those 30 years and younger (15).

4.2. Gender

It is known that men are at a higher risk for CVD early on in life. However, the risk at CVD increases with age in women and even leads to higher mortality among older women than in older men (98). Therefore, understanding differences in effects of seasonality and temperature across gender could help improve management decisions of blood pressure care in LMICs. To date, results from most studies reporting on seasonality and blood pressure show that men have a higher seasonal variation in blood pressure compared to women. Tu et al., 2012, found that, in an adult population from Taiwan, overall blood pressure levels were higher by 5.3mmHg (SE=0.07) SBP in winter compared to summer. This difference was further reported to be more pronounced in men than in women (97). In a population with type 2 diabetes, studied by Lanzinger and colleagues, 2014, differences were found between men (0.8mmHg - 95% CI: 1.4mmH; 2.1mmHg) and women (0.1mmHg 95% CI: -1.00mmHg; 0.8mmHg) (99).

4.3. BMI

The varying effect of temperature and seasonality on BMI is particularly important among those with low BMI. The majority of studies reporting on the modifying effect BMI has on blood pressure, show that those with low BMI (≤18kg/m^2) are most sensitive to temperature and seasonal variation and therefore may potentially be at risk for seasonal and climate related outcomes. For example, In a study by Lewington and colleagues, 2012, it was reported that those with low BMI (15-18.4kg/m^2) had a 2% (0.3mmHg) higher SBP compared to those with high BMI (30-39kg/m2) for every 1°C change in outdoor temperature (15). Similarly, in a study by Madaniyazi and colleagues published in 2016, it was reported that those with a BMI of 18.5kg/m^2 or less, a 1°C change in outdoor temperature was associated with 0.379mmHg (95%CI: 0.089;0.668) higher SBP compared to those with a BMI of 23.9kg/m^2 and higher (0.133 95%CI: 0.086;0.181) (99). Conversely, some studies have reported opposite effects, with those with a high BMI having a 0.6mmHg (95% CI: 0.100;1.400) higher SBP for every 1°C change in outdoor temperature, compared to those with low BMI (0.2mmHg 95% CI: -0.200;0.400) (100).

4.4. Socio-economic status

A number of studies from HICs and LMICs have indicated that the effect of seasonality on blood pressure may vary by income group (37,68). For example, in a cross-sectional study by Kent et al., 2011, it was reported that the effect of daily minimum temperature was higher (8.0mmHg SBP, 95%CI: 7.2;8.7) in those with a yearly income of $20,000 or less compared to those earning between $35,000 and $75,000 (1.7mmHg, 95%CI: 1.0;2,3) (68). Similarly, Cois and Ehrlich's identified socioeconomic status as a modifier of the seasonal effect on blood pressure in their research on a South African adult population (37). The lowest income tertile and no education, indicators of socioeconomic status, were associated with a higher seasonal effect on blood pressure. This variation in blood pressure may be explained by access to indoor climate control condition and a consequently more varying degree and higher extremes of temperature exposure. Those from high income households are generally at lower risk for cardiovascular outcomes and in addition may have better access to household and indoor climate control conditions. Consequently, those of low income may be vulnerable to temperature associated effects and may be at greater risk for cardiovascular outcomes.

4.5. Antihypertension medication

The modifying effect of antihypertension agents on reducing seasonal variation in blood pressure was initially observed by Brennan and colleagues, 1982, in a comparative analysis of Bendrofluazide and Propranolol in England. After a 3 year follow up period, the authors observed lower seasonal difference in blood pressure in patients on Bendrofluazide (thiazide diuretics) treatment compared to Propranolol, more specifically in men (16). Similarly, a more recent Chinese study was done by Chen et al.,2013, on individuals exposed to varying seasonal temperature. Those on Benazepril, an angiotensin converting enzyme inhibitor (ACEI) treatment, appeared to have lower systolic blood pressure measured during a three year follow up of treatment (16,64). However, there is still a gap in evidence on the actual effect of antihypertension treatment on the relationship between seasonality and blood pressure as little is known about the resulting relationship after controlling for other modifying factors.

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APPENDIX 1 – Search Strategy

Search Strategy (Blood pressure, seasonal variation and outdoor temperature)

Keywords:

(Outdoor temperature OR ambient temperature OR air temperature) AND (season OR seasonality OR seasonal variation OR seasonal temperature) AND (blood pressure OR arterial blood pressure OR systolic blood pressure OR diastolic blood pressure)

Studies on outdoor temperature and blood pressure were sought irrespective of population characteristics. Databases searched included Scopus, Google scholar and EBSCO (Africa-Wide information and Medline). Keywords used were Outdoor temperature, seasonal variation and blood pressure. EBSCO gave best search results with **725 potential articles** identified. Abstracts (both English and non-English) were reviewed looking for articles on seasonality, outdoor temperature and blood pressure as subject of interest

610 Articles not linking the effect of seasonality and outdoor temperature on blood pressure were excluded

115 abstract were reviewed

73 studies excluded for not meeting the inclusion criteria

42 articles on seasonal variation and Outdoor temperature on blood pressure.

3 studies excluded because of data repetition by the same authors. 1 excluded due to inappropriate data (e.g.: data was exploratory with correlation result)

39 papers studied and analysed in detail

PART C
JOURNAL
MANUSCRIPT

Table of Contents

Temperature associated variation in clinic-measured blood pressure: secondary analysis of baseline data from the SMS-text Adherence support trial.

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Key words:

- **Outdoor temperature, seasonal variation, blood pressure**

1. Abstract

Rationale – Seasonal and diurnal variation of blood pressure measures have been shown to be associated with changes in outdoor temperature. This association may in part explain the excess incidence of hospitalisation and mortality due to a cardiovascular disease in winter. The present study investigates the relationship between outdoor temperature and blood pressure of adults living with high blood pressure and who were cared for in an outpatient primary care clinic with limited control to indoor climate.

Method – Blood pressure measurements from 2,494 participants screened for eligibility and entry in the SMS-text Adherence (StAR) trial study were used for this study. Clinic data from the trial was merged with the 24-hour outdoor temperature and air quality data from the nearest weather and air quality station in Cape Town, South Africa. Both temperature and air quality data were recorded using instruments and methods in line with the world meteorological and health organization guidelines. Inclusion criteria for the present study was participants screened and enrolled during the trial enrolment period (June 2012 and November 2012) and operating hours (7h00 and 17h00).

Result - 72% of individuals screened for the trial were female with a BMI of 31 kg/m^2 and generally had a higher mean blood pressure in winter and mornings (07h00-10h00) compared to spring and afternoons (≥13h00). The mean outdoor temperature during the trial enrolment was 16.7°C (3.7°C – 30.7°C) with lowest temperatures recorded in winter (June). Both, outdoor temperature and blood pressure were found to be associated with nitrogen and sulphur dioxide and therefore may be confounded by air pollution. In a multivariate analysis adjusting for the confounding effect of air pollution and humidity, a 10°C increase/decrease in outdoor temperature was associated with 7.5mmHg (95% CI: 3, 82 - 11, 18) change in systolic blood pressure. Similarly, the effects of temperature remained in a sensitivity analysis including a range of leading risk factors for CVD. Lastly, the effect of outdoor temperature on blood pressure were higher in those 65 years and older, those with a low BMI and those whose blood pressure were recorded in the morning (7h00 – 10h00).

Conclusion –The study shows an inverse association between outdoor temperature and clinic-based blood pressure measurements in South Africa. Given the fact that clinic-based blood pressure measures are used to the direct management of hypertension, greater attention needs to be given to environmental factors which may affect it. This may become of greater clinical relevance with changes in climate and extreme weather patterns, including extensive smog.

2. Introduction

In South Africa, high blood pressure accounts for 42% and 50% of stroke and ischaemic heart disease, making it the single leading cause of cardiovascular morbidity and mortality (1,2). As such, managing blood pressure in people living with high blood pressure is highlighted to be an important for prevention and control of cardiovascular diseases (CVD) (3,4). Currently, strategies and guidelines for diagnosis and management of high blood pressure focuses on monitoring and reducing the monthly mean blood pressure assessed at a once-a-month at the clinic visit (5). However, it is known that mean blood pressure measurements vary between weeks, months and seasons (6–12). This short and long-term variation of blood pressure is reported to be associated with an increased odds of hospitalisation and mortality due to CVD (12–16).

Mechanisms explaining this risk due blood pressure variation (BPV) are not yet clear. Few studies have indicated that outdoor temperature, an important marker of daytime and seasonal climate, may explain the variation in blood pressure measurement and therefore the risk associated with it (17–20). A recent systematic review and meta-analysis by Wang et al., 2017 showed that a 10°C decrease in mean outdoor temperature is associated with a 2.6mmHg (95% CI: 1.8 – 3.3) increase in SBP of the general population (17). At particular risk are individuals living with CVD as a 10°C decrease in temperature was shown to be associated with a 4.1mmHg (95% CI: 2.0 – 6.1) increase in SBP.

Notably, majority of studies (9 out of 14 studies) included in this meta-analysis were from high income countries (Europe and North America) and only one study from SSA (Ghana) was included. These findings may therefore not be generalizable to health care settings in SSA and many low-middle income countries where access to indoor temperature control may be limited; this is compared to high income countries which spends 50% of their hospital energy consumption on indoor heating (21). Lastly, most studies included in the meta-analysis did not adjust for important confounders like air pollution. This may potentially lead to over- or underestimation of temperature effects on blood pressure. It has been shown that leading air pollutants, such as nitrogen dioxide, sulphur dioxide and particulate matter are associated with blood pressure and some have been shown to increase the risk at CVD morbidity and mortality (22–26).

The present study aims to address the gap in evidence from Sub-Saharan Africa and more specifically explores the effect of outdoor temperature on blood pressure in a primary care setting with limited control to indoor temperature control. Additionally, we assess the confounding role of air quality on this association and discuss the overall implications for blood pressure management and care in South Africa and countries with similar settings.

3.Method

Participants and Study design

The study uses data from 2,494 participants assessed for eligibility and entry in the SMS-text Adherence (StAR) trial. Details of the study design and protocol have been reported previously (27). In brief, the StAR trial study is a randomised three-arm parallel group trial, evaluating the effects of a structured programme of hypertension treatment adherence support (delivered through either informational or interactive SMS-text messages) compared to the usual care of blood pressure management and treatment adherence at 12-months. All adult patients (≥21 years old) who were diagnosed with and being treated for high blood pressure were offered referral to the trial. Interested individuals, willing to give consent, were assessed for eligibility into the trial. Participants were enrolled between the 27th of June and the 31st of November in 2014 during outpatient hours from 08h00 - 17h00 South Africa Standard time (SAST). As part of the trial eligibility, data on participant's blood pressure, demographics and anthropometrics were captured in accordance to clinical trial best practice.

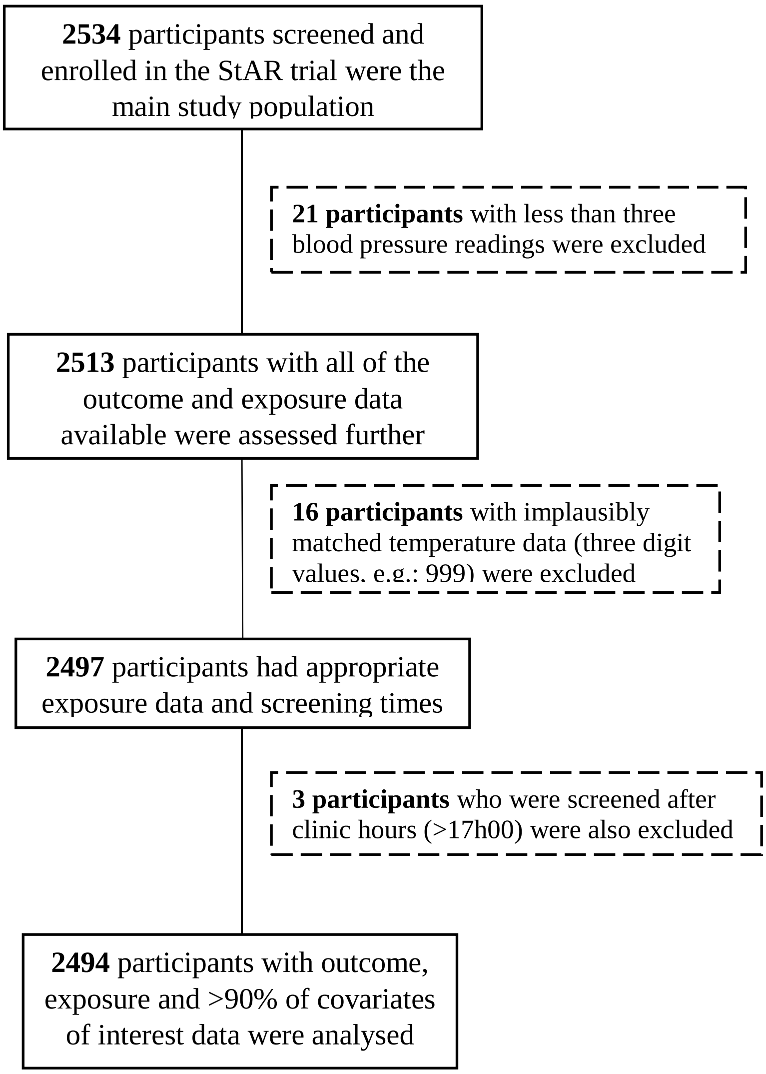
Inclusion criteria

Participants were included in the present study if they: i) had ≥ 3 blood pressure measurement and data over 90% of anthropometric, demographic and clinical variables ii) had available time records for blood pressure measurements, including the hour and date of enrolment iii) were enrolled during the trial operating times (between 07h00 – 17h00), and iv) had plausible hourly mean temperature (two digits, e.g.12°C not 199°C) and air quality data (four or more digits, e.g.23 $\mu g/m^3$ not 2339$\mu g/m^3$) that could be matched using the nearest hour of blood pressure measurement (**Figure 1**).

Ethics

Both the StAR study and the present study received ethics approval from the Human Research Ethics Committee of the University of Cape Town (HREC UCT 418/2011 and 267/2015 respectively) (See Appendix B) and are adherent to the Declaration of Helsinki guidelines for protection of human subjects. In addition, the StAR study received ethics approval from the Oxford Tropical Research Ethics Committee (OXTREC 03–12) and research governance approval from the Metro District Health Services of the Western Cape, South Africa. The trial was also registered with the South African National Clinical trials register (SANCTR DOH-27-211-386), subsequently included in the Pan African Trial Register (PACTR201411000724141) and registered at ClinicalTrials.gov (NCT02019823) prior to study protocol publication.

Figure 1 - Flow chart of study selection



Setting

Climate

The weather and air quality measures were obtained from a suburb in Cape Town in the Western Cape province of South Africa; a subtropical region characterised by a semi-arid climate and highly variable seasonal weather and temperature conditions (28). On a global scale, South Africa experiences much cooler winters compared to regions at the same latitude (e.g.: Brazil) and have temperature conditions ranging between minus 0°C in winter for areas at high altitude and 36°C in summer (29–31). On a country scale, regions such as north-east

Kwazulu Natal, experiences much cooler winters compared to areas in the south like the Western Cape. This regional difference in climate is largely driven by geographical variations in altitude and distance from the warm or cold current of the Indian and Atlantic Ocean (31). The Western Cape in particular, due to its close proximity to both warm and cold current oceans, experiences a “Mediterranean”-type of climate with mild temperatures, ranging between 5°C and 18°C, in winter and 20°C - 30°C in summer (31).

Primary care

Participants were recruited from the Vanguard Community Health Centre, a publicly funded free-at-point-of service primary care clinic serving two peri-urban communities, Langa and Bonteheweul, with a combined estimated population of 105,357 people (32,33). Approximately 28% of the population lives in informal dwellings and 62% have a household income of ≤ $250 (≤3200 ZAR) or less per month (32,33). The community health centre provides a range of health services including maternal, emergency and chronic disease management. Maternity and emergency services are provided for 24 hours, 7 days a week, whereas the chronic disease and other outpatient services are provided during an 8-hour weekday service. The facility is a brick and mortar building with indoor temperature control being provided by doors and windows only (i.e. no central heating/temperature control technology or apparatus). The clinic is representative of other primary care clinics in South Africa. According to a recent national health facility audit of primary care clinics in South Africa, there is no documentation or provision of indoor temperature control apparatuses and may therefore indicate no such provision cross-country (34)

Outcome measure

Clinic-based blood pressure measurement

For the purposes of the StAR trial, a canvas structure was erected within an internal courtyard of the clinic. The structure was adjacent to the room where the chronic diseases of lifestyle clinic is situated. The structure had a raised wooden and carpeted floor (levelled with the clinic), enclosed walls (with windows), a roof, and two doors. The temperature and overall climatic conditions of the trial tent were similar to the clinic. Thus, neither the clinic room nor the tent had access to air conditioning or other indoor climate control technology.

After 5 minutes of rest and with the participant seated, their blood pressure were taken by a trained fieldworker using a standardised and research validated instrument (IEM Stabilograph© Stolberg, Germany) (35). Up to 6 blood pressure measurements were taken and recorded at 3 minute intervals; of which the first reading was discarded and the mean of the remaining measures was captured (27). For the present study, the first three readings were considered and are used for the analysis..

Exposure measures

Meteorological

Daily surface air temperature and relative humidity measurements acquired during the trial enrolment period (June 2012 to 31 December 2014) were obtained from the closest South African Weather Service (SAWS) station, approximately 9 kilometres from the clinic. Hourly mean, minimum and maximum temperature data were recorded using a research-validated and standardised methods, in line with the World Meteorological Organisation's (WMO) guidelines for measuring outdoor temperature and relative humidity (36,37). In brief, air temperature and humidity data reported here are surface-level measurements captured by a frequently calibrated automated instrument, typically 30 meters (100 feet) away from a concrete or paved surface and 1.2 to 1.8 meters (4 – 6 feet) above the ground (38). The instrument calibration is set within the 90% - 95% accuracy of performance standards. The data obtained for the present study were stored and managed in line with the SAWS climate policy on handling climate data for research purposes (36).

Air quality

Air quality has been shown to be associated with blood pressure, particularly from studies in Asia where air pollution is known to be high (39,40) (41–43). For instance, results from Choi et al., 2006 study showed that air pollutants such as Nitrogen dioxide (NO2) and Ozone increase during winter and this increase was shown to be associated with changes in blood pressure in individuals living in Incheon city in South Korea. This effect of air quality on blood pressure among population living in urban areas may potentially confound the observed relationship between outdoor temperature and blood pressure.

For the present study, daily nitrogen dioxide (NO2), sulphur dioxide (SO2) and particulate matter with ≤ 10 micrometres in aerodynamic diameter (PM10) observations were obtained from the nearest City of Cape Town air quality monitoring station, approximately 5 km from the clinic (**Supplemental Figure 1**). Air quality was measured using a standardised automated method in line with the United States Environmental Protection agency (US EPA) and the World Health Organisation’s (WHO) guideline for monitoring air quality (44,45) All measurements taken at the monitoring station are checked for quality control on the city of Cape Town data management and organisation system before being distributed for research and commercial purposes (46).

Other

Demographic data such as age, gender and ethnicity were obtained using a field worker administered questionnaire (See Appendix A). Anthropometric measures (weight, height and subsequent calculation of BMI) were measured using standardised and validated research methods (27).

Statistical analysis

All of the study variables were explored and tested for normality and homogeneity (Bartlett's test for unequal variance). For normally distributed variables, mean and standard deviation (±SD) are reported, for skewed data, median and interquartile range is reported. Blood pressure data was further explored by age, sex and ethnicity. Lastly, correlation coefficients was calculated as part of the bivariate analysis between continuous variables. Potential collinearity was assessed and used to inform the model building.

Seasonal and daytime variation of clinical, weather and air quality variables

A two-way t-test for independent samples was used assess for seasonal variation of clinical, weather and air quality measures for the period of the StAR study screening and enrolment. Additionally, monthly and daytime variation in blood pressure, temperature and air quality was assessed using a one-way analysis of variance (ANOVA). Differences in daily, monthly and seasonal blood pressure measurement were important to explore as there is still limited data about clinical-based blood pressure variation in South Africa. (47,48)

Outdoor temperature and its association with clinic-based blood pressure

A multivariate regression analysis using variables selected a-priori was used to assess the relationship between outdoor temperature and blood pressure. Variables included in the model were age, ethnicity, gender, BMI, waist circumference, heart rate, time (hour) and month of enrolment, humidity, SO_2, NO_2 and PM10. Both SO_2, NO_2 and PM10 are known to be associated with changes in blood pressure, particularly in urban populations where exposure to high levels of outdoor air pollution is increased compared to rural areas. The present study is one of few studies that adjusts for their effect in the context of the temperature and blood pressure relationship. Additionally, given recent evidence that show older age groups and those with low BMI are most sensitive to temperature changes; interaction terms for age and BMI to assess for their modifying effect on blood pressure were generated (49).

The effect of temperature extremes on blood pressure in Cape Town

It has been shown that the risk and the outcomes associated with CVD varies across weather and temperature extremes (50–54). In particular, temperature ranges of -7°C and 13°C reported by Guo et al., 2013, were shown to be associated with nearly 2% higher risk of CVD mortality compared to warmer temperature ranges of 17-26°C(54). Based on this data, , temperature extreme (≤ 13°C and ≥20°C) on blood pressure of this population living with high blood pressure. The temperature extremes were selected based on temperature extremes seen in South African winters and summers.. The rationale for the analysis, is that simply modelling the linear relationship between the overall mean outdoor temperatures over a particular study period may not capture the varying effects that temperature extremes have on blood pressure and the risk associated with it. Therefore, to assess for this varying effect, the temperature data was categorised into three/tertile (T1-3) ranges associated with both cold (T1: ≤13°C), mild (T2: 13°C-20°C) and warm temperature conditions (≥20°C) for a mediterrean-like weather (for SA). A model adjusting for age, ethnicity, gender, BMI, waist circumference, heart rate, time (hour) and month of enrolment, humidity, SO_2, NO_2 and PM_{10} was used to assess the effect of temperature on blood pressure for each tertile temperature condition.

Sensitivity analysis

To further assess the robustness of the temperature model on blood pressure, several sensitivity analyses were done, adjusting for additional CVD risk factors. These were: smoking and drinking status, socioeconomic status, diet, exercise as well as participants' medical history of diabetes mellitus and vascular co-morbidities, such as stroke, high cholesterol, myocardial infarction, transient ischaemic attack and chronic cardiac failure.

4. Results

Population, weather and air quality characteristics

After excluding 40 participants for not meeting the inclusion criteria, the study reports blood pressure data from 2494 participants whose clinical measures could be matched with temperature and air quality data from the nearest weather and air quality station. **Table 1** summarises the study population characteristics. In brief, 72% and 53% of participants screened for the trial were female and of mixed ancestry, respectively. Participants mean age was 57 years old (±12, 4) and BMI of 31kg/m^2 and mean systolic and diastolic blood pressure of 137mmHg (sd ±19.7) 83mmHg (sd±13, 2), respectively. Blood pressure levels were higher in males and those 65 years and older and compared to females and those 50 years and younger (**Supplementary Table 1A and B**). Additionally, the mean outdoor temperature during the trial enrolment period was 16.7°C (3.7°C – 28.2°C) and 21.91 μg/m^3, 19.93 μg/m^3 and 14.17 μg/m^3 for PM_{10}, NO_2 and SO_2, respectively (**Supplementary Table 2A**).

Table 1 – Population characteristics

Characteristics	
Age – in years	
Mean (SD ±)	57 (±12,5)
Gender – in %	
Female	72
Ethnicity – in %	
Black African	47
Mixed ancestry	53
BMI – in Kg/m^2	
Mean (SD ±)	31.7
Waist – in cm	
Mean (SD ±)	99.21 (±14.6)
SBP – in mmHg	
Mean (SD ±)	137,7 (±19,7)
DBP – in mmHg	
Mean (SD ±)	83,3 (±13,2)
HR – in BPM	
Mean (SD ±)	72,3 (±13,4)

Furthermore, the overall mean outdoor temperature during the trial enrolment period was 16.7°C (3.7°C – 28.2°C) and for air quality, PM10, NO2 and SO2, the overall mean values were 21.91 µg/m^3, 19.93 µg/m^3 and 14.17 µg/m^3, respectively (**Supplementary Table 2A**). On a given day, the overall mean change in outdoor temperature (i.e.: difference between daily minimum and maximum temperature) was 4.3°C (min 1.4 °C - 14.6 °C max). The highest daily temperature differences were seen during winter (June-July) compared warmer periods (August and October).

Seasonal and daytime variation of clinical, weather and air quality measures

Table 2 provides a summary of seasonal and monthly variation of clinical, weather and air quality measurement across the trial enrolment period. In brief, a seasonal pattern was observed for blood pressure, outdoor temperature, humidity and all of the air quality variables. Between June 27 and November 31 2012, blood pressure was significantly different (p=0.0001) between those who enrolled during winter than those enrolled in spring. This inter-subject variation in blood pressure was not associated with age (p=0.928), BMI (p=0.71), heart rate (p=0.412) or demographic characteristics assessed. Conversely, outdoor temperature showed a significant increase during this period with a winter recording the lowest mean temperature compared to summer (14.3°C vs 18.3°C). Furthermore, humidity, NO2, SO2 and PM10 showed to decrease (*p=0.001 NO2, *p=0.001 SO2 and *p=0.001 PM10) during the same period with winter accounting for a higher humid and total air quality levels. Similar pattern was observed in daytime measurement, blood pressure showed to be higher during the mornings as temperatures levels were generally low. Participants assessed in the morning (8h00-10h00) had a 4mmHg higher systolic blood pressure (139mmHg vs 135.90mmHg, *p=0.01) compared to those assessed in the afternoon (>14h00). (**Supplementary Table 3**).

Table 2 – Monthly and seasonal variation in clinical, weather and air quality measures over the trial enrolment period.

	Winter			Spring			Winter - spring
	June	July	August	September	October	November	P-value*
Climate							
Temperature (°C), mean (min; max)	14,23 (3.7; 18.2)	14,61 (8; 26.4)	14,05 (7.7; 19.5)	15,48 (5.9; 22.1)	18,99 (13.7; 26.5)	20,66 (13.7; 28.9)	<0.0001
Humidity(%), mean (min; max)	65,137 (46; 84)	65,217 (15; 97)	65,067 (33; 97)	64,335 (30; 97)	57,326 (31; 88)	56,770 (27; 81)	<0.0001
Clinical							
Subjects, n	51	388	507	540	580	421	
Systolic BP(mmHg), mean (±SD)	145,87 (±21.91)	142,17 (±18.83)	140,65 (±20.9)	137,47 (±19.49)	136,69 (±19.80)	131,24 (±18.23)	<0.0001
Diastolic BP (mmHg), mean (±SD)	88,61 (±13.63)	85,21 (±11.68)	84,34 (±13.28)	83,88 (±13.36)	82,92 (±13.22)	79,48 (±13.55)	<0.0001
Heart rate (bpm), mean (±SD)	73,67 (±11.06)	71,23 (±13.71)	71,92 (±13.70)	72,52 (±12.98)	72,62 (±13.52)	72,98 (±13.02)	0.4212
Age (years) - mean **(±SD)**	56,10 (±15,18)	57,08 (±12,12)	57,70 (±12,57)	55,56 (±12,24)	57,36 (±12,42)	57,80 (±12,73)	0.9228
BMI (Kg/m²) - mean (±SD)	31,04 (±7,96)	32,03 (±7,80)	32,03 (±7,21)	31,71 (±7,64)	31,35 (±7,04)	31,69 (±7,96)	0.7097
Air quality							
PM10 (μg/m³), mean (min – max)	50.352 (16 - 103)	34.227 (4 – 220)	18.633 (3 – 107)	16.331 (3 – 46)	15.655 (0 – 55)	26.675 (7 – 72)	<0.0001
NO_2 (μg/m³)- mean (min – max)	52,65 (12 – 100)	50.03 (9 – 287)	24.97 (1 – 93)	13.43 (2 – 35)	6.87 (3 – 29)	7.73 (2 – 22)	<0.0001
SO_2 (μg/m³)- mean (min – max)	23.18 (13 – 38)	35.36 (0 – 153)	31.07 (10 – 103)	4.03 (0 – 37)	1.95 (0 – 80)	2.90 (0 – 71)	<0.0001

Outdoor temperature and its association with clinic-based blood pressure

In this population of people living with hypertension and on treatment, outdoor temperature was strongly associated with blood pressure change. This can be seen by the proportion of variation explained by temperature. For instance, in the main study model adjusting for temperature, humidity, NO2, SO2 and PM10, heart rate, age, sex, waist, ethnicity BMI, hour and month of enrolment, the model explained 5.6% variation (Adjusted R^2= 0.056) in blood pressure. From this proportion, temperature explained 3.7% variability after adjusting for potential confounders. Furthermore, prior analysis showed temperature was significantly correlated with both climate (humidity) and air quality variables (NO2, SO2 and PM10). In summary, outdoor temperature was inversely correlated with blood pressure (Pearson r = -0.194* SBP & -0.151* DBP), humidity, NO2 and SO2 (Pearson r= -0.64*, r= -0.32 and r = -0.25), respectively. There was generally a weak correlation between blood pressure and humidity, NO2, SO2 and PM10. (**Supplementary Table 4)**.

Nitrogen dioxide and sulphur dioxide were found to be associated with both outdoor temperature and blood pressure and therefore may confound the relationship between outdoor temperature and blood pressure (**Supplementary Table 5**). On a given day, the overall mean change in outdoor temperature (i.e.: difference between daily minimum and maximum temperature) was 4.3°C (min 1.4 °C - 14.6 °C max). The highest daily temperature differences were seen during winter (June-July) compared warmer periods (August and October).

Table 3 provides a summary of the adjusted effect of outdoor temperature on blood pressure. After adjusting for potential confounders and other important demographic and clinical characteristics, a 10°C increase/decrease in outdoor temperature was associated with 7.5mmHg change in systolic blood pressure.

Table 3 - Independent predictors of blood pressure

	Systolic blood pressure			Diastolic blood pressure		
	Coef.	**[95%Conf.Interval]**		**Coef.**	**[95%Conf.Interval]**	
Temperature (Δ 10°C)	-7,448	-11,176	-3,721	- 4,859	-7,264	-2,454
Heart rate	0,033	- 0,026	0,091	0,093	0,056	0,131
Age	0,075	0,012	0,139	-0,254	-0,295	-0,213
Sex						
Female	-1,979	-3,825	-0,132	-3,486	-4,677	-2,294
Ethnicity						
Mixed ancestry	-2,039	-3,667	-0,411	-0,335	-1,386	0,716
BMI	- 0,081	-0,194	0,031	- 0,171	-0,243	-0,099
Daytime hours	- 0,415	-1,048	0,218	- 0,159	-0,567	0,250
Months						
July	-3,804	-9,592	1,985	-2,729	-6,464	1,006
August	-4,464	-10,388	1,460	-2,901	-6,724	0,922
September	-5,743	-11,507	0,021	-3,639	-7,358	0,080
October	-4,349	-10,416	1,717	-2,554	-6,469	1,361
November	-8,875	-15,299	-2,451	-4,999	-9,145	-0,854
Humidity	-0,032	-0,104	0,039	-0,033	-0,080	0,013
SO2	0,006	-0,077	0,089	-0,015	-0,069	0,038
NO2	0,046	-0,015	0,107	0,040	0,000	0,079
PM10	-0,008	-0,064	0,047	-0,018	-0,054	0,018

Age was found to be an important modifier of this relationship, with those 50 years and older having higher effect change in blood pressure compared to those less than 50 years old (**Supplementary Table 6)**. Additionally, the overall mean outdoor temperature during the trial enrolment period was 16.7°C (3.7°C – 28.2°C) and for air quality, PM10, NO2 and SO2 had overall mean values of 21.91 μg/m^3, 19.93 μg/m^3 and 14.17 μg/m^3, respectively (**Supplementary Table 2a**).

The effect of temperature extremes on blood pressure in Cape Town

After categorising temperature data into the three groups that included two extreme temperature conditions (≤13 °C & ≥ 20°C) representative of Cape Town mediterrean-like winter and summer, it was seen that nearly 15% of individuals enrolled during trial period were exposed to hourly mean temperature, ranging between 3.6 and 13 °C (Tertile I). 67% were exposed to temperature ranges of 13-20 °C (Tertile II) and 18% to 20 – 29 °C (Tertile III) before or during their BP measurement.

Table 4 - Temperature extremes in Cape Town and their association with blood pressure of people living with hypertension

	N	SBP	DBP
		Coef (95% CI)	Coef (95% CI)
Temperature **(overall)**	2494	-0,750 (-1,184; -0,382)	-0,495 (-0,734;-0,257)
Tertile I **(≤13°C)**	363	0,333 (-1,374; 2,040)	0,029 (-1,084; 1,027)
Tertile II **(13°C-20°C)**	1688	-0,487 (-1,12; -0,139)	-0,045 (-0,445;0,355)
Tertile III **(>20°C)**	443	-2,044 (-3,348; -0,739)	-1,370 (-2,256;-0,482)

The tertile I-III are individual multivariate models adjusted for age, BMI, heart rate, sex, ethnicity, waist, hour and month of enrolment, humidity, NO2, SO2, PM10.

After adjusting for important confounding factors like air quality, humidity and age and gender; exposure to lower temperature of 13°C and less, was associated with 0.33mmHg (95%CI: -1,374; 2,040) increase in systolic blood pressure for every 1°C change in outdoor temperature.

Conversely, exposure to hourly mean temperatures of 13°C-20°C showed similar but inverse effect with decreasing blood pressure change for 1°C increase. Warmer temperatures of 20°C and above was associated with as much as 2.3mmHg decrease in systolic blood pressure. This difference in direction and varying effect of temperature on blood pressure may give insight into previously reported risk and outcome related to CVD during cold season and temperatures.

5. Discussion

Main findings

The study provides evidence showing that mean blood pressure measured in a clinical setting with limited control to indoor climate may be affected by changes in outdoor temperature. These changes in outdoor temperature were particularly seen between mornings and afternoons and winter and summer, and was associated with statistically significant differences in blood pressure. The model for association between temperature and blood pressure indicates that a 10°C decrease in mean hourly temperature, for example, could have detrimental effects on blood pressure and its care in patients at risk for outcomes related to CVD.

Comparison with other literature

To our knowledge, this is the first study to describe the relationship between outdoor temperature and blood pressure in people living with hypertension in South Africa and is one of the few studies from Sub-Saharan Africa. The findings follow a similar trend of association reported by others in LMICs (55,56). The study also highlights variation in daytime in temperature and air pollution levels patterns between months and seasons of the year. This is often under-reported in other studies (11,55,57) and may give insight about the day to day and seasonal variation in temperature and blood pressure. Furthermore, we report on clinic-based blood pressure captured in a thermal setting that is close to outdoor environments. Previous studies reporting on the relationship between outdoor temperature and blood pressure used blood pressure measurements assessed indoors. These studies have been criticised suggesting that using indoor temperature in this instance may be a better exposure measure than outdoor temperature (58). While this notion may hold also for our study, data from countries (e.g.: Brazil) with similar settings to South Africa have showed that outdoor and indoor temperatures are strongly correlated ($r=0.82$, $p<0.05$). In addition, in some studies that assessed for individual effects of indoor and outdoor temperature on blood pressure, independently, shows minimal differences in effects between the two temperature measures (55,58–60). Given the overall limited access to indoor temperature control technology in South Africa's primary care clinics (34), outdoor temperature effects reported here may still be relevant for understanding implications on blood pressure management in this setting.

Clinical and public health implications

Understanding the impact of temperature on blood pressure measurement and control is important for people living with hypertension. They are generally known to be at an elevated risk for morbidity and mortality due to CVD; More importantly, recent data shows that this risk varies across seasonal and temperature extremes regardless of climate and region (18,61,62). In the present study it was observed that daily temperature changes can vary as much as 14°C in a given day (**Supplementary Table 2b**). In particular the months of June and July showed large daily temperature variation between the morning and the afternoon. This variation in daily outdoor temperature may have clinical relevant implication for management of blood pressure on cold days, for example. In addition, based on evidence from Mitchell and colleagues on cardiovascular risk associated with climate, individuals from poor households are more likely to be exposed to colder climate and have a 25% and 45% higher risk to systolic and diastolic hypertension(63).

Limitations

The study uses cross-sectional data which may be confounded by intrinsic and extrinsic factors captured by residual measures in the model. Based on evidence from studies examining seasonality and cardiovascular health, several biological factors associated with blood pressure have shown to change with seasonality and could therefore potentially be influenced by temperature change. Intrinsic factors such as C-reactive protein, fibrinogen, haematocrit and cholesterol have a seasonal pattern and may therefore influence variation in blood pressure (64–66). Additionally, extrinsic factors, such as physical exercise, carbon monoxide and ozone concentration have also shown to be associated with seasonality and blood pressure and may influence temperature effects and blood pressure change (42,67). Furthermore, the current study does not take into account the impact of temperature on within-subject variation od blood pressure, best captured by a cohort study. Lastly, outdoor temperature and air quality data were taken at the nearest weather and air quality station which may vary with temperature and air quality surrounding the clinic.

6. Conclusion

To our knowledge, this study demonstrates for the first time in South Africa, the impact of outdoor temperature on clinic-based blood pressure measurement, and adds to the growing body of evidence showing the interacting effect of seasonality and temperature on blood pressure. It can be seen from this study that temperature may have clinically relevant implications for both measurement and management of blood pressure of cardiovascular disease patients in LMICs. These findings together with the growing body literature on the association between temperature and blood pressure, calls for re-assessment of policies and clinical guidelines for monitoring and managing blood pressure both at a clinical and public health level.

Author's Contributions

KB, NL and EH formulated the research question and designed the study from inception. EH prepared the protocol, the literature review and the manuscript with supervision from KB and NL.KB and KA provided input on managing missing data from the air quality station. DS provided assistance with the data management and the merging of air quality and clinic data. AF, NL and KB provided the right to access to the StAR study data. EH prepared the journal manuscript with KB and NL input.

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7. Figures

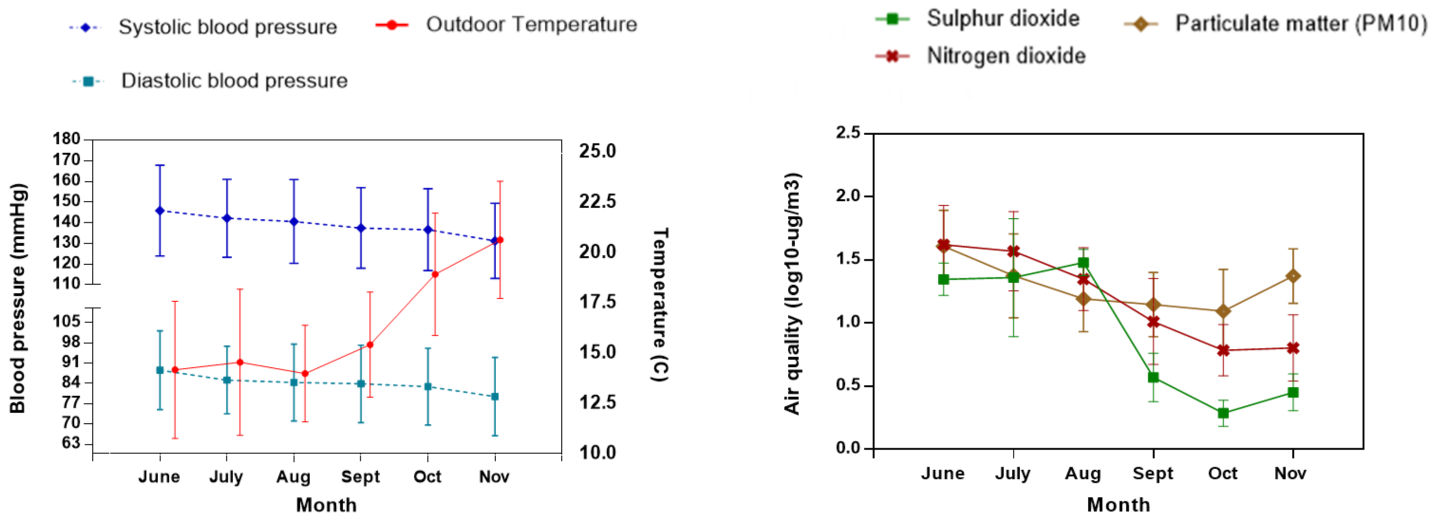

Figure 2: a) Mean distribution of blood pressure and outdoor temperature across months of trial enrolment (June – November 2012). **b)** Mean distribution (at log-scale) of nitrogen dioxide, sulphur dioxide and particulate matter during the trial enrolment period.

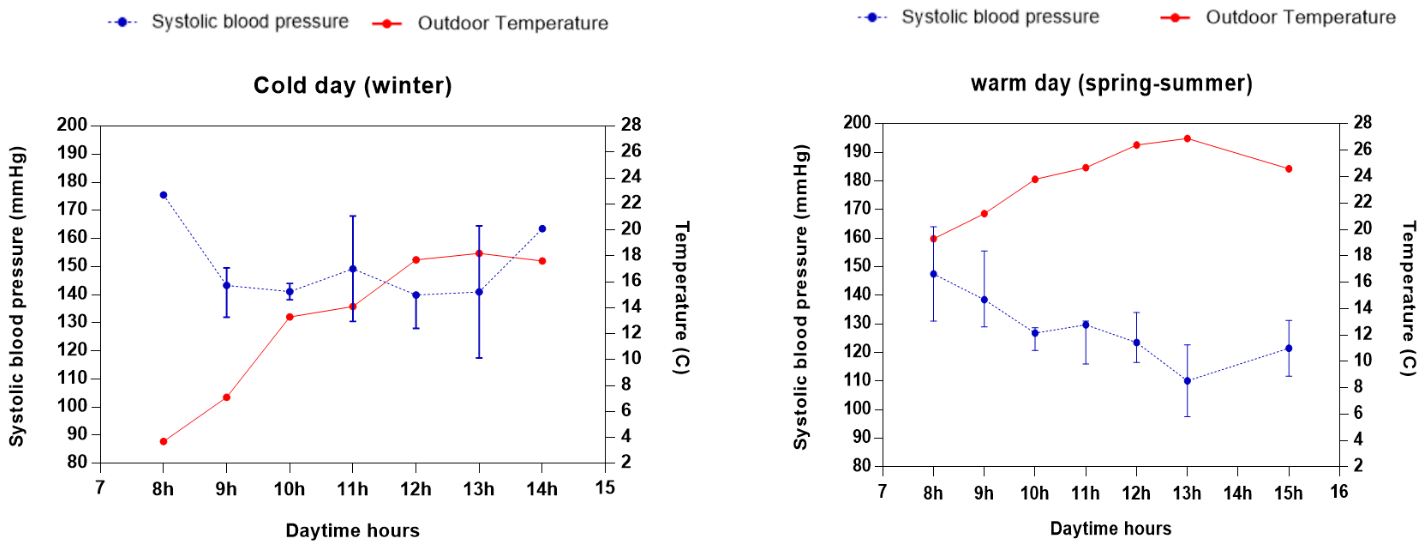

Figure 3: Distribution of daytime temperature and blood pressure on a winter's cold day and spring-summer's warm day

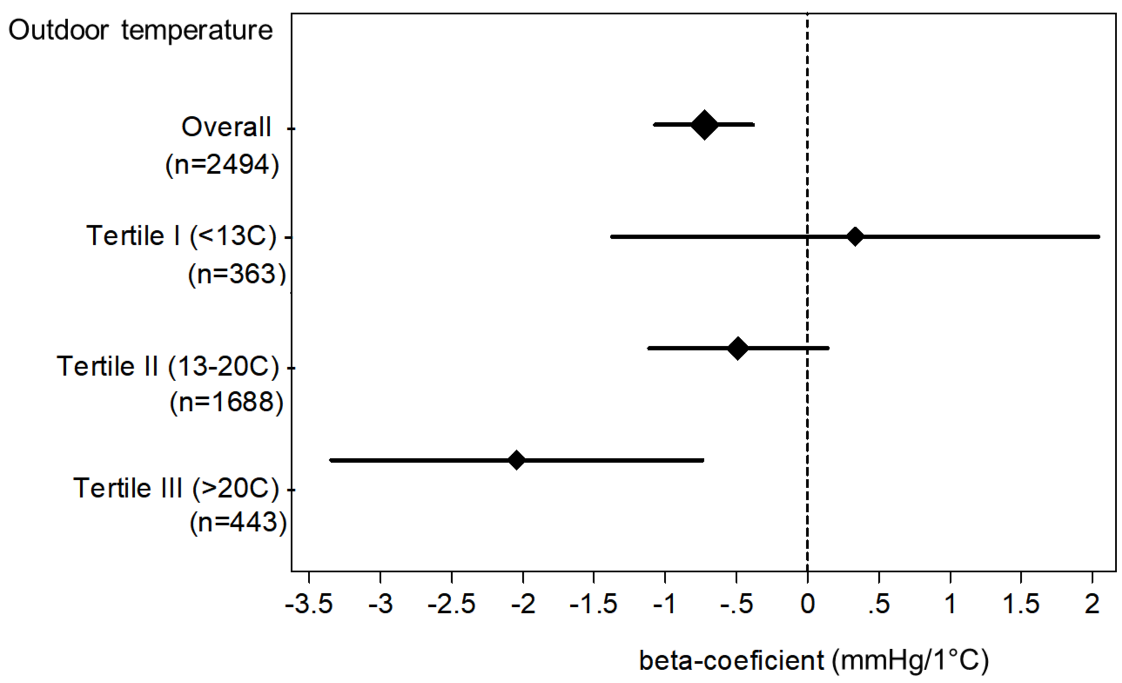

Figure 4: The effect of temperature extreme (≤13°C vs ≥20°C) in Cape Town on blood pressure adjusting for age, sex, ethnicity, BMI, humidity daytime hours, month, NO2, SO2 and PM10

8. Supplementary Tables and Figures

Supplementary Figure 1: City of Cape Town Air Quality Monitoring (AQM) stations and an approximated clinic area

A – Air quality station nearest to the study clinic

B – Approximate clinic area

Supplementary Table 1a: Population characteristics stratified by gender (mean, ±SD)

	Overall	Female	Male
Subject, n	2494	1971	703
Age - in years	57 (±12,49)	56,95 (±12,44)	57,312 (±12,62)
SBP - mmHg	137,79 (±19,79)	137,12 (±20,03)	139,50 (±19,07)
DBP - mmHg	83,32 (±13,23)	82,11 (±13,15)	86,39 (±12,93)
HR - bpm	72,32 (±13,35)	72,57 (±13,18)	71,72 (±13,75)
BMI - Kg/m2	31,72 (±7,504)	33,42 (±7,56)	27,38 (±5,31)
Waist - cm	99,21 (±14,64)	100,67 (±14,88)	95,50 (±13,31)

Supplementary Table 1b: Population characteristics stratified by age (mean, ±SD)

	< 50 years	51-65 years	> 65 years
Subject, n	744	1097	653
SBP - mmHg	134,5 (±17,89)	137,24 ±20,31)	139,85 (±20,81)
DBP - mmHg	86 (±12,75)	83,74 (±12,99)	78,63 (±12,79)
HR - bpm	74 (±12,83)	72,08 (±13,30)	69,44 (±13,36)
BMI - Kg/m2	31,623 (±7,79)	32,05 (±7,44)	30,32 (±7,1)
Waist - cm	98,65 (±15,12)	100,09 (±14,51)	97,83 (±14,22)

Supplementary Table 2a: Weather and air quality characteristics during the trial enrolment period (June – November 2012)

Variable	
Temperature (°C), mean (±SD)	16,73 (±3,88)
Humidity (%), mean (±SD)	61,71 (±14,87)
SO2 (µg/m^3), median (p25, p75)	4 (2, 31)
NO2 (µg/m^3), median (p25, p75)	13 (5, 25)
PM10 (µg/m^3), median (p25, p75)	18 (12, 25)

Supplementary Table 2b: Daily temperature differences (min-max) across the different months of trial enrolment (June – November 2012)

	Days of trial enrolment	Mean Difference	Min difference	Maximum difference
June	2	9,2 °C	3,9 °C	14,5 °C
July	18	5,45 °C	1,3 °C	14,6 °C
August	18	4,11 °C	1,7 °C	7,3 °C
September	17	5,05 °C	1,4 °C	13,3 °C
October	22	3,40 °C	1,4 °C	8,8 °C
November	18	3,29 °C	1,6°C	9,5 °C
Total	95	4,32 °C	1,4 °C	14,6 °C

Supplementary Table 3: Daytime distribution of key study variables (mean, ±SD and min-max)

	Daytime Hours			
	8h – 10h 1 (n=1230)	**11h -13h 2 (n=1122)**	**14h-17h3 (N=142)**	**p-value**
Temperature, °C - mean (± SD)	15,67 °C (±3,93)	17,67 °C (±3,48)	18,50 °C (±3,88)	<0,004 (1&2,1&3, 2&3)
SBP, mmHg - mean (± SD)	139 mmHg (±20,07)	136,64 mmHg (±19,50)	135,90 mmHg (±18,98)	0,010 (1&2)
DBP, mmHg – mean (± SD)	84,04 mmHg (±13,44)	82,54 mmHg (12,98)	83,23 mmHg (13,13)	0,018 (1&2)
Relative Humidity, % – mean (± SD)	66,58% (±14,69)	57,56% (±13,12)	52,37% (±15,14)	<0,001 (1&2,1&3, 2&3)
PM_{10}, µg/m^3- median, (p25; p75)	19 ug/m3 (12; 24)	16 ug/m3 (11; 24)	22 ug/m3 (15; 28)	<0,001 (1&2, 2&3)
NO_2 µg/m^3- median, (p25; p75)	16 ug/m3 (6; 25)	12 ug/m3 (5; 25)	11 ug/m3 (5; 25)	<0,001 (1&2)
SO_2 µg/m^3- median, (p25; p75)	4 ug/m3 (2; 30)	4 ug/m3 (2,31)	4 ug/m3 (3;31)	1,000

Supplementary Table 4: Correlation matrix of key study variables

	Age	BMI	Waist	Temperature	SBP	DBP	HR	Humidity	SO2	NO2	PM10	Daytime hours
Age	1,000											
BMI	- 0,117*	1,000										
Waist	-0,035	0,821*	1,000									
Temperature	0,005	- 0,02	-0,025	1,000								
SBP	0,059*	-0,059*	- 0,026	- 0,194*	1,000							
DBP	- 0,240*	-0,110*	0,083*	- 0,151*	0,724*	1,000						
HR	- 0,160*	0,021	0,062*	0,035	0,004	0,114*	1,000					
Humidity	0,019	0,013	0,040*	- 0,640*	0,097*	0,065*	0,019	1,000				
SO2	- 0,021	-0,003	-0,018	-0,318*	0,130*	0,089*	-0,032	-0,034*	1,000			
NO2	- 0,024	-0,003	-0,010	-0,254*	0,131*	0,102*	-0,018	0,023	0,762*	1,000		
PM10	- 0,022	0,024	-0,015	0,028	0,042*	0,029	0,008	-0,071*	0,451*	0,694*	1,000	
Daytime hours	-0,018	0,016	-0,031	0,278*	-0,064*	-0,045*	0,034	-0,369*	0,034	-0,072*	-0,046*	1,000

* p <0,05

Supplementary Table 5a: Adjusted and unadjusted effects of potential confounders (air quality and relative humidity) on blood pressure

Blood pressure (mmHg)				
	Unadjusted		Adjusted [a]	
	Coefficient (95%CI)	P>t	Coefficient (95%CI)	P>t
Nitrogen dioxide µg/m^3	0,10 (0,07; 0,13)	0,000	0,08 (0,03; 0,12)	0,001
Sulphur dioxide µg/m^3	0,01 (0,09;0,17)	0,000	0,06 (0,02;0,11)	0,010
Particulate matter (PM10), µg/m^3	0,04 (0,01; 0,08)	0,038	0,03 (0,08; 0,03)	0,038
Relative humidity %	0,13 (0,08; 0,18)	0,000	0,04 (0,11; 0,03)	0,262

[a] – Adjusted for age, sex, ethnicity, heart rate, BMI, temperature and NO2, SO2, PM10 and humidity, where necessary

Supplementary Table 5b: Adjusted and unadjusted effect of the study selected-a-priori potential confounders (air quality and relative humidity) on outdoor temperature

	SO2 (µg/m^3)		NO2 (µg/m^3)		PM10 (µg/m^3)	
	Unadjusted	Adjusted [b]	Unadjusted	Adjusted [b]	Unadjusted	Adjusted [b]
	Coef (95%CI)	Coef (95%CI)	Coef (95%CI)	Coef (95%CI)	Coef (95%CI)	Coef (95%CI)
Temperature (°C)	-1,59 (-1,77; -1,40)	- 0,93 (-1,11; -0,76)	- 1,75 (-2,01; -1,49)	-0,92 (-1,13; -0,73)	0,15 (-0,06; 0,36)	1,38 (1,17;1,58)

[b] – Adjusted for humidity, NO2, SO2 and PM10 where necessary,

Supplementary Table 6: The interaction between outdoor temperature and age and BMI on systolic blood pressure

Systolic blood pressure*	Coef,	95% Conf, Interval		P>t
Temperature (n=2494)	-7,502	-11,184	-3,820	0,001
50 – 65 (n=1097)	0,092	0,285	16,088	0,042
>65 (n=653)	2,700	-6,128	12,118	0,520
Temperature*Age ≤50	-0,523	-0,963	-0,083	0,020
Temperature*Age 50-65	-1,002	-1,416	-0,588	0,000
Temperature*Age≥65	-0,541	-1,029	-0,053	0,030
BMI (n=2494)				
25-30 (n=661)	2,359	0,044	4,675	0,409
30-45 (n=1220)	0,963	-1,230	3,157	0,871
45-65 (n=123)	-2,958	-6,950	1,034	0,499
Temperature*BMI <25	0,019	-0,934	0,972	0,969
Temperature*BMI 25 - 30	-0,285	-1,192	0,622	0,538
Temperature*BMI 30 - 45	0,125	-0,752	1,001	0,781

*All estimates were adjusted for sex, ethnicity waist, daytime hours, month, humidity and air quality,

Supplementary Table 7: Sensitivity analysis assessing the effect of outdoor temperature on systolic blood pressure adjusted for addition cardiovascular disease risk factor on a subset of the study population (n=1343)

	Coef	95% Conf. Interval		P>t
Temperature	-0,705	-1,197	-0,412	0,000
BMI	-0,155	-0,294	-0,017	0,028
Heart rate	0,009	-0,064	0,082	0,816
Sex	-3,025	-5,511	-0,540	0,017
Ethnicity	-3,764	-6,067	-1,460	0,001
Daytime hours	0,457	-0,245	1,159	0,202
Month	-1,182	-2,160	-0,204	0,018
Formal education	0,124	-0,270	0,518	0,536
Higher education	2,083	-0,921	5,087	0,174
Employment	0,973	-1,169	3,116	0,373
History of diabetes mellitus (DM)	0,323	-1,870	2,515	0,773
History of DM & cholesterol	0,231	-2,043	2,504	0,842
History of DM & stroke	-0,307	-4,660	4,046	0,890
History of DM & myocardial infarction	2,520	-1,792	6,832	0,252
History of DM& congenital cardiac failure	-2,238	-7,423	2,947	0,397
History of DM & TIA	-0,644	-4,735	3,447	0,758
History of DM & Angina	1,864	-1,126	4,854	0,222
Smoking	1,674	-0,877	4,224	0,198
Alcohol	-1,718	-4,311	0,874	0,194
Diet	-0,002	-0,415	0,411	0,993
Humidity	-0,026	-0,113	0,061	0,560
Sulphur Dioxide	-0,020	-0,097	0,058	0,621
Nitrogen dioxide	0,046	-0,019	0,111	0,169
PM10	-0,007	-0,069	0,055	0,816

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Appendices

Table of Contents

Appendix A: StAR trial Screening Questionnaire

StAR_clinical_measures_1.4 ELIGIBLITY STATUS: [ ] 04/06/12

* StAR

SECTION 1 – STICK LABEL OVER OR FILL IN							
1.1	CLINIC FOLDER NUMBER						
1.2	LAST NAME						
1.3	FIRST NAME						
1.4	DATE OF BIRTH	DD	MM	YYYY	1.5	GENDER	[1] M / [2] F

DATE: __ __/ __ __/ 2012

INTERVIEWER STAFF NUMBER/NAME

____

SECTION 1 - CONTINUED							OFFICE USE ONLY
1.5	If FEMALE, are you PREGNANT OR BREASTFEEDING?			[1] YES	[2] NO	[3] N/A	
1.6	SA ID NUMBER						
1.7	IN WHICH ETHNIC GROUP WOULD YOU CLASS YOURSELF?						
	[1] BLACK	[2] WHITE	[3] COLOURED	[4] INDIAN	[5] OTHER	[6]PREFER NOT TO SAY	
1.8	DO YOU HAVE REGULAR ACCESS TO A CELLPHONE?			[1] YES	[2] NO	[3] NOT SURE	
1.9	DO YOU HAVE HIGH BLOOD PRESSURE?			[1] YES	[2] NO	[3] NOT SURE	
	If NO go to Question 1.12, if YES answer 1.11.a						
1.10	DID YOU TAKE YOUR HIGH BLOOD PRESSURE MEDICINE TODAY?			[1] YES	[2] NO	[3] NOT SURE	
1.11	IF NO, PLEASE WILL YOU TELL ME WHY YOU HAVE NOT YET TAKEN YOUR PILLS TODAY? [TICK THE REASON THAT APPLIES]						
	[1] FORGOT	[2] I CAN'T TAKE THEM ON EMPTY STOMACH	[3] I RAN SHORT	[4] ONLY TAKE AT NIGHT	[5] MAKE ME NEED TOILET	[6] OTHER	

SECTION 3			
3.1	Weight	●	KG
3.2	Height	●	CM
3.3	Waist Circumference	●	CM
3.4	Mid Upper Arm Circumference	●	CM

SECTION 4				
4.1	Stabil-o-graph Number			
4.2	Cuff size used			
	[1] S (<24cm)	[2] M (24 -32cm)	[3] L (32-38cm)	[4] XL (38-55cm)
4.3	Allocated Arm	[1] L	[2] R	
4.4	Number of readings to be completed			

STICK OR WRITE IN BP

	[TIME]	SBP / DBP	HR
1.	____	___/___	___
2.	____	___/___	___
3.	____	___/___	___
4.	____	___/___	___
5.	____	___/___	___
6.	____	___/___	___
AVE		___/___	___

4.5	PLEASE LOOK ON THE PRESCRIPTION CHART (IN FOLDER) AND NOTE THE LAST FOUR CONSECUTIVE DATES THE PATIENT PICKED-UP CHRONIC MEDICINE FROM CLINIC. (FORMAT DD-MM-YY)								
4.6	PLEASE LOOK ON THE PATIENT MEDICINE PICK-UP CARD AND NOTE THE LAST FOUR CONSECUTIVE DATES (DD-MM-YY) THE PATIENT WAS SCHEDULED TO PICK CHRONIC MEDICINE FROM CLINIC. (FORMAT DD-MM-YY)								
	FOR EACH DATE PAIR DO THE DATES MATCH? (I.E. WITHIN 72 HOURS BEFORE OR AFTER SCHEDULED DATE)								
4.7	[1] YES	[2] NO	[1] YES	[2] NO	[1] YES	[2] NO	[1] YES	[2] NO	
	IF ALL FOUR DATES MATCH THEN PARTICIPANT IS "REGULAR" IF < 4 MATCH THEN PARTICIPANT IS "IRREGULAR". IF PARTICIPANT HAS < 4 AVAILABLE READINGS THEN PARTICIPANT IS "UNKNOWN"								
	[REGULAR]		[IRREGULAR]		[UNKNOWN]				

StAR_clinical_measures_1.4 ELIGIBLITY STATUS: [ ] 04/06/12

* StAR

SECTION 1: PARTICIPANT CONTACT DETAILS		
PLEASE COMPLETE SECTION 1 IF THE PARTICIPANT'S STREET ADDRESS IS NOT THE SAME AS IN THEIR CLINIC FOLDER		OFFICE USE
	INTERVIEWER TO COMPLETE [IN PEN]	
1.1	PARTICIPANT CLINIC FOLDER NUMBER	
1.2	PARTICIPANT MAIN CELL NUMBER	
1.3	WHAT IS THE STREET ADDRESS OF THE HOME WHERE YOU LIVE OR STAY MOST OFTEN (PLEASE REMEMBER WE KEEP THIS INFORMATION STRICTLY CONFIDENTIAL, WE WILL NOT SHARE IT WITH ANY CLINIC STAFF)	
	HOUSE NUMBER & STREET	
	SUBURB	
	ZONE (if applicable)	
	TOWN	
	PROVINCE	
	POST CODE	

PLEASE MAY WE HAVE THE CONTACT DETAILS OF TWO PEOPLE WHO KNOW YOU VERY WELL AND WHO WOULD BE ABLE TO REACH YOU IF WE ARE NOT ABLE TO? THEY CAN BE FAMILY OR FRIENDS OR OTHERS. [PLEASE REMIND PARTICIPANT THAT IT WOULD BE PREFERABLE FOR THESE TO BE PEOPLE WHO ARE NOT LIKELY TO MOVE IN THE NEXT 3 YEARS, ALSO IT DOESN'T MATTER IF THEY ARE NOT IN CAPE TOWN]

SECTION 2: NEXT OF KIN OR SIMILAR (1)		
	INTERVIEWER TO COMPLETE [IN PEN]	OFFICE USE
2.1	NAME	
2.2	SURNAME	
2.3	PHONE NUMBER (1)	
2.4	PHONE NUMBER(2)	
2.3	What is the street address of the home where they live or stay most often (PLEASE REMEMBER WE KEEP THIS INFORMATION STRICTLY CONFIDENTIAL, WE WILL NOT SHARE IT WITH ANY CLINIC STAFF)	
	HOUSE NUMBER & STREET	
	SUBURB	
	ZONE (if applicable)	
	TOWN	
	PROVINCE	
	POST CODE	

SECTION 3: NEXT OF KIN OR SIMILAR (2)		
	INTERVIEWER TO COMPLETE [IN PEN]	OFFICE USE
3.1	NAME	
3.2	SURNAME	
3.3	PHONE NUMBER (1)	
3.4	PHONE NUMBER(2)	
3.5	What is the street address of the home where they live or stay most often (PLEASE REMEMBER WE KEEP THIS INFORMATION STRICTLY CONFIDENTIAL, WE WILL NOT SHARE IT WITH ANY CLINIC STAFF)	
	HOUSE NUMBER & STREET	
	SUBURB	
	ZONE (if applicable)	
	TOWN	
	PROVINCE	
	POST CODE	

Appendix B: The UCT Human Research Ethics committee Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

04 May 2015

HREC REF: 267/2015

Prof N Levitt
Diabetic Medicine and Endocrinology
J47-85
OMB

Dear Prof Levitt

PROJECT TITLE: VARIATION IN BLOOD PRESSURE AND ITS ASSOCIATION WITH OUTDOOR TEMPERATURE AMONG ADULTS WITH HYPERTENSION IN A PRIMARY CARE SETTING IN SOUTH AFRICA (Sub-study linked to 418/2011) - Masters candidate Mr E Havyarimana)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th May 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Enock Havyarimana will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH

HREC 267/2015

Appendix C: The City of Cape Town air quality data request approval

CITY OF CAPE TOWN
ISIXEKO SASEKAPA
STAD KAAPSTAD

CITY HEALTH

Dr Hélène Visser
Manager: Specialised Health

T: 021 400 3981 F: 021 421 4894 M: 083 298 8718
E: Helene.Visser@capetown.gov.za

2015-07-13

Re: Research Request: Variation in blood pressure and its association with outdoor temperature among adults with hypertension in a primary care setting in South Africa (ID No: 10496)

Dear Mr Havyarimana,

Apologies for the delay in sending your approval letter. Your research request has been approved as per your protocol during the latter part of June.

Contact Person
Air Pollution: Mr I Gildenhuys (Head: Specialised Environmental Health)
Tel/Cell: (021) 590-5202 / 084 2200 139)

Please note the following:

1. All information obtained must be kept confidential.
2. A copy of the final report must be sent to the City Health Head Office, P O Box 2815 Cape Town 8001, within 6 months of its completion.
3. Your project has been given an ID Number (10496). Please use this in any future correspondence with us.
4. Any papers for publication must be submitted to City Health prior to publication.

Thank you for your co-operation and please contact me if you require any further information or assistance.

Kind regards,

ff Dr Visser

DR G H VISSER
MANAGER: SPECIALISED HEALTH

cc. Mr I Gildenhuys

CIVIC CENTRE IZIKO LOLUNTU BURGERSENTRUM
HERTZOG BOULEVARD CAPE TOWN 8001 P O BOX 2815 CAPE TOWN 8000
www.capetown.gov.za

Making progress possible. Together.

Appendix D: The South African Weather Service data disclosure statement

LS-Disclosure-001 4.docDisclosure Statement

DISCLOSURE STATEMENT

The provision of the data is subject to the User providing the South African Weather Service (SAWS) with a detailed and complete disclosure, in writing and in line with the requirements of clauses 1.1 to 2.4 (below), of the purpose for which the specified data is to be used. The statement is to be attached to this document as Schedule 1.

Should the User intend using the specified data for commercial gain then the disclosure should include the following: the commercial nature of the project/funded research project in connection with which the User intends to use the specified data; the names and fields of expertise of any participants in the project/funded research project for which the specified data is intended; and the projected commercial gains to the User as a result of the intended use of the specified data for the project/funded research project. Should the User intend using the specified data for the purposes of conducting research, then the disclosure should include the following: the title of the research paper or project for which the specified data is to be used; the details of the institution and supervisory body or person(s) under the auspices of which the research is to be undertaken; an undertaking to supply SAWS with a copy of the final results of the research in printed and/or electronic format; and the assurance that no commercial gain will be received from the outcome from the research.

If the specified data is used in research with disclosure being provided in accordance with paragraph 2 and the User is given the opportunity to receive financial benefit from the research following the publication of the results, then additional disclosure in terms of paragraph 1 is required. The condition of this disclosure statement is applicable to the purpose and data requirements of the transaction recorded in Schedule 1. This statement is effective from 24 May 2012.

SCHEDULE 1

Please note: The South African Weather Service will only act upon customer requirements noted on this disclosure statement and not from any other correspondence.

FULL PERSONAL DETAILS OF USER

Full Names	Enock Havyarimana
University	University of Cape Town, Chronic Diseases Initiative for Africa
Student Number (if applicable)	HVYENO001
Email address	ehavyarimana@gmail.com
Postal address	Groote Schuur Dr, Cape Town 7925, South Africa
Supervisor	Professor Naomi Levitt
Project Title	The effect of climatic conditions (temperature, humidity, pollution) on clinic blood pressure measurements and their potential influence on hypertension treatment decisions
Degree	Master's in Public Health

LS-Disclosure-001 4.docDisclosure Statement

THE PURPOSE (Please indicate a detailed description of the purpose for which the data will be used)

Published evidence suggests that for many populations blood pressure varies with outdoor temperature[1] . The extent to which climatic variables affect clinic-based blood pressure measurement in South Africa is not known. We have been conducting a 12-month parallel group trial of an SMS-based adherence support intervention in adult patients attending the Vanguard Community Health Centre. The research clinic is moderately affected by outdoor temperature and other climatic variables. Using SAWS data we have begun to characterise and describe the relationship between outdoor temperatures in Bontehuewel, Cape Town and blood pressures measured using a research-validated electronic device on one or more occasions. (Dr K Bobrow – permission and data accessed 04/03/14) As part of a these analyses we are exploring which clinical variables may affect this relationship and we would like to add to this by exploring the influence on this relationship of other climate variables which are known to influence other health conditions (e.g. asthma).

DATA REQUIRED (Please include the weather elements (e.g. rain, temperature), place/s and period)

Daily air-quality/air-pollution for the period 25 June 2012 to 28 February 2014 inclusive

Daily humidity for the period 25 June 2012 to 28 February 2014 inclusive

Daily precipitation for the period 25 June 2012 to 28 February 2014 inclusive

For each of these please may we have access to data which would be relevant for the Bontehuewel area of Cape Town?

I hereby accept that:

SAWS will be acknowledged in the resulting thesis/project or when published, for the data it provided. SAWS will be provided with a copy of the final results in printed or electronic format. The data received shall not be provided to any third party.

Signature of the User:

Date: 25/07/2014

(Please sign the document and do not type your name in as this is a legal document and requires a signature.)

---

[1] Lewington S, Li L, Sherliker P, Guo Y, Millwood I, Bian Z, Whitlock G, Yang L, Collins R, Chen J, Wu X, Wang S, Hu Y, Jiang L, Yang L, Lacey B, Peto R, Chen Z; China Kadoorie Biobank study collaboration. J Hypertens. 2012 Jul;30(7):1383-91. doi: 10.1097/HJH.0b013e32835465b5. Seasonal variation in blood pressure and its relationship with outdoor temperature in 10 diverse regions of China: the China Kadoorie Biobank.

Appendix E: Author Guidelines for the Journal of Hypertension

Guidance for Authors on the Preparation and Submission of Manuscripts to Journal of Hypertension

These instructions comply with those formulated by the International Committee of Medical Journal Editors. For further details, authors should consult the following article: International Committee of Medical Journal Editors, "Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals" at www.icmje.org.

The Journal is a member of the Committee on Publication Ethics (COPE) which aims to define best practice in the ethics of scientific publishing. COPE has established a number of guidelines including a Code of Conduct, and created flow charts that help editor's process cases of suspected misconduct (www.publicationethics.org).

Appeals on editorial decisions should be sent to the Editor. Complaints related to how your paper was processed during peer-review and not resolved by the Editor, should be referred to the person named as publisher in "About the Journal" under "Journal Info" contacts (http://journals.lww.com/jhypertension/Pages/aboutthejournal.aspx) or if unsatisfied to COPE (www.publicationethics.org).

Submitted articles undergo a preliminary review by the editor. Some articles may be returned to authors without further consideration. Those being considered for publication will undergo further assessment and peer-review by the editor and those invited to do so from the board and reviewer pool.

SCOPE

The Journal of Hypertension publishes papers reporting original clinical and experimental research which are of a high standard and which contribute to the advancement of knowledge in the field of hypertension. The Journal publishes full papers, reviews or editorials (normally by invitation), and correspondence.

SUBMISSIONS

Authors can submit their manuscripts through the web-based tracking system at http://www.editorialmanager.com/jh. Authors should submit the text of the paper as a word-processed document, and not as a PDF. The site contains instructions and advice on how to use the system. Authors should NOT post a hard copy submission to the editorial office, unless you have been instructed to do so. All submitted manuscripts should be addressed to the Editor-in-Chief, Professor Alberto Zanchetti.

Margins should be not less than 3 cm. Double spacing should be used throughout the manuscript, which should include the following sections, each starting on a separate page: title page, abstract and keywords, text, acknowledgements, references, individual tables and captions. Pages should be numbered consecutively, beginning with the title page, and the page number should be placed in the top right hand corner of each page. Abbreviations should be defined on their first appearance in the text; those not accepted by international bodies should be avoided.

Please note that as a new feature of the Journal of Hypertension, published articles will be followed by a short summary of strengths and weaknesses prepared by each of the reviewers.

Article Types

1. **Original manuscripts (Original clinical and experimental research)**
2. **Reviews (These also include Systematic Reviews and Meta-analyses)**
3. **Editorials and Editorial Comments (By invitation)**
4. **Consensus Documents and Guidelines (By agreement between Scientific Societies and the Editor)**
5. **Case reports**
6. **Correspondence (Mostly, brief comments on published papers and authors' replies)**
7. **ESH News (Submitted by the Scientific Society)**
8. **ISH News (Submitted by the Scientific Society)**

All manuscripts should be as concise as possible, with the number of Tables and Figures not exceeding those required for scientific information. The Editor may require reduction of length and illustrations, whenever convenient and will communicate this as necessary.

POINTS TO CONSIDER WHEN SUBMITTING YOUR PAPER TO ONE OF OUR JOURNALS
Please think carefully about the following points and make the appropriate declarations.

Redundant or duplicate publication
Submissions are accepted on the understanding that they have not been published in their current form or a substantially similar form (in print or electronically, including on a web site), that they have not been accepted for publication elsewhere, and they are not under consideration by another publication.

Conflicts of interest
Authors must state all possible conflicts of interest in the manuscript, including financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest. If there is no conflict of interest, this should also be explicitly stated as none declared. All sources of funding should be acknowledged in the manuscript. All relevant conflicts of interest and sources of funding should be included on the title page of the manuscript with the heading "Conflicts of Interest and Source of Funding:". For example:

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Patient consent forms
Patients have a right to privacy that should not be infringed without informed consent. Identifying details (written or photographic) should be omitted if they are not essential, but patient data should never be altered or falsified in an attempt to attain anonymity. Complete anonymity is difficult to achieve, and a consent form should be obtained if there is any doubt. For example, masking the eye region in photographs of patients is inadequate protection of anonymity. When informed consent has been obtained it should be indicated in the published article.

Ethics committee approval
The Editors reserve the right to judge the appropriateness of the use and treatment of humans or animals in experiments for publication in the journal.

Human experiments: All work must be conducted in accordance with the Declaration of Helsinki. Papers describing experimental work on human participants which carries a risk of harm must include (1) a statement that the experiments were conducted with the understanding and the consent of each participant, and (2) a statement that the responsible ethical committee has approved the experiments.

Animal experiments: In papers describing experiments on living animals, include (1) a full description of any anaesthetic and surgical procedure used, and (2) evidence that all possible steps were taken to avoid animals' suffering at each stage of the experiment.

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Articles in journals
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More than seven authors:
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Kim HC. SSA 01-1 Hypertension subtypes in rapidly aging East Asia. J Hypertens 2016; 34 (e-supp 1): e1

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Perk G, Bursztyn M. Changes in body position effect measurements during 24 hr ambulatory blood pressure monitoring [Letter]. J Hypertens 2001; 19:1513.

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Books
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