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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Submitted in partial fulfilment of the requirement for the degree of Master of Public Health

In the School of Public Health and Family Medicine

at the University Of Cape Town

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December 2017
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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
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Declaration

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Signature: _____________________

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.

I also would like to thank David Springer and Katye Altyeri for their technical support with the data management and analysis. And last but not least, the staff at the chronic disease initiative for Africa, thanks for your kind support, warm hearts and openness to help me at all times.
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Part A: Protocol

Part B: Literature Review

Part C: Journal Manuscript

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PART A
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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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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.
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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 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 (>65 years), 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.
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
STUDY PROTOCOL

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

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unit</th>
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<tr>
<td><strong>Outcome</strong></td>
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<tr>
<td><strong>Exposure</strong></td>
<td>Outdoor temperature</td>
</tr>
<tr>
<td><strong>Potential confounders</strong></td>
<td>Humidity</td>
</tr>
<tr>
<td></td>
<td>Particulate Matter (PM2.5/10)*</td>
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STUDY PROTOCOL

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<tbody>
<tr>
<td>Carbon dioxide (CO₂)*</td>
<td>Parts per million (ppm)</td>
<td></td>
</tr>
<tr>
<td>Nitrogen dioxide (NO₂)*</td>
<td>µgm⁻³</td>
<td></td>
</tr>
<tr>
<td>Ozone (O₃)*</td>
<td>µgm⁻³</td>
<td></td>
</tr>
<tr>
<td>Sulphur dioxide (NO₂)*</td>
<td>µg/m³</td>
<td></td>
</tr>
<tr>
<td>Carbon monoxide (CO)*</td>
<td>Parts per million (ppm)</td>
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<tr>
<th>Other</th>
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<tbody>
<tr>
<td>Age</td>
<td>Years</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>Weight/height square</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male or female</td>
<td></td>
</tr>
</tbody>
</table>

*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.
9. References


Andersen UO, Henriksen JH, Jensen G. Sources of measurement variation in blood pressure in large-scale epidemiological surveys with follow-up. Blood Press.
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Literature Review
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**Acronyms**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>LMICs</td>
<td>Low-middle income countries</td>
</tr>
<tr>
<td>HICs</td>
<td>High income countries</td>
</tr>
<tr>
<td>WMO</td>
<td>World Meteorology Organization</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>BPV</td>
<td>Blood pressure variation</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>95%CI</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>SE</td>
<td>Standard error</td>
</tr>
<tr>
<td>NO2</td>
<td>Nitrogen dioxide</td>
</tr>
<tr>
<td>SO2</td>
<td>Sulphur dioxide</td>
</tr>
<tr>
<td>PM2.5</td>
<td>Particulate matter with 2.5(\mu)m diameter aerodynamic</td>
</tr>
<tr>
<td>PM10</td>
<td>Particulate matter with 10(\mu)m diameter aerodynamic</td>
</tr>
</tbody>
</table>
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
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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 Feddeconstante 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

<table>
<thead>
<tr>
<th>Author</th>
<th>Population / data source</th>
<th>Setting &amp; period examined</th>
<th>Sample Size</th>
<th>Study design &amp; analysis</th>
<th>Seasons compared</th>
<th>Key results (Summer – Winter)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-middle income countries</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hightower et al., 2009 (42)</td>
<td>Rural residents of Kassena-Nankana, Ghana</td>
<td>Kinshasa, Congo (DRC)</td>
<td>232</td>
<td>Cross sectional time series Not mentioned</td>
<td>End of Winter vs end of summer</td>
<td>2.7mmHg SBP (SD ±2.6)</td>
</tr>
<tr>
<td>Lewington et al., 2012 (15)</td>
<td>General population from 10 provinces in China</td>
<td>10 cities, China 2004 - 2008</td>
<td>506673</td>
<td>Cross sectional, Multivariate linear regression</td>
<td>Winter vs summer</td>
<td>10 mmHg SBP (p&lt;0.0001)</td>
</tr>
<tr>
<td>Cois A &amp; Ehrlich R., 2015(37)</td>
<td>General population in South Africa</td>
<td>South Africa 2010 &amp; 2012</td>
<td>11440</td>
<td>Cross-sectional, multilevel linear structural equation model</td>
<td>All seasons</td>
<td><strong>Women:</strong> 4.25mmHg SBP (95% CI: 3.18 – 5.31), <strong>Men:</strong> 4.21mmHg SBP (95% CI: 2.98 – 5.44)</td>
</tr>
<tr>
<td>Tu et al., 2013 (43)</td>
<td>General population from 4 major cities in Taiwan</td>
<td>4 cities in Taiwan 1996 – 2006</td>
<td>68045</td>
<td>Prospective repeated &amp; single measures cohort GEE</td>
<td>All seasons</td>
<td>5.3mmHg SBP ( SE=0.07)</td>
</tr>
<tr>
<td>Askari et al., 2014 (44)</td>
<td>Urban Population from Tehran Iran (&gt;20 years)</td>
<td>Tehran, Iran 1998 - 2001</td>
<td>29777</td>
<td>Prospective cohort ANOVA &amp; post-hoc pairwise Turkey test</td>
<td>All seasons</td>
<td>3mmHg SP (P&lt;0.01)</td>
</tr>
<tr>
<td>Youn et al., 2007 (45)</td>
<td>Elderly people living with hypertension (≥ 55 years) patients</td>
<td>Yonsei, South Korea 2002 - 2005</td>
<td>85</td>
<td>Prospective cohort Multivariate linear regression</td>
<td>All seasons</td>
<td>9mmHg SBP (p&lt;0.001)</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Design</th>
<th>Methodology</th>
<th>Season Comparison</th>
<th>Blood Pressure Change (mmHg) (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinha et al., 2010 (46)</td>
<td>Adult females (&gt;18 years old) residing in a Peri-urban area of Gokulpiri, New Delhi, India</td>
<td>India, 2 years</td>
<td>Prospective cohort &amp; Paired t-test</td>
<td>Winter vs Summer</td>
<td>11mmHg (p&lt;0.001)</td>
</tr>
<tr>
<td>High Income countries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barnett et al., 2007 (48)</td>
<td>25 populations from 16 countries in Europe &amp; Oceania</td>
<td>Europe &amp; Oceania 1979 - 1997</td>
<td>Prospective cross-sectional GLMM(^1)</td>
<td>Mid-winter vs Mid-summer</td>
<td>2.06 mmHg (95% PI: 1.05; 3.08)</td>
</tr>
<tr>
<td>Kristal-Boneh et al., 1996 (59)</td>
<td>Factory workers, machining departments</td>
<td>Israeli, Not reported</td>
<td>Cross sectional ANOVA</td>
<td>Winter vs Summer</td>
<td>3.4mmHg SBP (p&lt;0.01)</td>
</tr>
<tr>
<td>Minami et al., 1998 (50)</td>
<td>Outpatients with essential hypertension</td>
<td>Japan, Not reported</td>
<td>Prospective cohort, ANOVA</td>
<td>Winter vs Summer</td>
<td>1.5mmHg (SD:±1.3)</td>
</tr>
<tr>
<td>Prasad GV, Nash M, Zaltzam S., 2001 (60)</td>
<td>Stable renal transplant recipients</td>
<td>Canada, Not reported</td>
<td>Cross sectional</td>
<td>Winter vs Summer</td>
<td>2.3mmHg (p&lt;0.01)</td>
</tr>
</tbody>
</table>
| Ulmer et al., 2004 (52)      | General population in Austria                                              | Austria 1985 - 1999  | 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 | 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)
<table>
<thead>
<tr>
<th>Study</th>
<th>Population Description</th>
<th>Location</th>
<th>N</th>
<th>Study Design</th>
<th>Analysis Type</th>
<th>Seasons</th>
<th>SBP Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hopstock et al., 2013 (54)</td>
<td>General population from Tromso, Norway</td>
<td>Tromso, Norway 1979 - 2008</td>
<td>38037</td>
<td>Cohort &amp; cross-section time series Multivariate &amp; mixed effect linear regression</td>
<td></td>
<td>All seasons</td>
<td>2mmHg SBP (p&lt;0.001).</td>
</tr>
<tr>
<td>Modesti PA et al., 2013 (55)</td>
<td>Outpatients referred for ABP monitoring in Florence, Italy</td>
<td>Florence, Italy 2005 - 2007</td>
<td>1897</td>
<td>Cross sectional Multivariate linear analysis</td>
<td></td>
<td>All seasons</td>
<td>2.7mmHg, (p&lt;0.001).</td>
</tr>
<tr>
<td>Fedeconstante M et al., 2012</td>
<td>Adults (≥ 18 years) with hypertension (75%) &amp; normal BP (25%) in Marche, Italy</td>
<td>Marche, Italy 2002 - 2011</td>
<td>1395</td>
<td>Cross sectional Logistic regression</td>
<td>Winter vs summer</td>
<td></td>
<td>People wt normal BP 2.4 mmHg (p&lt;0.001) People wt high BP 2.7mmHg (p=0.017) People wt Controlled high BP on treatment 0.9mmHg SBP (p&gt;0.05) People wt Uncontrolled high BP on treatment 2.7 mmHg (p&lt;0.009)</td>
</tr>
<tr>
<td>Seguro et al.,1992 (61)</td>
<td>People with hypertension on treatment in Cagliari</td>
<td>Cagliari, Italy 1981 – 1990</td>
<td>145</td>
<td>Prospective cohort Paired t-test</td>
<td></td>
<td>All season</td>
<td>5.0mmHg (P&lt;0.05)</td>
</tr>
<tr>
<td>Alperovitch et.al 2009 (62)</td>
<td>Elderly population (≥ 65 years) from Bordeaux, Dijon and Montpellier in France</td>
<td>3 Cities, France 1999 – 2002</td>
<td>9294</td>
<td>Prospective cohort &amp; Bartlett- Kolmogorov-Smirnov test</td>
<td></td>
<td>All seasons</td>
<td>5.0mmHg (p&lt;0.001)</td>
</tr>
<tr>
<td>Sega et al., 1996 (63)</td>
<td>Population of Monza area in Italy (25 – 64 years)</td>
<td>Monza, Italy 1989 – 1993</td>
<td>2051</td>
<td>Cross sectional Unpaired T-test</td>
<td></td>
<td>All seasons</td>
<td>Clinic BP 4.5mmHg (p&lt;0.05) Home SBP 6mmHg (P&lt;0.01) 24hr SBP 4.1mmHg (p&lt;0.001)</td>
</tr>
</tbody>
</table>
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 1.9 mmHg (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 1.6 mmHg 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

<table>
<thead>
<tr>
<th>Author</th>
<th>Population / data source</th>
<th>Sample Size</th>
<th>Setting &amp; period examined</th>
<th>Study design &amp; analysis</th>
<th>Temperature meas. used &amp; distance from BP meas.</th>
<th>Variables adjusted for</th>
<th>Key results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-middle income countries</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Kunutsor and Powles, 2010 (33)</td>
<td>Rural residents of Kassena-Nankana, Ghana</td>
<td>574</td>
<td>Kassena-Nankana, Ghana N/A</td>
<td>Cross-sectional Multivariate linear regression</td>
<td>Outdoor Not reported</td>
<td>Age, gender, BMI, waist, time of BP measurement</td>
<td>5mmHg SBP/ 10°C (P=0.047) Mean daytime temperature</td>
</tr>
<tr>
<td>Lewington et al., 2012 (15)</td>
<td>General population from 10 provinces in China</td>
<td>506673</td>
<td>10 provinces, China 2004 - 2008</td>
<td>Cross-sectional Multivariate linear regression</td>
<td>Outdoor 15km</td>
<td>Age, sex, BMI, study area, humidity</td>
<td>5.7mmHg SBP / 10°C (SE:0.04) (Mean daytime temperature &gt;5°C)</td>
</tr>
<tr>
<td>Su et al., 2014 (12)</td>
<td>Rural residents of Zhejiang province in China</td>
<td>57375</td>
<td>Zhejiang, China 2004 - 2008</td>
<td>Cross-sectional Multivariate linear regression</td>
<td>Outdoor</td>
<td>Age, sex, education, season (month), physical activity, diet and BMI</td>
<td>6.9mmHg SBP/10°C (no P-value or 95%CI reported) Mean daytime temperature</td>
</tr>
<tr>
<td>Sinha et al., 2010 (46)</td>
<td>Adult females (&gt;18 years old) residing in a Peri-urban area of Gokulpiri, New Dheli, India</td>
<td>132</td>
<td>New Dheli, India 2004 - 2005</td>
<td>Cross-sectional Multivariate linear regression</td>
<td>Outdoor Not reported</td>
<td>Age, BMI, day length</td>
<td>8.8mmHg/ 10°C (95% CI: -10.73; -3.06) Mean daytime temperature</td>
</tr>
<tr>
<td>Study</td>
<td>Population Description</td>
<td>Sample Size</td>
<td>Study Design</td>
<td>Study Duration</td>
<td>Outcome Parameters</td>
<td>Results</td>
<td></td>
</tr>
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</tr>
<tr>
<td>Chen et al., 2013 (64)</td>
<td>People with hypertension residing in an urban area in Shanghai</td>
<td>1831</td>
<td>Prospective cohort</td>
<td>1997–2001</td>
<td>Outdoor, Not reported</td>
<td>Age, sex, BMI, drinking &amp; smoking, urine, medication duration, urine, baseline BP</td>
<td>Baseline -2.66/10°C SBP (95% CI: -3.52; 0.181)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Multilevel model</td>
<td></td>
<td></td>
<td>3 year follow up -2.14mmHg SBP/10°C (95% CI: -2.22; -2.06)</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean daytime temperature</td>
<td></td>
</tr>
</tbody>
</table>

**High Income Countries**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population Description</th>
<th>Sample Size</th>
<th>Study Design</th>
<th>Study Duration</th>
<th>Outcome Parameters</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruce et al., 1991 (67)</td>
<td>Men from 24 towns in Britain</td>
<td>7735</td>
<td>Cross sectional Multivariate linear regression</td>
<td>1978–1980</td>
<td>Outdoor, Not reported</td>
<td>Age, sex, BMI, smoking, diet</td>
</tr>
<tr>
<td>Andersen et al., 2002 (14)</td>
<td>General population of Copenhagen, Denmark</td>
<td>19698</td>
<td>Cross sectional Multivariate time series linear regression</td>
<td>1976–1994</td>
<td>Outdoor, Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Madsen and Nafstad., 2006 (53)</td>
<td>Residents of Oslo, Norway</td>
<td>18770</td>
<td>Cross sectional Multivariate &amp; General linear regression (GLM)</td>
<td>2000–2001</td>
<td>Outdoor, Not reported</td>
<td>Age, sex, BMI, education, alcohol, day, month, year &amp; TSM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Women 2.4 mmHg SBP/10°C (95% CI – 1.6; 3.2)</td>
</tr>
<tr>
<td>Study</td>
<td>Population Description</td>
<td>Sample Size</td>
<td>Study Design</td>
<td>Measurement Location</td>
<td>Measurement Variables</td>
<td>Analysis Method</td>
</tr>
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</tr>
<tr>
<td>Barnett et al., 2007 (48)</td>
<td>25 populations from 16 countries in Europe &amp; Oceania</td>
<td>115434</td>
<td>16 countries (Europe &amp; US)</td>
<td>Cross-sectional time-series</td>
<td>Bayesian hierarchal model</td>
<td>Outdoor</td>
</tr>
<tr>
<td>Kent et al., 2011 (36)</td>
<td>General population (&gt;45 years old) from 48 states in the USA</td>
<td>20623</td>
<td>48 conterminous USA 2003-2006</td>
<td>Cross-sectional Multivariate linear regression</td>
<td>Outdoor</td>
<td>Not reported</td>
</tr>
<tr>
<td>Modesti et al., 2013 (55)</td>
<td>Outpatients referred for ambulatory BP monitoring to Hypertension clinic</td>
<td>1897</td>
<td>Florence, Italy 2005 - 2007</td>
<td>Cross-sectional Multivariate linear regression</td>
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<td>Not reported</td>
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³ CA: California, MA: Massachusetts, NC: North Carolina
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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 (NO₂) and sulphur dioxide (SO₂), 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 NO₂ and SO₂ 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 NO₂ and 2.4 ppb for SO₂, 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
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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
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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/m³ 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 findings by Liu et al., 2013, showed that a short-term exposure (1-24 hrs) to PM 2.5, at an inter-quartile range increase of 9.6µg/m³ 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/m²) 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/m²) 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/m² 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/m² 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.

5. References

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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
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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/m² 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 µg/m³ not 2339 µg/m³) 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

2534 participants screened and enrolled in the StAR trial were the main study population

21 participants with less than three blood pressure readings were excluded

2513 participants with all of the outcome and exposure data available were assessed further

16 participants with implausibly matched temperature data (three digit values, e.g.: 999) were excluded

2497 participants had appropriate exposure data and screening times

3 participants who were screened after clinic hours (>17h00) were also excluded

2494 participants with outcome, exposure and >90% of covariates of interest data were analysed

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\textsubscript{2}, NO\textsubscript{2} and PM\textsubscript{10}. Both SO\textsubscript{2}, NO\textsubscript{2} and PM\textsubscript{10} 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\textsubscript{2}, NO\textsubscript{2} and PM\textsubscript{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/m² 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/m³, 19.93 µg/m³ and 14.17 µg/m³ for PM₁₀, NO₂ and SO₂, respectively (Supplementary Table 2A).
Table 1 – Population characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – in years</td>
<td>Mean (SD ±) 57 (±12,5)</td>
</tr>
<tr>
<td>Gender – in %</td>
<td>Female 72</td>
</tr>
<tr>
<td>Ethnicity – in %</td>
<td>Black African 47</td>
</tr>
<tr>
<td></td>
<td>Mixed ancestry 53</td>
</tr>
<tr>
<td>BMI – in Kg/m²</td>
<td>Mean (SD ±) 31.7</td>
</tr>
<tr>
<td>Waist – in cm</td>
<td>Mean (SD ±) 99.21 (±14.6)</td>
</tr>
<tr>
<td>SBP – in mmHg</td>
<td>Mean (SD ±) 137.7 (±19.7)</td>
</tr>
<tr>
<td>DBP – in mmHg</td>
<td>Mean (SD ±) 83.3 (±13.2)</td>
</tr>
<tr>
<td>HR – in BPM</td>
<td>Mean (SD ±) 72.3 (±13.4)</td>
</tr>
</tbody>
</table>

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/m³, 19.93 µg/m³ and 14.17 µg/m³, 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.

<table>
<thead>
<tr>
<th></th>
<th>Winter</th>
<th>Spring</th>
<th>Winter - spring</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Climate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature (°C), mean</td>
<td>14.23</td>
<td>14.61</td>
<td>14.05</td>
<td>15.48</td>
</tr>
<tr>
<td></td>
<td>(3.7; 18.2)</td>
<td>(8; 26.4)</td>
<td>(7.7; 19.5)</td>
<td>(5.9; 22.1)</td>
</tr>
<tr>
<td>Humidity(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>65.137</td>
<td>65.217</td>
<td>65.067</td>
<td>64.335</td>
</tr>
<tr>
<td></td>
<td>(46; 84)</td>
<td>(15; 97)</td>
<td>(33; 97)</td>
<td>(30; 97)</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects, n</td>
<td>51</td>
<td>388</td>
<td>507</td>
<td>540</td>
</tr>
<tr>
<td>Systolic BP(mmHg), mean (±SD)</td>
<td>145.87 (±21.91)</td>
<td>142.17 (±18.83)</td>
<td>140.65 (±20.9)</td>
<td>137.47 (±19.49)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg), mean (±SD)</td>
<td>88.61 (±13.63)</td>
<td>85.21 (±11.68)</td>
<td>84.34 (±13.28)</td>
<td>83.88 (±13.36)</td>
</tr>
<tr>
<td>Heart rate (bpm), mean (±SD)</td>
<td>73.67 (±11.06)</td>
<td>71.23 (±13.71)</td>
<td>71.92 (±13.70)</td>
<td>72.52 (±12.98)</td>
</tr>
<tr>
<td>Age (years) - mean</td>
<td>56.10 (±15.18)</td>
<td>57.08 (±12.12)</td>
<td>57.70 (±12.57)</td>
<td>55.56 (±12.24)</td>
</tr>
<tr>
<td>BMI (Kg/m²) - mean</td>
<td>31.04 (±7.96)</td>
<td>32.03 (±7.80)</td>
<td>32.03 (±7.21)</td>
<td>31.71 (±7.64)</td>
</tr>
<tr>
<td>Air quality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM10 (µg/m³), mean</td>
<td>50.352</td>
<td>34.227</td>
<td>18.633</td>
<td>16.331</td>
</tr>
<tr>
<td>NO₂ (µg/m³) - mean</td>
<td>52.65</td>
<td>50.03</td>
<td>24.97</td>
<td>13.43</td>
</tr>
<tr>
<td>SO₂ (µg/m³) - mean</td>
<td>23.18</td>
<td>35.36</td>
<td>31.07</td>
<td>4.03</td>
</tr>
<tr>
<td></td>
<td>(13 – 38)</td>
<td>(0 – 153)</td>
<td>(10 – 103)</td>
<td>(0 – 37)</td>
</tr>
</tbody>
</table>
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

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

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/m³, 19.93 µg/m³ and 14.17 µg/m³, 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 mediterranean-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

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>SBP</th>
<th></th>
<th>DBP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Coef (95% CI)</td>
<td></td>
<td>Coef (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Temperature (overall)</td>
<td>2494</td>
<td>-0.750 (-1,184; -0.382)</td>
<td>-0.495 (-0.734; -0.257)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile I (≤13°C)</td>
<td>363</td>
<td>0.333 (-1,374; 2,040)</td>
<td>0.029 (-1.084; 1.027)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile II (13°C-20°C)</td>
<td>1688</td>
<td>-0.487 (-1.12; -0.139)</td>
<td>-0.045 (-0.445; 0.355)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile III (&gt;20°C)</td>
<td>443</td>
<td>-2.044 (-3.348; -0.739)</td>
<td>-1.370 (-2.256; -0.482)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 of 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.

Acknowledgements

This study uses data from the SMS-Text message Adherence support trial (StAR) study, the South African Weather Services (SAWS) and the City of Cape Town environmental health department. The StAR study was supported by the Wellcome Trust and the Engineering Institute for Physical Sciences Research Council. Access to SAWS and City of Cape Town air quality data was in agreement with SAWS and AQMN data policy that the data would be used for research and not for any commercial purposes.
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)

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

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

<table>
<thead>
<tr>
<th></th>
<th>&lt; 50 years</th>
<th>51-65 years</th>
<th>&gt; 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject, n</td>
<td>744</td>
<td>1097</td>
<td>653</td>
</tr>
<tr>
<td>SBP - mmHg</td>
<td>134,5</td>
<td>137,24</td>
<td>139,85</td>
</tr>
<tr>
<td>(±17,89)</td>
<td>(±20,31)</td>
<td>(±20,81)</td>
<td></td>
</tr>
<tr>
<td>DBP - mmHg</td>
<td>86</td>
<td>83,74</td>
<td>78,63</td>
</tr>
<tr>
<td>(±12,75)</td>
<td>(±12,99)</td>
<td>(±12,79)</td>
<td></td>
</tr>
<tr>
<td>HR - bpm</td>
<td>74</td>
<td>72,08</td>
<td>69,44</td>
</tr>
<tr>
<td>(±12,83)</td>
<td>(±13,30)</td>
<td>(±13,36)</td>
<td></td>
</tr>
<tr>
<td>BMI - Kg/m2</td>
<td>31,623</td>
<td>32,05</td>
<td>30,32</td>
</tr>
<tr>
<td>(±7,79)</td>
<td>(±7,44)</td>
<td>(±7,1)</td>
<td></td>
</tr>
<tr>
<td>Waist - cm</td>
<td>98,65</td>
<td>100,09</td>
<td>97,83</td>
</tr>
<tr>
<td>(±15,12)</td>
<td>(±14,51)</td>
<td>(±14,22)</td>
<td></td>
</tr>
</tbody>
</table>
Supplementary Table 2a: Weather and air quality characteristics during the trial enrolment period (June – November 2012)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Temperature (°C), mean (±SD)</th>
<th>Humidity (%), mean (±SD)</th>
<th>SO2 (µg/m³), median (p25, p75)</th>
<th>NO2 (µg/m³), median (p25, p75)</th>
<th>PM10 (µg/m³), median (p25, p75)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16,73 (±3,88)</td>
<td>61,71 (±14,87)</td>
<td>4 (2, 31)</td>
<td>13 (5, 25)</td>
<td>18 (12, 25)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Days of trial enrolment</th>
<th>Mean Difference</th>
<th>Min difference</th>
<th>Maximum difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>June</td>
<td>2 9,2 °C</td>
<td>3,9 °C</td>
<td>14,5 °C</td>
</tr>
<tr>
<td>July</td>
<td>18 5,45 °C</td>
<td>1,3 °C</td>
<td>14,6 °C</td>
</tr>
<tr>
<td>August</td>
<td>18 4,11 °C</td>
<td>1,7 °C</td>
<td>7,3 °C</td>
</tr>
<tr>
<td>September</td>
<td>17 5,05 °C</td>
<td>1,4 °C</td>
<td>13,3 °C</td>
</tr>
<tr>
<td>October</td>
<td>22 3,40 °C</td>
<td>1,4 °C</td>
<td>8,8 °C</td>
</tr>
<tr>
<td>November</td>
<td>18 3,29 °C</td>
<td>1,6 °C</td>
<td>9,5 °C</td>
</tr>
<tr>
<td>Total</td>
<td>95 4,32 °C</td>
<td>1,4 °C</td>
<td>14,6 °C</td>
</tr>
</tbody>
</table>
Supplementary Table 3: Daytime distribution of key study variables (mean, ±SD and min-max)

<table>
<thead>
<tr>
<th>Daytime Hours</th>
<th>8h – 10h (n=1230)</th>
<th>11h -13h (n=1122)</th>
<th>14h-17h (N=142)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Temperature, °C - mean (± SD)</strong></td>
<td>15,67 °C (±3,93)</td>
<td>17,67 °C (±3,48)</td>
<td>18,50 °C (±3,88)</td>
<td>&lt;0,004 (1&amp;2,1&amp;3, 2&amp;3)</td>
</tr>
<tr>
<td><strong>SBP, mmHg - mean (± SD)</strong></td>
<td>139 mmHg (±20,07)</td>
<td>136,64 mmHg (±19,50)</td>
<td>135,90 mmHg (±18,98)</td>
<td>0,010 (1&amp;2)</td>
</tr>
<tr>
<td><strong>DBP, mmHg - mean (± SD)</strong></td>
<td>84,04 mmHg (±13,44)</td>
<td>82,54 mmHg (12,98)</td>
<td>83,23 mmHg (13,13)</td>
<td>0,018 (1&amp;2)</td>
</tr>
<tr>
<td><strong>Relative Humidity, % - mean (± SD)</strong></td>
<td>66,58% (±14,69)</td>
<td>57,56% (±13,12)</td>
<td>52,37% (±15,14)</td>
<td>&lt;0,001 (1&amp;2,1&amp;3, 2&amp;3)</td>
</tr>
<tr>
<td><strong>PM&lt;sub&gt;10&lt;/sub&gt;, µg/m³ - median, (p25; p75)</strong></td>
<td>19 ug/m³ (12; 24)</td>
<td>16 ug/m³ (11; 24)</td>
<td>22 ug/m³ (15; 28)</td>
<td>&lt;0,001 (1&amp;2, 2&amp;3)</td>
</tr>
<tr>
<td><strong>NO₂ µg/m³ - median, (p25; p75)</strong></td>
<td>16 ug/m³ (6; 25)</td>
<td>12 ug/m³ (5; 25)</td>
<td>11 ug/m³ (5; 25)</td>
<td>&lt;0,001 (1&amp;2)</td>
</tr>
<tr>
<td><strong>SO₂ µg/m³ - median, (p25; p75)</strong></td>
<td>4 ug/m³ (2; 30)</td>
<td>4 ug/m³ (2,31)</td>
<td>4 ug/m³ (3;31)</td>
<td>1,000</td>
</tr>
</tbody>
</table>
Supplementary Table 4: Correlation matrix of key study variables

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>BMI</th>
<th>Waist</th>
<th>Temperature</th>
<th>SBP</th>
<th>DBP</th>
<th>HR</th>
<th>Humidity</th>
<th>SO2</th>
<th>NO2</th>
<th>PM10</th>
<th>Daytime hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>-0.117*</td>
<td>1,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist</td>
<td>-0.035</td>
<td>0.821*</td>
<td>1,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>0.005</td>
<td>-0.02</td>
<td>-0.025</td>
<td>1,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>0.059*</td>
<td>-0.059*</td>
<td>-0.026</td>
<td>-0.194*</td>
<td>1,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>-0.240*</td>
<td>-0.110*</td>
<td>0.083*</td>
<td>-0.151*</td>
<td>0.724*</td>
<td>1,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>-0.160*</td>
<td>0.021</td>
<td>0.062*</td>
<td>0.035</td>
<td>0.004</td>
<td>0.114*</td>
<td>1,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humidity</td>
<td>0.019</td>
<td>0.013</td>
<td>0.040*</td>
<td>-0.640*</td>
<td>0.097*</td>
<td>0.065*</td>
<td>0.019</td>
<td>1,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SO2</td>
<td>-0.021</td>
<td>-0.003</td>
<td>-0.018</td>
<td>-0.318*</td>
<td>0.130*</td>
<td>0.089*</td>
<td>-0.032</td>
<td>-0.034*</td>
<td>1,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO2</td>
<td>-0.024</td>
<td>-0.003</td>
<td>-0.010</td>
<td>-0.254*</td>
<td>0.131*</td>
<td>0.102*</td>
<td>-0.018</td>
<td>0.023</td>
<td>0.762*</td>
<td>1,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM10</td>
<td>-0.022</td>
<td>0.024</td>
<td>-0.015</td>
<td>0.028</td>
<td>0.042*</td>
<td>0.029</td>
<td>0.008</td>
<td>-0.071*</td>
<td>0.451*</td>
<td>0.694*</td>
<td>1,000</td>
<td></td>
</tr>
<tr>
<td>Daytime hours</td>
<td>-0.018</td>
<td>0.016</td>
<td>-0.031</td>
<td>0.278*</td>
<td>-0.064*</td>
<td>-0.045*</td>
<td>0.034</td>
<td>-0.369*</td>
<td>0.034</td>
<td>-0.072*</td>
<td>-0.046*</td>
<td>1,000</td>
</tr>
</tbody>
</table>

* p < 0.05
### Supplementary Table 5a: Adjusted and unadjusted effects of potential confounders (air quality and relative humidity) on blood pressure

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted a</th>
<th></th>
<th>Unadjusted</th>
<th>Adjusted a</th>
<th></th>
<th>Unadjusted</th>
<th>Adjusted a</th>
<th></th>
<th>Unadjusted</th>
<th>Adjusted a</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient (95%CI)</td>
<td>P&gt;t</td>
<td>Coefficient (95%CI)</td>
<td>P&gt;t</td>
<td>Coefficient (95%CI)</td>
<td>P&gt;t</td>
<td>Coefficient (95%CI)</td>
<td>P&gt;t</td>
<td>Coefficient (95%CI)</td>
<td>P&gt;t</td>
<td>Coefficient (95%CI)</td>
<td>P&gt;t</td>
</tr>
<tr>
<td>Nitrogen dioxide</td>
<td>0,10 (0,07; 0,13)</td>
<td>0,000</td>
<td>0,08 (0,03; 0,12)</td>
<td>0,001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulphur dioxide</td>
<td>0,01 (0,09;0,17)</td>
<td>0,000</td>
<td>0,06 (0,02;0,11)</td>
<td>0,010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Particulate matter (PM10)</td>
<td>0,04 (0,01; 0,08)</td>
<td>0,038</td>
<td>0,03 (0,08; 0,03)</td>
<td>0,038</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative humidity</td>
<td>0,13 (0,08; 0,18)</td>
<td>0,000</td>
<td>0,04 (0,11; 0,03)</td>
<td>0,262</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>SO2 (µg/m³)</th>
<th>NO2 (µg/m³)</th>
<th>PM10 (µg/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted b</td>
<td>Unadjusted</td>
</tr>
<tr>
<td></td>
<td>Coef (95%CI)</td>
<td>Coef (95%CI)</td>
<td>Coef (95%CI)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>-1,59 (-1,77; -1,40)</td>
<td>-0,93 (-1,11; -0,76)</td>
<td>-1,75 (-2,01; -1,49)</td>
</tr>
</tbody>
</table>

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=1997)         | 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)

<table>
<thead>
<tr>
<th></th>
<th>Coef</th>
<th>95% Conf. Interval</th>
<th>P&gt;t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>-0.705</td>
<td>-1.197</td>
<td>-0.412</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.155</td>
<td>-0.294</td>
<td>-0.017</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.009</td>
<td>-0.064</td>
<td>0.082</td>
</tr>
<tr>
<td>Sex</td>
<td>-3.025</td>
<td>-5.511</td>
<td>-0.540</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>-3.764</td>
<td>-6.067</td>
<td>-1.460</td>
</tr>
<tr>
<td>Daytime hours</td>
<td>0.457</td>
<td>-0.245</td>
<td>1.159</td>
</tr>
<tr>
<td>Month</td>
<td>-1.182</td>
<td>-2.160</td>
<td>-0.204</td>
</tr>
<tr>
<td>Formal education</td>
<td>0.124</td>
<td>-0.270</td>
<td>0.518</td>
</tr>
<tr>
<td>Higher education</td>
<td>2.083</td>
<td>-0.921</td>
<td>5.087</td>
</tr>
<tr>
<td>Employment</td>
<td>0.973</td>
<td>-1.169</td>
<td>3.116</td>
</tr>
<tr>
<td>History of diabetes mellitus (DM)</td>
<td>0.323</td>
<td>-1.870</td>
<td>2.515</td>
</tr>
<tr>
<td>History of DM &amp; cholesterol</td>
<td>0.231</td>
<td>-2.043</td>
<td>2.504</td>
</tr>
<tr>
<td>History of DM &amp; stroke</td>
<td>-0.307</td>
<td>-4.660</td>
<td>4.046</td>
</tr>
<tr>
<td>History of DM &amp; myocardial infarction</td>
<td>2.520</td>
<td>-1.792</td>
<td>6.832</td>
</tr>
<tr>
<td>History of DM &amp; congenital cardiac failure</td>
<td>-2.238</td>
<td>-7.423</td>
<td>2.947</td>
</tr>
<tr>
<td>History of DM &amp; TIA</td>
<td>-0.644</td>
<td>-4.735</td>
<td>3.447</td>
</tr>
<tr>
<td>History of DM &amp; Angina</td>
<td>1.864</td>
<td>-1.126</td>
<td>4.854</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.674</td>
<td>-0.877</td>
<td>4.224</td>
</tr>
<tr>
<td>Alcohol</td>
<td>-1.718</td>
<td>-4.311</td>
<td>0.874</td>
</tr>
<tr>
<td>Diet</td>
<td>-0.002</td>
<td>-0.415</td>
<td>0.411</td>
</tr>
<tr>
<td>Humidity</td>
<td>-0.026</td>
<td>-0.113</td>
<td>0.061</td>
</tr>
<tr>
<td>Sulphur Dioxide</td>
<td>-0.020</td>
<td>-0.097</td>
<td>0.058</td>
</tr>
<tr>
<td>Nitrogen dioxide</td>
<td>0.046</td>
<td>-0.019</td>
<td>0.111</td>
</tr>
<tr>
<td>PM10</td>
<td>-0.007</td>
<td>-0.069</td>
<td>0.055</td>
</tr>
</tbody>
</table>
9. References


60. Nguyen JL, Dockery DW. Daily indoor-to-outdoor temperature and humidity relationships: a sample across seasons and diverse climatic regions. 2015;


Appendices
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Appendix A: StAR trial Screening Questionnaire

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


INTERVIEWER STAFF NUMBER/NAME

DATE: ___/___/2012

SECTION 1 - CONTINUED

1.6 SA ID NUMBER

1.7 IN WHICH ETHNIC GROUP WOULD YOU CLASS YOURSELF?

[6] PREFER NOT TO SAY

1.8 DO YOU HAVE REGULAR ACCESS TO A CELLPHONE?


1.9 DO YOU HAVE HIGH BLOOD PRESSURE?


IF NO go to Question 1.10, if YES answer 1.11.a

1.10 DID YOU TAKE YOUR HIGH BLOOD PRESSURE MEDICINE TODAY?


1.11 IF NO, PLEASE WILL YOU TELL ME WHY YOU HAVE NOT YET TAKEN YOUR PILLS TODAY?


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

Cuff size used


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)


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”
### SECTION 1: PARTICIPANT CONTACT DETAILS

Please complete Section 1 if the participant’s street address is not the same as in their clinic folder.

1. **Interviewer to complete [in pen]**
2. **Participant clinic folder number**
3. **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]**

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]**

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 ES2-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 - Facsimile [021] 406 6411
Email: shureita.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
347-85
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

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,

[Signature]

DR G H VISser
MANAGER: SPECIALISED HEALTH

c. Mr I Gildenhuys
Appendix D: The South African Weather Service data disclosure statement

LS-Disclosure-001 4.doc Disclosure 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 of 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

<table>
<thead>
<tr>
<th>Full Names</th>
<th>Enock Havyarimana</th>
</tr>
</thead>
<tbody>
<tr>
<td>University</td>
<td>University of Cape Town, Chronic Diseases Initiative for Africa</td>
</tr>
<tr>
<td>Student Number (if applicable)</td>
<td>HVYENO001</td>
</tr>
<tr>
<td>Email address</td>
<td><a href="mailto:ehavyarimana@gmail.com">ehavyarimana@gmail.com</a></td>
</tr>
<tr>
<td>Postal address</td>
<td>Groote Schuur Dr, Cape Town 7925, South Africa</td>
</tr>
<tr>
<td>Supervisor</td>
<td>Professor Naomi Levitt</td>
</tr>
<tr>
<td>Project Title</td>
<td>The effect of climatic conditions (temperature, humidity, pollution) on clinic blood pressure measurements and their potential influence on hypertension treatment decisions</td>
</tr>
<tr>
<td>Degree</td>
<td>Master’s in Public Health</td>
</tr>
</tbody>
</table>
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 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.)

---

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:

Conflicts of Interest and Source of Funding: A has received honoraria from Company Z. B is currently receiving a grant (#12345) from Organization Y, and is on the speaker’s bureau for Organization X – the CME organizers for Company A. For the remaining authors none were declared.

Copyright: In addition, each author must complete and submit the journal's copyright transfer agreement, which includes a section on the disclosure of potential conflicts of interest based on the recommendations of the International Committee of Medical Journal Editors, (www.icmje.org/update.html).

A copy of the form is made available to the submitting author within the Editorial Manager submission process. Co-authors will automatically receive an Email with instructions on completing the form upon submission.

Permissions to reproduce previously published material
Authors should include with their submission copies of written permission to reproduce material published elsewhere (such as illustrations) from the copyright holder. Authors are responsible for paying any fees to reproduce material.
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 anesthetic and surgical procedure used, and (2) evidence that all possible steps were taken to avoid animals’ suffering at each stage of the experiment.

*Experiments on isolated tissues:* Indicate precisely how you obtained the donor tissue.

Systematic Reviews and Meta-analysis
Authors should follow the PRISMA guidelines ([www.prisma-statement.org](http://www.prisma-statement.org)) on reporting items for systematic reviews and meta-analyses. Such reviews often serve as a basis for many health policy decisions and direction for further research, and following these guidelines will assist in improving the quality of reports available.

Clinical Trials and Behavioural and Public Health Evaluations
Authors reporting results of randomised controlled trials should include with their submission a complete checklist from the CONSORT statement ([www.consort-statement.org](http://www.consort-statement.org)). For behavioural and public health evaluations involving non-randomised designs, authors should include with their submission a complete checklist from the TREND statement ([www.cdc.gov/trendstatement/](http://www.cdc.gov/trendstatement/)).

Registration of clinical trials: As a condition for publication of a clinical trial in the Journal, registration of the trial in a public registry is required. The editor does not advocate one particular registry but require that the registry utilised meet the criteria set out in the statement of policy of the ICMJE ([www.icmje.org](http://www.icmje.org)).

Authorship
All authors must meet the criteria for authorship as established by the International Committee of Medical Journal Editors, that they believe that the paper represents honest work, and that they are able to verify the validity of the results reported.

In the case of a large study group involvement, please list the names of authors that meet the ICMJE criteria on the title page of the paper and include a study group name, if required, to encompass other author contributors. The study group name on the title page should be marked with a superscript asterisk, with a footnote on the title page stating "*A list of other author contributors are listed in the Acknowledgement section." Clearly identify in the Acknowledgement section those individuals who meet the author criteria after a superscript asterisk and study group
name and the text "author contributors:“. Other study sites and participants should be identified and listed separately to this study group.

**Compliance with NIH and Other Research Funding Agency Accessibility Requirements**

A number of research funding agencies now require or request authors to submit the post-print (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. As a service to our authors, LWW will identify to the National Library of Medicine (NLM) articles that require deposit and will transmit the post-print of an article based on research funded in whole or in part by the National Institutes of Health, Wellcome Trust, Howard Hughes Medical Institute, or other funding agencies to PubMed Central. The revised Copyright Transfer Agreement provides the mechanism.

**Copyright assignment**

Papers are accepted for publication on the understanding that exclusive copyright in the paper is assigned to the Publisher. Authors are asked to submit a signed copyright assignment form with their submission. They may use material from their paper in other works published by them after seeking formal permission.

**PRESENTATION OF PAPERS**

**Title Page**

The title page should carry:

- full title of the paper, consisting of no more than 20 words (only common abbreviations should be used if absolutely necessary); titles should be clear and brief, conveying the message of the paper
- a brief short title, which will be used as running head (consisting of not more than 40 characters, including spaces)
- all authors’ names: the full first name, middle initial(s) and last (family name) name of each author should appear; if the work is to be attributed to a department or institution, its full name and location should be included. The last (family name) must appear in CAPITAL letters. Persons listed as authors should be those who substantially contributed to the study’s conception, design, and performance
- the affiliations of all the authors; when authors are affiliated to more than one institution, their names should be connected using a,b,c, etc. These letters should follow the surname but precede the address; they should be used for all addresses
- information about previous presentations of the whole or part of the work presented in the article
- the sources of any support, for all authors, for the work in the form of grants, equipment, drugs, or any combination of these
- Disclose funding received for this work from any of the following organizations: National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI); and other(s).
- a statement on potential conflicts of interest: if authors have financial interests relevant to the research or constituting a conflict of interest, these must be stated. If not applicable, state NONE disclaimers, if any
- the name and address of the author responsible for correspondence concerning the manuscript, and the name and address of the author to whom requests for reprints should be made. If reprints are not to be made available, a statement to this effect should be included. The peer-review process as well as publication will be delayed if you do not provide up to date telephone and fax numbers, and E-mail address, if available
Authors are encouraged to submit colour and non-colour versions of illustrative figures, should the editor choose to publish gratis the colour version online only. Colour images should be prepared to the standards indicated in the section below on illustrations, and take into account that colour and non-colour versions need to be interpretable by the reader. Please ensure that the different versions of the illustrations are labelled for easy identification.

Authors are also encouraged to submit supplementary digital content that may include figures, tables, a PowerPoint slide deck, audio or videos. Material submitted should not duplicate what is in the paper but contain extra material that a reader would find useful to access, but not critical for interpretation of the study. Audio or video should be no longer than 5 minutes in length. Please consult the Supplementary Digital Content section below for further advice.

Abstracts
The second page should carry a structured abstract of no more than 250 words. The abstract should state the Objective(s) of the study or investigation, basic Methods (selection of study subjects or laboratory animals; observational and analytical methods), main Results (giving specific data and their statistical significance, if possible), and the principal Conclusions. It should emphasise new and important aspects of the study or observations.

Review articles and case reports should include an unstructured summary of no more than 150 words.

Condensed Abstracts
A condensed abstract will be published in the ‘forthcoming contents’ section of the issue preceding the published article. This should be supplied with the submission, and should consist of no more than 100 words, this abstract should briefly summarise the main findings of your study.

Key Words
The abstract should be followed by a list of 3–10 keywords or short phrases which will assist the cross-indexing of the article and which may be published. When possible, the terms used should be from the Medical Subject Headings list of the Index Medicus (http://www.nlm.nih.gov/mesh/meshhome.html).

Abbreviations and symbols
Use only standard abbreviations. Avoid abbreviations in the title and abstract. A short list of non-standard abbreviation definitions that may not be familiar to readers should be included in a separate mandatory document submitted with your paper.

Text
Full papers of an experimental or observational nature may be divided into sections headed Introduction, Methods (including ethical and statistical information), Results and Discussion (including a conclusion), although reviews may require a different format.

Acknowledgements
Acknowledgements should be made only to those who have made a substantial contribution to the study. Authors are responsible for obtaining written permission from people acknowledged by name.
in case readers infer their endorsement of data and conclusions. Please see "Authorship" section for listing of author contributors in Study Groups.

References
References should be numbered consecutively in the order in which they first appear in the text. They should be assigned Arabic numerals, which should be given in brackets, e.g. [17]. References should include the names of all authors and any Study Group named in the primary author list when six or fewer; when seven or more, list only the first six names and add et al. Members of the Study Group should not be listed. References should also include full title and source information. Journal names should be abbreviated as MEDLINE (www.nlm.nih.gov/tsd/serials/jhi.html).

Articles in journals

More than seven authors:

Supplements:
Kim HC. SSA 01-1 Hypertension subtypes in rapidly aging East Asia. J Hypertens 2016; 34 (e-supp 1): e1

Letter/Abstract:


Books
Book:
Katz AM, Konstam MA. Heart Failure. Pathophysiology, Molecular Biology, and Clinical Management. Philadelphia: Lippincott Williams & Wilkins; 2008

Chapter in a book:

Personal communications and unpublished work should not feature in the reference list but should appear in parentheses in the text. Unpublished work accepted for publication but not yet released should be included in the reference list with the words ‘in press’ in parentheses beside the name of the journal concerned. References must be verified by the author(s) against the original documents.

Tables
Each table should be typed on a separate page in double spacing. Tables should not be submitted as photographs. Each table should be assigned an Arabic numeral, e.g. (Table 3) and a brief title. Vertical rules should not be used. Place explanatory matter in footnotes, not in the heading. Explain in footnotes all non-standard abbreviations that are used in each table. Identify statistical measures of variations, such as standard deviation and standard error of the mean.
Be sure that each table is cited in the text. If you use a table or data from another published or unpublished source, obtain permission and acknowledge the source fully.

Illustrations

A) Creating Digital Artwork

1. Learn about the publication requirements for Digital Artwork: [http://links.lww.com/ES/A42](http://links.lww.com/ES/A42)
2. Create, Scan and Save your artwork and compare your final figure to the Digital Artwork Guideline Checklist (below).
3. Upload each figure to Editorial Manager in conjunction with your manuscript text and tables.

B) Digital Artwork Guideline Checklist

Here are the basics to have in place before submitting your digital artwork:

- Artwork should be saved as JPEG, TIFF, EPS, or MS Office (DOC, PPT, XLS) files. High resolution PDF files are also acceptable.
- Crop out any white or black space surrounding the image.
- Please use either Arial or Helvetica font size 7 for any text or labels within illustrations.
- Diagrams, drawings, graphs, and other line art must be vector or saved at a resolution of at least 1200 dpi. If created in an MS Office program, send the native (DOC, PPT, XLS) file.
- Photographs, radiographs and other halftone images must be saved at a resolution of at least 300 dpi.
- Photographs and radiographs with text must be saved as postscript or at a resolution of at least 600 dpi.
- Each figure must be saved and submitted as a separate file. Figures should not be embedded in the manuscript text file.

Remember:

- Cite figures consecutively in your manuscript.
- Number figures in the figure legend in the order in which they are discussed.
- Upload figures consecutively to the Editorial Manager web site and enter figure numbers consecutively in the Description field when uploading the files.
- Photomicrographs must have internal scale markers.
- If photographs of people are used, their identities must be obscured or the picture must be accompanied by written consent to use the photograph.
- If a figure has been published before, the original source must be acknowledged and written permission from the copyright holder for both print and electronic formats should be submitted with the material. Permission is required regardless of authorship or publisher, except for documents in the public domain.
- Figures may be reduced, cropped or deleted at the discretion of the editor.
- Colour illustrations for reproduction in print are acceptable but authors will be expected to cover the extra reproduction costs (for current charges, contact the publisher).

Legends for Illustrations

Captions should be typed in double spacing, beginning on a separate page. Each one should have an Arabic numeral corresponding to the illustration to which it refers. Internal scales should be explained and staining methods for photomicrographs should be identified.

Supplemental Digital Content (including Video Abstracts)
Authors may submit SDC via Editorial Manager to LWW journals that enhance their article's text to be considered for online posting. SDC may include standard media such as text documents, graphs, audio, video, etc. On the Attach Files page of the submission process, please select Supplemental Audio, Video, or Data for your uploaded file as the Submission Item. If an article with SDC is accepted, our production staff will create a URL with the SDC file. The URL will be placed in the call-out within the article. SDC files are not copy-edited by LWW staff, they will be presented digitally as submitted. For a list of all available file types and detailed instructions, please visit http://links.lww.com/A142.

**Video Abstracts**
Authors are encouraged to submit a Video Abstract to accompany their article. Guidelines for preparation of the Video Abstract, along with links to sample Video Abstracts, can be found here.

**SDC Call-outs**
Supplemental Digital Content must be cited consecutively in the text of the submitted manuscript. Citations should include the type of material submitted (Audio, Figure, Table, etc.), be clearly labelled as "Supplemental Digital Content," include the sequential list number, and provide a description of the supplemental content. All descriptive text should be included in the call-out as it will not appear elsewhere in the article.

Example:
We performed many tests on the degrees of flexibility in the elbow (see Video, Supplemental Digital Content 1, which demonstrates elbow flexibility) and found our results inconclusive.

**List of Supplemental Digital Content**
A listing of Supplemental Digital Content must be submitted at the end of the manuscript file. Include the SDC number and file type of the Supplemental Digital Content. This text will be removed by our production staff and not be published.

Example:
Supplemental Digital Content 1. wmv

**SDC File Requirements**
All acceptable file types are permissible up to 10 MBs. For audio or video files greater than 10 MBs, authors should first query the journal office for approval. For a list of all available file types and detailed instructions, please visit http://links.lww.com/A142.

**Units of measurement**
Measurements of length, height, weight, and volume should be reported in metric units (metre, kilogram, or litre) or their decimal multiples. Temperatures should be given in degrees Celsius. Blood pressures should be given in millimetres of mercury.

All haematologic and clinical chemistry measurements should be reported in the metric system in terms of the International System of Units (SI). Editors may request that alternative or non-SI units be added by the authors before publication.

**Open access**
Authors of accepted peer-reviewed articles have the choice to pay a fee to allow perpetual unrestricted online access to their published article to readers globally, immediately upon publication. Authors may take advantage of the open access option at the point of acceptance to ensure that this choice has no influence on the peer review and acceptance process. These articles are subject to the journal's standard peer-review process and will be accepted or rejected based on their own merit.
The article processing charge (APC) is charged on acceptance of the article and should be paid within 30 days by the author, funding agency or institution. Payment must be processed for the article to be published open access. For a list of journals and pricing please visit our Wolters Kluwer Open Health Journals page.

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