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Determinants of day-night difference in blood pressure in subjects of African ancestry

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CHAPTER 1

INTRODUCTION

Inter-ethnic differences in cardiovascular disease and risk factors: Potential relevance of ambulatory blood pressures.

1. Introduction

As this dissertation refers to a study conducted on the determinants of nocturnal decreases of blood pressure (BP) in an urban, developing community of African descent, I will adhere to the following structure in the literature review. First I will indicate why it is particularly important to study aspects of BP control in black Africans, a group that I will hereafter refer to as persons of African descent or ancestry. Second, I will indicate why nocturnal decreases in BP are of particular importance when studying BP control in any ethnic group. Third, I will review the evidence to indicate that the characteristic nocturnal BP profiles in groups of African descent may contribute toward a particularly high cardiovascular risk in this ethnic group. Fourth, I will indicate the factors that could contribute toward the characteristic nocturnal BP profiles in groups of African descent and highlight the deficiencies in these data. Lastly, in this literature review I will list the aims of this dissertation in the context of the preceding discussion.

1.1 Cardiovascular disease and risk factors

There are many shared mechanisms and risk factors responsible for diseases of the vasculature and heart that result in strokes, myocardial infarction (MI), renal failure, heart failure, sudden cardiac death and peripheral vascular disease (PVD). As a consequence of the considerable overlap in the causes of these disease entities, they are broadly termed “cardiovascular diseases”. Cardiovascular diseases are amongst the leading cause of death in adults in both developed (reviewed by guidelines committees including World Health Organization, International Society of Hypertension Writing

Group. 2003; European Society of Hypertension-European Society of Cardiology Guidelines Committee 2003; Chobanian et al 2003; Williams et al 2004) and developing (Kahn et al 1999) countries and hence an understanding of these disease processes and how to manage them is of critical relevance. A significant proportion of the risk of developing cardiovascular diseases is attributed to hypertension, smoking, diabetes mellitus, dyslipidaemias (increases in low density lipoprotein cholesterol [LDL cholesterol] concentrations, decreases in high density lipoprotein cholesterol [HDL cholesterol] concentrations or increased triacylglyceride [TG] concentrations) and aging (reviewed by guidelines committees including World Health Organization, International Society of Hypertension Writing Group. 2003; European Society of Hypertension-European Society of Cardiology Guidelines Committee 2003; Chobanian et al 2003; Williams et al 2004). Nevertheless, there is still a substantial portion of risk that has yet to be accounted for (Ionita et al 2005).

Hypertension, smoking, diabetes mellitus and dyslipidaemias can be successfully modified through either lifestyle or pharmacological intervention programs (reviewed by guidelines committees including World Health Organization, International Society of Hypertension Writing Group. 2003; European Society of Hypertension-European Society of Cardiology Guidelines Committee 2003; Chobanian et al 2003; Williams et al 2004). Lifestyle interventions include an increased physical activity, weight loss programs, a reduced salt intake, an increased potassium intake, modifications in carbohydrate and fat intake and the cessation of smoking (The Trials of Hypertension Prevention Collaborative Research Group 1997; Whelton et al 1998; He et al 2000; Sacks et al 2001; Vollmer et al 2001; World Health Organization, International Society of Hypertension Writing Group. 2003; European Society of Hypertension-European Society of Cardiology Guidelines Committee 2003; Chobanian

et al 2003; Williams et al 2004). Despite the promise of primordial prevention through lifestyle modification there is scepticism regarding the ability to sustain these programs. Nevertheless, if BP, blood glucose concentrations or lipid aberrations are not modified by lifestyle changes to target levels, effective pharmacological intervention programs may be initiated (reviewed by guidelines committees including World Health Organization, International Society of Hypertension Writing Group. 2003; European Society of Hypertension-European Society of Cardiology Guidelines Committee 2003; Chobanian et al 2003; Williams et al 2004). Despite the established efficacy of pharmacological intervention programs, these programs may represent a cost burden to health-care systems that over the short term could reach substantial levels, the consequence being inefficient health care delivery. Over the long-term, however, cardiovascular morbidity and mortality related to inappropriate risk factor management strategies could result in even higher costs. Primordial prevention programs are obviously a potential solution to reducing the costs of pharmacological intervention programs.

1.1.1 Ethnic differences in cardiovascular disease

In developed countries there is a greater prevalence of some cardiovascular diseases in ethnic groups of African origins. Indeed, in the United States of America (USA), the prevalence of strokes and major cardiovascular intermediate phenotypes for stroke, namely left ventricular hypertrophy and urinary albumin-to-creatinine ratios, are higher amongst groups of African as compared to European origins (Gillum 1999; Hollar et al 2004; McGruder et al 2004; Jamerson 2004; Howard 2001, Sacco et al 2001, Nunez et al 2005, Skelton et al 2003, Lorber et al 2003, Kizer et al 2004,

Rodriguez et al 2004, Drazner et al 2005, Murtaugh et al 2003, Bryson et al 2006). In developing countries in Africa, there is evidence to indicate that stroke is highly prevalent in urban communities (Connor et al 2007). Although until recently ischemic heart disease (IHD) was thought to be a rare entity in sub-Saharan Africa, based on hospital admissions, the prevalence is thought to be increasing at a dramatic level. Moreover, the risk of coronary artery disease may be just as high in patients of African ancestry with stroke as it is in patients of European ancestry with stroke (Joubert et al 2000). As stroke is a common cause of morbidity and mortality in sub-Saharan Africa it may therefore be argued that IHD is also common in these countries, but that it goes largely undetected or is not expressed as an important clinical phenotype. However, true prevalence data for IHD in these countries has yet to be reported on.

Importantly, it is generally agreed on that a major mechanism responsible for the higher prevalence of some cardiovascular diseases in groups of African ancestry, including stroke, is through a higher prevalence of hypertension in these ethnic groups (see section 1.2.1). However, it is not just an increase in the prevalence of hypertension that may account for a high prevalence of stroke in this ethnic group, but also apparent ethnic differences in the characteristics of 24 hour BP profiles (Phillips et al 2000). This issue will be reviewed in section 3.1.

1.1.2 Hypertension as an important cause of cardiovascular disease

Epidemiological data provide strong support for the notion that an increased BP in the developed and the developing world is a major risk factor for strokes, MI, heart failure, renal failure and sudden cardiac death (reviewed by guidelines committees including World Health Organization, International Society of Hypertension Writing

Group. 2003; European Society of Hypertension-European Society of Cardiology Guidelines Committee 2003; Chobanian et al 2003; Williams et al 2004). Moreover, primordial, primary and secondary prevention studies indicate that treating hypertension results in a decrease in strokes, MI, heart failure, renal failure, and sudden cardiac death (reviewed by guidelines committees including World Health Organization, International Society of Hypertension Writing Group. 2003; European Society of Hypertension-European Society of Cardiology Guidelines Committee 2003; Chobanian et al 2003; Williams et al 2004). Although a comprehensive and critical discussion of all of these studies would be interesting, this goes beyond the scope of the present dissertation and hence these studies will not be elaborated on. Clearly, however, hypertension is a disorder that requires careful detection and management in any community.

1.2 How well is hypertension being treated?

Despite the importance of hypertension as a risk factor for cardiovascular disease, the current status of BP control in hypertension world-wide is appalling. Only 29-34% of hypertensives achieve BP control to target in developed countries (Erdine and Aran 2004; Glover et al 2005). In South Africa the proportion of hypertensives that achieve BP control is even lower (Steyn et al 2001).

Uncontrolled hypertension is clearly contributing to a substantial portion of cardiovascular events. Even in developed countries, prospective, population-based studies indicate that more than 90% of strokes can be attributed either to a lack of treatment or uncontrolled BP if treated (Li et al 2005). Consequently, there is little evidence to indicate that BP goals are being achieved to the extent that they could be or should be.

1.2.1 Ethnic differences in the prevalence of hypertension

Many studies have demonstrated a greater prevalence of hypertension amongst groups of African ancestry as opposed to groups of other ethnic origins (reviewed by Mayet et al 1998). As indicated above (section 1.1) this has been the major reason provided to explain the higher prevalence of strokes in this ethnic group. Despite the fact that it has been recognised for a number of years that individuals of African descent are predisposed to hypertension, this knowledge has not necessarily been translated into entirely effective prevention programs. Indeed, more recent analysis of the National Health and Nutrition Examination Surveys (NHANES) in the USA indicates that the prevalence of hypertension in those of African descent is 40.5% as compared to 27.4% in those of European descent (Glover et al 2005). These are quite extraordinary differences and represent an even greater difference in prevalence than previously reported on (Ashaye and Giles, 2003). The persistently higher prevalence of hypertension in groups of African descent despite a number of programs designed to intervene at the primordial care level in the USA, may be attributed to confusion concerning the aetiology of the higher prevalence rates of hypertension in this ethnic group. Targeting the wrong cause in primordial prevention is obviously likely to translate into ineffective prevention programs.

Although the prevalence of hypertension remains consistently higher in groups of African descent in the USA, whether the same higher prevalence rates exist in subjects of African descent living in Africa is in question. Indeed, data from South Africa indicate that prevalence rates in those of African ancestry may not necessarily be as high as that in the USA in this ethnic group (Steyn et al 2001).

1.2.2 Potential factors accounting for ethnic differences in hypertension prevalence

There could be many reasons for the sustained higher prevalence of hypertension amongst groups of African origins as compared to other ethnic groups. These reasons may be considered either as socio-economic (SE)/cultural/political or biological in origin. SE/cultural/political factors include poverty, dietary and lifestyle preferences, limited education, lack of awareness, distrust of health providers and health systems, perceived racism, anger inhibition, exposure to excessive violence, and transitional racial identity (excessive focus on one race group). SE/cultural/political factors are thought to mediate effects through environmental or extraneous forces such as a high salt and low potassium intake, undue anxiety and stress mediating an increased sympathetic nervous system activity, a predisposition to sedentary behaviour and obesity, or simply failing to seek health care. Biological factors include differences in responses to dietary or other causes of hypertension, such as an enhanced sensitivity to salt intake and a genetic predisposition to developing hypertension. Biological factors are thought to increase the propensity to developing hypertension irrespective of extraneous causes.

There are arguments both for and against SE/cultural/political and biological factors accounting for the higher prevalence rates of hypertension in groups of African ancestry. Unfortunately, social, cultural, political and economic barriers have primarily been used as the explanation for differences in hypertension prevalence rates (Martin and Norris 2004) and little attention has been given to the fact that biological differences may truly exist and account for a substantial portion of the burden of the

disease. Believing that SE/cultural/political effects are of principal importance has always been thought of as the optimistic point of view as these factors may be modified. However, credence has not been paid to the fact that the adverse effects of biological factors may also be modified as a substantial interaction between SE/cultural and biological factors is very likely.

There is no disputing that SE/cultural/political effects may have been a dominant force accounting for ethnic differences in hypertension prevalence rates in the USA in the past. However, despite sustained ethnic differences in prevalence, there are now more and not less hypertensives of African than European descent in the USA who are aware of their condition (70.3 vs 62.9%) and at least the same proportion whose BP is controlled to target levels (29.8 vs 29.8%)(Glover et al 2005). Even in the context of equivalent health promotion services between ethnic groups, subjects of African ancestry between the ages of 45-to-64 years are still 5.6 times more likely to be hospitalised for hypertension than their white counterparts (Holmes et al 2005). Moreover, higher prevalence rates of hypertension persist in those of African descent in the USA when adjusting for income and educational level (Howard et al 2000). Thus, under conditions of equivalent care, awareness, income and education, the higher prevalence rates in individuals of African descent are sustained. Whether this is because intrinsic biological factors are likely to play a more important role in determining ethnic differences in the prevalence of hypertension than previously thought, or because despite a better awareness and care, poor dietary practises, lack of activity and obesity and resentment toward policy makers, politicians and other ethnic groups still persist irrespective of SE status, is uncertain.

In South Africa, although the prevalence of hypertension in groups of African descent is not as high in those of African origins in developed countries, this group are

also less aware of their condition (Steyn et al 2001). Therefore, in South Africa at least there are clearly still strong SE/cultural forces operating to contribute toward prevalence rates of hypertension. However, whether biological differences also account for these prevalence rates is still unknown.

1.3 Are blood pressures measured during epidemiological studies appropriate?

Decisions regarding the risk of cardiovascular disease are to some extent based on epidemiological surveys, both cross-sectional and prospective. The strength of epidemiological surveys is the nature of the sampling (random and cross-sectional), the large sample sizes employed, and in some instances the prospective nature of the analysis. However, these approaches are offset by an inability to fully consider measurement limitations of the phenotype of interest. This is obviously not an issue when one considers measurements such as body weight or height, but measures such as BP vary considerably during the course of a day, with BP decreasing markedly at night or when resting and increasing dramatically during active or stressful periods (Mancia et al 1999). As BP is generally measured over a very short time-period in a day in population surveys (usually 3-to-5 times over 5 or so minutes), measures of BP obtained during these surveys may only represent crude estimates of BP as compared to measures obtained in subjects that are ambulatory over a 24 hour period.

Obviously, appropriate alternatives to crude estimates of BP made during population surveys would limit the ability to recruit large samples in a random and cross-sectional manner and would make these studies costly and time-consuming. The arguments used in favour of crude estimates of BP normally obtained in population-screening is firstly that these are the measurements that are employed clinically and

secondly that ambulatory BP monitoring is mainly (but not exclusively) used to exclude "white coat" effects or "white coat" hypertension (isolated office hypertension) (O'Brien et al on behalf of the European Society of Hypertension Working Group on Blood Pressure Monitoring 2003; Pickering et al 2005), where measurements made in an office environment are artificially elevated. As "white coat" responses occur in an office or clinic environment and not in a home environment there would seem to be no point to ambulatory BP replacing home BP measures. However, as will be discussed there are arguments to indicate that 24 hour ambulatory BP measurements are more appropriate indices of outcomes than measures made over short periods in a day irrespective of whether they are made in an "office" or a "home" environment.

1.3.1 Ambulatory versus conventional blood pressure measurements.

Many studies have demonstrated that 24 hour ambulatory BP is more closely correlated with target organ damage than office BP (Mancia and Parati 2000). This has been demonstrated for changes in carotid intimal-medial thickness (Zanchetti et al 1998) as well as left ventricular hypertrophy (Mancia et al 1997) with therapy. Moreover, ambulatory BP values are more closely correlated with microalbuminuria than office BP measurements (Palatini et al 1996). Ambulatory BP measurements are also better predictors of cardiovascular events than office BP measurements (Verdecchia et al 1995; Clement et al 2003; Staessen et al 1999; Verdecchia et al 1998 ; Verdecchia et al 1994; Imai et al 1996). However, as indicated above a large portion of the differences in relationships between office BP and target organ damage and 24 hour BP and target organ damage may be attributed to "white coat effects" or "white coat" hypertension.

1.3.2 Nocturnal decreases in BP as a determinant of cardiovascular disease

Subjects who do not decrease their BP at night by more than 10% (these individuals are called “non-dippers”, whilst those that do exhibit an appropriate decrease in BP are called “dippers” [Figure 1]) have a greater left ventricular mass (Verdecchia et al 1990), more silent cerebrovascular disease (Kario et al 1996), and a greater chance of microalbuminuria (Redon et al 1994) and progressive renal damage (Timio et al 1994). A meta-analysis by Fargard et al (1995) has indicated that a lack of nocturnal decreases in BP accounts for 15% of the variability in left ventricular mass. Importantly, when considering cardiovascular events as outcomes (so-called “hard” end-points), which clearly represent more important outcomes than just intermediate phenotypes such as left ventricular hypertrophy or carotid intimal-medial thickness (so-called “soft” end points), the relationship between BP and cardiovascular events is substantially better in those patients who do not decrease their BP by more than 10% at night (Verdecchia et al 1994, Verdecchia et al 1995). Indeed, in patients of European ancestry, a raised 24 hour BP predicts about three times more cardiovascular events as compared to if office BP alone is elevated, whereas a raised 24 hour BP and an inability to decrease BP at night predicts about ten times more cardiovascular events occurring as compared to if office BP alone is elevated (Verdecchia et al 1994; Verdecchia et al 1995). These effects of an attenuated decrease in nocturnal BP appear to occur mainly in women. Indeed, an attenuated nocturnal decrease in BP has been noted in hypertensive women of Caucasian ancestry in particular with future cardiovascular

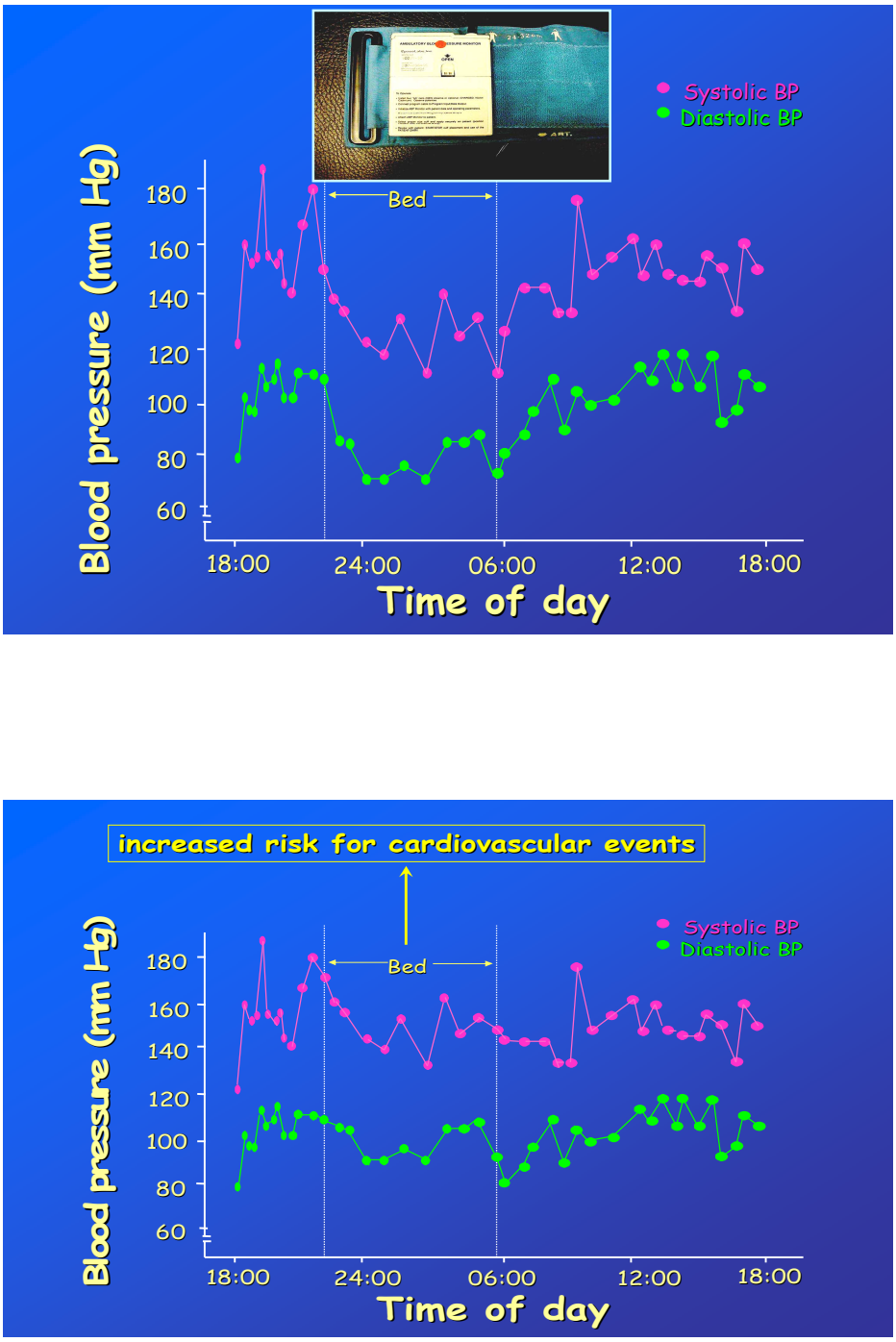


Figure 1. Example of BP values obtained using 24 hour ambulatory BP monitoring from a subject with a greater than 10% decrease in BP at night (upper panel-so-called "dipper") as opposed to BP values obtained from a subject with a less than 10% decrease in BP at night (lower panel-so-called "non-dipper").

events (Verdecchia et al 1993). Attenuated nocturnal decreases in BP have also been shown to be a strong predictor of cardiovascular events in Japanese subjects (Ohkubo et al 1997). Moreover, in patients with isolated systolic hypertension (Staessen et al 1999) or in the general population (Yan Li et al 2007) the night/day ratio of systolic ambulatory BP has been shown to be an independent predictor of cardiovascular events and nocturnal BP is a stronger predictor of cardiovascular events than daytime BP in the Japanese (Kikuya et al 2005, Suzuki et al 2000). In addition, in patients with stroke, a clear attenuation of the ability to decrease BP at night occurs in all ethnic groups (Phillips et al 2000). Whether this is a risk factor for the development of stroke or a consequence of an impaired central control of BP at night is not clear.

The importance of the relationship between nocturnal decreases in BP and cardiovascular disease is nevertheless not that clear. The definition of “dipping” and “non-dipping” status may not be that reproducible (Omboni et al 1998). Moreover, regression of left ventricular mass in hypertension has been shown in a large European study to be related to either daytime or night-time BP (Omboni et al 1998; Mancia et al 1997). Clearly, further data are required to determine whether either nocturnal BP or nocturnal decreases in BP are related to the regression of LV mass.

Although there is obviously still debate about the clinical relevance of nocturnal decreases in BP or nocturnal BP *per se*, at this point the detection of attenuated nocturnal decreases in BP or the measurement of nocturnal BP may be considered to be important in risk assessment and this in-turn requires ambulatory BP monitoring. Therefore, there is a case for considering 24 hour ambulatory BP measures when assessing the risk for a cardiovascular event in any study, whether it is an epidemiological cross-sectional study or a prospective follow-up study. In this regard

further large prospective studies utilising ambulatory rather than office or home BP are currently being conducted to assess the predictive power of this measurement tool.

1.3.3 Ethnic differences in ambulatory blood pressures

There are presently no data describing the prevalence of an increased 24-hour BP in developing countries, as thresholds for normality of 24-hour recordings have not been determined. Moreover, no direct comparisons between 24-hour BP values have been made in specific settings (the same environmental, political and psychological circumstances) between ethnic groups. Nevertheless, comparisons of the characteristics of 24-hour ambulatory BP values have been made in persons of different ethnic origins. The study design and outcomes of these papers have been summarised in Table 1.

Many studies comparing ambulatory BP between ethnic groups have demonstrated that in both normotensives, hypertensives and treated hypertensives, nocturnal BP in patients of African ancestry does not decrease to the same degree as in groups of European ancestry (Belsha et al 1997; Chaturvedi et al. 1994; Fumo et al, 1992; Gretler et al, 1994; Harshfield et al 1993; Hebert et al 1996; James et al 1991; Mayet et al, 1998; Murphy et al 1991; Olutade et al 1998; Osei and Schuster, 1996; Treiber et al 1994; Harshfield et al, 1990; Harshfield et al, 2002a, Harshfield et al 2002b, Vaughan and Murphy,1994; Mancia et al. 1999, Hinderliter et al, 2004, Wang et al 2006). Moreover, a meta-analysis of these and other studies have provided evidence to support the notion that African-Americans have an attenuated nocturnal decline in blood pressure (Profant and Dimsdale 1999**).** If this holds true across the world, then there are major implications for translating epidemiological data with respect to inter-

Table 1. Summary of studies assessing the impact of ethnicity on nocturnal decreases in blood pressure (modified from Profant and Dimsdale 1999).

Geographical area	Study	Sample sizes	Age	Hypertensives or normotensives	Day and night definitions	BP effects	Nocturnal decrease in BP
Middlesex UK	Acharya et al 1996	56 Afro-Caribbeans 562 Whites	46±9 51±11	Essential hypertensives	Day:1200-1800 Night:2400-0600	Daytime SBP, DBP higher in Afro-Caribbeans	Night-time SBP, DBP higher in Afro-Caribbeans
Little Rock, Ark	Belsha et al 1997	32 Blacks 67 Whites	6-18	Normotensives, hypertensives	Participant diaries		Reduced nocturnal decline in BP of Blacks
London, UK	Chaturve di et al 1994	167 Afro-Caribbeans 152 Eropeans	40-64	Normotensives, hypertensives, untreated hypertensives	Day:0900-1100 Night:0300-0500	No difference in daytime SBP	Lower % decline nocturnal SBP of Afro-Caribbeans
Denver, Colo	Chase et al 1997	36 Blacks 50 Whites	20±0.67 22.4±0.52	Healthy	Day:0600-2200 Night:2200-0600	Daytime SBP higher in blacks; mean 24-h BP higher in blacks	-
Chicago, Ill Johannesburg, SA	Fumo et al 1992	22 African Americans 22 White Americans 22 Black South Africans	36±12	Self defined normal	Day:0600-2259 Night:0300-0559	Similar daytime BP in all groups	Higher nocturnal BP in American blacks;
Memphis, Tenn	Harshfield et al 1993	151 Blacks 149 Whites	14±2 13±2	Normotensives	Day:0800-2200 Night:2200-0800	-	Higher nocturnal SBP, DBP in blacks
Chicago, Ill	Gretler et al 1994	275 Blacks 256 Whites	20-79	326 previously untreated patients Presented to Hypertension Clinic Plus 195 volunteers	Participant diaries	Higher ABPM values in blacks	Lower decline in nocturnal BP of blacks
Franklin County County, Ohio	Osel and Schuster 1996	31 African Americans 27 African immigrants 31 White Americans	37.2±1.6 34.5±2.5 28.6±1.4	Normotensive, nondiabetic	Day:0800-2200 Night:2200-0800	SBP, DBP lower in whites than in blacks	-

Table 1. Continued.

Geographical area	Study	Sample sizes	Age	Hypertensives or normotensives	Day and night definitions	BP effects	Nocturnal decrease in BP
Columbus, Ohio Cincinnati, Ohio	Hebert et al 1996	62 Blacks 72 Whites	51.4±1.72 51.9±1.67	Essential hypertensives	Day:0600-2200 Night:0100-0500	-	Night BP higher in blacks
New York, NY	James 1991	27 Blacks 83 Whites	31.0±8.5 29.4±6.7	Normotensive women	Work:1100-1500 Home:1800-2200 Sleep:2200-0600	No daytime differences	Higher nocturnal BP in blacks
London, UK	Mayet et al 1998	46 Blacks 46 Whites	43±1.9 44±2.0	Previously untreated essential hypertensives	Day:0600-2400 Night:2400-0600	-	Smaller mean nocturnal dip in blacks
Chicago, Ill	Murphy et al 1991	44 Blacks 37 Whites	45±15 46±16	Possibly hypertensive	-	Similar daytime BP	Lower decline in nocturnal BP of blacks
Atlanta, Ga	Olutade et al 1998	34 Blacks 39 Whites	54±11 52±12	Mild to moderate essential hypertensives	-	-	Less nocturnal dip in blacks
Augusta, GA	Prisant et al 1991	25 Blacks 46 Whites	51.1±13.8 46.2±10.8	Essential hypertensives	Day:0800-1200 Night:2400-0400	No difference in day BP	No difference in nocturnal BP
New Orleans, LA	Rockstroh et al 1997	20 Blacks 40 Whites	43±7 45±11	Essential hypertensives	Day:0800-2200 Night:2200-0800	No significant racial differences	No significant racial differences
Birmingham, UK	Rowlands et al 1982	16 Blacks 16 Whites	42±10 42±11	Mild to moderate hypertensives	Participant diary	No significant racial differences	No difference in nocturnal BP
Los Angeles Calif	Shapiro et al 1996	56 Blacks 85 Whites	21.4±2.7 20.7±2.4	Healthy college students	Participant diary	Higher BP in blacks	-
Augusta, GA	Treiber et al 1994	64 Blacks 56 Whites	11.8±2.2 11.4±2.3	Children from hypertensive families	Day:0800-2000 Night:2200-0600	Higher 24-h BP in black children	Higher nocturnal SBP and DBP in black children
Augusta, GA	Wang et al 2006	312 Blacks 351 Whites	14.5±3.3 14.2±3.3	Normotensives Normotensives	Day:0800-2200 Night:2400-0600	Higher 24-h BP in Blacks	Higher nocturnal BP in Blacks

BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

ethnic differences in the impact of BP on cardiovascular risk. Importantly, for any given BP measured at home, the impact on risk assessment will be determined by the time of day that BP is measured. As BP measurements are usually determined during the day, the risk of a cardiovascular event may be underestimated in patients of African descent.

Despite innumerable papers describing an attenuated nocturnal decrease in BP in subjects of African ancestry (Belsha et al 1997; Chaturvedi et al. 1994; Fumo et al, 1992; Gretlier et al, 1994; Harshfield et al 1993; Hebert et al 1996; James et al 1991; Mayet et al, 1998; Murphy et al 1991; Olutade et al 1998; Osei and Schuster, 1996; Treiber et al 1994; Harshfield et al, 1990; Harshfield et al, 2002a, Harshfield et al 2002b, Vaughan and Murphy,1994; Mancia et al. 1999, Hinderliter et al, 2004, Wang et al 2006), studies performed in those of African ancestry living in Africa or countries other than the USA suggest that nocturnal declines in BP are comparable with other ethnic groups (Harshfield and Treiber, 1999). Indeed, when including African-Americans only in a meta-analysis, race predicts nocturnal decreases in BP; but when including all studies in a meta-analysis irrespective of where black subjects were living, the effect of race on nocturnal decreases in BP did not reach significance (Profant and Dimsdale, 1999). However, this is not a consistent finding in subjects of African ancestry living in London who also show a blunted nocturnal decline in BP (Chaturvedi et al 1994, 1994). With respect to South Africa, studies with very small sample sizes (n=22 in each group) performed in subjects of African descent also indicate that in contrast to groups of African descent living in the USA, nocturnal decreases in BP are equivalent to groups of European ancestry (Fumo et al, 1992). Nevertheless, the small sample sizes employed in the study by Fumo et al (1992) preclude any meaningfull conclusions being drawn from data obtained in Africa.

1.3.4 Determinants of nocturnal decreases in BP

The obvious question that begs an answer is the potential mechanism that may be involved in reducing the nocturnal decrease in BP in groups of African ancestry. Before discussing the current evidence that may explain ethnic differences in nocturnal decreases in BP, it is first worth considering the potential mechanisms that have been ascribed to nocturnal decreases in BP in any population.

As with absolute BP values, circadian variations in BP are influenced by both extrinsic (environmental) as well as intrinsic (physiological and pathophysiological) factors. The circadian variation in BP is predictably determined mainly by levels of activity, with marked decreases in BP occurring when going to bed and increases again when getting up from bed (environmental factor). However, from a physiological and pathophysiological perspective there are a number of factors that determine the extent to which these changes occur. Importantly the changes in BP induced by activity are mediated mainly by sympathetic nervous system activation (Furlan et al 1990; Somers et al 1993). However, a number of factors influence diurnal BP profiles either through effects on the sympathetic nervous system or through alternative mechanisms.

Through unexplained mechanisms, after the age of 70 years a marked reduction in the decline in nocturnal BP may occur in both men and women (Staessen et al 1997). Probably because daytime BP values are higher and hence the day-night difference is also higher, smoking, employment outside of the home, mean clinic BP (Staessen et al 1997) and alcohol (Pickering and James 1993) are all associated with a greater nocturnal decrease in BP. More recently data obtained in a large study have demonstrated that obesity is associated with a reduced nocturnal decline in BP (Kotsis et al 2005). From a pathophysiological perspective, presumably through an autonomic

neuropathy, diabetes mellitus also reduces nocturnal decreases in BP (Lindsay et al 1995). Moreover, exogenous glucocorticoids (Imai et al 1989) and cardiac transplantation, probably through the administration of immuno-supressants such as steroids and cyclosporine (Reeves et al 1986) can markedly attenuate nocturnal decreases in BP.

1.3.5 Potential determinants of ethnic differences in nocturnal decreases in BP

Studies have been performed to attempt to determine why ethnic differences in nocturnal decreases in BP may occur. A number of proposals, summarised in figure 2, have been put forward which include both SE/cultural/political and biological factors. These include high levels of hostility and anger (Thomas et al 2004), anger inhibition (Steffen et al 2003), victimization and increased exposure to violence (Wilson et al 2002), particular characteristics of male gender (Harshfield et al 1990; Harshfield et al 2002), an enhanced catecholamine excretion and sensitivity to α_1 adrenoreceptor responsiveness (Sherwood et al 2002), a greater impact of obesity on BP at night (Harshfield et al 2000), salt intake in those with salt-sensitive hypertension (Damasceno et al 2000; Okuguchi et al 1999), salt intake affecting nocturnal rather than daytime BP (Harshfield et al 1991), and salt-sensitive hypertension *per se* (Wilson et al 1999).

Unquestionably it is important to understand the mechanisms responsible for a blunted nocturnal decrease in BP in groups of African descent as effective intervention programs will be required to address this ethnic difference. To-date, however, all of these studies have been conducted in small study samples and no study has assessed the contribution of these factors to attenuated nocturnal decreases in BP in a randomly selected community-based sample. Moreover, no study has assessed whether these

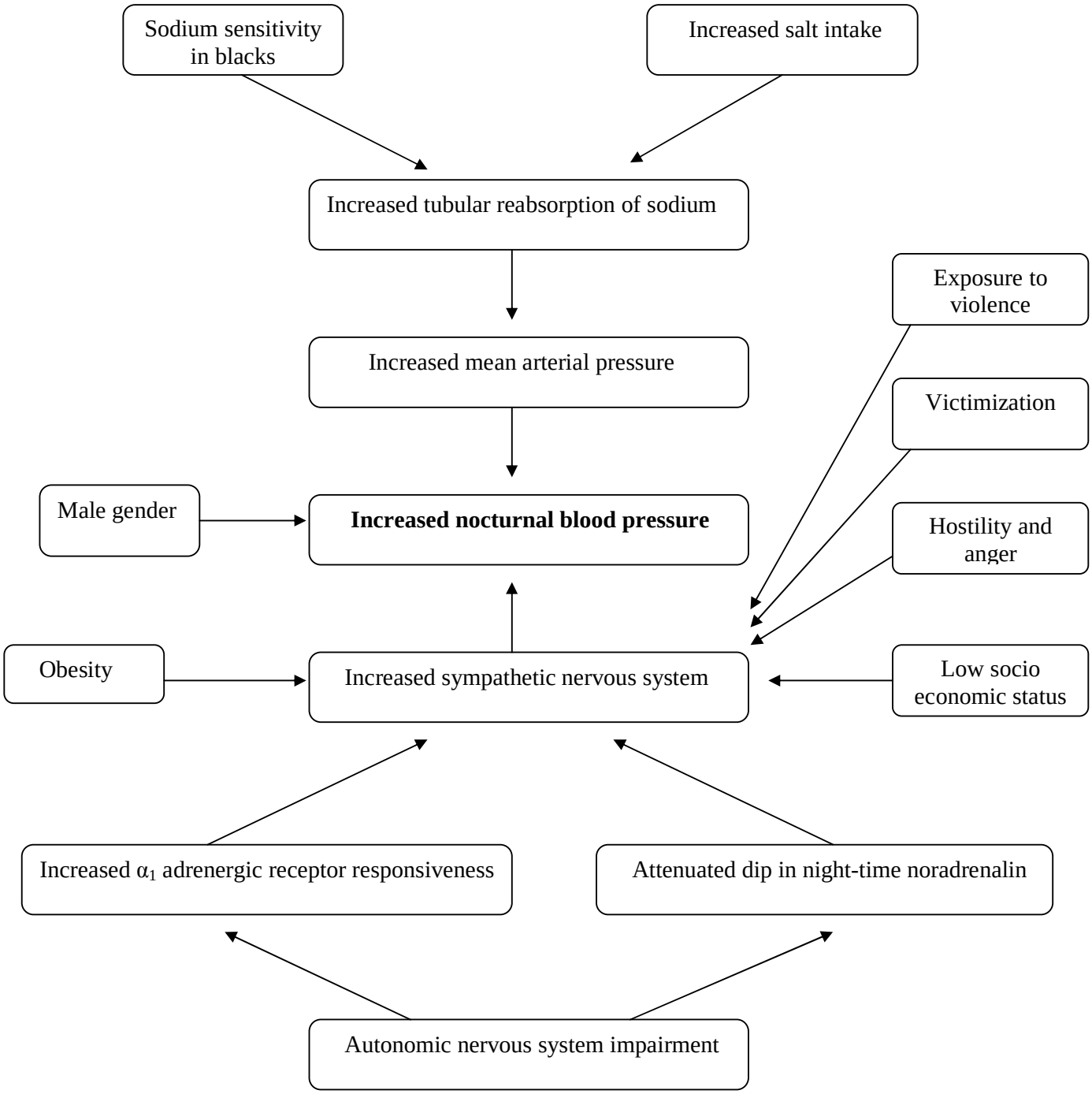


Figure 2. Summary of proposed mechanisms responsible for attenuated decreases in nocturnal BP in people of African descent. References to these mechanisms are cited in the text.

factors determine nocturnal decreases in BP in persons of African descent living in Africa.

Undoubtedly it is important to identify modifiable factors that determine an attenuated nocturnal decline in BP. In this regard, inappropriate salt intake and excess adiposity are two factors that may be modified in primordial prevention programs. However, with respect to salt intake, there is no evidence to suggest that primordial prevention programs will modify nocturnal decreases in BP. Indeed, the consistent relationship between salt intake and nocturnal decreases in BP is in hypertensives who are salt-sensitive (Damasceno et al 2000; Okuguchi et al 1999). In neither salt-resistant hypertensives, nor normotensives would there appear to be an association between salt intake and nocturnal decreases in BP (Damasceno et al 2000; Okuguchi et al 1999). However, it is estimated that a high proportion of persons who are of African descent are salt-sensitive (Sowers et al 1998). Moreover, without selecting individuals who are salt-sensitive, nocturnal rather than daytime BP appears to be particularly sensitive to salt intake in African-Americans (Harshfield et al 1991). This could influence the diurnal BP profile in this ethnic group. Therefore, at a community level in black Africans, there is still nevertheless a possibility that salt intake influences nocturnal decreases in BP.

With respect to the potential of weight reduction programs modifying nocturnal decreases in BP, there is some evidence to suggest that this may be an option. Although no studies have been performed to specifically assess whether weight reduction programs may modify attenuated nocturnal decreases in BP, a recent study conducted with 3216 outpatients has indicated that excess adiposity is indeed associated with an attenuated nocturnal decline in BP (Kotsis et al 2005). Moreover, the reduced nocturnal decline in BP noted in women is abolished after adjusting for body mass index

(Staessen et al 1997), suggesting that body size is an important determinant of nocturnal decreases in BP. However, there are presently no community-based data available in groups of African ancestry to support the notion that attenuated nocturnal decreases in BP are indeed associated with excessive adiposity. Moreover, ambulatory BP studies conducted in groups of African descent have largely been with small samples of selected individuals (Profant and Dimsdale 1999). Thus, a community-based study with a relatively large study size is still required to determine whether the degree of adiposity is associated with nocturnal decreases in BP in groups of African descent.

Clearly, the importance of assessing the role of excessive adiposity and salt intake on nocturnal decreases in BP is largely dependent on whether the community at large has a high prevalence of excess adiposity and exceeds the thresholds for salt intake. Although clear thresholds for indices of adiposity have been defined, thresholds for salt intake have only recently been established (see section 1.3.6). Thus, although the high prevalence of excess adiposity has previously been reported on in communities of African descent (Puonane et al 2002), whether salt intake in communities of African descent exceeds the recommended thresholds for salt intake has not been reported on. Therefore, as the first part of this study I assessed to what degree salt intake in the community exceeds the threshold for salt intake.

1.3.6 Optimal thresholds for salt intake

Thresholds for salt intake have recently been established from both previous and recent studies (MacGregor et al 1989; The Trials of Hypertension Prevention Collaborative Research Group. 1997; Whelton et al. 1998; He et al 2000; Sacks et al 2001; Vollmer et al 2001), reviews (Cutler et al 1997; Law et al 1997; He et al 1999;

Chobanian et al 2000) and consensus opinions amongst experts (Chobanian et al 2000; Whelton et al 2002; Appel et al 2006). It is now widely acknowledged that reductions in sodium (Na^+) intake are likely to be beneficial in the management of hypertension. A decrease in Na^+ intake will lower blood pressure (BP) in hypertensives (MacGregor et al 1989; The Trials of Hypertension Prevention Collaborative Research Group. 1997; Whelton et al 1998; He et al 2000; Sacks et al 2001; Vollmer et al 2001; Cutler et al 1997; Law 1997; He and Whelton 1999; Chobanian and Hill 2000; Whelton et al 2002; Appel et al 2006), reduce the need for pharmacological therapy (He et al 2000) and prevent the development of hypertension (MacGregor et al 1989; The Trials of Hypertension Prevention Collaborative Research Group.1997; Whelton et al 1998). Consequently, without exception, all major guidelines (World Health Organization, International Society of Hypertension Writing Group. 2003; Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension; Chobanian et al 2003; Williams et al 2004) express the opinion that part of lifestyle management should include a reduction in Na^+ intake. The most recent consensus indicates that this reduction in salt intake should be to less than 65 mmol/day (1.5 g of Na^+/day) (Appel et al 2006). Not only is a reduction in Na^+ intake recommended for the management of hypertension, but also an increase in K^+ intake (Appel et al 2006; Whelton et al 1997). Nevertheless, the majority of subjects in population studies lie below the recommended levels of K^+ intake of 120 mmol/day (4.7 g of K^+/day) (Institute of medicine; 2004).

Modifications in dietary Na^+ and K^+ are particularly pertinent to groups of African descent as the impact of lowering Na^+ (He et al 2000) and increasing K^+ (Whelton et al 1997) intake on BP is substantially greater in hypertensives of African as opposed to European descent. Although alterations in dietary electrolytes have been

recommended for the management of hypertension, particularly for groups of African descent, there are no data to indicate whether these suggestions are being implemented in randomly selected subjects in primary health care settings in Africa. Thus, prior to assessing the relationship between salt intake and nocturnal decreases in BP in the present study, I first, evaluated to what extent recommended daily allowances (RDA) of dietary Na^+ and K^+ are being adhered to at a community level in urban South Africa. Second, I evaluated whether Na^+ intake is reduced or K^+ intake increased in hypertensive patients aware of their condition and receiving therapy for it as compared to untreated hypertensives or normotensive subjects. The hypothesis in this regard was that if receipt and implementation of appropriate dietary advice had been applied at a community level then this should have result in a decreased Na^+ and increased K^+ intake in hypertensives being treated and aware of their condition as compared to hypertensives not receiving therapy.

1.3.7 Objectives of the dissertation

The primary objective of this dissertation was therefore to identify whether modifiable factors previously proposed as determinants of nocturnal decreases in BP (salt intake and excess adiposity) contribute toward nocturnal decreases in BP in urban, developing communities of African descent in South Africa. This study was conducted in a large community-based sample. To achieve the aims of this study I used a two-step approach.

1. First the prevalence of excess adiposity, and inappropriate salt intake was established in randomly selected nuclear families in Soweto.

2. Second, having established a high prevalence of excess adiposity and inappropriate salt intake, the second aim of this study was to assess whether any of these factors was associated with nocturnal decreases in BP in this community.

CHAPTER 2

METHODS

2.1 Subjects

The study protocol was approved by the University of the Witwatersrand Committee for Research in Human Subjects (approval number: M02-04-72) and forms part of the African Project on Genes in Hypertension (APOGH). To ensure quality control of the present study, investigators were trained at the University of Leuven in Belgium. In the present study, subjects of African ancestry were recruited from the South-Western township (Soweto) of Johannesburg. Random recruitment of spouses and siblings living in households from formal dwellings (Figure 3) represented in the last census conducted (2001) was performed. Street names and addresses of households with at least one parent and two siblings or two parents and one sibling were obtained from the Department of Home Affairs**.** These households were allocated numbers and numbers were selected from a random number generator. People residing in informal dwellings (Figure 3) or institutions/homes were not recruited.

Recruitment for the present study was initiated in October 2003 and data obtained up until November 2005 were used for the present dissertation. The study design has been described in brief in a recent publication (Shiburi et al 2006). Substantially more participants have been recruited subsequent to this original analysis (Shiburi et al 2006). Up until November 2005, of the 760 subjects that were invited to be part of the study, 453 subjects (62%) agreed to participate. Of the 438 participants enrolled, we discarded 128 that did not meet pre-specified quality criteria for 24-hour urine collection as described below, and a further 19 who did not have conventional BP measurements obtained on three separate occasions as part of this study.

The minimum age for participation in the study was 17 years, but there was no upper age limit. A lower age limit was included as BP rapidly increases with age below



Figure 3. Examples of formal (upper panel) dwellings where people were recruited for this study and informal (lower panel) dwellings not included in the recruitment for this study.

this value. Two hundred and ninety eight (68%) of the subjects recruited were of the Nguni chiefdom (Zulu, Xhosa, Ndebele, Swati) and 140 (32%) were of the Sotho chiefdom (South Sotho, North Sotho and Tswana). The lack of representation from the Venda chiefdom reflects a lack of individuals of this chiefdom residing in these areas of Johannesburg. No subjects of mixed, Asian, or European ancestry were recruited and no Khoi-San subjects were recruited. All subjects gave written, informed consent to participate in the study.

2.2 Questionnaire

Subjects completed a standard questionnaire. In order to avoid translational errors, the questionnaire was not translated into an African language, but study assistants familiar with all languages spoken in these townships and who either previously lived in Soweto or currently reside in Soweto assisted with the completion of each questionnaire. Only same sex assistants were used to assist each family member with the completion of the questionnaire. Assistance was only provided when requested. The majority of subjects were reasonably proficient in English. Study assistants first visited homes of subjects that agreed to participate in the study in order to develop a trusting relationship. The questionnaire was only completed at a subsequent clinic visit and then ambiguities checked by performing a follow-up home visit. If family members were absent at follow-up home visits, data was checked with them personally via telephonic conversations whenever possible. Ambiguities in answers to the questionnaire were detected by an independent observer prior to the second home visit. A pilot study was conducted in 20 subjects to ensure that data

obtained in the questionnaires were reproducible when obtained with the assistance of two separate study assistants.

The questionnaire requested specific answers to date of birth, gender, previous medical history, the presence of hypertension, diabetes mellitus and kidney disease, prior and current drug therapy (analgesic use included), prior and current occupation, level of education, smoking status (including the number of cigarettes smoked in the past and at the present time), daily alcohol consumption (beer, traditional beer or other forms of alcohol and the daily quantity), caffeine consumption (number of cups of tea or coffee and whether they are decaffeinated and the number of cola's a day), exercise frequency and family history of hypertension and cardiovascular events. For females, menstrual history, history of pregnancies and oral contraceptive use was evaluated. Most of the questions simply required a "Yes"-"no" answer, but understanding was assessed by requesting some short answers. If subjects were unable to provide the name of medication taken these were obtained on the second home visit. Although a crude assessment of SE status (SES) was calculated from the combined levels of education, present occupations and annual income, these data have not been analysed at this point as an appropriate score has not been derived.

2.3 Conventional blood pressure measurements

Trained nurse-technician observers measured BP using a standard mercury sphygmomanometer during two home visits and a clinic visit. These were not doctors as they are perceived by the community as being in positions of authority and hence may elicit "white-coat" effects. After being trained in the procedure, including being shown the pitfalls of BP measurement (positioning of the cuff, positioning of the arm, first

estimating systolic BP using a radial pulse measure in order to avoid increasing cuff pressures too high, detecting auscultatory gaps, releasing valve pressure at the correct speed, using the correct cuff size, etc.), assistants had to demonstrate an ability to perform the procedure on 20 subjects. The study assistants were then tested on their ability to measure BP in two ways. First they were asked to measure BP on a separate group of 20 subjects including patients with hypertension and their readings had to be within 4 mm Hg of an experienced investigators readings obtained with a stethoscope with two ear pieces. Second, study assistants were asked to watch a video showing a simulated mercury column with Korotkoff sounds where observers were tested on their ability to detect phase I and V sounds under different circumstances including in the presence of a wide auscultatory gap and where phase V Korotkoff was taken as a "muffling" rather than a "disappearance" of sounds (Blood Pressure Measurement, British Medical Journal, BMA House London). To qualify as observers all readings (n = 20) had to be within 4 mm Hg of the reference standard. Assistants who failed on the assessment the first time were given more time to practise on subjects and then asked to repeat the tests.

Home visits were conducted 3-to-4 weeks apart and the clinic visit occurred between the two home visits. A standard cuff with a 12×24 cm inflatable bladder was used, but if upper arm circumference exceeded 31 cm, larger cuffs with a 15×35 cm inflatable bladder were used. After 10 minutes of rest in the seating position, five consecutive BP readings were taken 30 to 60 seconds apart with the subject in a sitting position, followed by a pulse rate count. The cuff was deflated at approximately 2 mm Hg per second and phase I (systolic) and phase V (diastolic) BP recorded to the nearest 2 mm Hg according to the recommendations of the European Society of Hypertension (O'Brien et al 1999). The mean of the five measurements taken at the first home visit

was recorded as the home BP. Between the two home visits subjects were invited the School of Physiology Hypertension Clinic where a nurse, following the same procedure as the first home visit, measured the subject's blood pressure under comfortable surroundings (Figure 4). The average of the five readings was taken as the office BP.

In the present study quality control of conventional BP assessments was assessed as previously described (Kuznetsova et al 2002). Only 0.23% of visits had fewer than the planned BP recordings. The frequency of identical consecutive recordings was 1.15% for systolic BP and 2.08% for diastolic BP. The occurrence of BP values recorded as an odd number was 0.02 %. Of the 8722 systolic and diastolic BP readings, 26% ended on a zero (expected =20%). A diagnosis of hypertension was made if subjects were receiving antihypertensive therapy and/or if the average of the mean values for the home and clinic readings was ≥140/90 mm Hg.

2.4 Anthropometric measurements

Body height, weight, waist and hip circumference and triceps and subscapular skin-fold thickness (Harpenden Skinfold Calliper, Bedfordshire, UK) were measured during the clinic visit by a trained observer. Height and weight were measured with the participants standing and wearing indoor clothes with no shoes. Waist circumference and hip circumference were measured according to conventional techniques (World Health Organisation, 2003). Body mass index was calculated as weight in kilograms divided by the square of height in meters and waist-to-hip ratio calculated as an index of central obesity.





Figure 4. Hypertension clinic in the School of Physiology. Bottom picture shows reception area and the top picture is the general clinical room.

2.5 Blood measurements

Blood samples were obtained on the day of the clinic visit and sent to the NHLS to perform a full blood count and differential count, to measure urea, creatinine and electrolyte concentrations, to assess liver function (from alanine transaminase, aspartate transaminase, gamma gluteryl transaminase, alkaline phosphatase, albumin, total protein and plasma albumin, total bilirubin, and conjugated and unconjugated bilirubin concentrations) and plasma urate concentrations, to obtain a lipid profile (total cholesterol, low density lipoprotein cholesterol concentrations, high density lipoprotein cholesterol concentrations and triglyceride concentrations), a blood glucose measurement, percentage glycated haemoglobind (HbA_{1c}) and a follicle stimulating hormone concentration in females. These data were used to identify medical conditions, syndromes that may affect BP and to confirm menopausal status in females. A “spot” urine analysis was also performed to screen for major clinical conditions, such as diabetes mellitus and renal pathology. The NHLS was utilised for blood measurements to ensure reproducibility and reliability as these laboratories have been accredited as fulfilling all criteria of “good laboratory practise” (GLP). In those subjects without a prior history of diabetes mellitus, an HbA_{1c} rather than a fasting blood glucose concentration was utilised in the APOGH study to assess blood glucose control (Peters et al 1996).

2.6 Urinary sodium and potassium excretion

Timed urine samples were obtained over at least a 24-hour period after discarding urine obtained immediately prior to the collection period. Urine Na^+, K^+, and

creatinine concentrations were measured by the National Health Laboratories (NHLS) accredited for these measurements. Twenty-four hour urine Na^+ and K^+ excretion rates were calculated from the product of urine volume and urine electrolyte concentration. Creatinine clearance was determined from the product of urine volume and urine creatinine concentrations/plasma creatinine concentration.

The quality of urine samples was determined by constructing regression relations between 24-hour urine creatinine and body weight and 24-hour urine volume and age in gender-specific groups. Based upon the 95% confidence intervals for each group, a 24-hour urine sample was considered acceptable if 24-hour urine creatinine (mmol) was >3.5 and <35 for males and >3.5 and <30 for females. Samples with urine volumes <300 mls/day were also assumed to be incomplete urine collections. These approaches are standard approaches and have been published on numerous occasions by other groups (Stolartz et al 2004, Kuznetsova et al 2004).

2.7 Ambulatory blood pressure measurements

On the same day as 24-hour urine samples were obtained, 24-hour ambulatory BP monitoring was performed using oscillometric monitors (SpaceLabs, model 90207) (see Figure 4). Ambulatory monitors were calibrated monthly against a mercury manometer. The non-dominant arm was selected for BP monitoring. The size of the cuff was the same as that which was used for conventional BP measurements. The monitors were programmed to measure BP at 15-minute intervals from 06:00 to 22:00 and then 30-minute intervals from 22:00 to 06:00. Subjects kept a diary card for the duration of the recordings to note the time of going to bed in the evening and getting



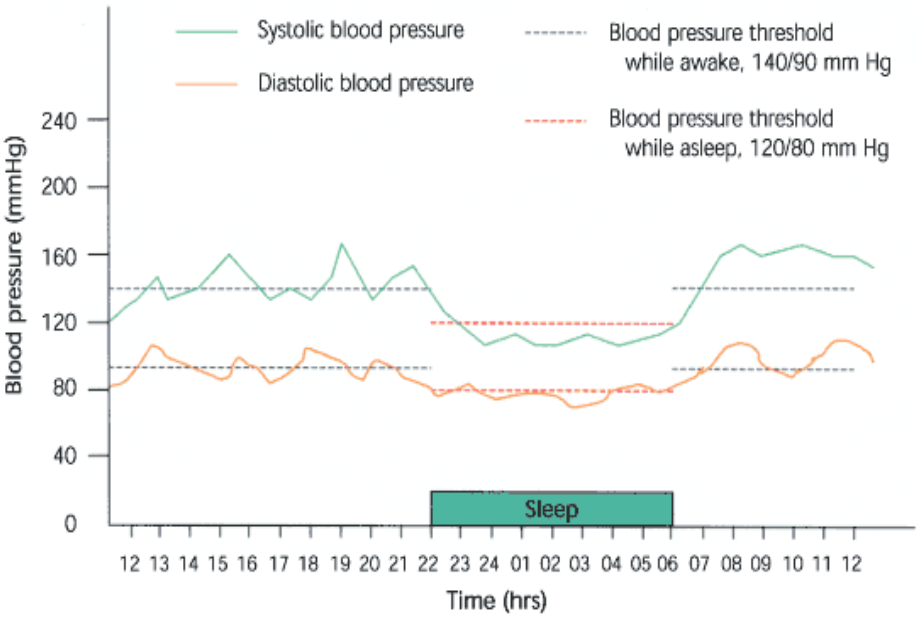


Figure 5. Spacelabs model 90207 ambulatory BP monitor (upper panel) and representative data obtained for analysis purposes (lower panel).

up in the morning. The times when going to bed and getting out of bed in the morning were used to determine the awake and sleep periods of the day. Subjects were also asked to record the time when taking medication in those receiving medication and any times when they either smoked or took caffeine-containing or alcoholic beverages. Subjects were asked to pursue their normal daily activities and to keep the cuff arm steady during measurements. From the subject's diary card data we determined the awake and asleep periods. On average the subjects went to bed at 19:00 h and woke up at 05:00 h. Considering these patterns of daily activities the daytime and night-time intervals were defined as time intervals ranging from 09:00 h to 19:00 h and from 23:00 h to 05:00 h respectively. These fixed clock-time intervals (Thijs et al 1992) were defined in order to eliminate the transition periods (evening and morning) during which BP changes rapidly in most subjects. On completion of the recording, the data were transferred to a computer for analysis. Intra-individual means of the ambulatory measurements were weighted by the time-interval between successive recordings (Thijs et al 1992). Of the participants enrolled in the study, I discarded 124 from the analysis, because the ambulatory BP measurements did not meet pre-specified quality criteria (more than 20 hours of recordings and more than 10 and 5 readings for the computation of daytime and night-time means respectively). Ambulatory BP data were expressed as 24-hour average systolic and diastolic BP, the percentage decrease in BP at night (mean day-mean night/ mean day x 100), the difference between day and night BP and the ratio of day-to-night BP.

2.8 Definitions and analysis

Definitions for hypertension from auscultatory measurements (≥140 mmHg systolic BP or 90 mmHg diastolic BP) and ambulatory BP (≥130 mmHg systolic BP or 80 mmHg diastolic BP) values were based on published guidelines (World Health Organization, International Society of Hypertension Writing Group 2003; Guidelines Committee of the European Society of Hypertension-European Society of Cardiology 2003; Chobanian et al 2003; Williams et al 2004; Pickering et al 2005, O'Brien et al 2003). The presence of hypertension was identified if subjects were either receiving antihypertensive medication, or had an elevated auscultatory BP value obtained in a clinic environment. Overweight and obesity were defined using body mass index thresholds of between 25-29.9 kg/m^2 for overweight and ≥30 kg/m^2 for obesity.

Database management and statistical analyses were performed with SAS software, version 9.1 (The SAS Institute Inc., Cary, North Carolina, USA). Data from individual subjects were averaged and expressed as mean±SD. The X^2-statistic was used to compare proportions. Comparisons between normotensives, hypertensives aware of their condition and hypertensives unaware of their condition and not receiving treatment for it were made using an ANOVA when no adjustments for confounding variables were required and multivariate regression analysis when adjustments were required. To determine whether awareness and treatment of hypertension was an independent determinant of electrolyte intake, covariates included in the regression model were age, gender, BMI, tobacco and alcohol intake, the class of antihypertensive agent employed and the presence or absence of diabetes mellitus. To identify the predictors of 24-hour ambulatory BP, stepwise multivariate adjusted regression analysis was performed with age, gender, antihypertensive medication, the presence or absence

of diabetes mellitus or abnormal blood glucose control, indices of adiposity, 24-hour electrolyte excretion rates and urine Na^+:K^+ ratio included in the regression model. Probability values were obtained with further adjustments for non-independence of family members (mixed model as outlined in the SAS package). To identify the predictors of indices of nocturnal decreases in BP, stepwise regression analysis was performed with age, gender, the presence or absence of hypertension, antihypertensive medication, the presence or absence of diabetes mellitus or abnormal blood glucose control, indices of adiposity, 24-hour electrolyte excretion rates and urine Na^+:K^+ ratio used in the regression model. Again, probability values were obtained with further adjustments for non-independence of family members (mixed model as outlined in the SAS package). Importantly, adjustments for age, gender, the presence or absence of hypertension, the presence or absence of antihypertensive medication, the presence or absence of diabetes mellitus or abnormal blood glucose control, and adjustments for non-independence of family members were made in all regression analyses, whereas BMI, waist circumference, waist-to-hip ratio and skin-fold thickness were assessed in separate models from each other, and electrolyte excretion rates were assessed in models separate from those with urine Na^+:K^+ ratios.

Chapter 3

Results

3.1 Characteristics of the study groups

Of the 438 subjects recruited, 314 had 24-hour ambulatory BP values that met pre-specified quality control criteria (Table 2). Of the 438 subjects recruited, 291 subjects had appropriate 24-hour urine samples (Table 2) of which 228 subjects had both appropriate 24-hour urine and 24-hour BP data (Table 2).

Tables 2 and 3 give the demographic, anthropometric and general clinical characteristics of the participants in each of these study groups, i.e. the characteristics of all subjects, subjects with appropriate urinary salt excretion, ambulatory BP; and both urinary salt excretion and ambulatory BP data. More women than men were recruited (Table 2). A high proportion of subjects had an increased adiposity with 38-41% being obese (Table 2). Approximately 12% used tobacco products on a regular basis and 21-25% regularly consumed alcohol (Table 2). Approximately 21% of subjects were receiving antihypertensive therapy, 6.1-7.2% had treated diabetes mellitus and ~3% were not receiving glucose lowering agents and had an HbA_{1c} >7.0% (Table 3). Approximately 40-47% of women were postmenopausal (Table 3). Importantly, the demographic, anthropometric and general clinical characteristics of the groups generally did not differ (Tables 2 and 3).

Table 2. Demographic and anthropometric characteristics of all study subjects and study subjects with appropriate ambulatory BP monitoring, urinary salt excretion and both ambulatory BP and urinary salt excretion data.

	All subjects recruited	Subjects with appropriate:		
		Urinary salt excretion data	Ambulatory BP data	Ambulatory BP and salt excretion data
Number	438	291	314	228
Age (years)	42±18	44±18	43±18	44±18
Females (%)	64	63	63	62
Weight (kg)	75.4±18.6	76.4±19.1	75.1 ± 18.4	76.0±18.8
Height (cm)	161.2±8.6	160.9±8.2	161.3 ± 8.5	161.1±8.0
BMI (kg/m^2)	29.2±7.4	29.6±7.6	29.0±7.3	29.4±7.5
Waist circumference (cm)	89.5±15.2	90.5±15.6	89.4±15.1	90.3±15.4
Waist-to-hip ratio	0.84±0.1	0.85±0.10	0.84±0.10	0.85±0.10
% overweight/obese	27.4/39.5	29.6/40.9	29.0/37.9	32.0/38.6
Tobacco intake (%)	11.2	12.7	12.1	12.3
Alcohol intake (%)	20.8	25.9	22.0	24.6

BMI, body mass index. ± values are the standard deviation

Table 3. Clinical characteristics of all study subjects and study subjects with appropriate ambulatory BP monitoring, urinary salt excretion and both ambulatory BP and urinary salt excretion data.

	All subjects	Subjects with appropriate:		
		Urinary salt excretion data	Ambulatory BP data	Ambulatory BP and salt excretion data
Number	438	291	314	228
% receiving antihypertensives	20.6	22.3	20.4	22.4
% Hypertensive	30.6	31.3	30.6	31.6
% Diabetes Mellitus	7.1	6.9	6.1	6.6
% Uncontrolled blood glucose*	2.1	2.4	2.6	3.1
Postmenopausal women (%)	39.9	44.3	42.4	46.5

* Based on the absence of a clinical diagnosis of diabetes mellitus, but with an HbA1c >7.0%

3.2 Salt intake

The following section describes the data obtained that was employed to assess salt intake in the community studied.

3.2.1 General demographic and clinical characteristics of the participants with appropriate 24-hour urine samples grouped according to hypertension status

Table 4 gives the general demographic and clinical characteristics of participants grouped according to hypertension status. Thirty-one persent of the study group were hypertensive, 21% (67% of the hypertensives) were aware of their condition and receiving treatment for it, and 10% (33% of the hypertensives) were unaware of their condition and not receiving treatment for it. None of the subjects receiving treatment were unaware of the reasons for their therapy. The gender distribution was similar between the groups (Table 4). Hypertensives were older, had a higher BMI, more subjects who were either overweight or obese and more subjects with diabetes mellitus (Table 4). The hypertensive groups had more postmenopausal women (Table 4). Tobacco use and alcohol consumption were lower in the hypertensives aware of their condition and receiving treatment for it (Table 4). Importantly, no differences in age, gender, BMI, alcohol consumption, proportion of subjects who were overweight or obese or proportion of women who were postmenopausal were noted when comparing hypertensives aware of their condition and receiving treatment for it, and hypertensives unaware of their condition and not receiving treatment for it (Table 4). However, fewer hypertensives unaware of their condition had diabetes mellitus than hypertensives

aware of their condition and receiving treatment for it (Table 4). Moreover hypertensives unaware of their condition had a lower HbA_{1C} than hypertensives aware of their condition and receiving treatment for it (Table 4).

3.2.2 Antihypertensive medication

Table 5 gives the class of antihypertensive agents employed by the study group and the proportion of patients receiving these agents. The most commonly used class of antihypertensive agent used was a thiazide diuretic agent, followed by angiotensin-converting enzyme inhibitors and then long-acting calcium channel blockers of the dihydropyridine class (Table 5). Few patients were receiving selective β_1-adrenoreceptor blockers (Table 5). No patients were receiving loop diuretics, K^+ supplements, centrally acting agents, angiotensin II receptor blockers, aldosterone receptor antagonists, non-dihydropyridine calcium channel blockers, short-acting dihydropyridine calcium channel blockers, or non-selective β-adrenoreceptor blockers.

3.2.3 Blood pressures

Table 5 also gives the clinic and home BP values for the participants. Both systolic and diastolic clinic and home BP values were higher in the hypertensive groups than in the normotensive groups (Table 5). Moreover, BP values were consistently higher in hypertensives unaware of their condition than in hypertensives aware of their condition and receiving treatment for it (Table 5).

Table 4. Demographic, anthropometric and clinical characteristics of study subjects with appropriate 24-hour urine samples.

	Normotensives	Hypertensives aware and receiving treatment	Hypertensives unaware and not receiving treatment
Sample number (%)	200 (69%)	61 (21%)	30 (10%)
Number of females (%)	121 (61%)	45 (74%)	17 (57%)
Age (years)	37±16	60±12**	56±12**
BMI (kg/m^2)	28.9±15.3	34.2±7.8*	30.6±6.0
Overweight+obese n (%)	123 (61.5)	57 (93.4)**	25 (83.3)**
Smokers n (%)	31 (16)	1 (2)*	5 (17) †
Alcohol intake n (%)	60 (30)	8 (13)*	7 (23)
Diabetes mellitus + abnormal blood glucose control n (%)	8 (4)	18 (30)	2 (7)†
HbA_{1C} (%)	5.9±0.8	6.9±1.7**	6.1±0.9†
Postmenopausal n (%)	30 (25)	39 (87)**	12 (71)**

BMI, body mass index; HbA_{1C}, glycated haemoglobin; n, sample number. * $p<0.05$ **$p<0.0001$ versus normotensives; † $p<0.001$ versus hypertensives aware and receiving treatment. ± values are the standard deviation.

Table 5. Blood pressures (BP) and antihypertensive therapy of study subjects with appropriate 24-hour urine samples.

	Normotensives	Hypertensives aware and receiving treatment	Hypertensives unaware and not receiving treatment
Blood pressures (mm Hg)			
First home visit	122±13/79±10	145±25**/88±14*	151±16**†/98±10**††
Second home visit	120±12/76±10	141±26**/86±16*	148±15**†/96±11**††
Clinic visit	123±14/81±9	149±26**/91±14*	161±24**††/101±13**††
Average	122±11/79±8	145±23**/88±13**	153±15**†/98±9**††
Antihypertensive therapy n (%)			
Thiazide diuretics	0	38 (62)	0
ACE inhibitors	0	19 (31)	0
Calcium channel blockers	0	4 (7)	0
Beta-blockers	0	1 (2)	0
Others	0	7 (11)	0

Values for BP are for systolic BP/diastolic BP. * $p<0.001$ **$p<0.0001$ versus normotensives; † $p<0.05$, †† $p<0.0001$ versus hypertensives aware and receiving treatment. All comparisons between BP values are after adjusting for age and body mass index. ± values are the standard deviation.

3.2.4 Electrolyte excretion rates

Table 6 gives the urine volumes, urine electrolyte concentrations, electrolyte excretion rates, and creatinine clearance values of the participants. The average 24-hour urinary Na^+ excretion rate for the whole group was 114±55 mmol/day, well above the RDA for Na^+ intake of 65 mmol/day. Thus most of the study group (82%) were consuming more than the RDA for Na^+ intake. All subjects and patients had 24-hour urinary K^+ excretion rates less than the RDA for K^+ intake of 120 mmol/day.

No differences were noted between the groups in urine volumes, urine electrolyte concentrations, electrolyte excretion rates and the proportion of participants with 24-hour urinary Na^+ excretion rates greater than 65 mmol/day (Table 6). On multivariate regression analysis, a younger age and male gender were the only independent determinants of 24-hour urinary Na^+ excretion (age: β-coefficient=-0.59±0.25, $p<0.02$; gender: β-coefficient=15.9±7.8, $p<0.05$). Male gender was the only independent predictor in the proportion of subjects with a 24-hour urinary Na^+ excretion rate greater than 65 mmol/day (β-coefficient=23±8, $p<0.005$). Awareness of hypertension was not associated with 24-hour urinary Na^+ excretion or the proportion of participants with 24-hour urinary Na^+ excretion rates greater than 65 mmol/day.

Table 6. Urinary values of study subjects

	Normotensives	Hypertensives aware and receiving treatment	Hypertensives unaware and not receiving treatment
Urine volume (ml/day)	1335±696	1446±666	1418±838
U_{Na+} (mmol/l)	106±59	87±42	86±37
U_{K+} (mmol/l)	30±20	26±14	26±15
$U_{creatinine}$ (mmol/day)	12±7	13±8	13±10
Creatinine clearance (ml/min)	118±65	122±71	107±79
Urine Na^+ excretion (mmol/day)	117±56	112±54	102±49
Urine K^+ excretion (mmol/day)	33±17	32±16	28±13
24-hour urine Na^+ >65 mmol/day n (%)	168 (84%)	49 (80%)	22 (73%)

U_{Na+}, U_{K+} and $U_{creatinine}$ indicate urine concentrations of Na^+, K^+ and creatinine. There were no significant differences between the groups before or after adjusting for covariates. ± values are the standard deviation.

3.3 Determinants of 24 hour ambulatory BP and nocturnal decreases in BP

The following section describes the data obtained to assess the determinants of ambulatory BP and nocturnal decreases in BP in the community studied.

3.3.1 Ambulatory BP values in subjects with appropriate urine samples

Tables 7 and 8 show ambulatory BP data obtained in all subjects with 24-hour ambulatory BP values that met pre-specified quality control criteria, and in subjects with both appropriate 24-hour urine and 24-hour BP data. As would be expected, daytime BP values were considerably higher than night-time values (Table 7) and a marked decline in BP occurred at night (Tables 7 and 8). Importantly, data obtained in subjects with appropriate 24-hour urine samples were similar to that obtained for all subjects with 24-hour BP data.

3.3.2 Urinary salt excretion in subjects with appropriate 24 hour BP data

Table 9 shows urinary values in all subjects with appropriate 24 hour urine samples and urinary values in subjects with appropriate urine samples as well as 24-hour ambulatory BP data. Importantly, no differences were noted between these two groups.

Table 7 Ambulatory blood pressures in all subjects with 24-hour ambulatory BP data (mmHg) and subjects with 24-hour urine excretion data.

	All subjects (n=314)					Subjects with 24-hour urine data (n=228)				
Index	Mean	SD	P5	P50	P95	Mean	SD	P5	P50	P95
24 hour SBP	118.7	15.7	100.0	115.3	150.8	118.5	15.3	100.7	114.6	150.5
24 hour DBP	72.8	10.4	58.4	71.2	93.6	72.5	10.2	58.9	71.2	93.6
Daytime SBP	123.1	15.3	103.8	120.0	154.5	122.9	15.1	104.7	119.6	152.8
Daytime DBP	77.9	10.7	62.8	76.0	97.8	77.5	10.7	63.1	75.7	97.8
Night-time SBP	111.7	18.2	90.0	107.6	152.9	111.4	17.7	90.1	107.0	148.1
Night-time DBP	65.0	12.0	49.4	63.2	88.7	64.8	11.5	49.8	63.0	86.5

SD, P5, P10, P50, P90, and P95 indicate standard deviation and percentiles; SBP, systolic BP; DBP, diastolic BP.

Table 8. Indices of nocturnal decreases in blood pressure (BP) in all subjects with 24-hour ambulatory BP data and subjects with 24-hour ambulatory BP and 24-hour urine excretion data.

	All subjects (n=314)					Subjects with 24-hour urine data (n=228)				
Index	Mean	SD	P5	P50	P95	Mean	SD	P5	P50	P95
% decrease in SBP	9.4	8.4	-5.4	10.5	20.9	9.4	7.9	-5.2	10.6	20.9
% decrease in DBP	16.5	10.1	-1.4	17.2	33.6	16.3	9.9	-1.4	16.9	32.9
Night-day SBP	-11.4	10.3	-26.4	-12.4	7.7	-11.5	10.0	-26.3	-12.6	7.7
Night-day DBP	-12.9	8.0	-26.8	-12.8	1.10	-12.7	7.8	-26.1	-12.7	1.10
Night SBP/day SBP	0.91	0.08	0.79	0.90	1.05	0.91	0.08	0.79	0.89	1.05
Night DBP/day DBP	0.83	0.10	0.66	0.83	1.01	0.84	0.10	0.67	0.83	1.01

SD, P5, P10, P50, P90, and P95 indicate standard deviation and percentiles; SBP, systolic BP; DBP, diastolic BP.

Table 9. Urinary values of all study subjects and study subjects with appropriate 24-hour ambulatory BP values.

	All subjects n=291	With 24-hour BP data n=228
Urine volume (ml/day)	1366.9±704.7	1348.1±695.8
U_{Na+} (mmol/l)	99.7±54.2	97.3±49.7
U_{K+} (mmol/l)	28.7±18.1	29.0±18.8
$U_{creatinine}$ (mmol/day)	12.5±7.7	12.5 ±7.6
Creatinine clearance (ml/min)	117.9±67.9	115.6±66.6
Urine Na^+ excretion (mmol/day)	114.4±54.6	110.4±47.5
Urine K^+ excretion (mmol/day)	32.1±16.2	31.9±15.6

See table 6 for abbreviations. ± values are the standard deviation.

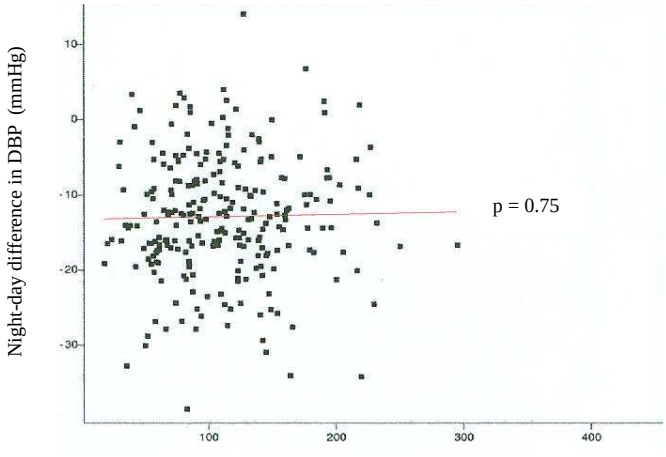
3.3.3. Determinants of ambulatory blood pressures

Table 10 summarises the results of stepwise regression analysis for relationships between a number of demographic and clinical characteristics and 24-hour blood pressures. Age, male gender, BMI, and waist circumference were independently associated with 24-hour BP (Table 10). Moreover, skin-fold thickness was independently associated with 24-hour BP (data not shown). However, waist-to-hip ratio was not an independent predictor of 24-hour BP (data not shown). Neither urinary Na^+, nor K^+ excretion, nor urine Na^+:K^+ ratios were associated with 24-hour BP (Table 10). Models for day and night BP are not shown, and models with waist-to-hip ratio and skin-fold thickness are not shown). Neither the use of antihypertensive medication, regular tobacco or alcohol intake, nor the presence or absence of diabetes mellitus or abnormal blood glucose control were associated with 24-hour BP (data not shown). Essentially the same predictors of BP were noted as indicated in Table 10 in stepwise regression models with day and night periods determined separately (data not shown).

3.3.4. Determinants of nocturnal decreases in ambulatory blood pressures

Figure 6 shows the multivariate between urine sodium excretion and day-night difference, figure 7 shows the relationship between urine potassium excretion and day-night difference, figure 8 shows the relationship between the sodium to potassium ratio and the day-night difference and figure 9 shows the relationship between BMI and the day-night difference. Tables 11 and 12 summarise the results of stepwise regression analysis for relationships between a number of demographic and clinical characteristics and either day-night differences in BP (Table 11) or the ratio of night to day blood

pressure (Table 12). Twenty-four hour BP and male gender were the only independent predictors of day-night differences in BP (Table 11) and the ratio of night to day blood pressure (Table 12). Neither indices of salt excretion nor adiposity were significantly associated with any index of nocturnal decreases in BP (Figures 6, 7, 8 and 9, Tables 11 and 12). Moreover, neither the presence of hypertension, the use of antihypertensive medication, nor the presence or absence of diabetes mellitus or an abnormal blood glucose control were associated with nocturnal decreases in BP (data not shown).



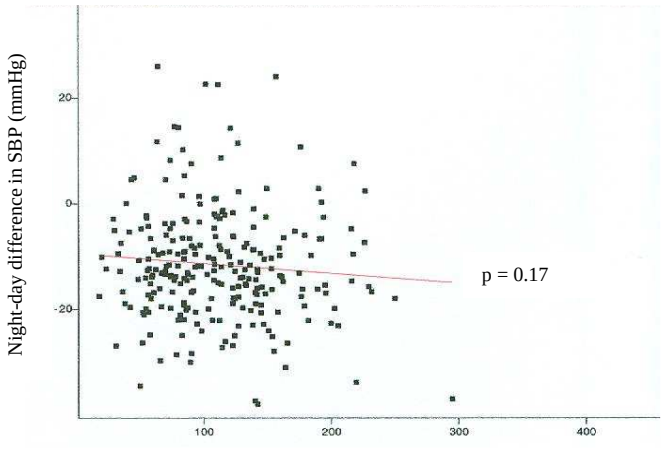
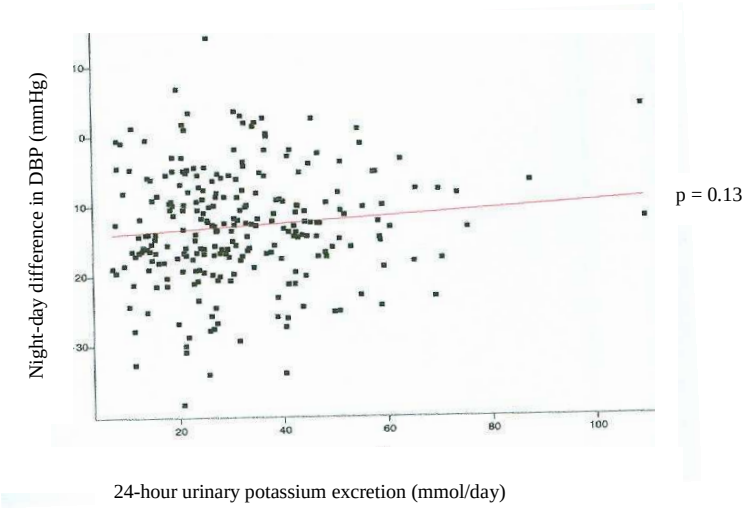


Fig 6 Relationship between urinary sodium excretion and night-day difference in BP



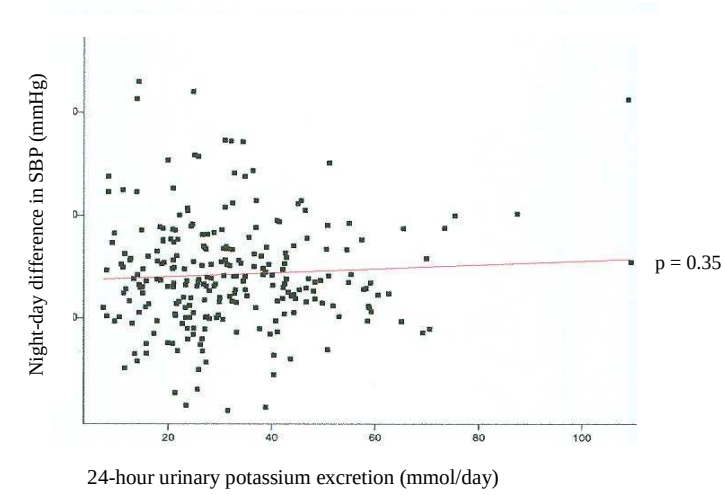
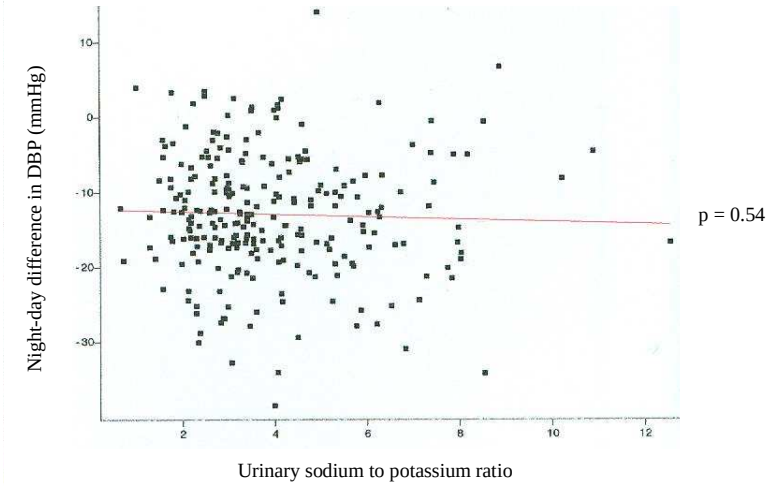


Fig 7 Relationship between urinary potassium excretion and night-day difference in BP



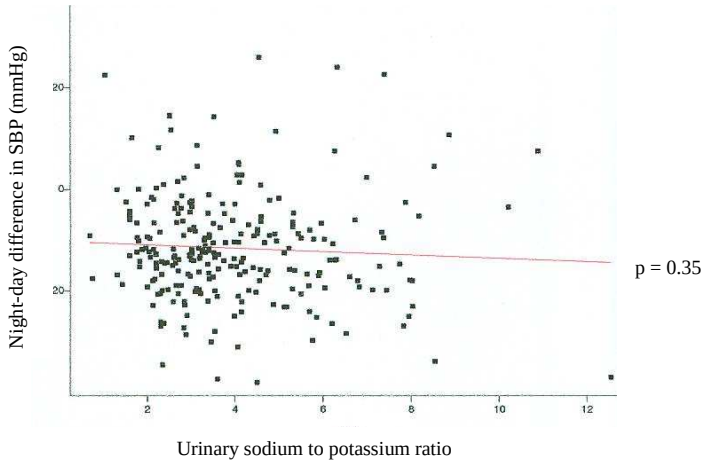
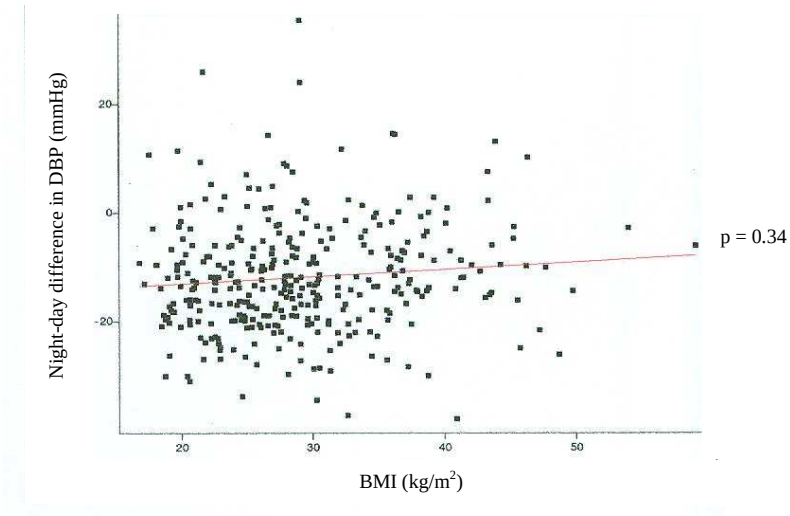


Fig 8 Relationship between sodium to potassium ratio and night-day difference in BP



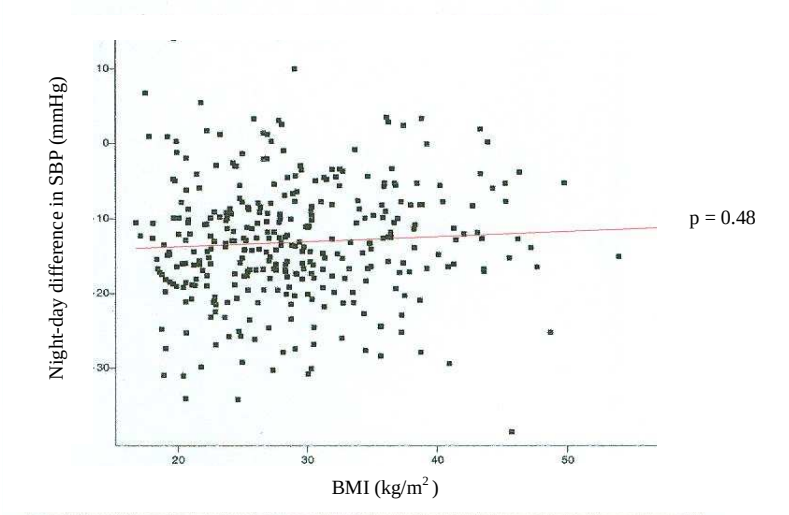


Fig 9 Relationship between BMI and night-day difference in BP

Table 10. Determinants of 24-hour blood pressure in study subjects.

	24-hour systolic BP				24-hour diastolic BP			
	Na^+ and K^+ in model		Na^+/K^+ in model		Na^+ and K^+ in model		Na^+/K^+ in model	
	Parameter estimate*	P value	Parameter estimate*	P value	Parameter estimate*	P value	Parameter estimate*	P value
				Models with waist circumference				
Age (years)	0.26±0.07	**<0.0005**	0.27±0.07	**<0.0005**	0.15±0.05	**<0.005**	0.16±0.05	**<0.002**
Male gender	5.02±2.41	**=0.038**	-4.92±2.39	**=0.04**	2.11±1.62	=0.19	1.83±1.62	=0.26
Waist circumference (cm)	0.18±0.08	**<0.03**	0.17±0.08	**<0.03**	0.13±0.05	**<0.02**	0.12±0.05	**=0.03**
Urine Na^+ excretion (mmol/day)	0.02±0.02	=0.36	-	-	-0.01±0.02	=0.82	-	-
Urine K^+ excretion (mmol/day)	-0.11±0.07	=0.12	-	-	-0.08±0.05	=0.13	-	-
Urine Na^+/K^+	-	-	0.67±0.56	=0.23	-	-	0.02±0.38	=0.95
				Models with body mass index (BMI)				
Age (years)	0.29±0.07	**<0.0001**	0.30±0.07	**<0.0001**	0.17±0.05	**<0.0005**	0.18±0.05	**<0.0001**
Male gender	5.02±2.49	**=0.02**	5.70±2.47	**<0.03**	2.81±1.68	=0.10	2.49±1.67	=0.14
BMI	0.36±0.16	**<0.03**	0.35±0.16	**<0.04**	0.25±0.11	**<0.03**	0.22±0.11	**<0.05**
Urine Na^+ excretion (mmol/day)	0.02±0.02	=0.65	-	-	-0.01±0.02	=0.73	-	-
Urine K^+ excretion (mmol/day)	-0.11±0.07	=0.13	-	-	-0.07±0.05	=0.18	-	-
Urine Na^+/K^+	-	-	0.56±0.55	=0.30	-	-	-0.06±0.37	=0.88

* From stepwise regression analysis with listed factors as well as treatment for hypertension, regular alcohol and tobacco, diabetes mellitus or an HbA1c>7.0% forced into the model. Further adjustments of probability values were made for relatedness. ± values are the standard deviation.

Table 11. Determinants of night-day differences in blood pressure in study subjects.

	Day-night systolic BP				Day-night diastolic BP			
	Na^+ and K^+ in model		Na^+/K^+ in model		Na^+ and K^+ in model		Na^+/K^+ in model	
	Parameter Estimate*	P value	Parameter estimate*	P value	Parameter estimate*	P value	Parameter estimate*	P value
Models with waist circumference								
24-hour BP	0.13±0.05	**<0.02**	0.12±0.05	**=0.02**	-0.03±0.06	=0.67	0.03±0.06	=0.62
Age (years)	-0.02±0.05	=0.70	-0.02±0.05	=0.77	0.03±0.04	=54	0.02±0.04	=0.60
Male gender	3.17±1.66	=0.06	3.07±1.64	=0.06	2.63±1.32	**<0.05**	2.72±1.31	**<0.04**
Waist circumference (cm)	-0.02±0.06	<0.70	-0.02±0.06	=0.72	0.00±0.04	=0.97	0.00±0.04	=0.92
Urine Na^+ excretion (mmol/day)	-0.02±0.02	=0.35	-	-	0.00±0.01	=0.90	-	-
Urine K^+ excretion (mmol/day)	-0.03±0.05	=0.61	-	-	0.02±0.04	=0.62	-	-
Urine Na^+/K^+	-	-	-0.07±0.39	=0.86	-	-	-0.12±0.31	=0.69
Models with body mass index (BMI)								
24-hour BP	0.12±0.05	**<0.02**	0.12±0.05	**<0.02**	-0.03±0.06	=0.66	-0.03±0.06	=0.62
Age (years)	0.03±0.04	=0.45	-0.02±0.05	=0.74	0.03±0.04	=0.45	0.03±0.04	=0.50
Male gender	3.14±1.72	=0.07	2.99±1.70	=0.08	2.69±1.38	**=0.05**	2.78±1.36	**=0.04**
BMI	-0.03±0.11	=0.78	-0.04±0.11	=0.75	0.00±0.09	=0.96	0.00±0.09	=0.92
Urine Na^+ excretion (mmol/day)	-0.02±0.02	=0.36	-	-	0.00±0.01	=0.89	-	-
Urine K^+ excretion (mmol/day)	0.02±0.05	=0.68	-	-	0.01±0.04	=0.72	-	-
Urine Na^+/K^+	-	-	-0.03±0.38	=0.94	-	-	-0.09±0.30	=0.78

* From stepwise regression analysis with listed factors as well as treatment for hypertension, regular alcohol and tobacco, diabetes mellitus or an HbA1c>7.0% forced into the model. Further adjustments of probability values were made for relatedness. ± values are the standard deviation.

Table 12. Determinants of the ratio of night-to-day blood pressure in study subjects.

	Night-to-day ratio of systolic BP				Night-to-day ratio diastolic BP			
	Na^+ and K^+ in model		Na^+/K^+ in model		Na^+ and K^+ in model		Na^+/K^+ in model	
	Parameter Estimate*	P value	Parameter estimate*	P value	Parameter estimate*	P value	Parameter estimate*	P value
Models with waist circumference								
24-hour BP	0.0013±0.0004	**<0.001**	0.0013±0.0003	**<0.001**	0.0014±0.0007	**=0.05**	0.0014±0.0007	=0.06
Age (years)	-0.0001±0.0004	=0.80	-0.0000±0.0004	=0.86	0.0003±0.0005	=0.58	0.0002±0.0005	=0.62
Male gender	0.0250±0.0128	**=0.05**	-0.0242±0.0127	=0.06	0.034±0.016	**=0.03**	0.034±0.016	**=0.03**
Waist circumference (cm)	0.0000±0.0004	=0.95	-0.0000±0.0004	=0.96	0.0001±0.0005	=0.79	0.0002±0.0005	=0.76
Urine Na^+ excretion (mmol/day)	-0.0001±0.0001	=0.31	-	-	0.0000±0.0002	=0.96	-	-
Urine K^+ excretion (mmol/day)	0.0002±0.0004	=0.58	-	-	0.0002±0.0005	=0.74	-	-
Urine Na^+/K^+	-	-	-0.0007±0.003	=0.79	-	-	-0.001±0.004	=0.77
Models with body mass index (BMI)								
24-hour BP	0.0013±0.00004	**=0.0005**	0.0013±0.0003	**<0.001**	0.0014±0.0007	**=0.05**	0.0014±0.0007	**=0.05**
Age (years)	0.0000±0.00037	=0.80	0.0000±0.0004	=0.89	0.0003±0.0005	=0.47	0.0003±0.0005	=0.49
Male gender	0.0254±0.0132	=0.06	0.0241±0.0131	=0.07	0.035±0.017	**<0.05**	0.036±0.017	**=0.03**
BMI	0.0000±0.00087	=0.99	0.0000±0.0008	=0.96	0.0002±0.001	=0.82	0.0003±0.0011	=0.80
Urine Na^+ excretion (mmol/day)	0.0001±0.0001	=0.31	-	-	0.0000±0.0002	=0.95	-	-
Urine K^+ excretion (mmol/day)	0.0001±0.0004	=0.63	-	-	0.0001±0.0005	=0.83	-	-
Urine Na^+/K^+	-	-	-0.0006±0.0029	=0.84	-	-	-0.0007±0.0037	=0.85

- From stepwise regression analysis with listed factors as well as treatment for hypertension, regular alcohol and tobacco, and diabetes mellitus or an HbA1c>7.0% forced into the model. Further adjustments of probability values were made for relatedness. ± is SD.

CHAPTER 4

DISCUSSION

A number of issues were considered in the present dissertation. The community studied is of African ancestry and hence could have an attenuated nocturnal decrease in BP as compared to groups of European descent. Consequently, this discussion will initially focus on ethnic associations with nocturnal changes in BP and the potential factors that could contribute toward these changes. Second, prior to assessing the relationship between either salt intake or excess adiposity and nocturnal decreases in BP, I established that a high prevalence of inappropriate salt intake and adiposity exists in the community studied. Therefore, in the next part of this chapter I will discuss the implications of the data obtained on indices of salt intake obtained in the community studied. Lastly, the role of salt intake and adiposity as determinants of nocturnal decreases in BP in this and other studies will be discussed.

4.1 Nocturnal decreases in BP in groups of African descent

Earlier studies with relatively small sample sizes have reported on comparisons of nocturnal decreases in BP between groups of African and European origins (Belsha et al 1997; Chaturvedi et al. 1994; Fumo et al, 1992; Gretler et al, 1994; Harshfield et al 1993; Hebert et al 1996; James et al 1991; Mayet et al, 1998; Murphy et al 1991; Olutade et al 1998; Osei and Schuster, 1996; Treiber et al 1994; Harshfield et al, 1990; Harshfield et al, 2002a, Harshfield et al 2002b, Vaughan and Murphy,1994; Mancia et al. 1999, Hinderliter et al, 2004; Profant and Dimsdale 1999; Harshfield and Treiber, 1999). Although a number of these studies reported on an attenuated nocturnal decrease in BP in those of African ancestry, data that has largely been summarised in a meta-analysis (Profant and Dimsdale 1999), the outcome of the meta-analysis did not support this outcome, except when considering African-American as compared to European-

American groups alone (Profant and Dimsdale 1999). Consequently, large studies in randomly selected subjects were required. In this regard, more recent data obtained in a large study sample have provided clear evidence that African-Americans have a marked attenuation in the nocturnal decline in BP as compared to European-Americans (Wang et al 2006).

Comparisons of indices of nocturnal decreases in BP between groups of African and European descent living in countries other than North America have revealed discrepant data. Although some groups have shown an attenuated decline in nocturnal BP (Mayet et al J, 1998; Chaturvedi et al 1993), others have failed to reproduce these data (Chaturvedi et al.1993; Fumo et al 1992). Nevertheless, meta-analysis showing an attenuated nocturnal decline in BP when considering African-American as compared to European-American groups alone, but not when including groups of African descent living in non-American countries in the analysis (Profant and Dimsdale 1999), would suggest that the effect is environmental rather than biological.

Whether a reduced nocturnal decline in BP has implications for cardiovascular disease or outcomes in groups of African descent is not clear. There are fairly substantial data to indicate that a reduced nocturnal decline in BP or nocturnal BP *per se* is independently associated with cardiovascular outcomes in Caucasian and Asian groups (Verdecchia et al 1993; Verdecchia et al 1994; Verdechia et al 1995; Ohkubo et al 1997; Staessen et al 1999; Kikuya et al 2005, Suzuki et al 2000). However, when assessing the regression of left ventricular mass with antihypertensive therapy, both daytime and night-time BP appear to be equally well correlated with changes in LV mass (Mancia et al 1997). Moreover, in some studies, daytime rather than night-time BP was a better predictor of cardiovascular outcomes (Devereux et al 1991). Presently the only data to show the relationship between diurnal BP profiles and either

cardiovascular target organ effects or outcomes in persons of African descent is a four month study conducted in black South Africans showing that both daytime and night-time BP were equally well correlated with the regression of LV mass on-treatment (Skudicky et al 2002). Further cross-sectional and prospective analysis is currently underway under the umbrella of the APOGH study to assess the clinical importance of nocturnal decreases in BP in subjects of African descent living in South Africa.

4.2 Environmental and phenotypic factors other than adiposity or salt intake that may influence nocturnal decreases in BP

As indicated in the above discussion it is likely that the factors that determine ethnic differences in nocturnal decreases in BP are environmental in origin. A number of environmental factors may influence the ability of BP to decrease at night. Elevated 24-hour values, treatment status and alternative disease processes, such as diabetes mellitus, may modify nocturnal BP profiles (Profant and Dimsdale 1999; Lurbe et al 2002; Sturrock et al 2000). In the present dissertation, the presence or absence of hypertension, treatment status and the presence or absence of diabetes mellitus were included in the regression models as covariates. None of these factors were associated with nocturnal decreases in BP. However, this does not exclude the possibility that diabetes mellitus produces an attenuated decline in nocturnal BP in this population. In the present study only ~7-9% of subjects were receiving treatment for diabetes mellitus or had an abnormal blood glucose control as determined from HbA1c values>7.0%.

Levels of activity, socioeconomic factors, levels of stress, type of work, age, and gender have all been reported to contribute to diurnal patterns of BP (Staessen et al 1997; Schillaci et al 1996). I also included age and gender as covariates in the

regression analysis and neither of these factors was associated with nocturnal decreases in BP. Importantly, however, fewer men than women participated and thus the outcomes of the present study may reflect that of the predominant gender, that is females. I could not perform sex-specific analyses as the study sample size in men limited the statistical power to perform this analysis. Moreover, I was not statistically powered to assess parents and siblings in separate analyses, thus separating younger from older individuals. In addition, the attenuation of the nocturnal decline in BP is thought to occur at the age of 70 years (Staessen et al 1997) and few of the subjects in the present study were over the age of 70 years. Consequently, the present data do not exclude the possibility that either age or gender contribute toward attenuated nocturnal decreases in BP. Levels of activity, socioeconomic factors and type of work have not been analysed to-date as there is no clear method of analysing activity scores and socioeconomic status in the South African context. Although data on occupation, income, and level of education has been obtained, a meaningful score still have to be decided upon. Levels of stress were not assessed as part of the present study.

4.3 Salt intake in the study group

As adiposity and salt intake are two modifiable factors that have previously been reported to increase nocturnal BP or reduce nocturnal decreases in BP (Harshfield et al 2000; Damasceno et al 2000; Okuguchi et al 1999; Harshfield et al, 1991; Kotsis et al 2005; Staessen et al 1997), the main aim of the present study was to assess whether adiposity and salt intake are associated with nocturnal decreases in BP in an urban developing community of African descent. Previous studies have indicated that there is a high prevalence of adiposity in urban developing communities of African descent

(Puonane et al 2002). These data are supported by the present study where ~67% of subjects recruited were either overweight or obese. The high prevalence of excess adiposity in this community indicated that excess adiposity was worth studying as a potential mechanism of attenuated nocturnal decreases in BP. However, there is no clear evidence as to whether inappropriate salt intake characterises this community. Therefore as one aspect of this study I also explored the dietary salt patterns in this community.

The main findings of the study designed to assess whether inappropriate/appropriate salt intake characterises this community are as follows: First, 82% of people living in urban, developing communities surrounding Johannesburg have 24-hour urinary Na^+ excretion rates greater than the RDA of 65 mmol/day. Second, all persons living in urban, developing communities surrounding Johannesburg have 24-hour urinary K^+ excretion rates less than the RDA of 120 mmol/day. Third, awareness and treatment of hypertension (determined from a clinical history, the current use of pharmacological agents and an understanding of their purpose) was not associated with 24-hour urinary Na^+ or K^+ excretion rates in an urban developing South African community. There were no differences in 24-hour urinary Na^+ or K^+ excretion rates or the proportion of participants with 24-hour urinary Na^+ excretion rates greater than 65 mmol/day between patients aware of their disorder and receiving treatment for it and those unaware of their disorder. These data suggest that reductions in Na^+ intake and increases in K^+ intake in hypertensives as recommended in all guidelines and consensus opinions for the diagnosis and management of hypertension (World Health Organization, International Society of Hypertension Writing Group. 2003; Guidelines Committee of the European Society of Hypertension-European Society of Cardiology

2003; Chobanian et al 2003; Williams et al 2004; Appel et al 2006) are not being achieved in urban, developing communities of African ancestry in South Africa.

Although 24-hour urinary Na^+ excretion is a close reflection of Na^+ intake with only a minor component lost in the gastrointestinal tract and through sweat (Palacios et al. 2004), a substantial portion of total K^+ intake is excreted via the gastrointestinal tract rather than in the urine (Barlow et al 1986). Consequently, I am likely to have substantially underestimated K^+, but not Na^+ intake from urinary excretion rates. Therefore, in the present study I could have overestimated the frequency of individuals whose K^+ intake is below the RDA. Nevertheless, assuming that faecal K^+ excretion was approximately one-third of urinary K^+ excretion as previously reported (Barlow et al 1986) adding a third to the mean urinary K^+ excretion rate of each individual would still have resulted in all participants consuming less than the RDA for K^+ intake of 120 mmol/l (Appel et al 2006).

In the present study 87% of treated hypertensive patients were receiving thiazide diuretic agents, which are well recognised to promote a natriuresis and kaliuresis. However, measurements of 24-hour urinary Na^+ and K^+ excretion rates are generally considered to reflect salt intake rather than pharmacologically-induced changes in renal function. Indeed, treatment of hypertensives for two years with a thiazide diuretic failed to modify 24-hour urinary Na^+ excretion rates (Bing et al 1979). However, to avoid misinterpretation of data because of a potential confounding effect of the use of antihypertensive agents, in the analysis I also adjusted for drug class.

Participants were not followed prospectively in the present study. Therefore, it may be argued that hypertensives aware of their condition may have reduced their dietary Na^+ and increased their dietary K^+ intake to values comparable with those noted in normotensives. However, this cannot explain the comparable 24-hour urinary Na^+

and K^+ excretion rates between hypertensives aware of their condition and receiving treatment for it and hypertensives unaware of their condition and not receiving treatment for it. Presumably hypertensives unaware of their condition and not receiving antihypertensive therapy would have received little if any dietary advice. Hence, these subjects should have 24-hour urinary Na^+ and K^+ excretion rates that represent values in hypertensives presently aware of their condition and receiving antihypertensive agents for it prior to when dietary advice could have been implemented.

The mean 24-hour urinary Na^+ and K^+ excretion rates reported on in the present study are lower than those reported on in some studies conducted in populations of European and of African descent (Hoosen et al 1985; Hoosen et al 1990; Ganguli et al 1999). It may therefore be argued that at a population level dietary habits have tended toward a lower Na^+ intake in South Africa and therefore that dietary changes are possibly occurring at a population level rather than just in hypertensives. However, in the questionnaire, few subjects reported having received dietary advice. Despite measures taken to prevent incomplete urine collection, this possibility may however still explain lower mean Na^+ excretion values noted in the present study as compared to other studies (Hoosen et al 1985; Hoosen et al 1990; Ganguli et al 1999). Nevertheless, urinary K^+ excretion rates in the present study are comparable with those previously reported on in subjects of African descent under conditions where patients were carefully monitored (Palacios et al 2004). Moreover, quality control of urine collection was determined using standard approaches. Thus incomplete 24-hour urine collection is an unlikely explanation. Importantly, although mean Na^+ excretion values were lower in the present study as compared to other studies (Hoosen et al 1985; Hoosen et al 1990; Ganguli et al 1999), the majority of treated (80%) and untreated (73%) hypertensives were imbibing more than the recommended daily Na^+ intake. Considering that

hypertensives of African descent are particularly responsive to decreases in Na^+ intake (He et al 2000), the present study is a serious indictment of dietary management in hypertensives at a primary care level in urban, developing communities in South Africa. From a clinical perspective, if mean Na^+ intake in hypertensives were decreased to RDA values, BP values could be reduced on average by ~3 mm Hg systolic BP and ~1.6 mm Hg diastolic BP (He et al 2002). As indicated by the present study, because BP control is substandard in treated hypertensives, this approach could improve the proportion of patients who achieve target BP levels.

The reasons for the lack of association between awareness of hypertension and indexes of dietary Na^+ intake were not explored in the present study. These could include a lack of availability of low Na^+, high K^+ food products, a lack of dietary advice provided by health care workers, or failure of patients to respond to the dietary advice given. Failure to provide dietary advice may occur because of time constraints in overburdened clinics, a lack of dietary knowledge by health care workers, or a lack of faith by health care workers in diet as a form of therapy for hypertension. Failure to respond to dietary advice could occur because of the limited availability of appropriate food products, a reluctance to change dietary habits, or a lack of understanding of the advice being given.

4.4 Relationship between salt intake or excess adiposity and ambulatory BP and nocturnal decreases in BP

Having confirmed that excess adiposity does indeed characterise the study group and having established that the majority of people in the community consume more Na^+ and less K^+ than the recommended daily allowances, I then assessed whether either

adiposity or electrolyte intake are associated with nocturnal decreases in BP. In the present study, although indices of adiposity were associated with nocturnal BP, neither indices of adiposity nor indices of electrolyte intake were associated with indices of nocturnal decreases in BP.

Few studies have assessed the impact of salt intake on nocturnal decreases BP or nocturnal BP *per se*. The lack of relationship between salt intake and nocturnal decreases in BP in the present study are not in contrast to previous data exploring the relationship between salt intake and nocturnal decreases in BP (Damasceno et al 2000; Okuguchi et al 1999). In these previous studies (Damasceno et al 2000; Okuguchi et al 1999) a relationship between salt intake and nocturnal decreases in BP was only apparent in salt-sensitive individuals. In this regard, irrespective of salt intake, salt-sensitivity is associated with nocturnal decreases in BP (Wilson et al., 1999). However, salt intake has been shown to be associated with nocturnal, but not daytime BP in persons of African descent (Harshfield et al, 1991), data that would suggest a potential modifying impact of salt intake in general on nocturnal decreases in BP. Moreover, the relatively high prevalence of salt-sensitivity in persons of African descent could have resulted in a relationship between salt intake and nocturnal decreases in BP in the community studied by myself. Nevertheless, as the present data show, this relationship was not apparent and hence at a community level, the question arises as to whether modifying salt intake is likely to influence the nocturnal decline in BP. Further studies in this regard are required.

The lack of association between salt intake and nocturnal decreases in BP in the present study may also be attributed to the general lack of relationship between salt intake and ambulatory BP noted in the community studied. Although K^+ intake was inversely associated with 24-hour diastolic BP in the present study, neither Na^+ intake

nor urinary Na^+:K^+ ratios were associated with 24-hour BP. Based on these outcomes it may be argued that salt intake measurements in our study may have been inaccurate and limited my ability to detect a relationship with either BP or nocturnal decreases in BP. However, the quality control measures used in the present study to ensure that appropriate urinary salt excretion data were obtained were the same as those reported on in numerous publications (see methods section). Moreover, the relationship between salt intake and either conventional or ambulatory BP in previous studies has generally been inconsistent (INTERSALT Cooperative Research Group 1988; Smith et al 1988), possibly because this relationship is only likely to become apparent in subjects who are salt-sensitive (Okuguchi et al 1999). Therefore, further studies are required to determine whether salt intake in the community studied is related to absolute 24 hour BP or nocturnal decreases in BP in those subjects who are salt-sensitive. Indeed, we are presently assessing the capacity of specific regions of the tubule to handle salt using lithium clearance techniques. These data are however presently available on only a portion of the subjects studied and would go beyond the scope of an MSc dissertation.

4.5 Relationship between adiposity and ambulatory BP and nocturnal decreases in BP

As with the present study, a number of studies with large sample sizes have previously demonstrated a relationship between adiposity and conventional BP (for example Zhu et al 2005; Okosun et al, 1998; Harris et al 2000). However, it is only recently that a study with a large sample size has been published demonstrating a relationship between indices of adiposity and 24-hour BP (Kotsis et al 2005). As with

this prior study (Kotsis et al 2005), the present study shows a clear relationship between indices of adiposity and 24 hour ambulatory BP.

Obesity has previously been demonstrated to have a greater impact on BP at night than during the day (Harshfield et al 2000). The obvious conclusion from this is that excess adiposity should influence the difference between day and night BP. Indeed, in a large study conducted in a group of European ancestry obesity was associated with attenuated nocturnal decline in BP (Kotsis et al 2005). However, despite showing a relationship between indices of adiposity and ambulatory BP in the present study, I was unable to show a relationship between indices of adiposity and nocturnal decreases in BP. Differences between this and a previous study could be related to a number of factors. First, Kotsis et al (2005) assessed subjects referred to them for the assessment of hypertension, rather than randomly recruiting in the population at large. Hence, a selection bias may have occurred in the study by Kotsis et al (2005). However, the present study is limited by the predominance of one gender (females) recruited and our inability to assess gender-specific effects because of the limited number of male subjects recruited. In contrast, in the study by Kotsis et al (2005) there was an equal distribution of genders. The mean age of the study subjects recruited by Kotsis et al (2005) was 10 years older than the subjects studied by us and as previously mentioned age is major determinant of nocturnal decreases in BP (Staessen et al 1997). Lastly, the methods of assessing the relationship between nocturnal decreases in BP and indices of adiposity were different. In the study conducted by Kotsis et al (2005) nocturnal decreases in BP were assessed as discrete data, with subjects classified on the basis of whether they had a nocturnal decrease in BP that was >10% of the daytime value. In the present study I assessed nocturnal decreases in BP as continuous data for a number of reasons. First, thresholds for what constitutes an abnormal nocturnal decrease in BP

have not been described in the present population. Second, the reproducibility of "dipping" and "non-dipping" status based on indices of nocturnal BP changes has been questioned (Omboni et al 1998). Third, indices of nocturnal decreases in BP may have a Gaussian distribution which is nevertheless skewed, and hence although the indices may be transformed to provide a normal distribution, they probably should not be assessed as a discrete trait. The current study sample was too small to determine the distribution and skewness of the distribution of indices of nocturnal decreases in BP in healthy, normotensive, non-diabetic individuals. This is the topic of ongoing studies in the laboratory.

4.6 Relationship between female gender and attenuated nocturnal decreases in blood pressure

Although not a particularly strong effect, an independent relationship between female gender and an attenuated nocturnal decrease in BP was noted in the present study. This is in contrast to previous studies conducted with large sample sizes in both African-Americans and European-Americans showing a lack of effect of gender on nocturnal decreases in BP (Wang et al 2006). It is possible that the gender-specific effect noted in the present study represents a false positive finding. Further, even if this was a real finding in the present population sample, this was not an *a priori* hypothesis of the present study and hence it would be speculative to suggest potential mechanisms of the observed effect. Nevertheless, our group has initiated a study to determine whether this observation has merit.

4.7 Potential study limitations and future studies and analysis

A number of potential study limitations need to be mentioned and the potential solutions to these limitations posed. Many of these limitations have already been discussed above, but are worth emphasising. From a general perspective there were a greater number of women than men recruited in the present study. This could obviously bias the data in favour of effects noted in women. However, gender was included as a covariate on regression analysis. Once sample sizes are substantially greater I also intend to assess whether interactions between gender and either indexes of adiposity or salt intake are associated with nocturnal decreases in BP.

Although in the present study, random selection procedures were employed, nuclear families rather than individuals were randomly selected. This approach was utilised in the present study as we are ultimately going to assess familial aggregation of phenotypes. Moreover, for prospective analysis we also needed to obtain groups of subjects in whom it is ultimately going to be easier to follow-up (family units). However, as many of the subjects were related, a correction factor for non-independence of family members was introduced into the regression analysis using non-linear regression analysis (a mixed procedure).

As nuclear families were recruited, there are clearly two distinct age-groups, one for the parents and the other for the siblings. As age may determine some of the outcomes assessed, it would be important to perform the analysis in just the parents. However, age was included in the regression analysis and hence the fact that two distinct age-groups were studied, is unlikely to have affected the outcomes of the present study.

The present study was cross-sectional rather than prospective and interventional. With respect to salt intake studies it is now well recognized that although the

relationships between BP and salt intake are controversial (INTERSALT Cooperative Research Group 1988; Smith et al 1988), reductions in salt intake produce relatively consistent decreases in BP (MacGregor et al 1989; The Trials of Hypertension Prevention Collaborative Research Group 1997; Whelton et al 1998; He et al 2000; Sacks et al 2001; Vollmer et al 2001; Cutler et al 1997). Whether the same holds true for salt intake and nocturnal decreases in BP has not been assessed. Further prospective, intervention studies with dietary programs are presently underway and are likely to give me a clearer indication as to whether reductions in adiposity or decreases in salt (Na^+) intake can modify diurnal BP profiles.

As indicated in the above discussion I did not assess salt-sensitivity. Hence although the present data indicate that modifications in salt intake are unlikely to influence nocturnal decreases in BP at a community level, I cannot draw conclusions about the relationship between salt intake and nocturnal decreases in BP in individuals susceptible to the effects of salt.

In the present study, 24-hour urinary Na^+ excretion measurements were obtained only once. The extent to which these measurements reflect salt intake over prolonged periods is uncertain. Further studies with repeated 24-hour urinary Na^+ excretion measurements are therefore required to confirm the data from the present study.

In the present study the reproducibility of diurnal variations in ambulatory BP was not determined. Indeed, the reproducibility of nocturnal decreases in BP has been questioned (Omboni et al 1998). However, more recent data has demonstrated the reproducibility of differences in diurnal patterns between African-American and European-American youths over a 2-year study period (Harshfield et al 2002). Hence, the extent of nocturnal decreases in BP is likely to be sustained.

4.8 Conclusions

In conclusion the present dissertation has demonstrated that in a random selected urban community sample of African descent, although excess adiposity, and an increased Na^+ intake and a decreased K^+ intake (as indexed by 24-hour urine electrolyte excretion rates) characterizes this community, none of these factors are associated with attenuated nocturnal decreases in BP. However, an unexpected finding of the present study was an independent association between female gender and an attenuated nocturnal decrease in BP. Further studies are nevertheless required to determine whether Na^+ or K^+ intake are associated with nocturnal changes in BP in salt-sensitive individuals and whether the gender effect on nocturnal decreases in BP observed in the present study represents a chance finding.

REFERENCES

Acharya DU, Heber ME, Dore CJ, Raftery EM ambulatory intra-arterial blood pressure in essential hypertension: effects of age, sex, race and body mass: the Northwick Park Hopsital Database Study. Am J Hypertens 1996;9:943-952.

Appel LJ, Brands MW, Daniels SR, Karanja N, Elmer PJ, Sacks FM. Dietary approaches to prevent and treat hypertension: A scientific statement from the American Heart Association. Hypertension 2006;47:296-308.

Ashaye MO, Giles WH. Hypertension in blacks: a literature review. Ethn Dis 2003;13:456-462.

Barlow RJ, Connel MA, Milne FJ. A study of 48-hour faecal and urinary electrolyte excretion in normotensive black and white South African males. J Hypertens 1986;4:197-200.

Belsha CW, Spencer HJ, Berry PL, Plummer JK, Wells TG. Diurnal blood pressure patterns in normotensive and hypertensive children and adolescents. J Hum Hypertens 1997;11:801-806.

Belsha CW, Wells TG, McNiece KL, Seib PM, Plummer JK, Berry PL. Influence of diurnal blood pressure variations on target organ abnormalities in adolescents with mild hypertension. Am J Hypertens 1998;11:410-417.

Bing RF, Thurston H, Swales JD. Salt intake and diuretic treatment of hypertension. Lancet 1979;2:121-123.

Bryson CL, Ross HJ, Boyko EJ, Young BA. Racial and ethic variations in albuminuria in the US Third National Health and Nutrition Examination Survey (NHANES III) population: associations with diabetes and level of CKD. Am J Kid Dis 2006;48:720-726.

Charlton KE, Steyn K, Levitt NS, Zulu JV, Jonathan D, Veldman FJ, Nel JH. Ethnic differences in intake and excretion of sodium, potassium, calcium and magnesium in South Africans. Eur J Cardiovasc Prev Rehabil 2005;12:355-362.

Chaturvedi N, McKeigue PM, Marmot MG. Resting and ambulatory blood pressure differences in Afro-Caribbeans and Europeans. Hypertension 1993;22:90-96.

Chaturvedi N, Athanassopoulos G, McKeigue PM, Marmot MG, Nihoyannopoulos P. Echocardiographic measures of left ventricular strducture and their relation with rest and ambulatory blood pressure in blacks and whites in the United Kingdom. J Am Coll Cardiol 1994;24:1499-1505.

Chobanian AV, Hill M. National Heart, Lung, and Blood Institute Workshop on Sodium and Blood Pressure: a critical review of current scientific evidence. Hypertension 2000;35:858-863.

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, JOnes DW, Materson BJ, Oparil S, Wright JT Jr, Rocella EJ, and the National Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and treatment of high blood pressure. Hypertension 2003;42:1206-1252.

Clement DL, De Buyzere ML, DE Bacquer DA, de Leeuw PW, DuPrez DA, Fagard RH, Gheeraert PJ, Missault LH, Braun JJ, Six RO, Van Der NP, O'Brien E. Office versus ambulatory pressure study investigators. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. N Engl J Med 2003;348:2407-2415.

Connor MD, Modi G, Warlow CP. Accuracy of the Siriraj and Guy's Hospital stroke scores in urban South Africans. Stroke 2007;38:62-68.

Cutler JA, Follman D, Allender P. Randomized controlled trials of sodium reduction: an overview. Am J Clin Nutr 1997;65:643S-651S.

Damasceno A, Caupers P, Santos A, Lobo E, Sevene E, Bicho M, Polonia S. Influence of salt intake on the daytime-nightime blood pressure variation in normotensive and hypertensive black subjects. Rev Port Cardiol 2000;19:315-329.

Devereux RB, Pickering TG. Relationship between the level, pattern and variability of ambulatory blood pressure and target organ damage in hypertension. J Hypertension 1991;8:S34-S38.

Drazner MH, Dries DL, Peshock RM, Cooper RS, Klassen C, Kazi F, Willett D, Victor RG. Left ventricular hypertrophy is more prevalent in blacks than whites in the general population: the Dallas Heart Study. Hypertension 2005;46(1):124-129.

Erdine S, Aran SN. Current status of hypertension control around the world. Clin Exp Hypertens 2004;26: 731-738.

Fagard RH, Staessen JA, Thijs L. The relationship between left ventricular mass and daytime and night-time blood pressures: a meta-analysis of comparative studies. J Hypertens 1995;13:823-829.

Fumo MT, Teeger S, Lang RM, Bednarz J, Sareli P, Murphy MB. Diurnal blood pressure variation and cardiac mass in American blacks and whites and South African blacks. Am J Hypertens 1992;5:111-116.

Furlan R, Guzzetti S, Crivellaro W, Dassi S, Tinelli M, Baselli G Cerutti S, Lambardi F, Pagani M, Mallian A. Continuous 24-hour assessment of the neural regulation of systemic arterial pressure and RR variabilities in ambulant subjects. Circulation 1990;81:537-547.

Ganguli MC, Grimm RH Jr, Svendsen KH, Flack JM, Grandits GA, Elmer PJ. Urinary sodium and potassium profile of blacks and whites in relation to education in two different geographic urban areas. TOMHS Research Group. Treatment of Mild Hypertension Study. Am J Hypertens 1999;12:69-72.

Gillum RF. Risk factors for stroke in blacks: a critical review. Am J Epidemiol 1999;150:1266-1274.

Glover MJ, Greenland KJ, Ayala C, Croft JB. Racial/ethnic disparities in prevalence, treatment and control of hypertension. United States-1999-2002. CDC-MMWR 2005;54:7-9.

Godwin M, Delva D, Seguin R, Casson I, Mac Donalds, Birtwhisle R, Lam M. Relationship between blood pressure recorded on patients' charts in family physicians' offices and subsequent 24 hour ambulatory blood pressure monitoring. BMC Cardiovascular Disorders 2004; 4:2.

Gretler DD, Fumo MT, Nelson KS, Murphy MB. Ethnic differences in circadian hemodynamic profile. Am J Hypertens 1994;7:7-14.

Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J of Hypertens 2003;21:1011-1058.

Harris MM, Stevens J, Thomas N, Schreiner P, Folsom AR. Associations of fat distribution and obesity with hypertension in a bi-ethnic population: The ARIC Study. Obesity Res 2000;8:516-524.

Harshfield GA, Hwang C, Grim CE. Circadian variation of blood pressure in blacks: influence of age, gender and activity. J Hum Hypertens 1990;4:43-47.

Harshfield GA, Alpert BS, Pulliam DA, Willey ES, Somes GW, Stapelton FB. Sodium excretion and racial differences in ambulatory blood pressure patterns. Hypertension 1991;18:813-818.

Harshfield GA, Pulliam DA, Somes GW, Alpert BS. Ambulatory blood pressure patterns in youth. Am J Hypertens 1993;6:968-973.

Harshfield GA, Treiber FA. Racial differences in ambulatory blood pressure monitoring-derived 24 h patterns of blood pressure in adolescents. Blood Press Monit 1999;4:107-110.

Harshfield GA, Barbeau P, Richey PA, Alpert BS. Racial differences in the influence of body size on ambulatory blood pressure in youths. Blood Press Monit 2000;5:59-63.

Harshfield[a] GA, Wilson ME, Treiber FA, Alpert BA. A comparison of ambulatory blood pressure patterns across populations. Blood Press Monit 2002;7:265-269.

Harshfield[b] GA, Treiber FA, Wilson ME, Kapuku GK, Davis HC. A longitudinal study of ethnic differences in ambulatory blood pressure patterns in youth. Am J Hypertens 2002;15:525-530.

He J, Whelton PK. What is the role of dietary sodium and potassium in hypertension and target organ injury? Am J Med Sci 1999;317:152-159.

He J, Whelton PK, Appel LJ, Charleston J, Klag MJ. Long-term effects of weight loss and dietary sodium restriction on incidence of hypertension. Hypertension 2000;35:544-549.

He FJ, MacGregor GA. Effect of modest salt reduction on blood pressure: a meta-analysis of randomized trials: implications for public health. J Hum Hypertens 2002;16:761-770.

Hebert LA, Agarwal G, Ladson-Wofford SE, Reif M, HIremath L, Carlton SG, Nahman NS, Jr, Falkenhain ME, Agarwal A. Nocturnal blood pressure in treated hypertensive African Americans compared to treated hypertensive European Americans. J Am Soc Nephrol 1996;7:2130-2134.

Hinderliter AL, Blumethal JA, Waugh β, Chilukuri M, Sherwood A. Ethnic differences in left ventricular structure: relations to hemodynamics and diurnal blood pressure. Am J Hypertens 2004;17:43-49.

Hollar D, Agatston AS Hennekens CH. Hypertension : trends, risks, drug therapies and clinical challenges in African Americans. Ethn Dis 2004;14:23-25.

Holmes JS, Arispe IE, Moy E. Heart disease and prevention: race and age differences in heart disease prevention, treatment, and mortality. Med Care 2005;43:133-141.

Hoosen S, Seedat YK, Bhigjee AI, Neerahoo RM. A study of urinary sodium and potassium excretion rates among urban and rural Zulus and Indians. J HYpertens 1985;3:351-358.

Hoosen S, Seedat YK, Bhigjee AI. A study of urinary and intracellular sodium and potassium, renin, aldosterone and hypertension in blacks and Indians in Natal. Cardiovasc Drugs and Therapy 1990;4:363-365.

Howard G, Anderson RT, Russell G, Howard VJ, Burke GL. Race. Socioeconomic status, and cause-specific mortality. Ann Epidemiol 2000;10:214-223.

Howard GH. Ethnic disparities in stroke: the scope of the problem. Ethn Dis 2001;11:761-768.

Imai Y, Abe K, Sasaki S, Minami N, Munataka M, Nihei M, Sekino H, Yoshinaga K. Exogenous glucocorticoid eliminates or reverse circadian blood pressure variations. J Hypertens 1989 ;7 :113-120.

Imai Y, Tsuji I, Nagai K, Sakuma M, Ohkubo T, Watanabe N, Ito O, Satoh H, Hisamichi S, Abe K. Ambulatory blood pressure monitoring in evaluating the prevalence of hypertension in adults in Ohasama, a rural Japanese community. Hypertens Res 1996;19:207-212.

Institute of medicine: Dietary Reference Intakes: Water, Potassium, Sodium Chloride, and Sulfate. 1st ed. Washington. DC: National Academy Press; 2004.

Ionita CC, Xavier AR, Kirmani JF, Dash S Divani AA, Qureshi AI. What proportion of stroke is not explained by classic risk factors. Prev Cardiol 2005;8:41-46.

INTERSALT Cooperative research group. INTERSALT: An international study of electrolyte excretion and blood pressure: Results for 24-hour urinary sodium and potassium excretion. Brit Med J 1988;297:319-328.

Jamerson KA. The disproportionate impact of hypertensive cardiovascular disease in African-Americans: getting to the heart of the issue. J Clin Hypertens 2004;6:4-10.

James GD. Race and perceived stress independently affect the diurnal variation of blood pressure in women. Am J Hypertens 1991;4:382-384.

Joubert J, McClean CA, Reid CM, Davel D, Pilloy W, Delport B, Steyn I, Walker AR. Ischemic heart disease in black South African stroke patients. Stroke 2000;31:1294-1298.

Kahn, K, Tollman, SM. Stroke in rural South Africa-contributing to the little known about a big problem. SAMJ 1999; 89:1,63.

Kario K, Matsuo T, Kobayashi H, Imiya M, Matsuo M, Shimada K. Nocturnal fall in blood pressure and silent cerebrovascular damage in elderly hypertensive subjects: advanced silent cerebrovascular damage in extreme dippers. Hypertension 1996;27:130-135.

Kikuya M, Ohkubo T, Asayama K, Metoki H, Obara T, Saito S, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Ambulatory blood pressure and 10-year risk of cardiovascular and noncardiovascular mortality. The Ohasama Study. Hypertension 2005;45:240-245.

Kizer JR, Arnett DK, Bella JN, Paranicars M, Rao DC, Province MA, Oberman A, Kitzman DW, Hopkins PN, Liu JE, Devereux RB. Differences in Left Ventricular Structure Between Black and White Hypertensive Adults. Hypertension 2004;43:1182-88.

Kotsis V, Stabouli S, Bouldin M, Low A, Toumanidis S, Zokopoulos N. Impact of obecit on 24-hour ambulatory blood pressure and hypertension. Hypertension 2005;45;602-607.

Kuznetsova T, Staessen J, Kawecka-Jaszcz K, Babeanu S, Casiglia E, Filipovsky J, Nechev C, Nikitin Y, Paleska J, O'Brien E. Quality control of the blood pressure phenotype in the European Project on Genes in Hypertension. Blood Pressure Monitoring 2002; 7: 215-224.

Law MR. Epidemiological evidence on salt and blood pressure. Am J Hypertens 1997;10:42S-45S.

Li C, Engstrom G, Hedblad B, Berglund G, Janzon L. Blood pressure control and risk of stroke. A population-based prospective cohort study. Stroke 2005; 36: 725-730.

Lindsay RS, Stewart MJ, Nairn IM, Baird JD, Padfield PL. Reduced diurnal variation of blood pressure in non-insulin dependent diabetic patients with microalbuminuria. J Hum Hypertens 1995;9:223-227.

Lorber R, Gidding SS, Daviglus ML, Coangelo LA, Liu K, Gardin JM. Influence of systolic blood pressure and body mass index on left ventricular structure in healthy African-American and white young adults: the CARDIA study. J Am Coll Cardiol 2003;19;41(6):955-960.

Lurbe E, Redon J, Kesani A, Pascual JM, Tacons J, Alvarez V, Battle D. Icrease in nocturnal blood pressure and progression to microalbuminuria in type I diabetes. N Engl J Med 2002;347:797-805.

MacGregor GA, Markandu ND, Sagnella GA, Singer DR, Cappuccio FP. Double-blind study of three sodium intakes and long term effects of sodium restriction in essential hypertension. Lancet 1989;2:1244-1247.

Mancia G, Parati G. Ambulatory blood pressure monitoring and organ damage. Hypertension 2000; 36;894-900.

Mancia G, Zanchetti A, Agabiti-Rosei E, Benemio G, De Cesaris B, Fogari B, Pessina A, Porcellati C, Rapelliu A, Salvetti A, Trimarco B. Ambulatory blood pressure is superior to clinic blood pressure in predicting treatment-induced regression of left ventricular hypertrophy. Circulation 1997;95:1464-1470.

Mancia G, O'Brien E, Imai Y, Redon J. Task force II: Ambulatory blood pressure monitoring in population studies. Blood Pressure Monit 1999;4:295-301.

Manning G, Rushton L, Millar-Graig MW. Twenty-four hour blood pressure: a sample from a normal British population. Journal of Human Hypertension1998; 12: 123-127.

Martins D, Norris K. Hypertension treatment in African-Americans: physiology is less important than sociology. Cleve Clin J Med 2004;71:735-743.

Mayet J, Chapman N, Li CK, Shahi M, Poulter NR, Sever PS, Foale RA, Thom SA. Ethnic differences in the hypertensive heart and 24-hour blood pressure profile. Hypertension 1998;31:1190-1194.

McGruder HF, Malarcher AM, Antoine TL, Greenlund KJ, Croft JB. Racial and ethnic disparities in cardiovascular risk factors among stroke survivors: United States 1999-2001. Stroke 2004;35:1557-1561.

Murphy MB, Fumo MT, Gretler DD, Nelson KS, Lang RM. Diurnal blood pressure variation: differences among disparate ethnic groups. J Hypertens 1991;9:S45-S47.

Murtaugh MA, Jacobs DR, Yu X, Gross MD, Steffes M. Correlates of urinary albumin excretion in young adult blacks and whites : The Coronary Artery Risk Development in Young Adults study. Am J Epidemiol 2003;158:676-686.

Nunez E, Arnett DK, Benjamin EJ, Liebson PR, Skelton TN, Taylor H, Andrew M. Otimal threshold value for left ventricular hypertrophy in blacks in the Atheroscelrosis Risk in Communities study. Hypertension 2005;45:58-63.

O'Brien E, Murphy J, Tyndall A, Atkins N, Mee F, Mc Carthy G, Staessen J, Cox J,

O'Malley K. Twenty-four-hour blood pressure in men and women aged 17 to 80 years: the Allied Irish Bank Study. Journal of Hypertension 1999; 9: 355-360.

O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P; European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. J Hypertens 2003; 21:821-848.

Ohkubo T, Imai Y, Tsuji I, Nagai K, Watanabe N, Minami N, Kato J, Kikuchi N, Nishiyama A, Aihara A, Sekino M, Satoh H, Hisamichi S. Relation between nocturnal decline in blood pressure and mortality. The Ohasama study. Am J Hypertens 1997;10:1201-1207.

Okosun IS, Cooper RS, Rotimi CN, Osotimehin B, Forrester T. Association of waist circumference with risk of hypertension and type 2 diabetes in Nigerians, Jamaicans and African Americans. Diabetes Care 1998;21:1836-1842.

Okuguchi T, Osanai T, Kamada T, Kimura M, Takahashi K, Okumura K. Significance of sympathetic nervous system in sodium-induced nocturnal hypertension. J Hypertens 1999;17:947-957.

Olutade BO, Gbadebo TD, Porter VD, Wilkening B, Hall WD. Racial differences in ambulatory blood pressure and echocardiographic left ventricular geometry. Am J Med Sci 1998;315:101-109.

Omboni S, Parati G, Palatini P, Vanasia A, Muiesan ML, Cuspidi C, Mancia G. Reproducibility and clinical value of nocturnal hypotension: prospective evidence from the SAMPLE study. J Hypertens 1998;16:733-738.

Omvink P, Gerhardsen G. The Norwegian office, home and ambulatory blood pressure study. Blood Pressure 2003; 12: 211-219.

Osei K, Schuster DP. Effects of race and ethnicity on insulin sensitivity , blood pressure and heart rate in three ethnic populations: comparative studies in African-Americans, African immigrants (Ghanaians), and white Americans using ambulatory blood pressure monitoring. Am J Hypertens 1996;9:1157-1164.

Palatini P, Craniero CR, Mormino P, Mattarei M, Sanzuol F, Cignacco GB, Gregori S, Garavelli G, Pegoraro F, Maraglino G, Bortolazzi A, Accurso V, Dorigatti F, Graniero F, Gelisio R, Businaro R, Accurso V, Dorigatti F, Graniero F, Gelisio R, Businaro R, Vriz O, Follo MD, Camarotto A, Pessina AC. Prevalamce and clinical correlates of Microalbuminuria in stage 1 hypertension. Am J Hypertens 1996;9:334-341.

Peters AL, Davidson MB, Schriger DL, Hasselblad V. A clinical approach for the diagnosis of diabetes mellitus: an analysis using glycosylated hemoglobin levels. Meta-analysis Research Group on the Diagnosis of Diabetes Using Glycated Hemoglobin Levels. JAMA 1996;276: 1246-52.

Phillips RA, Sheinart KF, Godbold JH, Mahboob B, Tuhrim S. The association of blunted nocturnal blood pressure dip and stroke in a multiethnic population. Am J Hypertens 2000;13:1250-1255.

Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Roccella EJ. Recommendations for blood pressure measurement in humans and experimental animals. Part 1: Blood pressure measurement in humans. Hypertension 2005;45:142-161.

Pickering TG, James GD. Determinants and consequences of the diurnal rhythm of blood pressures. Am J Hypertens 1993;6(suppl):166S-169S.

Prisant LM, Thompson WO, Bottini PB, Carr AA, Rhoades R. Racial aspects of ambulatory blood pressure. J Hum Hypertens 1991;5:369-373.

Profant J, Dimsdale JE. Race and diurnal blood pressure patterns: A review and meta-analysis. Hypertension 1999;33:1099-1104.

Puonane T, Steyn K, Bradshaw D, Laubscher R, Fourie J, Lambert V, Mbananga N. Obesity in South Africa: The South African demographic and health survey. Obes Res 2002;10:1038-1048.

Rasmusse S. L, Torp-Pedersen C, Borch-Johnsen K, Ibsen H. Normal values for ambulatory blood pressure and casual blood pressure: results from a Danish population survey. J Hypertens 1998; 16: 1415-1424.

Redon J, Liao Y, Lozano JV, Miralles A, Pascual JM, Cooper RS. Ambulatory blood pressure and microalbuminuria in essential hypertension : role of circadian variability. J Hypertens 1994;12:947-953.

Reeves RA, Shapiro AP, Thompson ME, Johnson AM. Loss of nocturnal decline in blood pressure after cardiac transplantation. Circulation 1986;73:401-408.

Rockstroh JK, Schmieder RE, Schlaich MP, Messerli FH. Renal and systemic haemodynamics in black and white hypertensive patients. Am J Hypertens 1982;4:817-820.

Rodriguez CJ, Sciacca RR, Diez –Roux AV, Boden-Albala B, Sacco RL, Homma S, DiTullo MR. Relation between socioeconomic status, race-ethnicity, and the left ventricular mass: the Northern Manhattan study. Hypertension 2004;43(4):775-779.

Rowlands DB, de Giovanni J, McLeay RA, Watson RD, Stallard TJ, Littler WA. Cardiovascular response in black black and white hypertensives. Hypertension 1982;4:817-820.

Sacco RL, Boden-Albala B, Abel G, Lin IF, Elkind M, Hauser WA, Paik MC, Shea S. Race-ethnic disparities in the impact of stroke risk factors: the northern Manhattan stroke study. Stroke 2001;32:1725-1731.

Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER 3rd, Simons-Morton DG, Karanja N, Lin PH; DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and

the Dietary Approaches to Stop Hypertension (DASH) diet. DASH Sodium Collaborative Research Group. N Engl J Med 2001;344:3-10.

Schillaci G, Verdecchia P, Borgioni C, Ciucci A, Gattobigio B, Sacchi N, Benemio G, Porchellati C. Predictors of diurnal blood pressure changes in 2042 subjects with essential hypertension. J Hypertens 1996;14:1167-1173.

Shapiro D, Goldstein IB, Jamner LD. Effects of cynical hostility, anger out, anxiety, and defensiveness on ambulatory blood pressure in black and white college students. Psychosom Med 1996;58:354-364.

Sherwood A, Steffen PR, Blumenthal JA, Kuhn C, HInderliter AL. Nighttime blood pressure dipping: the role of the sympathetic nervous system. Am J Hypertens 2002;15:111-118.

Shiburi CP, Staessen JA, Maseko M, Wojciechowska W, Thijs L, van Bortel LM, Woodiwiss AJ, Norton GR. Reference values for Sphygmocor measurements in South Africans of African ancestry. Am J Hypertens 2006;19:40-46.

Skelton TN, Andrew ME, Arnett DK, Burchfiel CM, Garrison RJ, Samdarshi TE, Taylor HA, Hutchinson RG. Echocardiographic left ventricular mass in African-Americans: the Jackson cohort of the Atheroscierosis Risk in Communities Study. Echocardiography 2003;20(2): 111-120.

Skudicky D, Sareli P, Libhaber E, Candy G, Radevski I, Valtcanova Z, Tshele E, Thijs L, Wang J-G, Staessen JA. Relationship between treatment-induced changes in left ventricular mass and blood pressure in black African hypertensive patients. Circulation 2002;105:830-836.

Smith WCS, Crombie IK, Tavendale RT, Gulland SK, Tunstall-Pedoe HD. Urinary electrolyte excretion, alcohol consumption and blood pressure in the Scottish Heart Health Study. Brit Med J. 1988;297:329-330.

Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med 1993;328:303-307.

Sowers JR, Zemel MB, Zemel P, Beck FW, Walsh MF, Zawada ET. Salt sensitivity in blacks. Salt intake and natriuretic substances. Hypertension 1998; 12: 485-490.

Staessen J, Bulpitt CJ, Fagard R, Joosens JV, Lijnen P, Amery A. Familial aggregation of blood pressure, anthropometric characteristics urinary excretion of sodium and potassium: A population study in two Belgian towns. Journal of Chronic Diseases 1985; 38: 397-407.

Staessen JA, Bieniaszewski L, O'Brien E, Gosse P, Hayashe H, Imai Y, et al. Nocturnal blood pressure fall on ambulatory monitoring in a large international database. Hypertension 1997;29:30-39.

Staessen J, Thijs L, Fagard B, O'Brien E, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J. Predicting cardiovascular risk using conventional versus ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. JAMA 1999;282:539-546.

Steffen PR, McNeilly M, Anderson N, Sherwood A. Effects of perceived racism and anger inhibition on ambulatory blood pressure in African Americans. Psychomosom Med 2003;65:746-750.

Steyn K, Gaziano TA, Bradshaw D, Laubscher R, Fourie J, for the South African demographic and health coordinating team: Hypertension in South African adults: results from the demographic and health survey, 1998. J Hypertens 2001;19:1717-1725.

Sturrock ND, George E, Pound N, Stevenson J, Peck GM, Sowter H. Non-dipping diurnal blood pressure and renal impairment are associated with increased mortality in diabetes mellitus. Diabet Med 2000;17:360-364.

Suzuki Y, Kuwajima I, Aono T, Kanemaru A, Nishiniga M, Shibata H, Ozawa T. Prognostic value of nighttime blood pressure in the elderly: a prospective study of 24-hour blood pressure. Hypertens Res 2000;23:323-330.

Tatiana K, Sofia M, Elena P, Lutgarde T, Yuri N, Staessen J.A. Ambulatory blood pressure in Novosibirsk, Russia: interim report on a population study. Blood Pressure Monitoring 2000;5:291-296.

The Trials of Hypertension Prevention Collaborative Research Group. Effects of weight loss and dietary sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. Arch Intern Med 1997;157:657-667.

Thijs L, Staessen J, Fagard R. Analysis of the diurnal blood pressure curve. High Blood Press Cardiovasc Prev 1992;1:17-28.

Thomas KS, Nelesen RA, Dimsdale JE. Relationships between hostility, anger expression and blood pressure dipping in an ethnically diverse sample. Psychosom Med 2004;66:298-304.

Timio M, Venanzi S, Lolli S, Lippi C, Verdura E, Guerrini E, Monarca C. Night-time blood pressure and progression of renal insufficiency. High Blood Pressure Cardiovasc Prev 1994;3:39-44.

Treiber FA, Murphy JK, Davis H, Raunikar RA, Pflieger K, Strong WB. Pressor reactivity, ethnicity, and 24-hour ambulatory monitoring in children from hypertensive families. Behav Med 1994;20:133-142.

Vaughan CJ, Murphy MB. The use of ambulatory blood pressure monitoring in the evaluation of racial differences in blood pressure. J Cardiovasc Risk 1994;1:132-135.

Verberk WJ, Kroon AA, Kessels AGH, Dirksen C, Nelemans PJ, Lenders JW, Thien TA, van Montfrans GA, Smit AJ, de Leeuw PW. Home versus office blood pressure

measurements: Reduction of unnecessary treatment study: Rationale and study design of the HOMERUS trial. Blood Pressure 2003; 12:326-333.

Verdechia P, Schillaci G, Guerrieri M, Gatteschi C, Benemio G, Boldrini F, Porcellati C. Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. Circulation 1990;81:528-536.

Verdechia P, Schillaci G, Zampi I, Gatteschi C, Battistelli M, Bartoccini C, Porcellati C. Blunted nocturnal fall in blood pressure in hypertensive women with future cardiovascular morbid events. Circulation 1993;88:986-992.

Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Guirrieri M, Gatteschi C, Zampi I, Santucci A. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. Hypertension 1994;24:793-801.

Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Guirrieri M, Gatteschi C, Zampi I, Santucci A. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. Hypertension 1995;25:4621.

Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Pede S, Porcellati C. Ambulatory pulse pressure: A potent predictor of total cardiovascular risk in hypertension. Hypertension 1998;32:983-988.

Vollmer WM, Sacks FM, Ard J, Appel LJ, Bray GA, Simons-Morton DG, Conlin PR, Svetkey LP, Erlinger TP, Moore TJ, Karanja N; DASH-Sodium Collaborative Research Group. Effects of diet and sodium intake on blood pressure: subgroup analysis of the DASH-sodium trial. Ann Intern Med 2001;135:1019-1028.

Wang X, Poole JC, Treiber FA, Harshfield GA, Hanevold CD, Snieder H. Ethnic and gender differences in ambulatory blood pressure trajectories: Results from a 15-year longitudinal study in youth and young adults. Circulation 2006; 114: 2780-2787.

Whelton PK, He J, Cutler JA, Brancati FL, Appel LJ, Follmann D, Klag MJ. Effects of oral potassium on blood pressure: meta-analysis of randomised controlled clinical trials. JAMA 1997;277:1624-1632.

Whelton PK, Appel LJ, Espeland MA, Applegate WB, Ettinger WH Jr, Kostis JB, Kumanyika S, Lacy CR, Johnson KC, Folmar S, Cutler JA. Sodium reduction and weight loss in the treatment of hypertension in older persons: A randomized controlled trial of non-pharmacological interventions in the elderly (TONE). JAMA 1998;279:839-846.

Whelton PK, He J, Appel LJ, Cutler JA, Havas S, Katchen TA, Roccella EJ, Stout β, Vallbona C, Winston MC, Karimbakas J; National High Blood Pressure Education Program Coordinating Committee. Primary prevention of hypertension. Clinical and public health advisory from the National High Blood Pressure Education Program. JAMA 2002;288:1882-1888.

Wilson DK, Sica DA, Miller SB. Ambulatory blood pressure nondipping status in salt-sensitive and salt-resistant black adolescents. Am J Hypertens 1999;12:159-165.

Wilson DK, Kliewer W, Teasley N, Plybon L, Sica DA. Violence exposure, catecholamine excretion, and blood pressure nondipping status in African American male versus female adolescents. Psychosom Med 2002;64:906-915.

Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, Sever PS, Thom McG. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. J Hum Hypertens 2004;18:139-185.

World Health Organization, International Society of Hypertension Writing Group. 2003 World Health Organisation (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens 2003;21:1983-1992.

Yan Li, Staessen JA,Lu L, Wang G, Wang J. Is isolated nocturnal hypertension a novel clinical entity?: Findings from a Chinese population study. Hypertension 2007; 50; 333-339.

Zanchetti A, Bond G, Henning M, Neiss A, Mancia G, Dal Palu C, Hanson L, Magnani B, Rahn K, Reid J, Rodicio J, Safar M, Eckes L, Ravinetto R. Risk factors associated with alterations in carotid intima-media thickness in hypertension: baseline data from the European lacidipine study on atherosclerosis. J Hypertens 1998;16:949-961.

Zhu S, Heymsfield SB, Toyoshima H, Wang Z, Pietrobelli A, Heshka S. Race-ethnicity specific waist circumference cuttoffs for identifying cardiovascular disease risk factors. Am J Clin Nutr 2005;81:409-415.