VARIOUS DIETARY RISK MARKERS OF HYPERTENSION IN BLACK SOUTH AFRICANS: THE THUSA AND THUSA BANA STUDY

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Various dietary risk markers of hypertension in black South Africans: The THUSA and THUSA BANA study

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Thesis submitted for the degree Philosophia Doctor in Physiology at the School for Physiology, Nutrition and Consumer Science of the Potchefstroomse Universiteit vir Christelike Hoër Onderwys

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Ps. 8:5,6,10

Wat is die mens dat U aan hom dink, en die mensekind dat U hom besoek? U het hom 'n weinig minder gemaak as 'n goddelike wese en hom met eer en heerlikheid gekroon.

O HERE, onse Here, hoe heerlik is u Naam op die ganse aarde!

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Afrikaanse titel: ***Verskeie dieetverwante risikomerkers vir hipertensie van swart Suid-Afrikaners: Die THUSA en THUSA BANA studie***

Opsomming

Motivering: Hipertensie is een van die belangrikste oorsake van siektetoestande en sterftes in Suid-Afrika. Volgens die Wêreld Gesondheidsorganisasie vind die ontwikkeling van kardiovaskulêre siektes skrikwekkend vinnig in ontwikkelende lande plaas, en daar is min direkte bewyse omtrent die bepalers van algemene kardiovaskulêre siektes in hierdie groot populasies van suidelike Afrika. Hoewel genetika steeds die belangrikste rol in die etiologie van hipertensie speel, het verskeie studies reeds bewys dat sekere dieetfaktore bloeddruk betekenisvol kan verlaag en ook die verbetering van 'n aantal risikofaktore vir kardiovaskulêre siektes tot gevolg kan hê. Daar is steeds spesifieke onsekerhede, teenstrydighede en 'n tekort aan data in die literatuur aangaande die effekte van die meeste dieetfaktore op bloeddruk.

Doelstellings: Die hoofdoel van die vier manuskripte wat in hierdie proefskrif saamgevat word is om te bepaal watter dieetfaktore geïdentifiseer kan word as risikomerkers vir die voorkoms van hipertensie in swart Suid-Afrikaanse kinders. Die rol van dieetinname word ook in verhouding met ander bekende hipertensie risikofaktore geplaas.

Metodologie: Die manuskripte wat in Hoofstuk 3, 4 en 5 vervat is, het gebruik gemaak van die dwarsdeursnee THUSA BANA projek, waar swart Suid-Afrikaanse kinders ewekansig vanuit skole in die Noordwes Provinsie as proefpersone gekies is. Hierdie kinders is as normo- en hipertensief geklassifiseer nadat uitgebreide bloeddrukmetings plaasgevind het. Antropometriese metings en dieetinname is ook bepaal. Betekenisvolle verskille tussen normo- en hipertensiewe proefpersone is deur middel van onafhanklike t-toetse bepaal. Stapsgewyse meervoudige regressie analises is ook uitgevoer om die mees betekenisvolle bepalers van hipertensie in die proefgroepe aan te wys. Die studie wat in Hoofstuk 6 vervat is het gebruik gemaak van twee dwarsdeursnee studies, naamlik die THUSA en THUSA BANA projekte. Die THUSA proefpersone was oënskynlik gesonde swart volwassenes vanuit ewekansig geselekteerde gebiede in die Noordwes Provinsie. Verskeie kardiovaskulêre parameters, demografiese vraelyste, antropometriese metings en dieetinnames is bepaal. Bloedmonsters is geneem vir die bepaling van plasma fibrinogeen, serum lipiede, gamma glutamiel-transferase en insulien analises. Faktor analise is op die data toegepas om struktuur in die verhoudinge van die veranderlikes te identifiseer.

Alle THUSA proefpersone en al die ouers van die THUSA BANA proefpersone het ingeligte toestemming gegee en beide studies is goedgekeur deur die Etiese Komitee van die Potchefstroomse Universiteit vir CHO. Die leser word verwys na die afsonderlike opsommings wat aan die begin van elke manuskrip in Hoofstuk 3-6 voorkom vir die duidelike beskrywing van die proefpersone, studie ontwerp en analitiese metodes wat gebruik is.

Resultate en gevolgtrekkings van die individuele manuskripte:

- ❑ Resultate van die THUSA BANA studie het daarop gedui dat dieselfde dieetfaktore wat met die bloeddruk van hipertensiewe kinders geassosieer word, ook merkwaardiglik dié dieetfaktore is waarvan die laerskoolkinders gebrekkige innames gehad het. Dit sluit die volgende dieetfaktore in: totale energie inname, biotien, foliensuur, pantoteensuur, sink, yster, magnesium en vitamien A inname. Hierdie dieetfaktore was ook die beste merkers vir sistoliese, diastoliese en gemiddelde bloeddruk in swart hipertensiewe kinders. Dieetresultate tesame met die kardiovaskulêre parameters het aangedui dat hoër foliensuur innames met laer bloeddruk geassosieer is, terwyl hoër biotien innames met 'n toename in sistoliese en diastoliese bloeddruk geassosieer is. Inname van beide hierdie nutriënte was onvoldoende.
- ❑ Met 'n opvolgstudie van die eerste manuskrip was die doel hoofsaaklik daarop gestel om die uitwerking van dieetfaktore op kardiovaskulêre parameters van die perifere bloedvate te toets, naamlik arteriële meegewendheid en perifere weerstand. Polsdruk en slagvolume is egter ook bepaal. Resultate het gedui dat veral makronutriëntinname, soos koolhidrate, proteïene, versadigde vette en mono-onversadigde vette, maar ook

magnesium, yster en mangaan geassosieer is met verhoogde polsdruk en verlaagde arteriële meegewendheid. Biotieninname het teenstrydige resultate getoon, naamlik 'n assosiasie met 'n verhoging in slagvolume, maar ook 'n verhoging in die arteriële meegewendheid van hipertensiewe swart kinders. Biotien was die enigste nutriënt wat met die verbetering van arteriële meegewendheid geassosieer is.

- Die resultate van die eerste twee manuskripte het gelei tot verdere ondersoeke aangaande die effekte en moontlike meganisme waarop biotien in die kardiovaskulêre stelsel funksioneer. Die volgende teenstrydigheid is steeds gekenmerk: biotieninname is geassosieer met 'n verhoogde sistoliese en diastoliese bloeddruk, en verhoogde slagvolume, maar dit het ook die voordelige effek om arteriële meegewendheid te verhoog. Of die onvoldoende biotieninname van die kinders verantwoordelik vir hierdie verskynsel is, is onseker, maar dit is moontlik dat 'n suboptimale biotienstatus die ontwikkeling van hipertensie in 'n persoon wat geneties gepredisposisioneer is om hipertensief te wees, kan versnel of inisieer.
- Deur statistiese faktor analise is vyf basiese patrone van risikofaktore vir hipertensie saamgestel: (1) *verstedelikte wanvoedingsverskynsel*, gekenmerk deur verstedeliking en hoë inname van versadigde vette, dierproteïene en natrium; (2) *metaboliese sindroom X*, gekenmerk deur hoë ouderdom, insulienweerstand, obesiteit, dislipidemie, hipertensie, rookgewoonte en hiperfibrinogenemie; (3) *hipercholesterolemie en obesiteitskompleks*, geassosieer met hoë ouderdom, obesiteit, en 'n eenvoudige kombinasie van totale cholesterol en LDL; (4) *alkoholiese hipertrigliseriedemie*, geassosieer met ouderdom, gamma glutamiel-transferase, plasma trigliseriedes, rookgewoonte en sentrale obesiteit; en (5) *sentrale en perifere kardiovaskulêre effek* wat aandui dat hipertensie by kinders positief geassosieer word met kardiale omset en negatief met perifere vaskulêre weerstand, waar volwassenes die omgekeerde toon. Daar vind dus 'n verskuiwing vanaf 'n sentrale beheermeganisme (hoë kardiale omset) na 'n meer perifere meganisme (hoë perifere vaskulêre weerstand) in ouer persone plaas.

Gesamentlike bespreking: Die bydrae wat hierdie studie gelewer het is die aanduiding dat biotieninname 'n merker vir hipertensie by swart kinders is. Maar ook die resultate aangaande die uitwerking van dieetfaktore op spesifieke kardiovaskulêre parameters, soos arteriële meegewendheid, slagvolume, perifere vaskulêre weerstand en polsdruk, maak hierdie studie uniek. 'n Onlangse oorsigartikel het daarop gewys dat daar 'n tekort bestaan aan studies wat die uitwerking van meervoudige nutriënte en makronutriënte in hipertensie by kinders ondersoek. Die resultate van hierdie studie dra dus by tot hierdie leemte. Volgens die Wêreld Gesondheidsorganisasie is daar ook 'n tekort aan bewyse van bepalers van hipertensie in groot populasies, soos die van suidelike Afrika. Hierdie leemte is ook aangespreek deur die beskrywing van vyf patrone van hipertensie risiko's wat in 'n swart Suid-Afrikaanse populasie voorkom.

Die resultate van hierdie studie lewer 'n bydrae tot bestaande kennis van die voorkoms van hipertensie in die swart bevolking en hierdie resultate kan ook rigting vir toekomstige navorsingsprojekte in hierdie populasie verskaf. Die meganisme waarvolgens die vitamiene bloeddruk en ander kardiovaskulêre faktore beïnvloed, behoort ondersoek te word.

Resultate van die vier manuskripte lei tot die formulering van bykomende aanbevelings omtrent die inname van mikronutriënte, soos foliensuur, biotien, vitamien A, vitamien E, askorbiensuur en makronutriënte, soos koolhidrate en versadigde vette. Hoewel hierdie studie nie ontwerp is om nutriënttekorte vas te stel nie, kan aanbevelings moontlik die ontwikkeling van hipertensie voorkom. Aanbevelings spreek ook die korreksie van 'n risikofaktorpatroon aan, eerder as die regstelling van 'n enkele risikofaktor, byvoorbeeld die aanpassing van 'n persoon se hele dieet en nie slegs die beperking van soutinname nie. Hierdie aanbevelings kan deur beleidsbepalers en gesondheidsdepartemente van die regering, asook die voedselindustrie en professionele gesondheidswerkers gebruik word ten einde kardiovaskulêre siektes te voorkom.

Sleutelwoorde: hipertensie, risikofaktore, dieet, eetgewoontes, biotien, swart kinders, Suid-Afrika, faktor analise

Summary

Motivation: Hypertension is one of the most important causes of mortality and morbidity in South Africa. An alarming and rapid development of cardiovascular disease is now flowing through developing countries according to the World Health Organisation. There is also very little direct evidence about the determinants of common cardiovascular diseases in large populations such as those of sub-Saharan Africa. Although genetic make-up plays the most important role in the aetiology of hypertension, various studies have shown that certain dietary factors significantly lowers blood pressure and also improve multiple risk factors for patients with cardiovascular disease. There are, however, still some uncertainties, inconsistencies and a lack of data in the literature regarding the effects of most dietary factors on hypertension.

Objectives: The main objective of the papers presented in this thesis is to determine which dietary factors could be identified as risk markers that might be associated with the prevalence of hypertension and specific cardiovascular parameters in black South African children. Also, to examine the role of dietary intake in relation to other known hypertension risk factors.

Methodology: Manuscripts presented in Chapters 3, 4, and 5 made use of the cross-sectional THUSA BANA project, where black South African children were recruited from randomly selected schools of the North West Province. These children were classified as normotensive and hypertensive after extensive blood pressure measurement. Anthropometric measurements were also taken and dietary intakes were assessed. Significant differences between normotensives and hypertensives were determined by means of independent t-tests. Stepwise regression analyses were done to determine the most significant determinants of hypertension in subject groups. The study presented in Chapter 6 made use of two cross-sectional studies: the THUSA and THUSA BANA studies. The THUSA subjects were apparently healthy black adults from randomly selected sites throughout the North West Province. These participants were subjected to extensive blood pressure measurement, demographic questionnaires, anthropometric measurements and dietary intake assessments. Blood samples were taken for plasma fibrinogen, serum lipids, gamma glutamyl-transferase and insulin analyses. Factor analysis was applied to detect structure in the relationships between variables.

All THUSA subjects and all parents of the THUSA BANA subjects gave informed consent and both studies were approved by the Ethics Committee of the Potchefstroom University for CHE. The reader is referred to the abstracts at the beginning of each separate paper in Chapters 3-6 for a description of the subjects, study design and analytical methods used in each paper.

Results and conclusions of the individual manuscripts:

- Results from the THUSA BANA study showed that dietary factors associated with blood pressure of hypertensive children are remarkably similar to those indicated as deficient intakes in primary school children in South Africa. These dietary factors included: total energy, biotin, folic acid, pantothenic acid, zinc, iron, magnesium and vitamin A intakes. These dietary factors were the strongest markers for systolic, diastolic and mean blood pressure in black hypertensive children. Dietary results coupled with cardiovascular parameters identified folic acid to be associated with lower blood pressure and biotin intakes to be associated with an increase in systolic and diastolic blood pressure, although intake of both nutrients were deficient.

- By following up on the first paper, the aim was focused mainly on the associations of dietary nutrients on cardiovascular parameters of the peripheral vasculature, such as arterial compliance and peripheral vascular resistance, but also on pulse pressure and stroke volume. It were especially macronutrient intakes, such as carbohydrates, protein, saturated fat, and monounsaturated fat, but also magnesium, iron and manganese, that were associated with higher pulse pressure and decreased arterial compliance. Dietary biotin intake showed somewhat contradictory results, namely being associated with increased stroke volume, but also with increased arterial compliance of hypertensive black children – being the only nutrient to be associated with increased arterial compliance.

- Results of the first two papers forced further investigations concerning the association and possible mechanism of action of biotin on the cardiovascular system. The following contradiction still exists: biotin intake is associated with increasing systolic blood pressure, diastolic blood pressure, and stroke volume, but also having the beneficial effect of an association with increased arterial compliance. Whether the insufficient biotin intakes of these children are the cause of this phenomenon is uncertain, but it could be possible that a suboptimal biotin status might accelerate or initiate the development of hypertension in a person who is genetically predisposed to be hypertensive.

- Factor analysis extracted five basic patterns of risk factors for hypertension: (1) *urban malnutritional phenomenon*, characterised by urbanisation and high dietary intake of saturated fat, animal protein and sodium; (2) *metabolic syndrome X*, characterised by old age, insulin resistance, obesity, dyslipidaemia, hypertension, smoking habit and hyperfibrinogenaemia; (3) *hypercholesterolaemia and obesity complex*, associated with increased aging, obesity, and a simple combination of total cholesterol and LDL; (4) *alcoholic hypertriglyceridaemia*, associated with age, gamma-glutamyltransferase, plasma triglycerides, smoking habit and central obesity; and (5) *central and peripheral cardiovascular effects* indicated that hypertension in children is positively associated with cardiac output and negatively with vascular peripheral resistance, while adults showed inverse results. Therefore a shift from a centrally acting mechanism (high cardiac output) to a more peripheral mechanism (high peripheral vascular resistance) in older subjects.

Combined discussion: The major contributions of this study lie in the results of biotin intake as marker for hypertension, but also in the results found with specific cardiovascular parameters, such as arterial compliance, stroke volume, peripheral vascular resistance and pulse pressure. Since a recent review of publications stated that there is a paucity of studies examining the effects of multiple nutrients and macronutrients regarding hypertension in children, manuscripts in this thesis have also contributed to this area to a great extent. According to the World Health Organisation evidence is lacking regarding the determinants of hypertension in large populations such as in sub-Saharan Africa. This is addressed by proposing five patterns of hypertension risks that occur in a black South African population.

The results of this study are therefore valuable in contributing to the current knowledge regarding hypertension in the black population and it could also give direction for future research in this population. The mechanism of the effect of vitamins on blood pressure and other cardiovascular parameters should be investigated.

Results from the four papers led to the formulation of additional recommendations regarding the intake of micronutrients, such as folic acid, biotin, vitamin A, vitamin E, ascorbic acid and macronutrients, such as carbohydrates and saturated fat. Although this study was not designed to determine nutrient needs, the recommendations could possibly prevent the development of hypertension. Recommendations also addressed the correction of a pattern of risk factors rather than a single factor, for example adjusting a person's whole diet, and not only restricting sodium chloride consumption. These recommendations can be used by policy makers and health departments of government, the food industry and health professionals for prevention of cardiovascular diseases.

Key words: hypertension, risk factors, nutrition, biotin, diet, black children, South Africa, factor analysis

Preface

For the purpose of this study it was decided to use the article format. This means that Chapters 3, 4, 5 and 6 are manuscripts in the form of articles as required by the regulations of the Potchefstroom University for CHE. All of these manuscripts were submitted for publication in peer reviewed journals, with Chapter 4 being conditionally accepted for publication. Although the appropriate and relevant literature backgrounds are discussed in each separate manuscript, Chapter 2 also gives a broad literature survey of relevant cardiovascular parameters and the effects of dietary factors on hypertension. In all of the manuscripts the promoter and co-promoters are named as co-authors, as well as persons who participated in the initial concept and design of the larger THUSA and THUSA BANA studies. However, the main and first author initiated and was responsible for most stages of each manuscript, including literature searches, involved in the collection of most of the cardiovascular data, statistical analysis, interpretation of results and writing the papers. The co-authors therefore acted in their role as promoter and co-promoters. All co-authors gave consent that the manuscripts could be used in this thesis.

The four manuscripts were submitted to the European Journal of Clinical Nutrition, Cardiovascular Journal of South Africa (conditionally accepted), South African Journal of Clinical Nutrition and the Journal of Hypertension, respectively. The relevant references are provided at the end of each chapter according to the authors instructions of the specific journal in which the papers were published or submitted for publication.

Authors' contributions

The contribution of each of the researchers involved in this study is given in the following table:

Name	*Role in the study*
Mrs. AE Schutte M.Sc. (Physiologist)	Responsible for literature searches, statistical analysis, processing of cardiovascular data (especially the THUSA BANA study), design and planning of manuscripts, interpretation of results and writing of all manuscripts. Together with Dr. van Rooyen and Dr. Huisman, were responsible for the collection of cardiovascular data.
Dr. JM van Rooyen D.Sc. (Physiologist)	Promoter. Supervised the writing of the manuscripts, responsible for collection of cardiovascular data, as well as initial planning and design of manuscripts.
Dr. HW Huisman Ph.D. (Physiologist)	Co-promoter. Supervised the writing of the manuscripts, responsible for collection of cardiovascular data, as well as initial planning and design of manuscripts.
Dr. HS Kruger Ph.D. (Dietitian, Nutritionist)	Co-promoter. Supervised the collection of dietary data, and of writing up the data. Also gave guidance in the interpretation of dietary data in the final manuscripts.
Prof. NT Malan D.Sc. (Physiologist)	Helped in the initial design and planning of the manuscripts and supervised the writing of two of the manuscripts.
Prof. JH de Ridder Ph.D. (Anthropometrist Class III)	Supervised the collection of anthropometric data and contributed in the writing of the methods of anthropometrical measurements in the manuscripts.

The following is a statement from the co-authors confirming their individual role in each study and giving their permission that the four articles may form part of this thesis.

I declare that I have approved the above-mentioned articles, that my role in the study, as indicated above, is representative of my actual contribution and that I hereby give my consent that it may be published as part of the Ph.D. thesis of Alta Schutte.

Dr. JM van Rooyen

Dr. HW Huisman

Dr. HS Kruger

Prof. NT Malan

Prof. JH de Ridder

Abbreviations

%BF	-	percentage body fat
AI	-	adequate intake
BMI	-	body mass index
BP	-	blood pressure
C	-	arterial compliance
CHD	-	coronary heart disease
CO	-	cardiac output
CVD	-	cardiovascular disease
DASH	-	Dietary Approaches to Stop Hypertension
DBP	-	diastolic blood pressure
DRI	-	dietary reference intakes
DRV	-	daily reference values
EAR	-	estimated average requirements
Finapres	-	Finger Arterial Pressure apparatus
HDL/HDLC	-	high density lipoprotein cholesterol
HT	-	hypertensive
LDL/LDLC	-	low density lipoprotein cholesterol
MAP	-	mean arterial pressure
MRFIT	-	Multiple Risk Factor Intervention Trial
n	-	number of subjects
NHBPEP	-	National High Blood Pressure Education Program
NT	-	normotensive
P	-	pressure
PAI-1	-	plasma plasminogen activator inhibitor-1
PP	-	pulse pressure
QFFQ	-	quantitative food frequency questionnaire
RDA	-	recommended dietary allowance
SA	-	South Africa
SBP	-	systolic blood pressure
SD	-	standard deviation
s-GGT	-	serum gamma-glutamyl transferase
SV	-	stroke volume
TC	-	total cholesterol
TG	-	triglycerides
THUSA BANA	-	Transition, Health and Urbanisation of South African Children (Bana=children, in Setswana)

THUSA	-	Transition, Health and Urbanisation in South Africa (Thusa=help, in Setswana)
TPR	-	total peripheral resistance
V	-	volume
WHO	-	World Health Organization
WHR	-	waist-to-hip ratio

1

Introduction

1 Background, motivation and outline of the study

This thesis reports on dietary factors as risk markers of hypertension in black South Africans. In this chapter hypertension as an important cause of mortality and morbidity in South Africa will be discussed. The known risks for hypertension will be highlighted and the possible role of dietary factors on hypertension will be summarised. The results of this study are reported as manuscripts in the form of publications. A short motivation for each manuscript will be given. The aims and objectives of the study will be stated and the structure of the thesis explained.

Essential hypertension in South Africa

Hypertension is a massive problem not only for economically developed countries, but also for developing countries (Hu & Tian, 2001:487), such as South Africa. An alarming and rapid development of cardiovascular disease is now flowing through developing countries (WHO, 1999). It is evident that death and disability from coronary heart disease and cerebrovascular disease are increasing so rapidly in the developing world that they will rank no. 1 and no. 4, respectively, as causes of the global burden of disease by the year 2020 (Murray & Lopez, 1996). There is also very little direct evidence about the determinants of common cardiovascular diseases in large populations such as those of sub-Saharan Africa (WHO, 1999). Since hypertension presents such a serious public health concern in black populations (Olatunbosun *et al.*, 2000:249) it seems necessary to conduct further research about the development of hypertension in these populations.

The close connection of hypertension with cardiovascular diseases such as coronary heart disease, cerebrovascular disease, congestive heart failure and renal disease make the prevention and control of hypertension the more important. Especially in developing countries which show a growing occurrence of hypertension and where pharmaceutical treatment is expensive and may not always be a reality. In 1991 it was estimated that cardiovascular diseases, excluding rehabilitation and follow-up visits, cost South Africa between 4.1 and 5 billion Rand (Pestana *et al.*, 1996). Efforts to reduce the prevalence of hypertension by implementing nonpharmacologic approaches, such as lifestyle modifications and specific nutritional approaches would be more feasible in different ethnic groups and should also have a reduced economic impact.

Although clinical hypertension occurs less frequently in children than adults (Joint National Committee, 1993; Sinaiko, 1982; Sinaiko, 1989), ample evidence now supports the concept that the roots of essential hypertension extend back to childhood. Of particular importance is the documentation that elevated blood pressure in childhood often correlates with hypertension in early adulthood, thereby supporting the need to track blood pressure in children (Lauer & Clarke, 1984; Simons-Morton *et al.*, 1997).

In South Africa age-corrected prevalence studies showed that in the adult population of Durban, hypertension (WHO criteria) was the highest in urban Zulus (25%) when compared to whites (17.2%) and Indian people (14.2%) (Seedat, 1999). In the North West Province 22.8% of apparently healthy subjects had systolic and 20.7% diastolic blood pressures above 140/90 mmHg (Van Rooyen *et al.*, 2000). Therefore, hypertension is not an uncommon phenomenon in the black South African population. A comprehensive cardiovascular disease programme is therefore necessary in Africa, although social, economic, and cultural factors are known to impair control of hypertension in developing countries (Seedat, 2000). Despite these factors, it is of the utmost importance that hypertension be addressed and that strategies to prevent the occurrence of hypertension be developed. One such strategy is the assessment and management of the risk factors for hypertension.

Known risk factors for hypertension

Comprehensive epidemiological studies were mainly responsible for the identification of the many risk factors of hypertension. Once the risk factors have been identified, intervention studies have to be undertaken to establish a cause-and-effect relationship (Hornstra *et al.*, 1998). It is well known that in most populations, the risks of cardiovascular disease rise steeply with increasing age (WHO, 1999). The risks for cardiovascular diseases are also greater in men than in women, although this difference declines with increasing age (WHO, 1999). Lifestyle habits, such as smoking (Doll *et al.*, 1994), consumption of alcohol (Wannamethee & Shaper, 1996) and malnutrition (Appel *et al.*, 1997) have been shown to increase the risk of hypertension. Blood levels of fibrinogen are positively associated with cardiovascular diseases (Woodward *et al.*, 1998). Increasing levels of both total and low-density lipoprotein cholesterol are associated with increases in the risks (Law *et al.*, 1994), whereas high-density lipoprotein appears to be associated with a reduction in the risk of cardiovascular disease (Gordon *et al.*, 1989). Obesity has been shown to cause an almost threefold greater risk of cardiovascular disease (Rimm *et al.*, 1995), whereas physical activity reduces the risk (Leon *et al.*, 1997).

Lower levels of socio-economic status have been observed to be associated with higher risks of cardiovascular disease (Davey-Smith *et al.*, 1996). Ethnicity is also powerfully related to the risk of most common cardiovascular diseases, where African Americans show a generally greater risk of cardiovascular diseases than Caucasians from the United States (WHO, 1999). Pre-existing diseases may also predispose an individual to become hypertensive. Diseases such as renal disease, diabetes or other cardiovascular diseases like congestive heart failure, cerebrovascular disease or a history of myocardial infarction or angina are known to be associated with hypertension (WHO, 1999). The greatest determining factor, however, remains the genetic make-up of the individual which explains 20-60% of the occurrence of hypertension (Williams *et al.*, 1991). Environmental factors, on the other hand, are known to contribute to the occurrence of hypertension in those who are genetically predisposed to be hypertensive, and more information concerning the exact role of environmental factors in the development of hypertension is needed.

Whether hypertension is of genetic or environmental origin, the control of environmental factors, such as dietary intake, has a place in the management and prevention of cardiovascular diseases (McCarron, 1998). It is, after all, only environmental factors that could be adjusted in order to prevent the occurrence of hypertension.

The possible role of diet on hypertension

Much epidemiologic, experimental, and clinical data confirm the relevance of nutritional factors in determining blood pressure in the population as a whole, and among subjects with hypertension (Resnick *et al.*, 2000). Diseases associated with significant morbidity, such as hypertension, are closely linked with dietary intake, as an aetiologic or exacerbating factor (Shikany & White, 2000). With nutritional epidemiology certain findings have been consistently reproduced in multiple studies and serve as the foundation for formulating dietary recommendations for the general population (Shikany & White, 2000). Although the mechanisms of most nutrients in blood pressure control are not clear (Das, 2001) the mechanisms of certain nutrients, such as the improving of endothelial dysfunction by vitamin E, are clear (Touyz *et al.*, 2000). Further research is therefore necessary to investigate the mechanisms of individual nutrients and the combined effects of nutrients.

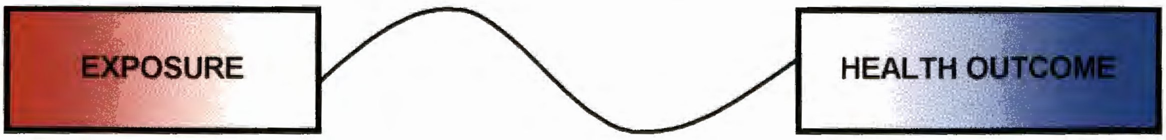
Although genetic make-up plays the most important role in the aetiology of hypertension, various studies have shown that certain dietary factors significantly lowers blood pressure, because nutritionally balanced meals could improve multiple risk factors for patients with cardiovascular disease (Appel *et al.*, 1997; McCarron *et al.*, 1997).

Sodium chloride limitation in food has historically been considered to be the critical change for reducing blood pressure. Changes in sodium intake do lower systolic and diastolic blood pressure of normotensive persons (Sacks *et al.*, 2001), as well as in those with hypertension, diabetes and older persons (Hermansen, 2000). But the role that sodium plays in population blood pressure has proven to be extremely controversial (McCarron, 2000; Kaplan, 2000). A recent meta-analysis indicates that adequate intake of minerals, such as potassium and calcium, rather than the restriction of sodium, should be the focus of dietary recommendations (Hermansen, 2000). Minerals such as calcium, potassium, magnesium, vitamins and antioxidants act together to determine the ultimate degree of blood pressure in a given individual. Thus, a diet rich in fruits, vegetables, and low-fat dairy foods with reduced saturated and total fats would contribute to a substantially lower blood pressure (Das, 2001; Conlin *et al.*, 2000).

The associations of all dietary factors on hypertension will therefore be the main focus point of this thesis, and not sodium chloride intake as such. A comprehensive summary (Table 2.2) of the effects of nutrients on cardiovascular parameters are presented in Chapter 2.

In order to promote healthy diets as an essential part of the prevention and management programme for hypertension in South Africa, it is important that the dietary recommendations are supported by valid and consistent data, targeted at the South African population's specific health issues. In this thesis results are reported in which the dietary risk markers for hypertension are identified in black children and the role of diet is placed in relation to other hypertension risk factors. These studies especially focussed on issues where a lack of data, inconsistent results and uncertainties in the literature still exist, concerning especially the black population in South Africa.

Since the design of the projects used in this thesis are epidemiological and cross-sectional (therefore observational), an association between a possible causative or protective dietary factor (*exposure*) and hypertension (*health outcome*) should not be considered as cause and effect. Interpretation of association is often problematic because causation cannot be directly inferred. Only in randomised trials and other experiments can an observed effect reasonably be ascribed to be causal, because of the controlled nature of the investigation.



Although a specific relationship exists between the exposure and health outcome the interpretation of the observed association needs great care. If an association between two variables are observed, there are several possible explanations (Altman, 1991). Excluding the possibility that it is a chance finding, it may be because: A influences (or 'causes') B; B influences A; or both A and B are influenced by one or more other variables. Although certain background knowledge or literature exists regarding associations and causal relationships of specific dietary factors and cardiovascular disease, inferring a causal link is not justified, but could give an indication based on relevant literature.

Another possibility is when a specific exposure is associated with a health outcome, whereas this health outcome could indirectly be an exposure to another health outcome. For example the intake of specific nutrients (*exposure*) is associated with obesity (*health outcome*), whereas obesity itself (*exposure*) could be associated with hypertension (*health outcome*).

Results from this thesis (which are given as associations) should therefore be regarded as potentially important indicators or markers of cardiovascular disease that warrant further study. By means of a clinical case-control or cohort study, which could investigate causal factors, could definite cause-and-effect relationships be established.

Motivation for each paper in this study

This thesis consists of four manuscripts submitted for publication, with one conditionally accepted. Since the relevant literature background is discussed in the papers, only a brief motivation for each paper will be provided here.

1.1 Dietary risk markers that contribute to the development of hypertension in black South African children (Chapter 3)

The prevalence of hypertension in adult black South Africans is higher than in any other racial group of South Africa (Seedat, 1999), the cost of hypertension treatment is out of reach for many and most hypertensive persons are apparently healthy and not aware of their condition (Van Rooyen *et al.*, 2000). It is therefore particularly important to study the association of diet and blood pressure in black, hypertensive children, because children with elevated blood pressure are at risk of developing hypertension in adulthood (Simons-Morton & Obarzanek, 1997).

A recent review of studies examining dietary nutrients and blood pressure in children of westernised countries concluded that there is a paucity of studies examining the effects of multiple nutrients and the influence of macronutrients on blood pressure in children (Simons-Morton & Obarzanek, 1997). The literature on the relationships between micronutrients and blood pressure is controversial, and the literature on macronutrients and blood pressure is sparse, particularly in children (Simons-Morton *et al.*, 1997). It is therefore decided to include multiple dietary factors of black South African children together, and evaluate their interactions with systolic and diastolic blood pressure, in order to detect specific associations between dietary factors and blood pressure. Thereby working with a population group of which very little information regarding dietary effects on blood pressure is available.

The THUSA BANA study (Setswana word for *help the children*; THUSA is the acronym for Transition, Health and Urbanisation in South Africa) is one of the first studies focusing on the rate of hypertension and dietary intake of black children in South Africa. Malnutrition and undernutrition have been observed in these parts (Vorster *et al.*, 1997) and the possible effects of undernutrition on blood pressure will be evaluated in this paper. These results would be essential in order to compare the prevalence of hypertension to other racial groups in South Africa and to children in other parts of the world. Specific dietary factors contributing to the occurrence of hypertension could be identified in the results. Since pharmacological or medical treatment is out of reach for many, lifestyle modifications, such as a healthy dietary approach would be more feasible in the prevention of hypertension. These results could then be used by health professionals in dietary recommendations to the public, and especially to the children in order to prevent hypertension in adulthood.

1.2 Dietary markers of hypertension associated with pulse pressure and arterial compliance (Chapter 4)

Although blood pressure is the most frequently measured parameter of the peripheral vasculature, other properties such as compliance, may be a more subtle index of vascular dysfunction associated with aging (Van Bortel & Spek, 1998) and diseases such as hypertension (Resnick *et al.*, 2000) where the endothelium may be damaged. Pulse pressure is also a more accurate predictor of death than systolic or diastolic blood pressure and various studies have shown that pulse pressure is a better predictor of cardiovascular disease than any other blood pressure parameter (Franklin *et al.*, 1999; Dart & Kingwell, 2001).

Although it has been shown that pulse pressure is a powerful predictor of cardiovascular morbidity and mortality, the association of pulse pressure with diet has not been well studied. The association of pulse pressure with modifiable dietary factors suggests that dietary interventions may decrease pulse pressure and its health risks (Hajjar & Grim, 2000). A targeted approach to lower pulse pressure will emerge from an increase in arterial compliance (Dart & Kingwell, 2001). Increases in arterial compliance can be achieved by dietary manipulations (Safar *et al.*, 1988).

With a quarter of South Africa's children stunted, coupled to high prevalences of micronutrient deficiencies, as well as very high prevalences of obesity among adults, there could be a double burden of both under and overnutrition (Vorster *et al.*, 1997). Strategies to address undernutrition should not lead directly to overnutrition in later life. Ample evidence also supports the concept that the roots of essential hypertension extend back to childhood (Simons-Morton & Obarzanek, 1997). The effects of malnutrition on the health of South African children might therefore have unhealthy consequences in adult life. Research on the prevention of hypertension by means of correct dietary approaches is necessary. It was therefore decided to extend the results of Chapter 1 by examining the relationship of dietary intake with pulse pressure, arterial compliance, total peripheral vascular resistance, and stroke volume, in black South African children who participated in the THUSA BANA study.

Results will not only provide information concerning the rate of hypertension in black children or deficiencies in their diet, but will also give an indication what the effects of their diet are on specific cardiovascular parameters, such as pulse pressure, arterial compliance, stroke volume and peripheral vascular resistance. By interpreting these results recommendations could be made to address their deficiencies by a fortification programme in order to prevent cardiovascular disease in later life.

1.3 The potential role of biotin as dietary risk marker for hypertension in black children (Chapter 5)

Despite increasing interest in biotin as nutritive, considerable basic information concerning biotin bioavailability and nutritional status remains unknown (Said, 1999). The speculation that the human biotin requirement can always be met by the contribution of biotin produced by the gut microflora (Schanler, 1997), is in contradiction with the report of an infant who developed biotin deficiency while consuming a biotin-free, elemental formula (Higuchi *et al.*, 1996). However, whether biotin deficiencies could occur remains controversial (Zempleni & Mock, 1999). It is therefore clear from the literature that further research is necessary to confirm whether biotin deficiencies could occur and whether this could lead to cardiovascular disease.

According to Ho and Cordain (2000) there may be a substantial link between cereal grain intakes and cardiovascular disease stemming from both biotin and essential fatty acid insufficiencies, because it has been shown that cereal grains have a low biotin bioavailability. Since black South African children are known to have a high prevalence of multiple micronutrient deficiencies (Vorster *et al.*, 1997), this population group might possibly be predisposed to develop biotin deficiency as well. It was therefore decided to examine the biotin intakes of normotensive and hypertensive South African children and to examine the associations of biotin intake with a range of cardiovascular parameters, namely systolic and diastolic blood pressure, stroke volume, arterial compliance, pulse pressure and total peripheral resistance.

The urgent need for further research concerning the potential role of biotin deficiency as cardiovascular risk factor serves as motivation for this paper. These results might contribute to basic information concerning biotin and biotin deficiencies. If biotin intake is shown to be associated with cardiovascular health, it might be used by health professionals in dietary recommendations for this population group.

1.4 Factor analysis of possible risks for hypertension in a black population (Chapter 6)

Age (WHO, 1999), gender (WHO, 1995), urbanisation (Van Rooyen *et al.*, 2000), obesity (Stampfer *et al.*, 1991), smoking (Doll *et al.*, 1994), alcohol consumption (Wannamethee & Shaper, 1996) and certain dietary factors (Stamler *et al.*, 1996a; Stamler *et al.*, 1996b; He & Whelton, Kaplan, 2000) have all been shown to strongly influence the occurrence of essential hypertension. These factors only demonstrate that the genesis of hypertension is complex and cannot readily be simplified. In any given patient one factor may be more important than others, but often hypertension is multifactorial (Opie, 1998).

To date only a small number of studies investigated the pattern of associations within a set of hypertension risk factors or markers. A similar idea came from the work of Maruši (2000) who examined the interrelationship of standard coronary heart disease risk factors and obtained a four-factor solution that involved dyslipidaemic and haemostatic complex, pure hypercholesterolaemia, metabolic syndrome X and family and medical histories.

By performing the exploratory factor analysis it is possible to determine whether given risks tend to form patterns. This analysis could thus be successfully used to identify a small number of underlying hypertension risk patterns which explain most of the variance observed in a much larger number of risks (Joliffe & Morgan, 1992).

Although other attempts have been made (Wright *et al.*, 1992; Maruši , 2000) to determine structure in coronary heart disease risk factors, no previous attempts have been made to detect underlying structure and patterns of hypertension risk factors by means of factor analysis. It was therefore decided to examine the associations of a large group of hypertension risks in order to detect underlying structure in the specific black South African population.

Since many of the risks for coronary heart disease overlap with hypertension risks, it is expected that some hypertension patterns will also overlap with those of coronary risks (Maruši , 2000). Results of this paper will, however, focus only on a black South African population, and not a mainly Caucasian population as used by Maruši (2000), since there is very little direct evidence about the determinants of common cardiovascular diseases in the black populations of South Africa (WHO, 1999).

Results of this paper will propose existing hypertension risk patterns of the black population in South Africa. For a successful therapeutic intervention study it will be necessary to focus on and change a whole pattern, rather than individual risk factor correction to improve the prevention of hypertension. By correcting a pattern of hypertension risks, health professionals would be able to implement lifestyle modification programmes successfully. Results will also assist in future research studies concerning risk factors of the black populations of sub-Saharan Africa.

2 Aims and objectives

The aims and objectives of the four manuscripts included in this thesis are:

2.1 **Main aim:** To determine which dietary factors could be identified as risk markers that might be associated with the prevalence of hypertension in randomly selected male and female black South African children who participated in the THUSA BANA project.

Objectives:

a) To determine the blood pressure values, body mass index, waist-to-hip ratio, dietary intake and age of the subjects;

b) To determine deficient dietary intakes of the subjects;

c) To classify subjects as normotensive and hypertensive according to the standards of the National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents (1996);

d) To examine the relationships between dietary intake and cardio-vascular parameters of normotensive and hypertensive subjects of both sexes.

2.2 **Main aim:** To determine which dietary factors contribute to the impairment of arterial compliance, stroke volume, total peripheral resistance and pulse pressure, and could thereby be identified as risk markers in the development of hypertension in randomly selected male and female black South African children who participated in the THUSA BANA study.

Objectives:

a) To determine arterial compliance, pulse pressure, total peripheral resistance, stroke volume, body mass index, waist-to-hip ratio, dietary intake and age of the subjects, classified as normotensive and hypertensive;

b) To extend the results of the first manuscript by examining the relationships between dietary intake and arterial compliance, pulse pressure, total peripheral resistance and stroke volume of normotensive and hypertensive subjects of both sexes.

2.3 **Main aim:** To determine whether biotin intake might be associated with the prevalence of hypertension in randomly selected male and female black South African children who participated in the THUSA BANA study.

Objectives:

a) To extend the results of the first two manuscripts by focusing on deficient biotin intakes;

b) To examine the relationships between biotin intake and all measured cardiovascular parameters (systolic and diastolic blood pressure, arterial compliance, pulse pressure, total peripheral resistance, stroke volume) of normotensive and hypertensive children of both sexes.

2.4 **Main aim:** To examine the interrelationships and patterns of main hypertension risk factors: age, urbanisation, smoking, alcohol consumption, lipid profile, obesity, cardiovascular variables, certain dietary factors, plasma fibrinogen and fasting insulin of randomly selected male and female subjects of a black South African population by combining the results of the THUSA and THUSA BANA study.

Objectives:

a) To determine the values of the following parameters and to examine their associations on the rate of hypertension by using the statistical method, exploratory factor analysis:

- age,
- cardiovascular parameters: systolic blood pressure, diastolic blood pressure, peripheral resistance, arterial compliance, pulse pressure, cardiac output;
- anthropometric variables: body mass index, waist-to-hip ratio, fat percentage;
- level of urbanisation as presented by strata;
- smoking habit;
- serum gamma-glutamyl transferase (indication of alcohol consumption);
- serum lipoproteins: total cholesterol, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL) and triglycerides;
- dietary intake of animal protein, plant protein, saturated fat, dietary fibre, dietary sodium chloride, dietary vitamin A, vitamin B_6 and vitamin E;
- plasma fibrinogen;
- fasting serum insulin;

b) To classify subjects as normotensive and hypertensive according to the standards of the National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents (1996) and according to WHO criteria of 140/90 mmHg for adults (WHO, 1999);

c) To identify underlying structural patterns of hypertension risk factors.

Definitions of risk marker, risk factor and predictor

An association between a nutrient and disease is not the same as cause and effect relationship (Shikany & White, 2000). That is why nutrients associated with hypertension will be referred to as *risk markers* for hypertension.

A *predictor* or *risk factor* for hypertension is a factor proved by epidemiological research to cause hypertension or to predict that the subjects will suffer the disease in later life.

3 Structure of this thesis

This thesis consists of three manuscripts submitted for publication and one conditionally accepted for publication. Following this introductory chapter, Chapter 2 gives an overview of the influence of dietary factors on hypertension. This chapter provides the background necessary for the interpretation of the data from the papers in this thesis. At the beginning of each of the Chapters 3, 4, 5 and 6, which contain the four manuscripts, a short *Instruction to the Authors* section concerning the requirements of the specific journal will be presented. Format of the manuscripts have, however, been adapted to the style of this thesis. Chapter 3 addresses the dietary risk markers of hypertension in black children. The dietary markers of hypertension that are associated with pulse pressure and arterial compliance are discussed in Chapter 4. Chapter 5 examines the potential role of biotin as dietary risk marker for hypertension in black children. A factor analysis of possible risks for hypertension in a black South African population are presented in Chapter 6. Chapters 3, 4, 5 and 6 were submitted for publication in peer reviewed journals, with Chapter 4 conditionally accepted. In Chapter 7 a general discussion and summary of all the results are provided, recommendations are made and conclusions are drawn. Although the appropriate and relevant literature backgrounds are discussed in each separate manuscript, Chapter 2 also gives a broad literature survey of relevant cardiovascular parameters and the effects of dietary factors on hypertension. The relevant references are provided at the end of each chapter according to the authors instructions of the specific journal in which the papers were published or submitted for publication. The relevant references used in the unpublished chapters 1, 2 and 7 are provided according to the mandatory style stipulated by the Potchefstroom University for Christian Higher Education, Potchefstroom, South Africa. The technical style used in chapters 1, 2 and 7 are therefore uniform, but differs in the other chapters according to the authors instructions of the specific journals.

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2

HYPERTENSION:
The influence of dietary factors

1 Introduction

The relationship between diet and cardiovascular disease, such as hypertension, has been the focus of substantial investigative effort for several decades. Despite this there are still great numbers of people over the world suffering from hypertension or hypertension-related disease. South Africa is no exception, where 25% of urban Zulus in the Natal province are classified as hypertensive (Seedat, 1999). Similar results have been found in the North West province where 22.8% of apparently healthy predominantly Setswana-speaking subjects had systolic, and 20.7% had diastolic blood pressures above 140/90 mmHg (Van Rooyen *et al.*, 2000).

The physiological basis underlying the effects of diet on blood pressure remains uncertain (Resnick *et al.*, 2000), although different effects of specific nutrients have been shown to have substantial influences on blood pressure. Although several authors have reviewed the effect of specific dietary factors on blood pressure, discrepancies occur. The role that sodium plays in population blood pressure, for example, has proven to be extremely controversial (McCarron, 2000; Kaplan, 2000).

There is a lack of reviews that provide a comprehensive overview of the contribution of most nutrients to lower cardiovascular risk or the role of nutrients in the aetiology of hypertension. Identifying dietary factors associated with blood pressure in children and adolescents would help guide recommendations for prevention of elevated blood pressure in later years (Simons-Morton & Obarzanek, 1997). This section will present an overview of the literature to indicate the effects that specific nutrients in isolation exert on cardiovascular parameters. Several studies have demonstrated that manipulations of isolated nutrients may influence some people with selected conditions (McCarron & Reusser, 2000), and from these studies it is stressed that nutrients are not consumed in isolation. Their physiologic interactions and combined effects on cardiovascular parameters are the subjects of much of the current research in the area of diet and hypertension (Reusser & McCarron, 1994).

2 Hypertension and cardiovascular parameters associated with it

The validated Finapres (finger-arterial pressure) apparatus will be used to record blood pressure continuously. The vascular unloading technique of Penáz together with the Physiocal criteria of Wesseling provide reliable, non-invasive and continuous estimates of blood pressure (McAuley *et al.*, 1997; Silke & McCauley, 1998). This technique is thus an alternative to the invasive intra-arterial measurements in many cases, without the risks and ethical questions inherent to invasive measurements. Since the pressure waveform is available continuously, computations such as pulse contour and Modelflow cardiac output provide further information on the dynamics of the cardiovascular system on a beat-to beat basis, similar to intra-arterial measurements (Langewouters *et al.*, 1998; Imholz *et al.*, 1998; Harms *et al.*, 1999; Wesseling *et al.*, 1993).

The manuscripts and articles of this thesis will mainly focus on the following cardiovascular parameters: *systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), arterial compliance (C), total peripheral resistance (TPR)* and *cardiac output (CO)*. These parameters will be discussed as follows:

2.1 Systolic blood pressure (SBP)

Systolic pressure represent the highest points of the blood pressure oscillation around a given mean value (Safar & London, 1989).

Persuasive evidence suggests that cardiovascular risk is more closely associated with systolic than diastolic pressure (He & Whelton, 1999a). A person can be diagnosed with isolated systolic hypertension when his systolic blood pressure exceeds 140 mmHg, but the diastolic pressure is still lower than 90 mmHg (WHO, 1999). Recent trials in isolated systolic hypertension have shown with remarkable consistency the benefits of lowering systolic blood pressure (Swales, 2000).

Numerous trials have reported the beneficial and detrimental effects of certain dietary factors on systolic blood pressure (Langley & Jackson, 1994; Liu & Medeiros, 1986; Preuss *et al.*, 1998; Gu *et al.*, 2001; Perry & Erlanger, 1982; Pfeifer, 2001; Saltzman *et al.*, 2001). It is clear from these literature that dietary factors could play a most important role to influence blood pressure. But further information in this field is still an urgent need since controversies regarding the effects of specific dietary factors such as sodium occur amongst researchers (Kaplan, 2000; McCarron, 2000). The effects of a combination of dietary factors on blood pressure has recently been recognised as most important and specific attention to this matter is urgently needed (Falkner *et al.*, 2000).

2.2 Diastolic blood pressure (DBP)

Diastolic pressure represent the lowest points of the blood pressure oscillation around a given mean value (Safar & London, 1989).

Many controversies exist on the important contribution of diastolic pressure against systolic pressure to hypertension, but according to Swales (2000) have physicians emphasised diastolic pressure too much in the past and should they rather focus on systolic pressure. But many general practitioners in the United Kingdom are still sceptical about the significance of systolic blood pressure and showed that their focus was still on diastolic blood pressure (Swales, 1999). Whichever parameter of the two is the most substantial, it is clear that diastolic pressure pulls its weight when referring to cardiovascular health.

A person can be diagnosed with isolated diastolic hypertension when his/her diastolic pressure exceeds 90 mmHg, but the systolic pressure remains below 140 mmHg (WHO, 1999)

Certain studies have already confirmed the belief that specific dietary factors could exert an influence on diastolic pressure (Block *et al.*, 2001; Goldhamer *et al.*, 2001; Hermansen, 2000; Falkner *et al.*, 2000).

The lowering of diastolic pressure in hypertensives remains an important priority. Data from different review articles and randomised tests recommend that a lowering of 2 mmHg in diastolic pressure will lead to a 17% lowering in the prevalence of hypertension, as well as a 6% decrease in the risk for cardiovascular heart diseases and a 15% decrease in risk for stroke and angina (Cook *et al.*, 1995).

2.3 Classification of hypertension

According to the World Health Organisation (1999) hypertension in adults over the age of 18 years are defined as a SBP of 140 mmHg or greater and/or a DBP of 90 mmHg or greater in subjects who are not taking antihypertensive medication. Table 1 provides a classification of blood pressure levels in adults.

Table 2.1 Definitions and classification of high blood pressure (mmHg) levels in adults
(WHO, 1999)

Category	Systolic	Diastolic
Optimal	< 120	< 80
Normal	< 130	< 85
High-normal	130-139	85-89
Grade 1 Hypertension (mild)	140-159	90-99
Subgroup: borderline	140-149	90-94
Grade 2 Hypertension (moderate)	160-179	100-109
Grade 3 Hypertension (severe)	≥ 180	≥ 110
Isolated systolic hypertension	≥ 140	< 90
Subgroup: borderline	140-149	< 90

When a patient's systolic and diastolic blood pressures fall into different categories, the higher category should apply.

Hypertension in children is diagnosed by using the normative blood pressure tables for children and adolescents provided in the Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents (1996). These normative blood pressure tables include height percentiles, age and gender. *Normal* blood pressure is defined as systolic and diastolic blood pressure less than the 90th percentile for age and sex. *High-normal* blood pressure is defined as average systolic or diastolic blood pressure greater than or equal to the 90th percentile but less than the 95th percentile. *Hypertension* is defined as average systolic or diastolic blood pressure greater than or equal to the 95th percentile for age and sex.

2.4 Pulse pressure (PP)

Pulse pressure – the dynamic component of the blood pressure – is mainly determined by stroke volume, the timing of reflected pulse waves, and the compliance of arterial capacitance vessels, which are predominantly large arteries (Safar, 1989).

The three most important factors altering the pulse pressure are (1) the pattern of ventricular ejection, (2) the changes in arterial distensibility, and (3) the timing of reflection waves. The latter two factors pointing to the contribution of large arteries in the mechanisms of raised blood pressure (Safar & London, 1989). Specifically, the pulse pressure that is produced by a ventricular ejection would be greater if the volume of blood ejected is increased, if the speed at which it is ejected is increased, or if the arteries are less compliant. Any condition that influences one of these factors, will also influence the pulse pressure. When a person is very old or when the arteries are hardened during artherosclerosis, will the pulse pressure increase to a level twice that of the normal (Dart & Kingwell, 2001).

The importance of pulse pressure as a risk factor for cardiovascular disease is increasingly recognised by researchers. Especially in persons older than 59 years of age pulse pressure is a more accurate predictor for mortality than systolic or diastolic blood pressure. Various studies have shown pulse pressure to be a better predictor of cardiovascular disease than other blood pressure parameters (Dart & Kingwell, 2001; Franklin *et al.*, 1999).

Although it has been shown that pulse pressure is a powerful predictor of cardiovascular morbidity and mortality, the association of pulse pressure with diet has not been well studied. The association of pulse pressure with modifiable dietary factors suggests that dietary interventions may decrease pulse pressure and its health risks (Hajjar & Grim, 2000). A targeted approach to lower pulse pressure will come from an increase in arterial compliance (Dart & Kingwell, 2001). Increases in arterial compliance can be achieved by dietary manipulations, for example reduced salt intake (Safar *et al.*, 1988).

2.5 Arterial compliance (C)

Compliance is simply a measure of the capacity of a volume-containing structure, in this case the arterial system, to accommodate further increases in volume (Δ volume / Δ pressure) (Dart & Kingwell, 2001; Guyton & Hall, 2000). A close connection exists between arterial compliance and pulse pressure. Compliance can be estimated by the simple approach of: C = stroke volume / pulse pressure (Dart & Kingwell, 2001).

The term *compliance* is better understood when compared to the term *distensibility*. Compliance and distensibility are quite different. A highly distensible vessel that has a slight volume may have far less compliance than a much less distensible vessel that has a large volume because compliance is equal to distensibility *times volume* (Guyton & Hall, 2000). Or compliance is related to distensibility and arterial diameter (Van Bortel & Spek, 1998).

Compliance is a more subtle index of vascular dysfunction associated with aging (Van Bortel & Spek, 1998), and diseases such as coronary heart disease, diabetes mellitus, congestive heart failure or hypertension (Resnick *et al.*, 2000). Research have shown, for example, that significant differences exist between vascular compliance of untreated hypertensive and normotensive subjects, where values for overall vascular compliance, calculated as stroke volume/pulse pressure (SV/PP), were being suppressed in the unmedicated hypertensive subjects (Resnick *et al.*, 2000).

Although blood pressure is the most frequently measured property of the peripheral vasculature, other properties such as *arterial compliance*, reflecting the change in vascular dimensions relative to the pulse pressure, may be a more subtle index of vascular dysfunction associated with aging and diseases such as hypertension (Resnick *et al.*, 2000).

Changes in arterial compliance can be achieved by means of dietary manipulations. Although this subject has not been widely studied, a few studies have reported increases in arterial compliance, for example by a reduced salt intake (Safar *et al.*, 1988). Nestel and co-workers (2001) reported a decrease in systemic arterial compliance of 25 to 27% after a fat meal, and it appears as if remnant lipids and plasma total triglyceride contributed to the fall in arterial compliance. Dietary n-3 fatty acids in flax oil, on the other hand, confer a novel approach to improve arterial compliance (Nestel *et al.*, 1997).

2.6 Total peripheral resistance (TPR) and Cardiac output (CO)

Resistance is the impediment to blood flow in a vessel, but it cannot be measured by any direct means. Instead, resistance must be calculated from measurements of blood flow and pressure difference between two points in the vessel. If the pressure difference between two points is 1 mmHg and the flow is 1 ml/sec, the resistance is said to be 1 peripheral resistance unit, usually abbreviated PRU. Another unit used to describe total peripheral resistance is dyne x s x cm^{-5}/m^2. TPR can be indexed to a patient's body size by dividing by Body Surface Area (BSA) to yield Systemic Vascular Resistance Index (SVRI) (Guyton & Hall, 2000).

The resistance of the entire systemic circulation, called the *total peripheral resistance*, is about 1 PRU. In conditions in which all the blood vessels throughout the body become strongly constricted, the total peripheral resistance occasionally rises to as high as 4 PRU. Conversely, when the vessels become greatly dilated, the resistance can fall to as little as 0.2 PRU (Guyton & Hall, 2000). The pathophysiological basis of age-related changes in blood pressures include arterial and arteriolar stiffening and increased peripheral resistance (Stott & Bowman, 2000).

Cardiac output is the quantity of blood pumped into the aorta each minute by the heart. This is also the quantity of blood that flows through the circulation and is responsible for transporting substances to and from the tissues. Therefore, cardiac output is perhaps the most important factor to be considered in relation to the circulation (Guyton & Hall, 2000). Under most normal conditions, the long-term cardiac output level varies reciprocally with the changes in total peripheral resistance (Guyton & Hall, 2000).

At any given level of cardiac output and ventricular ejection, blood pressure is influenced by two principal factors, namely (a) the level of vascular resistance which determines mean arterial pressure and hence diastolic pressure; and (b) the level or arterial distensibility and arterial compliance which determines pulse pressure and hence systolic blood pressure (Middlemost, 1999).

A close relationship exists between vascular resistance and hypertension. A study reported that men at risk for development of hypertension had significantly higher blood pressures accompanied by higher vascular resistances at rest and during mental stress when compared to a low risk group (Marrero *et al.*, 1997). There are opposing views concerning the transition from normotension to hypertension. Older theories suggest that the change commences with an elevated cardiac output (Lund-Johansen, 1967; Frohlich *et al.*, 1969; Sannerstedt, 1969). The competing theory is that the initial phase is characterized by increased peripheral resistance associated with trophic factors in the blood vessel wall. Marrero and co-workers (1997), also reported this in an aforementioned study.

In persons with hypertension there are morphological changes of the arterial wall in response to increased arterial pressure. These changes, as well as active contraction of the arterial wall, are mediated by the endothelial cell layer. Even in treated hypertensive patients the conduit function and the viscoelastic properties of the arterial function remain decreased (Heintz, 1994). Endothelium dysfunction is therefore associated with chronic hypertension (Kaya & Utkan, 1994). This relationship of endothelium dysfunction and hypertension are indirectly mediated by an increase in peripheral resistance, which is closely associated with essential hypertension.

Certain dietary factors have been shown to exert an effect on vascular resistance. Sodium chloride causes an increase in vascular resistance in hypertensive Dahl rats, with the renal vasculature undergoing the largest resistance increase (Boegehold *et al.*, 1991). Dietary calcium, however, decreases blood pressure without decreasing renal vascular resistance (Passmore *et al.*, 1997). The close relationship of cardiac output and peripheral resistance implicates that a nutritional factor, or any other factor that influences one of these parameters also influences the other parameter indirectly.

It is clear that a number of factors affect the resistance state of the entire systemic circulation. Whether it is age, dietary factors, or disease, adequate research remains the key factor to present effective treatment.

3 The effects of dietary factors on hypertension

There are abundant data to relate dietary factors to hypertension, the importance of which is the potential for prevention and intervention. The relation between diet and blood pressure may be viewed from an aetiologic, a therapeutic and a public health perspective

(Grobbee *et al.*, 1997). Manuscripts in this thesis will focus primarily on the aetiology of hypertension in black South African adults and children.

Malnutrition in adult life – often overnutrition regarding macronutrients and undernutrition regarding micronutrients (Shetty, 1997) – is associated with increased morbidity and mortality, mainly from diseases such as obesity, coronary heart disease, stroke, some cancers and hypertension. Although these diseases prevail in adult life, the origin usually stems from childhood. Factors related to blood pressure in children may be particularly important in this regard because blood pressure levels have been seen to track from childhood to adulthood (Simons-Morton *et al.*, 1997).

Repeated surveys in developing countries have shown an association between a dramatic increase in mean body mass index of the population and acculturation indices (Byers & Marshall, 1995). In these countries the rapid changes in dietary intake have been indicative of an increase in *per capita* availability of food. Countries like China have not only altered overall dietary adequacy but have also seen a marked change in dietary composition, with increasing proportions of the population consuming more than 30% of energy from fat. There has also been a concurrent marked change in physical activity levels and patterns (Shetty, 1997).

The exact consequences of one's diet on cardiovascular, and overall health remains to be determined.

3.1 Macronutrients

Three types of macronutrients can be differentiated:

3.1.1 Carbohydrates

Carbohydrates can be categorised as (a) monosaccharides, (b) di- and oligosaccharides, and (c) polysaccharides – starch and fibres (Ettinger, 2000). A growing body of evidence suggests that dietary carbohydrate, especially nonabsorbable oligosaccharides, and fibre exert significant impact on human physiology. It is now recognized that specific carbohydrates not only modulate whole body energy dynamics but also affect disease processes (Ettinger, 2000). The limited investigative attention to carbohydrate and blood pressure relationships is reflected in the fact that except for dietary fibre and blood pressure, this matter went unmentioned in the 1989 monograph *Diet and Health: Implications for Reducing Chronic Disease*.

Researchers agree that unusually high doses of refined sugar can alter blood lipids to promote heart disease. This effect is most dramatic in "carbohydrate-sensitive" individuals – people who respond to sucrose with abnormally high insulin secretion, which promotes the synthesis of excess triglycerides. Among dietary risk factors, several such as total fats, cholesterol and obesity have much stronger associations with cardiovascular disease than do sugar intakes (Whitney *et al.*, 1998).

The research paucity, concerning the effect of carbohydrates on blood pressure, has prevailed despite short-term studies in humans showing that ingestion of simple carbohydrates lead to salt and water retention and transient blood pressure increases. The MRFIT (Multiple Risk Factor Intervention Trial) findings report an independent positive relationship of dietary starch to blood pressure (Stamler *et al.*, 1996). However, in the Dietary and Nutritional Survey of British Adults, no relationship was found between starch and BP (Elliot *et al.*, 1992). The meanings of these controversial findings remain to be clarified by further research.

3.1.2 Proteins

Protein is indispensable to life and growth of individuals. Several essential bodily functions are performed by proteins, such as building materials, enzymes, hormones, acid-base regulators, fluid-electrolyte regulators, transporters and antibodies (Whitney *et al.*, 1998). In addition to these important functions, dietary protein also exerts an effect on blood pressure. In Japan has investigators had assessments of the protein and blood pressure relationship and found an inverse relation between the amount of protein in the diet, particularly animal protein and blood pressure (Kimura, 1977).

Larger studies such as the INTERSALT study (Stamler *et al.*, 1996) and the Dietary and Nutritional Survey of British Adults (Elliot *et al.*, 1992) found, in concordance with the first Japanese studies, a significantly inverse relationship of dietary protein to systolic and diastolic blood pressure. A few short-term randomised and controlled trials showed that consumption of vegetarian diets led to blood pressure falls in both normotensive and hypertensive adults. However, no blood pressure fall was reported in other trials with specific nutrient change from animal to vegetable protein at a fixed level of total protein. Furthermore, no blood pressure rise was reported with an increased intake of vegetable, dairy or meat protein (Sacks *et al.*, 1974; Sacks & Kass, 1988; Dwyer, 1988; Burke & Beilin, 1994).

Since substantial evidence exists that hypertension is common in the black population of Africa (Seedat, 2000), it is necessary to mention that a study of African Americans reported significant positive correlations of protein intake with both systolic and diastolic blood pressure (Melby *et al.*, 1994).

Recent research suggests that the amino acid *homocysteine* may be an independent risk factor for heart disease (Boushey *et al.*, 1995). Men with elevated homocysteine were three times as likely to have heart attacks. Researchers do not yet know what role homocysteine plays in heart disease, nor do they understand what raises homocysteine in the blood. Elevated homocysteine is associated with suboptimal concentrations of B-complex vitamins and can usually be corrected with vitamin B_{12}, vitamin B_6 and folate supplements. Whether such treatments will reduce the risk of heart attacks remain unknown (Whitney *et al.*, 1998; Chait *et al.*, 1999).

3.1.3 Lipids

Fats and lipids constitute approximately 34% of the energy in the human diet (Ettinger, 2000). Of all the nutrients, fat is most often linked with chronic diseases. A high-fat diet raises the risks of heart disease, some types of cancer, and obesity (Whitney *et al.*, 1998).

Saturated fats are most often implicated for raising LDL cholesterol, although not all saturated fats have the same cholesterol-raising effect (Mensink, 1993). Polyunsaturated fatty acids lower LDL cholesterol, and monounsaturated fatty acids have little or no independent effect (Anderson *et al.*, 1995; Carroll, 1991). Dietary cholesterol's influence on blood cholesterol is relatively minor. Some research suggests that polyunsaturated fats tend to lower both HDL and LDL, whereas monounsaturated fats raise HDL, thus improving the blood lipid profile. Other research indicates that both polyunsaturated and monounsaturated fatty acids lower both LDL and HDL (Nydahl *et al.*, 1994).

Among several ecological studies on relations of dietary lipids to blood pressure, most reported no significant association between average total fat intake and average blood pressure, but several reported a significant positive association between average intake of saturated fatty acids and average blood pressure (Sacks, 1989). Within-population cross-sectional studies on dietary lipid intake and blood pressure of individuals, 6 reported no significant relations, and 5 had either significant positive associations (saturated fatty acids and blood pressure) and/or inverse associations (polyunsaturated fatty acids and blood pressure) (Sacks, 1989).

Blood cholesterol is often used to predict the likelihood of a person's suffering a heart attack or stroke; the higher the cholesterol, the earlier and more likely the tragedy (Whitney *et al.*, 1998). The Western Electric Study, which considered dietary lipids one at a time, reported a significant positive independent relation of dietary cholesterol to systolic blood pressure change during an 8-year period (Stamler *et al.*, 1994).

Because of the increasing tendency towards urbanisation of prudent traditional diets, South Africans have higher fat and lower fibre intakes, thereby increasing the risk of chronic diseases of lifestyle (Vorster *et al.*, 1997).

3.2 Vitamins

The term *vitamin* has come to describe a group of essential micronutrients that generally satisfy the following criteria (Combs, 2000):

- An organic *compound* distinct from fats, carbohydrates, and proteins;
- A *natural component of foods* where it is usually present in minute amounts;
- *Not synthesized by the host* in amounts adequate to meet normal physiologic needs;
- Essential, also usually in minute amounts, for *normal physiologic function* (i.e., maintenance, growth, development, reproduction);
- By its absence or under utilization, causes a *specific deficiency syndrome*.

3.2.1 The Water-Soluble Vitamins: Vitamins B and C

This group of vitamins include the following:

- B vitamins
  - Thiamin (Vitamin B_1)
  - Riboflavin (Vitamin B_2)
  - Niacin (Nicotinic acid)
  - Biotin
  - Pantothenic acid
  - Vitamin B_6 (Pyridoxine)
  - Folate (Folic acid)
  - Vitamin B_{12}
- Vitamin C (Ascorbic acid)

The storage of most water-soluble vitamins is relatively slight. This applies especially to most vitamin B compounds, because when a person's diet is deficient in vitamin B compounds, clinical symptoms of the deficiency can sometimes be recognized within a few days (except for vitamin B_{12}, which can last in the liver in a bound form for a year or longer). Absence of vitamin C can cause symptoms within a few weeks and can cause death from scurvy within 20 to 30 weeks (Labadie, 1991). Vitamin C can react with free radicals, making it an antioxidant. By such reactions the vitamin can quench potentially toxic reactive oxygen species (Combs, 2000).

Apart from the normally recognized and essential bodily functions of vitamins, it is clear that certain vitamins also have antihypertensive effects. It has been noted in 1984 that intake of vitamin C was found to be low in a hypertensive group compared to the normal controls (McCarron *et al.*, 1984). The lower intake of vitamin C in hypertensives may reflect its close association in the diet with potassium (McCarron *et al.*, 1984). Treatment of hypertensive patients with ascorbic acid also lowers blood pressure (Duffy *et al.*, 1999). A hypothesis for this mechanism is that ascorbic acid may reduce blood pressure through a nitric-oxide mediated mechanism. Vitamin C has been shown to improve endothelium-dependent vasodilation in essential hypertension (Taddei *et al.*, 1998) and in patients with hypercholesterolaemia (Ting *et al.*, 1997), and to restore nitric oxide mediated flow-dependent dilation in patients with heart failure (Hornig *et al.*, 1998).

It has also been shown that the B vitamins could play a significant role in the prevention of cardiovascular disease, especially the lowering effect of certain B vitamins on serum homocysteine concentrations. An elevated serum total homocysteine concentration has been recognized as an important, independent risk factor for cardiovascular disease (Boushey *et al.*, 1995). Increased intakes of folate, vitamin B_{12} and vitamin B_6 was associated with a decrease in serum homocysteine concentrations (Chait *et al.*, 1999).

Apart from these findings other research studies reported that dietary vitamin B_6 supplementation attenuates hypertension in spontaneously hypertensive rats (Vasdev *et al.*, 1999). Ho and Cordain (2000) have indicated the potential role of biotin insufficiency on essential fatty acid metabolism and cardiovascular disease risk. Due to the coenzymatic activity of biotin in the holocarboxylase complexes, insufficient amounts of exogenous biotin could affect elongation and desaturation of essential fatty acids, contributing to endothelial cell dysfunction which may lead to higher cardiovascular disease risk.

Much research and clarification is necessary to fully understand the combined effects of vitamins in the prevention of cardiovascular disease.

3.2.2 The Fat-soluble Vitamins: A, D, E and K

The fat-soluble vitamins are found in the fats and oils of foods. They are insoluble in water, so they require bile for digestion and chylomicrons for absorption. Upon absorption, fat-soluble vitamins enter the lymphatic system before entering the bloodstream, where many of them require protein carriers for transport. The fat-soluble vitamins are stored in the liver and adipose tissue until they are needed; they are not readily excreted, as most of the water-soluble vitamins are. Having stored these vitamins, people can eat less than their daily need for days, weeks, or even months or years without ill effects. Blood concentrations are maintained because the body retrieves the vitamins from storage as needed. Because fat-soluble vitamins are stored, the risk of toxicity is greater than it is for the water-soluble vitamins (Whitney, 1998; Guyton & Hall, 2000).

McCarron and co-workers (1984; 1998) have found that reduced intakes of calcium, potassium, vitamin C and vitamin A were present most consistently in hypertensive individuals. Although they suggest that these deficiencies can predispose an individual to develop high blood pressure, its mechanism is not clear (Das, 2001). The lower intake of vitamin A in hypertensives may reflect, in part, its close association in the diet with calcium (McCarron *et al.*, 1984). Except for vitamin A treatment, vitamin E treatment has also shown to lower blood pressure, and increase membrane fluidity in rats (Pezeshk & Dalhouse, 2000). It has also been reported that vitamin E inhibit progression of hypertension and improve endothelial dysfunction as an antioxidant and reverse vascular remodelling. These beneficial effects of vitamin E, as antioxidant, in vascular damage associated with hypertension are related to alteration in vessel redox state (Touyz *et al.*, 2000).

Although not much is known about the effects of vitamin K and vitamin D in relation to blood pressure, Pfeifer and co-workers (2001) have reported that vitamin D_3 in combination with calcium lowers systolic blood pressure to a much higher extent than calcium supplementation alone. Other studies, however, reported that vitamin D intake had no significant effect on blood pressure (Jorde & Bønaa, 2000).

3.3 Minerals

The minerals represent a large class of micronutrients, most of which are considered essential. They are traditionally divided into *macrominerals* and *microminerals*. Most recently, the term *ultratrace* elements has been used to describe elements that are consumed in microgram (μg) quantities each day (Anderson, 2000).

Unlike the vitamins, which are organic compounds, minerals are inorganic elements that always retain their chemical identity. The minerals also differ from the vitamins in the amounts the body can absorb. Some minerals are easily absorbed into the blood, transported freely, and readily excreted by the kidneys, much like the water-soluble vitamins. Some minerals are more like fat-soluble vitamins in that they must have carriers to be absorbed and transported. While all the major minerals help to maintain the body's fluid balance, sodium, chloride, and potassium are most noted for that role (Whitney *et al.*, 1998).

Dietary minerals have long been known to affect blood pressure control and have been the subject of years of investigation to determine their specific role in the prevention and treatment of hypertension. Sodium, calcium, potassium, magnesium, and chloride are the primary micronutrients identified as having a role in blood pressure regulation and therefore have been the most extensively investigated (Reusser & McCarron, 1994).

Despite decades of investigation, the understanding of the impact of dietary sodium on blood pressure continues to be plagued with conflicting results and on-going controversy among the experts in this area of nutrition research (Reusser & McCarron, 1994). An overall average reduction of 40-60 mmol/d is being recommended in the United States. This recommendation has been widely made by multiple scientific and governmental agencies and is supported by a large body of evidence. However, an increasingly aggressive campaign was recently mounted against this recommendation in the belief that no benefit and possibly harm will occur if it is accomplished (Kaplan, 2000).

Evidence suggests that mineral interactions might be the cause of discrepancies in the results of various studies. It has been reported by Gruchow and co-workers (1988) that a higher sodium chloride intake with adequate calcium and potassium intakes was indeed related to lower blood pressure. It has also been pointed out that mineral deficiency likely accounts for much of the sensitivity to sodium, and that a nutrient-complete diet can produce far greater blood pressure improvements than can be achieved with sodium restriction. It has been acknowledged that there may be adverse effects associated with reduced sodium intake and that there is little evidence that lowering sodium intake will improve cardiovascular outcomes (McCarron, 2000).

To demonstrate the conflicting viewpoints: Sacks and co-workers (2001) have recently stated that blood pressure can be lowered in the consumers of either a typical diet in the United States or the DASH (Dietary Approaches to Stop Hypertension) diet by reducing the sodium intake from approximately 140 mmol per day to an intermediate level of approximately 100 mmol per day. They found that a reduction of dietary sodium significantly lowered the blood pressure of persons without hypertension who were eating a diet that is typical in the United States.

Various studies (Tannen, 1983; McCarron *et al.*, 1984; Harlan & Harlan, 1995) documented inverse associations of blood pressure with dietary potassium, calcium, and magnesium consumption. On the basis of these observations, however, it is difficult to relate blood pressure levels to specific nutrients because of strong correlations among dietary intakes of potassium, magnesium, fibre, and, to a lesser extent, calcium (Kotchen & McCarron, 1998). Concerning the cardiovascular effects of trace elements, it has been shown that no significant differences in zinc and copper exist between hypertensives and normotensives, though higher levels of serum copper are associated with increased risk of hypertension. Inverse correlations between blood pressure and serum zinc are observed (Bergomi *et al.*, 1997; Sentürk *et al.*, 2000).

The emphasis on sodium as the single dietary culprit is counterproductive (McCarron, 1998). A balance between all the ions seems more important than calcium, or, for that matter, any one ion in isolation (Das, 2001). Whether hypertension is genetic or environmental in origin, control of dietary mineral intake has a place in its management and prevention (McCarron, 1998).

In conclusion, a diet that emphasises fruits, vegetables, and low-fat dairy products, includes whole grains, poultry, fish, and nuts, and is reduced in fat, red meats, sweets, and sugar-containing beverages led to significant hypertension control in persons with Stage 1 hypertension (Conlin *et al.*, 2000).

3.4 Water

Water constitutes about 60% of an adult's body weight and a higher percentage of a child's. The body attempts to restore homeostasis as promptly as possible, adjusting both water intake and excretion is needed. The body cells, with a few exceptions, cannot move water from place to place; they need to use minerals and other constituents to regulate the distribution of body fluids. To control the movement of water, the body uses its major minerals, which form salts that dissolve in the body fluids. The cells direct the movement of these salts, and this determines the direction of the fluid movement (Whitney, 1998).

Osmotic pressure is directly proportional to the number of particles in solution and usually refers to the pressure at the cell membrane. The osmotic pressure of the extracellular fluid may be considered relative to its content of sodium, the major cation present in extracellular fluid. Although variation in the distribution of sodium and potassium ions is the principal causes of water shifts between the various fluid compartments, chloride and phosphate also influence water balance. Proteins, which are nondiffusible because of their molecular size, also play an important part in maintaining osmotic equilibrium (Whitmire, 2000).

A method of controlling blood pressure is by medically supervised water-only fasting. It appears to be a safe and effective means of normalising blood pressure and may assist in motivating health-promoting diet and lifestyle changes. Such a diet resulted in an average reduction in blood pressure of 37/13 mmHg, with the greatest decrease being observed for subjects with the most severe hypertension (Goldhamer *et al.*, 2001).

In its 1993 report, the National Institutes of Health (NIH) Joint National Committee on Detection, Evaluation, and Treatment of High blood Pressure (JNC V, 1993) acknowledged for the first time that dietary modifications may be a viable means of not only treating hypertension, but of preventing it as well. While many questions remain to be answered, our present understanding clearly indicates a primary role of dietary factors in blood pressure control (Reusser & McCarron, 1994).

4 The impact of ethnicity and diet on blood pressure and age-related changes in blood pressure

African Americans exhibit a high risk for hypertension and its sequelae, including coronary heart disease, renal disease, and stroke (Melby *et al.*, 1994). The frequency of hypertension in black citizens of the United States is amongst the highest in the world. Pathophysiological mechanisms suggest the frequency of salt-sensitive blood pressure is more common in black patients and older patients (Rutledge, 1994; Peters & Flack, 2000). Increased renal sodium reabsorption through epithelial sodium channels may underlie the development of high blood pressure in black people (Baker *et al.*, 2001). It also seems as if black people accumulate more sodium with increasing sodium intake than whites (Brier & Luft, 1994). A large, multicenter study by Chrysant and co-workers (1997), on the other hand, did not demonstrate any statistically significant effect of race, age, sex, and weight on blood pressure response to salt changes in salt-sensitive hypertensive patients.

Age-corrected prevalence studies of hypertension in South Africa showed that in the adult population of Durban, the prevalence of hypertension (according to WHO criteria) was highest in urban Zulus (25%), intermediate in whites (17.2%) and lowest in ethnically Indian people (14.2%) (Seedat, 2000). These results demonstrate that ethnicity plays a significant role in the prevalence of hypertension.

Compared with white adults, black individuals have been shown to exhibit a steeper increase in blood pressure with advancing age (Melby *et al.*, 1994). It is known from longitudinal studies in developed or urban populations that systolic blood pressure rises steadily with increasing age, at least into the ninth decade. In contrast diastolic blood pressure increases to a maximum around the sixth decade after which it tends to plateau or even decrease, which means that pulse pressure increases (Stott & Bowman, 2000). A high pulse pressure has been recognised as an important cardiovascular risk factor. The increase in pulse pressure with aging is mainly due to a decrease in large artery compliance. It has been shown that the distensibility and compliance of the common carotid artery is decreasing with aging, while diameter of the artery increases. A decrease in compliance leads to a high pulse pressure and isolated systolic hypertension (Van Bortel & Spek, 1998).

When elderly subjects were compared to a younger group it became clear that both elderly men and women had higher diastolic blood pressure. Blood pressure variability while subjects were awake was also higher in the elderly. This might indicate a relatively higher risk for end-organ damage (Jacquet *et al.*, 1998).

When concentrating on the impact of diet on age-related blood pressure changes it is reported that age-related changes in systolic blood pressure were attenuated by higher calcium and protein intakes. Magnesium was not associated with any changes in blood pressure (Hajjar *et al.*, 2001). The INTERSALT investigators concluded that urinary sodium excretion was predictive of the rate of rise in blood pressure with increasing age. But further research gave strong evidence that salt consumption was not predictive of increased blood pressure world wide (Hanneman, 1996). Dietary benefits on blood pressure observed that diets rich in a combination of nutrients derived from fruits, vegetables, and low-fat dairy products could contribute to primary prevention of hypertension when instituted at an early age (Falkner *et al.*, 2000).

5 Summary of the literature

Table 2.2 The effects of dietary factors on cardiovascular parameters

Dietary factor	Cardiovascular parameters				
	SBP	DBP	BP	PP	C	TPR
Macronutrients						
Total protein	↓[1, 2], ↑[3,4]	↓[1,2,4]	↓[15,16]	↑[3]		
Plant protein			↓[1]			
Animal protein			↓[1]			
Total fat	↑[2]	↑[2,4]	↑[17]			
Saturated fat	↑[2]	↑[2,4]	↑[1,17]			
Monounsaturated fat	↑[2]	↑[2]				
Polyunsaturated fat	↑[2]	↑[2]			↑[53]	
Cholesterol	↑[1,4], ↓[2]	↑[4], ↓[2]				
Total carbohydrate	↓[2]	↓[2]	⇔[1], ↑[18,1]			
Sucrose	↑[5]		⇔[19], ↑[20]			
Fibre	↓[2]	↓[2]	↓[15]			
Vitamins						
Fat-soluble						
Vitamin A			↑[21]			
Vitamin D			⇔[9]			
Vitamin E			↓[22,23]		↑[54]	
Water-soluble						
Thiamine						
Riboflavine						
Nicotinic acid			⇔[24]			
Vitamin B_6	↓[5]		↓[25]			
Vitamin B_{12}			↓[25,26]			
Folic acid		↓[14]	↓[25,26]			
Ascorbic acid	↓[7,8]	↓[7]	↓[27,28,30,23] ⇔[29]			↓[30,56]
Pantothenic acid			↓[58]			
Biotin						
Minerals						
Macrominerals						
Calcium	↓[2,9]	↓[2,9]	↓[31,32,33,27,34,35,36,37,38]			⇔[33]
Magnesium	↓[2]	↓[2]	↓[27,36,39,38]	↓[3]		⇔[57]
Sodium	↑[3]		↓[31], ↑[40,41,42,36,43,44,37,45,38]	↑[3]		
Potassium	↓[2,3,10,11]	↓[2,3,10]	↓[31,40,46,47,36,38]			⇔[57]
Microminerals/Trace elements						
Iron			⇔[49]			
Zinc			↓[50], ⇔[51,39]			
Copper	↑[12]		↑[50], ⇔[51,39]			
Water					↑[55]	
Alcohol	↑[3]	↓[3]	↑[52,36]	↑[3]		
Caffeine	↓[1], ↑[13]	↓[1], ↑[13]	↑[36]			

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BP: Blood pressure; PP: Pulse pressure; C: Arterial compliance; TPR: Total peripheral resistance

↑: Increase; ↓: Decrease; ⇔: No change

1 Stamler and co-workers (1996)
2 Simons-Morton and co-workers (1997)
3 Hajjar and co-workers (2001)
4 Melby and co-workers (1994)
5 Preuss and co-workers (1998)
6 Vasdev and co-workers (1999)
7 Block and co-workers (2001)
8 Vasdev and co-workers (2001)
9 Jorde and Bønaa (2000)
10 Whelton and co-workers (1997)

11 Gu and co-workers (2001)
12 Liu & Medeiros (1986)
13 Hartley and co-workers (2000)
14 Falkner and co-workers (2000)
15 He & Whelton (1999b)
16 Millward (1999)
17 Beegom & Singh (1997)
18 Liu and co-workers (2000)
19 Van der Schaaf and co-workers (1999)
20 Brands & Fitzgerald (2000)
21 Jacobson and co-workers (1999)
22 Pezeshk & Dalhouse (2000)
23 Touyz and co-workers (2000)
24 Kelly and co-workers (2000)
25 Prasad (1999)
26 Chait and co-workers (1999)
27 Das (2001)
28 Duffy and co-workers (1999)
29 Mark and co-workers (1998)
30 Taddei and co-workers (1998)
31 McCarron and co-workers (1984)
32 Kolata (1984)
33 Passmore and co-workers (1997)
34 Das (1985)
35 McCarron & Reusser (1999)
36 Nurminen and co-workers (1998)
37 Luft and co-workers (1989)
38 Kotchen & McCarron (1998)
39 Sentürk and co-workers (2000)
40 Hu & Tian (2001)
41 Johnson and co-workers (2001)
42 Sacks and co-workers (2001)
43 Ballesteros-Vasques and co-workers (1998)
44 Kaplan (2000)
45 Stamler (1997)
46 Das (1985)
47 Tannen (1983)
49 Hatton and co-workers (1991)
50 Bergomi and co-workers (1997)
51 Taittonen and co-workers (1997)
52 Okubo and co-workers (2001)
53 Nestel (2000)
54 Mottram and co-workers (1999)
55 Joannidès and co-workers (1997)
56 Jeserich and co-workers (1999)
57 Glänzer and co-workers (1984)
58 Schwabedal and co-workers (1985)

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3

Dietary risk markers that contribute to the aetiology of hypertension in black South African children: The THUSA BANA study

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ABSTRACT

Objective: The aim of this study was to determine which dietary factors could be identified as risk markers that might contribute to the aetiology of hypertension in black children.

Design: Cross-sectional epidemiological study.

Setting: North West Province, South Africa.

Subjects: Apparently healthy children between 10 and 15 years of age were recruited from each of 30 schools over a period of two years (2000 to 2001). These children comprised 321 black males and 373 females from rural to urbanised communities. The male (n=40) and female (n=79) groups consisted of subjects with identified high-normal to hypertensive blood pressure. The normotensive group consisted of 281 black male and 294 female subjects.

Results: In a stepwise regression analysis the following variables were significantly associated ($p \leq 0.05$) with blood pressure parameters of hypertensive males: biotin, folic acid, pantothenic acid, zinc and magnesium. Energy, biotin and vitamin A intakes were significantly associated with blood pressure parameters of hypertensive females. No significant dietary markers were indicated for any of the normotensive groups. Dietary intakes of all of these nutrients were well below the dietary reference intakes or recommended dietary allowances.

Conclusions: The dietary results coupled with the cardiovascular parameters of this study identified folic acid and especially biotin as risk markers that could contribute to the aetiology of hypertension in black persons. The low intakes of these nutrients, amongst others, is a matter of serious concern, as is the increasing tendency towards urbanisation.

Descriptors: biotin; folic acid; black children; hypertension, South Africa

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- ☐ Structured abstract of not more than 250 words is required, under the headings: Objective, Design, Setting, Subjects, Results, Conclusions, Descriptors.

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- ☐ Tables and Figures should have legends which enable them to be understood without reference to the text.

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- ☐ Ethical approval: Research studies involving human subjects should be approved by the relevant review committee, and such approval must be stated in the Methods section of the paper.

Introduction

Blacks in the USA have a several-fold higher mortality from hypertensive disease than the Caucasian population (Burt *et al*, 1995). The prevalence of hypertension in black people in the West Indies and in the USA is higher than the prevalence in any part of sub-Saharan Africa. This may be because African Americans have been acculturated for 300 years, whereas urban Zulus and Tswana-speakers have been acculturated only since the turn of the 20th century. It is possible that the blood pressure changes in the time since acculturation may explain the blood pressure differences between African Americans, West Indians, Nigerians, urban Zulus and Tswana-speaking people (Seedat, 2000). Nevertheless, hypertension is common in the black population of South Africa, including the North West Province (20.7% - 22.8%) (Seedat *et al*, 1982; Isaacson *et al*, 1989; Pick *et al*, 1990; Van Rooyen *et al*, 2000), and there is very little direct evidence about the determinants of common cardiovascular disease in large populations in sub-Saharan Africa (World Health Organization, 1999).

Although clinical hypertension occurs less frequently in children than in adults, (Joint National Committee, 1993; Sinaiko, 1982; Sinaiko, 1989) ample evidence now supports the concept that the roots of essential hypertension extend back to childhood. Of particular importance is the documentation that elevated blood pressure in childhood often correlates with hypertension in early adulthood, thereby supporting the need to track blood pressure in children (Lauer and Clarke, 1984; Simons-Morton *et al*, 1997).

The genetic make-up of the individual explains 20-60% of the occurrence of hypertension (Williams *et al*, 1991), whereas environmental factors, such as dietary factors, are much less important and explain 0-16 % of the causes of hypertension (Hornstra *et al*, 1998). Various studies, however, have shown that certain dietary factors not only significantly lower blood pressure, but nutritionally balanced meals could also improve multiple risk factors for patients with cardiovascular disease (Appel *et al*, 1997; McCarron *et al*, 1997). Whether hypertension is of genetic or environmental origin, the control of dietary intake has a place in the management and prevention of cardiovascular diseases (McCarron, 1998).

A recent review of studies examining dietary nutrients and blood pressure in children concluded that there is a paucity of studies examining the effects of multiple nutrients and/or the influence of macronutrients on blood pressure in children (Simons-Morton and Obarzanek, 1997). By including multiple dietary factors together and evaluating their interactions, it is possible to detect specific associations between dietary factors and blood pressure. It is particularly important to study the association of diet and blood pressure in black, hypertensive children, because elevated blood pressure in childhood is of concern since children within the upper distribution of blood pressure are at risk of developing hypertension in adulthood (Simons-Morton and Obarzanek, 1997).

The THUSA BANA study (Transition and Health during Urbanisation in South Africa in Children; Bana = Children) was designed to assess the relationship between the level of urbanisation and the health status of children of the North West Province of South Africa. The aim of this part of the study was to determine which dietary factors could be identified as risk markers that might contribute to the aetiology of hypertension in black children.

Methods

Study design

Thirty black schools were randomly selected from a list of schools of the North West Province. These schools were visited during the weeks preceding the collection of data, in order to obtain permission from the relevant school principals as well as from the parents of the children. Children within the schools were also randomly selected. Data collection took place during normal school hours. This study formed part of the THUSA BANA study.

Subjects
Apparently healthy children between 10 and 15 years of age were recruited from each of the 30 schools over a period of two years (2000 to 2001). These children comprised 321 black males and 373 females from rural to urbanised communities. The male (n=40) and female (n=79) hypertension groups consisted of subjects with identified high-normal to hypertensive blood pressure. Hereafter these groups will be referred to as "hypertensive". Hypertension in children is defined as an average systolic or diastolic blood pressure greater than or equal to the 90th percentile for age and sex (National High Blood Pressure Education Program, 1996). Height percentiles were also taken into consideration since body size is the most important determinant of blood pressure in childhood and adolescence (National High Blood Pressure Education Program, 1996). The normotensive group consisted of 281 black male and 294 female subjects with blood pressure lower than the 90th percentile for age and sex (Table 1).

The Ethics Committee of the University approved the study and all the parents of the subjects gave informed consent.

Data collection and measurements
The subjects were all introduced to the experimental setup, after which each one was separately subjected to the following procedures:

Blood Pressure
The subjects were connected to a Finapres (finger-arterial pressure) apparatus (Wesseling *et al*, 1986; Silke and McAuley, 1998) and blood pressure was recorded continuously. After a period of rest of at least 10 minutes, resting blood pressure values were obtained. Blood pressure was regarded as resting when the systolic blood pressure did not change with more than 10 mmHg during the last minute of this period, otherwise the resting period was extended. The resting blood pressure was then recorded continuously for 1 minute. The data was stored on magnetic tape by means of a Kyowa RTP-50A four-channel data recorder and digitised for further analysis by means of the Fast Modelflo software program (Wesseling *et al*, 1993). In this way the systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP) were obtained.

Weight and Height
Qualified anthropometrists took weight and height measurements. Height was measured to the nearest 0.1 cm and weight was measured to the nearest 0.1 kg by means of a calibrated electronic scale (Precision Health scale).The waist and hip circumferences of the subjects were measured with a flexible Lufkin anthropometric steel tape to the nearest 0.1 cm. The following equations were used to determine body mass index and WHR (Norton and Olds, 1996): BMI = body mass (kg)/stature^2 (m); WHR = waist girth (cm)/hip girth (cm).

Dietary intake
Dietary intake data were collected by fieldworkers trained by registered dieticians. A 24-hour dietary recall was collected face-to-face and the data collection interview method and nutrient coding were the same for all recalls. Food models and photo books for portion-size estimates were used for the recalls. This type of dietary assessment is widely used in international epidemiological studies (Simons-Morton *et al*, 1997; Falkner *et al*, 2000; Hajjar *et al*, 2001). Macronutrients (protein, fat, and carbohydrate) and fibre were calculated, and micronutrients (such as calcium, magnesium, sodium, potassium, and phosphorus), vitamins (such as A, B_6, B_{12}, C, D, E, and biotin) and cholesterol were calculated in the appropriate units, using a computer programme based on the South African food composition tables (Langenhoven *et al*, 1991).

Statistical analysis
All processed data were transferred to Excel and further statistically analysed by means of the software computer package STATISTICA (StatSoft, 2000). Due to skewed distributions all dietary variables were logarithmically transformed. Since the blood pressure parameters had a normal distribution, log transformations were not necessary. Multivariate analyses and forward stepwise regression analyses were used to assess the association between SBP, DBP and

MAP as dependent variables and the following (log-transformed) independent variables: dietary macronutrients (total protein, plant protein, animal protein, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, total carbohydrates, added sugar, energy), dietary fibre, dietary cholesterol, dietary micronutrients (calcium, magnesium, potassium, sodium, zinc, iron, phosphorus, copper) and dietary vitamins (vitamin A, thiamine, riboflavine, nicotinic acid, biotin, pantothenic acid, vitamin B_6, folic acid, vitamin B_{12}, ascorbic acid, vitamin E). Stepwise regression analyses were done to determine the most significant ($p \leq 0.05$) determinants of SBP, DBP and MAP in the four subject groups, namely normotensive males, hypertensive males, normotensive females and hypertensive females. Independent t-tests were used to determine if significant differences existed between two groups.

Results

The overall sample consisted of 695 participants divided into a male (46.2 %) and female (53.8 %) group. Each group was divided into a normotensive (NT) and hypertensive (HT) group (Table 1). Although significant differences ($p \leq 0.001$) existed between the SBP, DBP and MAP of the NT and HT groups of both sexes, no significant differences ($p \leq 0.05$) were detected between the BMI and WHR of the groups.

Table 1. Characteristics of subjects at baseline, blood pressure, age, body mass index and waist-to-hip ratio

Variable	Males		Females	
	Normotensive†	Hypertensive‡	Normotensive	Hypertensive
No. (%) of subjects	281 (88)	40 (12)	294 (79)	79 (21)
Age (years)	12.5 ± 1.7	12.4 ± 1.5	12.6 ± 1.7	12.0 ± 1.9
BMI	16.6 ± 2.5	17.3 ± 3.4	18.1 ± 3.8	18.9 ± 4.3
WHR	0.84 ± 0.07	0.83 ± 0.05	0.77 ± 0.06	0.78 ± 0.06
SBP (mmHg)	96 ± 12**	120 ± 11**	96 ± 11**	123 ± 9**
DBP (mmHg)	61 ± 8**	81 ± 8**	63 ± 8**	78 ± 8**
MAP (mmHg)	77 ± 8**	98 ± 8**	80 ± 8**	97 ± 8**

Values are mean ± standard deviation.

† Normotensive defined by blood pressure lower than the 90th percentile. Adjusted for age, sex and height.

‡ Hypertensive defined by blood pressure in the upper 10th percentile. Adjusted for age, sex and height.

** Significant $p \leq 0.001$

In the stepwise regression analyses the variables as shown in Table 2 were significantly associated ($p \leq 0.05$) with the blood pressure parameters. In this stepwise regression model, with SBP, DBP and MAP as the dependent variable and all the dietary factors used as independent variables, biotin ($p = 0.003$), folic acid ($p = 0.04$) and magnesium ($p = 0.01$) intakes were significant markers of SBP in hypertensive males. In hypertensive males these three variables, as well as added sugar ($p = 0.058$) intake, explained 27.5 % of the variance in SBP ($R^2 = 0.275$). Biotin ($p = 0.0006$), pantothenic acid ($p = 0.01$) and zinc ($p = 0.01$) intakes were significant markers of DBP in hypertensive males. Together with added sugar ($p = 0.12$) and energy ($p = 0.11$) intakes, these five variables account for 28.9 % of the variance in DBP. Biotin ($p = 0.007$) and folic acid ($p = 0.03$) along with zinc ($p = 0.053$) account for 23.7 % of the variance in the MAP of hypertensive males.

In hypertensive females no significant dietary markers were indicated for SBP, but energy ($p = 0.003$), biotin ($p = 0.02$), iron ($p = 0.001$) and vitamin A intakes ($p = 0.01$) were significant markers for DBP. Together with folic acid ($p = 0.06$) these parameters explained 22.4 % of the variance in DBP.
No significant dietary markers were indicated for any of the normotensive groups.

Table 2. Stepwise regression of SBP, DBP and MAP as dependent variables with independent variables. Regression coefficients beta (β) and level of significance, p are shown.

Independent variable	Males						Females					
	Normotensive (n = 281)			Hypertensive (n = 40)			Normotensive (n = 294)			Hypertensive (n = 79)		
	SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP	SBP	DBP	MAP
Energy	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	β = 0.44, p = 0.003	NS
Biotin	NS	NS	NS	β = 0.44, p = 0.003	β = 0.79, p = 0.001	β = 0.40, p = 0.007	NS	NS	NS	NS	β = 0.24, p = 0.02	NS
Folic acid	NS	NS	NS	β = -0.35, p = 0.04	NS	β = -0.32, p = 0.03	NS	NS	NS	NS	NS	NS
Pantothenic acid	NS	NS	NS	NS	β = -0.53, p = 0.01	NS	NS	NS	NS	NS	NS	NS
Magnesium	NS	NS	NS	β = 0.44, p = 0.01	NS	NS	NS	NS	NS	NS	NS	NS
Zinc	NS	NS	NS	NS	β = 0.40, p = 0.01	NS	NS	NS	NS	NS	NS	NS
Iron	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	β = -0.58, p = 0.001	NS
Vitamin A	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	β = -0.28, p = 0.01	NS

NS indicates not significant ($p > 0.05$). $p \leq 0.05$ for all values given in the table.

In Table 3 the dietary intakes of the aforementioned dietary markers are compared against the dietary reference intakes (DRI) or recommended dietary allowances (RDA) for the specific nutrients. From these data it is evident that energy, biotin, folic acid, pantothenic acid, zinc, iron and vitamin A intakes were well below the DRI or RDA. It was only magnesium intake that was close to the RDA, although still below it.

Table 3. Dietary intakes of subjects along with dietary reference intake for males and females aged 10 to 15 years.

Nutrient	Mean Dietary Intake†				Dietary reference intake
	Males		Females		
	Normotensive	Hypertensive	Normotensive	Hypertensive	
Energy (kJ/d)	7821.9 ± 3183.8	8008.1 ± 2764.7	7223.9 ± 2532.3	7307.1 ± 2701.5	9240‡
Biotin (μg/d)	16.1 ± 15.8	15.4 ± 12.0	16.8 ± 16.3	15.9 ± 13.4	20-25§¶
Folic acid (μg/d)	170.8 ± 147.6	174.3 ± 113.9	157.4 ± 111.2	150.6 ± 94.7	300-400¶
Pantothenic acid (mg/d)	3.1 ± 2.3	2.8 ± 1.2	3.5 ± 5.4	3.17 ± 2.4	4-5§¶
Magnesium (mg/d)	238.1 ± 122.9	229.7 ± 95.5	218.5 ± 94.6	207.6 ± 88.1	M: 240-410 F: 240-360¶
Zinc (mg/d)	8.1 ± 4.4	7.5 ± 3.5	7.4 ± 4.0	8.1 ± 4.1	M: 15 F: 12‡
Iron (mg/d)	8.4 ± 6.1	8.9 ± 4.6	8.1 ± 4.8	7.9 ± 3.8	M: 12 F: 15‡
Vitamin A (μg RE/d)	368.8 ± 613.4	459.2 ± 689.2	387.3 ± 685.1	467.4 ± 701.0	1000‡

† Values are means ± standard deviation.
‡ Recommended Dietary Allowances (RDA). Adapted from Food and Nutrition Board, 1989.
§ Adequate Intakes (AI)
¶ Adapted from Institute of Medicine, Food and Nutrition Board, 1998.

When comparing the dietary intakes of the normotensive and hypertensive groups there were almost no significant differences between the intakes of the groups. The only significant differences ($p \leq 0.05$) were a higher riboflavin intake in the hypertensive male group and a higher vitamin B_{12} and vitamin A intake in the hypertensive female group, compared to the normotensive group.

Discussion

This study examined relationships between dietary nutrients and blood pressure in growing children. The strengths of this study include the following: analysis of dietary recalls through a nutrient database that included both micronutrients and macronutrients; careful blood pressure measurement with quality control; data on major factors, such as weight and height, that affect blood pressure and are correlated with dietary intake. Updated normative blood pressure tables for children and adolescents are based on height percentiles because of the importance of height in determining blood pressure levels in children (National High Blood Pressure Education Program, 1996). The findings are best viewed as indicators of potentially important dietary components that warrant further study.

The BMI and WHR of the hypertensive groups were slightly higher than the normotensives, but there were no significant differences between the BMI and WHR of the groups of both sexes. From these results it seems as if obesity amongst black children is rare because of their dietary patterns, or the prevalence of hypertension among black children younger than 15 years cannot be ascribed to obesity.

When the dietary intakes of the normotensive and hypertensive groups were compared it was also evident that there were almost no significant differences between the intakes of the groups. Expected differences in dietary intakes such as sodium, potassium, calcium, protein, lipids or fibre did not occur. Intake of sodium in all groups (1468.5 – 1873.3 mg/d) was higher than the estimated minimum requirements (Food and Nutrition Board, 1989) of 500 mg but well below the upper limit of 6 g/day. Although the intake of sodium was slightly higher in the hypertensive groups, the difference was not substantial. Whether the dietary recall information was reliable is uncertain because it is almost impossible to quantify salt added during food preparation or at the table. However, it has been demonstrated that dietary recall information on sodium consumption parallels 24-hour urinary sodium excretion (Schlacter *et al*, 1980).

Dietary factors that contributed significantly to the blood pressures of hypertensive children are remarkably similar to those indicated as deficiencies in primary school children of South Africa (Vorster *et al*, 1997). Vorster and co-workers observed iron, vitamin A, folic acid and calcium deficiencies in pre-schoolers and primary school children. It was also evident that much less research has been done on adolescents, but iron and folic acid deficiencies were common and black children seem to have low vitamin A, E, B_6 and also calcium status.
According to this study energy, biotin, folic acid, pantothenic acid, magnesium, zinc, iron and vitamin A intakes are the strongest markers for SBP, DBP and MAP in black hypertensive children, although all markers were not applicable to each blood pressure parameter (Table 2). Intake of all of these nutrients were indicated as deficient in these children (Table 3), but not only these nutrients showed deficiencies. In accordance with the research of Vorster and co-workers (1997), deficient intakes of vitamin A, iron, folic acid (Table 3) and calcium were observed. Other deficient intakes that were observed, namely phosphorus, potassium, copper and fibre, were not indicated as markers for hypertension in this study, and were also observed in both normotensive and hypertensive children. In contrast to the findings of Vorster and co-workers (1997), deficient intakes of neither vitamin B_6 nor vitamin E were observed in this study. In fact, intake of all of the other dietary factors concurred well with the dietary reference values (Food and Nutrition Board, 1989; Institute of Medicine, Food and Nutrition Board, 1998).

It seems as if all the nutrients that showed low intakes were also the dietary markers for hypertension, except for phosphorus, potassium, sodium, copper and dietary fibre. Low intakes of potassium, calcium and magnesium, which are known for their anti-hypertensive abilities (Whelton *et al*, 1997; Miller *et al*, 2000; National High Blood Pressure Education Program, 1993) occurred in the hypertensive group, but these low intakes were also prevalent in the normotensive group. Thus hypertension could not be ascribed to the deficient intakes, but it could possibly be explained by a combination of genetic predisposition as well as specific nutritional deficiencies and probably other environmental factors.

On the other hand, since the low intakes occurred in both the normotensive and hypertensive groups, certain dietary factors could definitely be associated with hypertension. Whether a person shows a deficiency or not, the specific dietary factor could still be a marker for hypertension.

The following dietary markers of hypertensive subjects were provided by a forward stepwise regression analysis:

Energy
The strong positive relationship between BMI and blood pressure has repeatedly been indicated (Okasha *et al*, 2000; Geiβ *et al*, 2001) and it might be this relationship that could explain the positive link between diastolic blood pressure in females and energy intake.

Folic acid

The negative relationships of the SBP and DBP of hypertensive males with folic acid intakes are in accordance with previous studies (Chait *et al*, 1999; Prasad, 1999; Falkner *et al*, 2000). Folic acid has been shown to be beneficial and very effective in reducing plasma homocysteine levels. By reducing this risk factor for cardiovascular disease, folic acid intake contributes to the lowering of blood pressure (Chait *et al*, 1999; Prasad, 1999).

Pantothenic acid

The rather strong negative relationship of pantothenic acid with blood pressure is not commonly found in the literature. However, in endemic pantothenic acid deficiency of some Japanese populations, increased occurrence of hypertension has been described (Schwabedal *et al*, 1985). But all attempts to produce hypertension experimentally by means of pantothenic acid deficiency have failed. As a consequence, the observations made in Japan have largely been ignored. In later years it has been shown that pantothenic acid deficiency is a factor in the experimental origin of hypertension due to adrenal regeneration (Schwabedal *et al*, 1985). Whether the results of this study have the same origin or mechanisms as the Japanese study has to be determined.

Magnesium, Zinc, Iron and Vitamin A

The finding in this study, namely the positive relationship between magnesium intake and SBP in hypertensive males, is in contrast with previous research studies. Observational studies documented inverse associations of blood pressure with dietary magnesium consumption (Morris and Sebastian, 1995; Harlan and Harlan, 1995; Witteman *et al*, 1989; Stamler *et al*, 1997; Geleijnse *et al*, 1996).

The positive relationship of dietary zinc intake and DBP of hypertensive males is a result that could not be found in the literature. Weakly negative associations of zinc and blood pressure have been reported (Bergomi *et al*, 1997), but other studies have shown no relationships with blood pressure (Taittonen *et al*, 1997; Sentürk *et al*, 2000).

The only reported associations of iron with blood pressure are positive relationships with pregnancy-induced hypertension that are probably caused by an ongoing haemolytic reaction that is responsible for the increase in serum iron (Samuels *et al*, 1987; Das *et al*, 1994). The results of this study could definitely not be explained by these studies. However, this negative association between iron intake and DBP of hypertensive females should not be ignored, whatever the mechanism might be.

Vitamin A showed a negative relationship with DBP in hypertensive females. This relationship is not documented elsewhere. Relationships of vitamin A with blood pressure are the effect of elevated serum vitamin A on idiopathic intracranial hypertension (Jacobson *et al*, 1999), which does not explain the negative link.

The fact that magnesium, zinc, iron and vitamin A showed relationships only once, namely either with SBP or DBP, in hypertensive males or females, and no other relationships with blood pressure, could give an indication that these relationships might not be reliable. Whether these relationships could be ascribed to the low intakes of the nutrients in the children is unclear. The positive associations of zinc and magnesium with blood pressure may suggest that zinc and magnesium may act as markers for a specific eating pattern associated with higher blood pressure. The best food sources of zinc are animal protein foods, while the best sources of magnesium are milk products, whole-wheat cereals and dark green vegetables (Anderson, 2000). Further research concerning the magnesium, zinc, iron and vitamin A intake in hypertensive children in combination with blood pressure should address this problem.

Biotin

The most profound results are those found with dietary biotin. Strong positive associations of biotin were observed throughout with SBP, DBP and MAP in hypertensive males, and also with DBP in hypertensive females. The interpretation of these results are somewhat of a challenge, since it was clear that the dietary intake of biotin of the subjects in this study was insufficient. Although estimated average requirements for biotin are available, the human biotin requirements in specific populations and at various ages remain uncertain, in part because indicators of biotin status have not been validated up to this stage (Mock, 1999). Considerable basic information concerning biotin availability and nutritional status also remains unknown (Said, 1999).

From our results it is evident that the dietary intake of biotin was well below the Adequate Intakes proposed for 10-15 year old children by the Institute of Medicine, Food and Nutrition Board (1998). Whether their dietary biotin intake was physiologically deficient for bodily functions is not clear, but the results indicate that despite their low biotin intakes, biotin showed a strong positive association with blood pressure.

The data sets for biotin of the Food Composition Tables seem as if a few possibilities for biotin intake are not indicated (Langenhoven *et al*, 1991). But the data sets are basically complete, since the biotin content of food sources that were left out were food sources not normally ingested by children in these parts of South Africa.

The majority of biotin in meats and cereals appears to be protein-bound, and biotin is widely distributed in natural foodstuffs. But the absolute content of even the richest sources is low when compared with the content of most other water-soluble vitamins. Foods relatively rich in biotin include egg yolk, liver and some vegetables (Zempleni and Mock, 1999). Because the vitamin synthesised by the microflora in the colon can be absorbed, cases of deficiency are rare and there is a paucity of quantitative information about the biotin needs of humans (Combs, 2000).

Although biotin intake showed these strong relationships with blood pressure in hypertensives, no significant differences were indicated between the biotin intakes of the normotensive and hypertensive groups. It might be explained by a genetic predisposition of the hypertensive group, but since information about the determinants of bioavailability of biotin remains unknown (Said, 1999), the origin of the positive relationship to blood pressure in hypertensives remains unclear.

Research by Ho and Cordain (2000) indicated that symptoms of biotin deficiency are similar to that of essential fatty acid deficiencies (EFAD). Since EFAD have rarely been regarded as problematic in developed nations, studies have shown that insufficient levels of essential fatty acids could influence the aetiology of cardiovascular disease. Due to the prevalence of high carbohydrate/low fat diets in the population studied, there may be a concomitant increase in the prevalence of both biotin and essential fatty acid insufficiencies. Future studies should also consider the role that biotin insufficiencies play in hyperglycemia and diabetes mellitus (Ho and Cordain, 2000).

According to this information the physiological meaning of the relationship, namely the higher the biotin intake (although intakes are still insufficient), the higher the blood pressure of hypertensive children, could be explained. A specific threshold for biotin intake is proposed and could cause an inversion of the cardiovascular effect of biotin. This means that insufficient intake of biotin could cause an increase in cardiovascular risk of hypertension. A gradual increase in biotin intake could result in a higher risk until a threshold value is reached. From this point, which could also be a sufficient biotin intake, the cardiovascular risk could be lowered.

Conclusion

The DASH (Dietary Approaches to Stop Hypertension) study showed that a diet high in fruits, vegetables and non-fat dairy foods, and low in saturated fat and total fat, will decrease systolic blood pressure by an average of 6 to 11 mmHg (Appel *et al*, 1997) and is effective in the prevention and control of high blood pressure. It is clear that low energy density of weaning foods and of the diets of especially rural black school children, coupled with a low intake of fruits, vegetables, legumes and milk by many individuals, are the main deficiencies in the South African diet (Vorster *et al*, 1997). The nutrient intake data of the THUSA BANA study supports these observations.

The dietary results coupled with the cardiovascular parameters of this study identified folic acid and especially biotin as risk markers that could contribute to the aetiology of hypertension in black persons. The low intakes of these nutrients, amongst others, is a matter of serious concern, as is the increasing tendency towards urbanisation of prudent traditional diets, thereby increasing the risk of chronic lifestyle diseases.

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4

Dietary markers of hypertension associated with pulse pressure and arterial compliance in black South African children: The THUSA BANA study

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ABSTRACT

Aims: The aim of the study was to determine which dietary factors contribute to the impairment of arterial compliance, stroke volume, total peripheral resistance and pulse pressure, and could thereby be identified as risk markers in the development of hypertension in black children.

Methods: Children aged 10 to 15 years were recruited from 30 schools in the North West Province over two years (2000 to 2001). These children comprised 321 black males and 373 females from rural to urbanised communities and 40 male and 79 female subjects with identified high-normal to hypertensive blood pressure. Blood pressure were measured by means of a Finapres apparatus. Through analysis with the Fast Modelflo software program systemic arterial compliance, pulse pressure, total peripheral resistance and stroke volume were obtained. A 24-hour dietary recall questionnaire and weight and height measurements were taken.

Results: In a stepwise regression analysis the following nutrients were significantly associated ($p \leq 0.05$) with cardiovascular parameters of hypertensive subjects: protein, carbohydrates, total fat, polyunsaturated fat, monounsaturated fat, saturated fat, fibre, vitamin A, nicotinic acid, biotin, vitamin B_{12}, ascorbic acid, vitamin E, magnesium, manganese, phosphorus and iron. No significant dietary markers were indicated for the normotensive groups. Dietary intakes of most of these nutrients were below the dietary reference intakes for all groups.

Conclusions: The results indicate strong negative associations of protein, polyunsaturated fats, fibre, vitamin A, vitamin C, vitamin E, nicotinic acid, vitamin B_{12}, biotin and phosphorus with the rate of hypertension in black South African children.

KEY WORDS: hypertension, children, diet, South Africa

Cardiovascular Journal of South Africa (conditionally accepted)

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- Original research articles of 4 000 words or less, up to 6 tables and/or illustrations and up to 50 references, should report observations or research of relevance to cardiovascular medicine. Most submitted articles will be peer reviewed according to international standards.

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  Wyndham CH. Heatstroke and hyperthermia in marathon runners. *Ann NY Acad Sc* 1977;301:128-138.

- The work should comply with the requirements of the Helsinki declaration and should carry the approval of the Institutional review committee.

Introduction

Current guidelines for the diagnosis and management of hypertension describe cardiovascular risk as the elevation of systolic blood pressure and/or the elevation of diastolic blood pressure[1]. Although blood pressure is the most frequently measured parameter of the peripheral vasculature, other properties such as compliance, may be a more subtle index of vascular dysfunction associated with aging[2,3] and diseases such as hypertension[4].

The principal components of blood pressure consist of both a steady component (mean arterial pressure) and a pulsatile component, namely pulse pressure[5]. While mean arterial pressure is adequately described by cardiac output and total peripheral resistance, the origin of pulse pressure is more complex. Pulse pressure is not explicable by any single, simple model of the circulation, but can be discussed in terms of the Windkessel model[6].

Acting as an elastic buffering chamber, the aorta and proximal large arteries store half of the cardiac stroke volume during systole and propel it to the peripheral circulation in diastole, creating a nearly continuous peripheral blood flow[7]. This systolic-diastolic interplay, called the "Windkessel function," reduces cardiac afterload[8], and improves coronary blood flow[9] and left ventricular relaxation[10]. In its simplest, two-element form, the Windkessel model describes the circulation in terms of parallel resistance and capacitance components. The resistance element corresponds to measured peripheral vascular resistance, while the capacitance element corresponds to the compliance of the arterial circulation[6]. Vascular compliance is defined as the change in volume of the artery per unit of pressure ($\Delta V/\Delta P$)[3]. Arterial compliance (C) can also be estimated from the simpler approach of stroke volume (SV) divided by pulse pressure (PP)[6].

As arterial compliance decreases, a rise in systolic blood pressure with a fall in diastolic blood pressure occurs[11]. This indicates a pulse pressure amplification. An increase in pulse pressure, caused by large artery stiffening, is an independent cardiovascular risk factor, independent of the mean arterial pressure. In persons older than 59 years of age pulse pressure is a more accurate predictor of death than systolic or diastolic blood pressure and various studies have shown that pulse pressure is a better predictor of cardiovascular disease than any other blood pressure parameters[5,6].

Although it has been shown that pulse pressure is a powerful predictor of cardiovascular morbidity and mortality, the association of pulse pressure with diet has not been well studied. The association of pulse pressure with modifiable dietary factors suggests that dietary interventions may decrease pulse pressure and its health risks[12]. A targeted approach to lower pulse pressure will come from an increase in arterial compliance[6]. Increases in arterial compliance can be achieved by dietary manipulations, for example reduced salt intake[13].

Although environmental factors, such as diet, explain between 0 and 16% of the causes of hypertension, and genetic make-up explains 20-60%[14], certain dietary factors could still predispose an individual to develop hypertension in later years. Various studies have shown that certain dietary factors not only significantly lowers blood pressure, but nutritionally balanced meals could also improve other risk factors for patients with cardiovascular disease[15,16]. Whether hypertension is of genetic or environmental origin, the control of dietary intake has a place in the management and prevention of cardiovascular diseases[17].

A recent review of studies examining dietary nutrients and blood pressure in children concluded that there is a paucity of studies examining the effects of multiple nutrients and/or the influence of macronutrients on blood pressure in children[18]. Although clinical hypertension occurs less frequently in children than in adults[19], ample evidence supports the concept that the roots of essential hypertension extend back to childhood. Prevention of hypertension may become a reality by identifying, managing and controlling the factors that lead to the development of hypertension. It is particularly important to study the association of diet and blood pressure in black, hypertensive children, because children within the upper distribution of blood pressure, i.e. higher than the 90th percentile, are at risk of developing hypertension in adulthood[18].

The THUSA BANA study (Transition and Health during Urbanisation in South Africa in Children; Bana = Children) was designed to assess the relationship between the level of urbanisation and the health status of children of the North West Province of South Africa. The aim of this part of the study was to determine which dietary factors contribute to the impairment of arterial compliance, stroke volume, total peripheral resistance and pulse pressure, and could thereby be identified as risk markers in the development of hypertension in black children.

Methods

Study design

Thirty black schools were randomly selected from a list of schools in the five regions of North West Province of South Africa. These schools were visited during the weeks preceding the collection of data, in order to obtain permission from the relevant school principals as well as from the parents of the children. Children within the schools were also randomly selected from class lists. Data collection took place during normal school hours. This study formed part of the THUSA BANA study.

Subjects

Children between 10 and 15 years of age were recruited from each of the 30 schools over a period of two years (2000 to 2001). These children comprised 296 black males and 335 females from communities ranging from rural to urbanised. The male group consisted of 33 subjects with identified high-normal to hypertensive blood pressure and 263 normotensive subjects. The female group consisted of 65 subjects with identified high-normal to hypertensive blood pressure and 270 normotensive subjects (Table I). Groups with high-normal to hypertensive blood pressure will hereafter be referred to as "hypertensive". Hypertension in children is defined as average systolic or diastolic blood pressure greater than or equal to the 90th percentile for age and sex[20]. Height percentiles were also taken into consideration since body size is the most important determinant of blood pressure in childhood and adolescence[20]. Subjects with blood pressure lower than the 90th percentile for age and sex were considered normotensive.

The Ethics Committee of the University approved the study and all the parents of the subjects gave informed consent.

Data collection and measurements

The subjects were all introduced to the experimental setup, after which each one was separately subjected to the following procedures:

Cardiovascular parameters

The subjects were connected to a Finapres (finger-arterial pressure) apparatus[21,22] and blood pressure was recorded continuously. After a period of rest of at least 10 minutes, resting blood pressure values were obtained. Blood pressure was regarded as resting when the systolic blood pressure did not change with more than 10 mmHg during the last minute of this period, otherwise the resting period was extended. The resting blood pressure was then recorded continuously for 1 minute. The data was stored on magnetic tape by means of a Kyowa RTP-50A four-channel data recorder and digitised for further analysis by means of the Fast Modelflo software program[23]. In this way the systemic arterial compliance (C), pulse pressure (PP), total peripheral resistance (TPR) and stroke volume (SV) were obtained.

Weight and Height

Qualified anthropometrists took weight and height measurements. Height was measured to the nearest 0.1 cm and weight was measured to the nearest 0.1 kg by means of a calibrated electronic scale (Precision Health scale).The waist and hip circumferences of the subjects were measured with a flexible Lufkin anthropometric steel tape to the nearest 0.1 cm. The following equations were used to determine body mass index and WHR: BMI = body mass (kg)/stature^2 (m); WHR = waist girth (cm)/hip girth (cm).

Dietary intake

Dietary intake data were collected by fieldworkers trained by registered dieticians. A 24-hour dietary recall was collected face-to-face and the data collection interview method and nutrient coding were the same for all recalls. Food models and photo books for portion-size estimates were used for the recalls. This type of dietary assessment is widely used in international epidemiological studies[24,25]. Macronutrients (protein, fat, and carbohydrate) and fibre were calculated, and micronutrients (such as calcium, magnesium, sodium, potassium, and phosphorus), vitamins (such as A, B_6, B_{12}, C, D, E, and biotin) and cholesterol were calculated in the appropriate units, using a computer programme based on the South African food composition tables[26].

Statistical analysis

All processed data were transferred to Excel and further statistically analysed by means of the software computer package STATISTICA. Due to skewed distributions all dietary variables were logarithmically transformed. Multivariate analyses and forward stepwise regression analyses were used to assess the association between C, PP, TPR, and SV as dependent variables and the following (log-transformed) independent variables: dietary macronutrients (total protein, plant protein, animal protein, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, total carbohydrates, added sugar, energy), dietary fibre, dietary cholesterol, dietary micronutrients (calcium, magnesium, potassium, sodium, zinc, iron, phosphorus, copper) and dietary vitamins (vitamin A, thiamine, riboflavin, nicotinic acid, biotin, pantothenic acid, vitamin B_6, folic acid, vitamin B_{12}, ascorbic acid, vitamin E). Stepwise regression analyses were done to determine the most significant ($p \leq 0.05$) determinants of C, PP, TPR, and SV in the four subject groups namely normotensive males, hypertensive males, normotensive females and hypertensive females. Independent t-tests were used to determine if significant differences existed between two groups.

Results

The overall sample consisted of 631 participants divided into a male (46.9 %) and female (53.1 %) group. Each group was divided into a normotensive and hypertensive group (Table I). It was evident that the percentage of hypertensive females increased according to the level of urbanisation, whereas the male subjects living in the townships indicated the highest percentage of hypertension. The systolic (SBP) and diastolic blood pressure (DBP) of all the groups are indicated in Table I. Although significant differences ($p \leq 0.05$) existed between the normotensive and hypertensive male groups for SBP, DBP, PP and TPR, and between the normotensive and hypertensive female groups ($p \leq 0.001$) for C and PP, no significant differences ($p \leq 0.05$) were detected between the BMI and WHR of any of the normotensive and hypertensive groups.

Table I. Features of subjects: age, body mass index, waist-to-hip ratio and cardiovascular parameters

Variable	Males		Females	
	Normotensive[†]	Hypertensive[‡]	Normotensive	Hypertensive
No. (%) of subjects	263 (89)	33 (11)	270 (81)	65 (19)
% subjects living in rural setting	93.4	6.6	82.4	17.6
% subjects living in townships	81.3	18.7	80.9	19.1
% subjects in upperclass suburbs	90.9	9.1	77.6	22.4
Age (years)	12.5 ± 1.8	12.4 ± 1.7	12.6 ± 1.7	12.0 ± 1.9
BMI	16.5 ± 2.6	17.4 ± 2.7	18.2 ± 3.9	18.7 ± 4.4
WHR	0.84 ± 0.06	0.83 ± 0.05	0.77 ± 0.06	0.78 ± 0.07
SBP (mmHg)	95.1 ± 11.1**	118.7 ± 11.3**	98.8 ± 10.9**	123.0 ± 9.3**
DBP (mmHg)	60.9 ± 7.7**	80.8 ± 7.9**	62.4 ± 7.6**	77.4 ± 7.8**
C (ml/mmHg)	1.09 ± 0.40	0.98 ± 0.31	1.04 ± 0.36*	0.93 ± 0.38*
PP (mmHg)	34.1 ± 7.5*	38.1 ± 11.3*	36.5 ± 7.8**	45.7 ± 9.1**
TPR (mmHg.s/ml)	2.1 ± 1.2*	2.8 ± 1.4*	2.0 ± 0.8	2.2 ± 0.8
SV (ml)	34.14 ± 13.3	33.2 ± 11.3	34.2 ± 13.2	36.8 ± 14.5

Values are mean ± standard deviation

[†] Normotensive defined by blood pressure lower than the 90th percentile. Adjusted for age, sex and height.

[‡] Hypertensive defined by blood pressure in the upper 10th percentile. Adjusted for age, sex and height.

* Significant $p \leq 0.05$; ** Highly significant $p \leq 0.001$

In the stepwise regression analyses the independent variables as shown in Table II were significantly associated ($p \leq 0.05$) with the dependent variables PP, SV, TPR and C. With this model polyunsaturated fat (p = 0.007), ascorbic acid (p = 0.04), magnesium (p = 0.001), manganese (p = 0.03) and phosphorus (p = 0.01) intake were significant markers of PP ($p \leq 0.05$) in hypertensive males. In hypertensive males these five variables, as well as iron (p = 0.07), energy (p = 0.15) and animal protein (p = 0.45) intake, explained 47.3 % (it is $R^2 = 0.473$) of the variance in PP. Monounsaturated fat (p = 0.003), saturated fat (p = 0.008), fibre (p = 0.001), ascorbic acid (p = 0.04), vitamin E (p = 0.04), magnesium (p = 0.002) and iron (p = 0.001) were significant markers of PP in hypertensive females. Together with total fat (p = 0.07), biotin (p = 0.07), added sugar (p = 0.07) and pantothenic acid (p = 0.13), these variables accounted for 36.6 % of the variance in PP. Dietary factors that were significant markers ($p \leq 0.05$) for SV in hypertensive males were total carbohydrates (p = 0.007), saturated fat (p = 0.03), nicotinic acid (p = 0.04), biotin (p = 0.04) and ascorbic acid (p = 0.001). These five factors explained 42.5 % of the variance in SV in hypertensive males. In hypertensive females total protein (p = 0.005), total fat (p = 0.006), fibre (p = 0.002), vitamin A (p = 0.001) and vitamin B_{12} were significant markers ($p \leq 0.05$) for SV. Together with ascorbic acid (p = 0.19), calcium (p = 0.19) and vitamin B_6 (p = 0.11) these nutrients explained 23.4 % in the variance of SV. Phosphorus (p = 0.02) was the only significant marker ($p \leq 0.05$) for TPR in hypertensive males and explained 24.6 % of the variance of TPR together with iron (p = 0.08), nicotinic acid (p = 0.16) and pantothenic acid (p = 0.24). In hypertensive females no significant dietary markers were indicated for TPR. Significant dietary markers for C in the hypertensive male group were total carbohydrates (p = 0.01) and biotin (p = 0.04). Together with vitamin E (p = 0.22), nicotinic acid (p = 0.08), calcium (p = 0.07) and manganese (p = 0.17) these six variables explained 34.4 % of the variance in C. No significant dietary markers were indicated for C in the hypertensive females, neither were any significant dietary markers indicated for any of the normotensive groups.

Table II. Stepwise regression of C, PP, TPR, and SV as dependent variables with independent variables. Regression coefficients beta (β) and level of significance, p are shown.

Independent variable	Males								Females							
	Normotensive (n = 263)				Hypertensive (n = 33)				Normotensive (n = 270)				Hypertensive (n = 65)			
	PP	SV	TPR	C	PP	SV	TPR	C	PP	SV	TPR	C	PP	SV	TPR	C
Total Carbohydrates	NS	NS	NS	NS	NS	β = -0.94 p =0.007	NS	β = -0.46 p = 0.01	NS	NS	NS	NS	NS	NS	NS	NS
Total protein	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	β = 0.68 p =0.005	NS	NS
Total fat	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	β = -0.52 p =0.006	NS	NS
Mono-unsaturated fat	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	β = 1.34 p =0.003	NS	NS	NS
Poly-unsaturated fat	NS	NS	NS	NS	β = -0.53 p =0.007	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Saturated fat	NS	NS	NS	NS	NS	β = 0.77 p = 0.03	NS	NS	NS	NS	NS	NS	β = -0.98 p =0.008	NS	NS	NS
Fibre	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	β = -0.96 p =0.001	β = -0.47 p =0.002	NS	NS
Vitamin A	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	β = 0.51 p =0.001	NS	NS
Nicotinic acid	NS	NS	NS	NS	NS	β = 0.34 p = 0.04	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Biotin	NS	NS	NS	NS	NS	β = 0.30 p = 0.04	NS	β = 0.31 p = 0.04	NS	NS	NS	NS	NS	NS	NS	NS
Vitamin B_{12}	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	β = -0.40 p =0.03	NS	NS
Ascorbic acid	NS	NS	NS	NS	β = -0.32 p = 0.04	β = -0.51 p =0.001	NS	NS	NS	NS	NS	NS	β = -0.23 p = 0.04	NS	NS	NS
Vitamin E	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	β = -0.23 p = 0.04	NS	NS	NS
Magnesium	NS	NS	NS	NS	β = 1.39 p =0.001	NS	NS	NS	NS	NS	NS	NS	β = 0.85 p =0.002	NS	NS	NS
Manganese	NS	NS	NS	NS	β = 0.34 p = 0.03	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Phosphorus	NS	NS	NS	NS	β = -1.02 p = 0.01	NS	β = -0.59 p = 0.02	NS	NS	NS	NS	NS	NS	NS	NS	NS
Iron	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	β = 0.70 p =0.001	NS	NS	NS

NS indicates not significant (p > 0.05). Independent variables are regarded as a significant marker when $p \leq 0.05$.

In Table III the dietary intake of the dietary markers are compared against the dietary reference intake (DRI), recommended dietary allowances (RDA) or daily reference values (DRV) for the specific nutrients. From these data it is evident that most macronutrient intakes comply with the DRV. However, the intake of total carbohydrates and saturated fat of the female groups were below the prescribed DRV limits. The fibre, nicotinic acid, ascorbic acid, magnesium, phosphorus, iron and especially vitamin A and biotin intake of all the groups were well below the dietary reference intake. It was only vitamin B_{12} and manganese intake that were within the limits. Vitamin E intake of the female groups were within prescribed limits, but the male groups did not comply with the RDA values.

Table III. Dietary intake of subjects along with dietary reference intake for males and females aged 10 to 15 years.

Nutrient	Mean Dietary Intake[Ŧ]				Dietary reference intake
	Males		Females		
	Normotensive	Hypertensive	Normotensive	Hypertensive	
Total carbo-hydrates (g/d)	280.3 ± 108.9	278.8 ± 109.7	263.9 ± 97.2	253.9 ± 100.2	275-300[††]
Total protein (g/d)	62.8 ± 27.8	60.9 ± 25.9	58.6 ± 23.4	59.2 ± 23.0	50[††]
Total fat (g/d)	55.9 ± 39.9	59.8 ± 32.9	50.63 ± 30.9	52.4 ± 30.7	65[††]
Monounsatura-ted fat (g/d)	19.7 ± 14.9	20.8 ± 13.5	17.8 ± 11.6	19.2 ± 12.2	
Polyunsatura-ted fat (g/d)	12.2 ± 12.0	12.8 ± 8.4	11.1 ± 9.6	10.6 ± 8.6	
Saturated fat (g/d)	18.6 ± 14.8	19.8 ± 13.7	16.7 ± 11.4	17.8 ± 11.3	20[††]
Fibre (g/d)	15.4 ± 9.3	13.7 ± 6.2	14.2 ± 7.8	13.5 ± 7.5	25[††]
Vitamin A (μg RE/d)	369.3 ± 616.9	481.8 ± 752.1	406.8 ± 715.0	447.3 ± 684.5	1000[‡]
Nicotinic acid (mg NE/d)	11.9 ± 7.7	13.4 ± 7.4	11.6 ± 6.1	11.8 ± 6.7	M: 17 F: 15[‡]
Biotin (μg/d)	16.4 ± 16.2	15.2 ± 12.4	16.9 ± 16.9	14.1 ± 8.5	20-25[§¶]
Vitamin B_{12} (μg/d)	2.9 ± 4.7	2.4 ± 1.7	2.8 ± 4.7	2.9 ± 2.5	2[‡]
Ascorbic acid (mg/d)	42.4 ± 90.8	48.6 ± 74.3	36.2 ± 68.1	30.8 ± 41.1	50[‡]
Vitamin E (mg α-TE/d)	8.1 ± 7.7	7.4 ± 7.4	8.1 ± 8.1	8.8 ± 9.1	M: 10 F: 8[‡]
Magnesium (mg/d)	236.2 ± 125.6	229.3 ± 99.1	219.3 ± 95.6	207.9 ± 87.2	M: 240-410 F: 240-360[¶]
Manganese (μg/d)	2.3 ± 1.5	2.3 ± 1.2	2.2 ± 1.4	2.5 ± 1.5	2.0-5.0[¶]
Phosphorus (mg/d)	868.3 ± 432.3	887.1 ± 409.9	805.2 ± 374.9	787.6 ± 306.9	1250[‡]
Iron (mg/d)	8.4 ± 6.3	9.3 ± 4.6	8.1 ± 4.7	7.9 ± 3.9	M: 12; F: 15[‡]

[Ŧ] Values are means ± SD.
[‡] Recommended Dietary Allowances (RDA). Adapted from Food and Nutrition Board[27], 1989.
[§] Adequate Intakes (AI).
[¶] Adapted from Institute of Medicine, Food and Nutrition Board[42], 1998.
[††] Daily Reference Values (DRV) were established for adults and children over four years old. Adapted from Kurtzweil (1993), Food and Drug Administration[50].

When comparing the dietary intake of the normotensive and hypertensive groups there were almost no significant differences between the intake of the groups. The only significant difference ($p \leq 0.05$) was a higher manganese intake in the hypertensive female group compared to the normotensive group.

Discussion

This study examined relationships of dietary nutrients with pulse pressure, stroke volume, total peripheral resistance, and arterial compliance in growing children. The strengths of this study include the following: analysis of dietary recalls through a nutrient database that included both micro- and macronutrients; careful blood pressure measurement; data on major factors, such as weight and height, that affect cardiovascular parameters and are correlated with dietary intake. Updated normative blood pressure tables for children and adolescents are based on height percentiles because of the importance of height in determining blood pressure levels in children[20].

An association between a nutrient and disease is not the same as cause and effect which is why nutrients associated with hypertension are referred to as risk markers for hypertension. The findings are best viewed as indicators of potentially important dietary components that warrant further study.

The BMI of the male and female hypertensive groups were slightly higher than the normotensives, but there were no significant differences between the BMI and WHR of the groups of both sexes. From these results it seems as if obesity amongst black children are rare because of their dietary patterns and lifestyle, or alternatively the prevalence of hypertension among black children younger than 15 years cannot be ascribed to obesity.

When the dietary intakes of the normotensive and hypertensive groups were compared it was also evident that there were almost no significant differences between the intakes of the groups. The only significant difference ($p \leq 0.05$) that occurred was a higher manganese intake in the hypertensive female group when compared to the normotensive group. Expected differences in dietary intakes such as sodium, potassium, calcium, protein, lipids or fibre did not occur. Intake of sodium in all groups (1484.8 – 2071.6 mg/d) was higher than the estimated minimum requirements[27] of 500 mg but well below the upper limit of 6 g/day. Whether the dietary recall information of salt intake was reliable is uncertain because it is almost impossible to quantify salt added during food preparation or at the table. However, it has been demonstrated that dietary recall information on sodium consumption parallels 24-hour urinary sodium excretion[28].

Dietary factors that contributed significantly to the blood pressures of hypertensive children are similar to those indicated as deficiencies in primary school children of South Africa[29]. Vorster and co-workers[29] observed iron, vitamin A, folic acid and calcium deficiencies in pre-schoolers and primary school children. It was also evident that much less research has been done on adolescents, but iron and folic acid deficiencies were common and black children seem to have low vitamin A, E, B_6 as well as calcium status.

According to this study total carbohydrates, saturated fat, fibre, biotin, ascorbic acid, magnesium, phosphorus, total protein and fat, monounsaturated fat, polyunsaturated fat, vitamin A, nicotinic acid, vitamin B_{12}, vitamin E, manganese and iron intake are the strongest markers for PP, SV, TPR and C in black hypertensive children, although all markers were not applicable to every cardiovascular parameter (Table II). Most intakes of these nutrients were indicated as deficient in these children (Table III), but not only intake of these nutrients showed deficiencies. In accordance with the research of Vorster and co-workers[29], deficient intakes of vitamin A, vitamin B_6, iron, (Table III) and calcium were observed. Other deficient intakes, namely potassium, zinc, copper and pantothenic acid, were not indicated as markers for hypertension in this study, but were also observed in both normotensive and hypertensive children. It is evident that these children have sufficient intake of most macronutrients, namely total carbohydrates, total fat and total protein, but insufficient intake of most of the micronutrients. It is suspected that poverty, household food insecurity and other factors dictated by socio-economic realities, are important determinants of nutrient intakes and these insufficiencies are no exception to other nutritional studies done in South Africa[29].

Deficient intakes of potassium, calcium and magnesium, which are known for their anti-hypertensive properties[30,31,32] occurred in the hypertensive group, but the normotensive group also had low intakes of these nutrients. Thus hypertension could not be ascribed to the deficient intakes, but it could possibly be explained by a combination of genetic predisposition as well as specific nutritional deficiencies and probably other environmental factors.

Whether a person shows a deficient intake or not, the specific dietary factor could still be a marker for hypertension, which means that this dietary factor could accelerate or initiate the development of hypertension in a person who is genetically predisposed to be hypertensive.

The following relationships occurred only in the hypertensive subject groups and in none of the normotensive groups:

Macronutrients

The relationship between compliance, stroke volume and pulse pressure can be indicated as: C = SV/PP [6]. Thus, an inverse relationship exists between C and PP. Polyunsaturated fat showed and saturated fat showed inverse relationships with PP. Saturated fat has also shown a positive relationship with SV. From these results it seems as if polyunsaturated fat and saturated fat intake could be associated with lower pulse pressure. Total fat and monounsaturated fat, however, showed opposite results. A positive relationship between PP and monounsaturated fat and a negative association between total fat and SV might indicate that these types of fat are associated with an increase in pulse pressure. These results are in accordance to Nestel et al[33] who demonstrated that post-prandial remnant lipids appeared to impair arterial compliance, which might lead to an increase in pulse pressure.

The inverse relationship of carbohydrate intake with SV and with C comply with the relationship: C = SV/PP [6]. There is a paucity of literature to support this compliance lowering effect of carbohydrates. The findings from the Multiple Risk Factor Intervention Trial (MRFIT) reported an independent positive relationship of dietary starch to blood pressure[34]. Whether this positive relationship is due to a decrease in compliance, is unknown.

The INTERSALT study[35] and the Dietary and Nutritional Survey of British Adults[36] have found a significantly inverse relationship of dietary protein to systolic and diastolic blood pressure. The results of this study show that total protein has a positive relationship with SV, therefore indirectly also a positive relationship with C which might be associated with lower blood pressure. In another study of African Americans a significant positive correlation of protein intake with both systolic and diastolic blood pressure was reported[37].

The negative association of fibre intake with blood pressure has been well documented[24,38] and significant inverse associations of fibre intake with PP and SV suggest that fibre intake is associated with lower PP and SV.

Micronutrients

The relationships of vitamin A, vitamin B_{12} and nicotinic acid are not documented elsewhere. Relationships of vitamin A with blood pressure are the effect of elevated serum vitamin A on idiopathic intracranial hypertension[39], which does not explain the positive relationship with SV. Vitamin B_{12} has been shown to be beneficial and very effective in reducing plasma homocysteine levels. By reducing this risk factor for cardiovascular disease, vitamin B_{12} intake contributes to the lowering of blood pressure[40,41]. This association of vitamin B_{12} could be modulated by means of a SV or PP lowering effect.

Positive associations of biotin with SV and C were observed in the hypertensive male group. From our results it is evident that the dietary intake of biotin was well below the Adequate Intakes proposed for 10-15 year old children by the Institute of Medicine, Food and Nutrition Board[42]. Whether their dietary biotin intake was physiologically deficient for bodily functions is not clear, but the results indicate that despite their low biotin intakes, biotin showed a strong positive association with SV and C. Biotin was the only dietary nutrient positively associated with compliance. Because the vitamin synthesised by the microflora in the colon can be absorbed, cases of deficiency are rare and there is paucity of quantitative information about the biotin needs of humans[43].

Although biotin intake showed these relationships with C and SV in hypertensives, no significant differences were indicated between the biotin intakes of the normotensive and hypertensive groups. It might be explained by a genetic predisposition of the hypertensive group, but since information about the determinants of bio-availability of biotin remains unknown[44], the origin for the positive relationship to C and SV in hypertensives remains unclear. Whatever the origin might be, it seems as if biotin intake could play a preventative role in the aetiology of hypertension in black children.

Recent studies have documented that ascorbic acid improves endothelial function[45,46], and cause endothelial vasodilation by restoring nitric oxide activity. This might cause an increase in arterial compliance and explain the negative relationships in this study of ascorbic acid with PP.

Vitamin E treatment was found to lower blood pressure and increase membrane microviscosity and membrane permeability in rats[47]. It has also been shown that vitamin E improves arterial compliance in middle-aged men and women[48]. These findings are in agreement with the inverse relationship reported in this study between vitamin E intake and pulse pressure.

The strong positive associations of magnesium and PP are in contrast to the results of Hajjar and co-workers[25] who found a negative association between PP and magnesium. Reasons for these discrepancies might include racial differences, environmental factors or the fact that the children in this study showed deficient magnesium intakes.

Manganese also showed a positive relationship with PP and iron a positive relationship with PP. Studies in young spontaneously hypertensive rats showed that dietary iron caused no changes in blood pressure[49]. Whether this relationship of iron is caused by deficient intakes, is not clear. Manganese intakes, however, were sufficient, but the reason for this relationship remains unclear.

Strong inverse associations of phosphorus intake and PP and TPR were indicated. It seems as if phosphorus intake could play a role in reducing the vascular resistance (TPR), thereby reducing diastolic blood pressure.

Conclusions

The DASH (Dietary Approaches to Stop Hypertension) study showed that a diet high in fruits, vegetables and non-fat dairy foods, and low in saturated fat and total fat, will decrease systolic blood pressure by an average of 6 to 11 mmHg[15] and is effective in the prevention and control of high blood pressure. It is clear that low energy density of weaning foods and of the diets of especially rural black school children, coupled with a low intake of fruits, vegetables, legumes and milk by many individuals, are the main deficiencies in the South African diet[29]. The nutrient intake data of the THUSA BANA study supports these observations. In the present study hypertensive children had higher intakes (although not significant) of total fat and saturated fat and lower intakes of fibre than normotensive children (Table 3), which could indicate a trend in dietary patterns of the subjects.

Diets are made up of multiple nutrients, and one needs to take into account combinations of nutrients to estimate the effects of dietary patterns. Since dietary habits are potentially modifiable, the manipulation of diet could have a significant impact not only on blood pressure levels, but also on the rise in blood pressure with age. Since the impact of an individual nutrient on blood pressure is modified by the intake of other nutrients, it is important to assess the overall diet rather than any single nutrient in isolation when measuring the impact of diet on blood pressure[25].

In conclusion, the results of this study indicate strong associations of protein, polyunsaturated fats, fibre, vitamin A, vitamin C, vitamin E, nicotinic acid, vitamin B_{12}, biotin and phosphorus with the rate of hypertension in black South African children. The low intakes of these nutrients, amongst others, is a matter of serious concern, as is the increasing tendency towards urbanisation of prudent traditional diets, thereby increasing the risk of chronic lifestyle diseases such as hypertension. An optimal diet would thus be high in fruits and vegetables (fibre, vitamin A, C, B vitamins), whole-wheat cereals (B vitamins, fibre), milk, meat (protein, vitamin B_{12}, phosphorus) and nuts, for example peanuts (protein, vitamin E) and would probably contribute to a lower prevalence of future hypertension.

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5

The potential role of biotin as dietary risk marker for hypertension in black South African children: The THUSA BANA study

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ABSTRACT

Objective: The aim of this study was to determine whether biotin intake might contribute to the aetiology of hypertension in black children.

Design: Cross-sectional epidemiological study.

Setting: North West Province, South Africa.

Subjects: Children between 10 and 15 years of age were recruited from each of 30 schools over a period of two years (2000 to 2001). These children comprised 321 black males and 373 females from communities ranging from rural to urbanised. The male (n=40) and female (n=79) groups consisted of subjects with identified high-normal to hypertensive blood pressure. The normotensive group consisted of 281 black male and 294 female subjects.

Main outcome measures: Dietary intake, cardiovascular parameters.

Results: Biotin intake of all groups was below the adequate intake level of 20 μg/d. In the stepwise regression analysis biotin were significantly associated ($p \leq 0.05$) with systolic and diastolic blood pressure, along with arterial compliance and stroke volume of the hypertensive group. No significant associations were indicated for the normotensive group.

Conclusions: This study is the first to show that biotin might be regarded as a possible risk marker for the aetiology of hypertension in black children. Since dietary habits are potentially modifiable, the manipulation of diet could have a significant impact not only on blood pressure levels, but also on the rise in blood pressure with age. This means that there is a need for further research concerning the effect of biotin on adults.

KEY WORDS: biotin, hypertension, black children

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- Original articles of 3 000 words or less, with up to 6 tables or illustrations, should normally report observations or research of relevance to clinical medicine.

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  Price NC. Importance of asking about glaucoma. *BMJ* 1983; 286: 359-360.

Introduction

With especially smoking, obesity, hypertension and physical inactivity identified as the major risk factors for cardiovascular disease, recent scientific investigations have examined additional factors which contribute to the development of this disease[1]. Diet has been implicated as one of many factors that influence blood pressure[2] and hypertension is an important risk factor for cardiovascular disease and stroke.

Biotin is a water-soluble vitamin and its richest dietary sources include liver, kidneys, heart, pancreas, poultry, egg yolk and milk[3]. The majority of biotin in meats and cereals appears to be protein bound. But the absolute content of even the richest sources is low when compared to the content of most other water-soluble vitamins[4]. Biotin is also synthesised by the microflora in the colon. Free biotin is absorbed in the proximal small intestine by both facilitated and simple diffusion. Biotin can also be absorbed from the colon, which facilitates the utilization of the vitamin produced by hind gut microflora[5]. Despite increasing interest in biotin nutriture, considerable basic information concerning biotin bioavailability and nutritional status remains unknown[6].

Both marginal and frank biotin deficiencies occur rarely[1,4,6]. The only well-documented cases have occurred in association with total or near total intravenous feeding without biotin supplementation, chronic egg white feeding, or inborn errors of metabolism that lead to biotin wasting[7]. A single case that does not fit any of the three established associations is that of an infant fed a rice-based formula that was presumably very low in biotin[8].

According to Mock[9], however, reduced biotin status may not be rare. Except for the abovementioned cases biotin deficiency could occur in patients receiving long-term therapy with certain anti-convulsants[10,11], in children with severe protein-energy malnutrition[12] and in a substantial proportion of pregnant women with otherwise normal pregnancies[9,13].

The speculation that the human biotin requirement can always be met by the contribution of biotin produced by gut microflora[14] is in contradiction with the report of an infant who developed biotin deficiency while consuming a biotin-free, elemental formula[8].

The human biotin requirements in specific populations and at various ages remain uncertain and scientific knowledge is insufficient to provide estimated average requirements (EARs) and recommended dietary allowances (RDAs) in part because indicators of biotin status have not been validated[4,9]. Considerable basic information concerning biotin availability and nutritional status also remains unknown[6]. In cases such as this, adequate intakes (AIs) are provided[15]. Like RDAs, AIs are goals for the nutrient intake of individuals. The AI of biotin ranges from 20 μg (in 9-13 year olds) to 30 μg (in persons older than 19 years)[16].

Biotin functions as a mobile carboxyl carrier in four carboxylases of animals: pyruvate carboxylase, acetyl-CoA carboxylase, propionyl-CoA carboxylase, and 3-methylcrotonyl-CoA carboxylase. These roles of biotin link it to the metabolic roles of folic acid, pantothenic acid, and vitamin B_{12}[5].

According to Ho and Cordain[1] there may be a substantial link between cereal grain intakes and cardiovascular disease stemming from both biotin and essential fatty acid insufficiencies. The urgent need for further research concerning the potential role of biotin insufficiency as cardiovascular risk factor serves as motivation for this study.

Hypertension is common in the black population of Africa[17]. Studies in South Africa have shown that in the adult population of Durban, 25% of Zulus were hypertensive[18], where 20.7-22.8% of apparently healthy Tswana-speaking people were hypertensive in the North West Province[19].

By not only using cardiovascular parameters such as systolic and diastolic blood pressure, but also arterial compliance, pulse pressure and total peripheral resistance, a comprehensive study of the cardiovascular effects of biotin could be performed. Vascular compliance is defined as the change in volume of the artery per unit of pressure ($\Delta V/\Delta P$)[20] and could also easily be estimated from the simpler approach of stroke volume divided by pulse pressure[21].

As arterial compliance decreases, a rise in systolic blood pressure with a fall in diastolic blood pressure occurs[22]. This indicates pulse pressure amplifications. An increase in pulse pressure, caused by large artery stiffening, is an independent cardiovascular risk factor[23].

Dietary factors related to cardiovascular health of black children may be particularly important in this regard because blood pressure levels have been seen to track from childhood to adulthood[24,25] which means that high blood pressure levels in childhood may lead to hypertension in adulthood. It is also known that especially micronutrient deficiencies are present in black children in South Africa[26].

The THUSA BANA study (Transition and Health during Urbanisation in South Africa in Children; Bana = Children) was designed to assess the relationship between the level of urbanisation and the health status of children of the North West Province of South Africa. The aim of this part of the study was to determine whether biotin intake might contribute to the aetiology of hypertension in black children.

Methods

Study design

Thirty black schools were randomly selected from a list of schools of five regions of the North West Province in South Africa. These schools were visited during the weeks preceding the collection of data, in order to obtain permission from the relevant school principals as well as from the parents of the children. Children within the schools were also randomly selected. Data-collection took place during normal school hours.

Subjects

Children between 10 and 15 years of age were recruited from each of the 30 schools over a period of two years (2000 to 2001). These children comprised 321 black males and 373 females from communities ranging from rural to urbanised. The subject groups consisted of male (n=40) and female (n=79) groups with identified high-normal to hypertensive blood pressure. Hereafter these groups will be referred to as "hypertensive". Hypertension in children is defined as an average systolic or diastolic blood pressure greater than or equal to the 90th percentile for age and sex[27]. Height percentiles were also taken into consideration since body size is the most important determinant of blood pressure in childhood and adolescence[27]. The normotensive group consisted of 281 black male and 294 female subjects with blood pressure lower than the 90th percentile for age and sex (Table 1).

The Ethics Committee of the University of Potchefstroom approved the study and all the parents of the subjects gave informed consent.

Data collection and measurements

The subjects were all introduced to the experimental setup, after which each one was separately subjected to the following procedures:

Cardiovascular parameters

The subjects were connected to a Finapres (finger-arterial pressure) apparatus[28,29] and blood pressure was recorded continuously. After a period of rest of at least 10 minutes, resting blood pressure values were obtained. Blood pressure was regarded as resting when the systolic blood pressure did not change with more than 10 mmHg during the last minute of this period, otherwise the resting period was extended. The resting blood pressure was then recorded continuously for 1 minute. The data were stored on magnetic tape by means of a Kyowa RTP-50A four-channel data recorder and digitised for further analysis by means of the Fast Modelflo software program[30]. In this way the systolic (SBP) and diastolic blood pressure (DBP), stroke volume (SV), pulse pressure (PP), total peripheral resistance (TPR) and arterial compliance (C) were obtained.

Dietary intake

Dietary intake data were collected by fieldworkers trained by registered dieticians. A 24-hour dietary recall was collected face-to-face and the data collection interview method and nutrient coding were the same for all recalls. Food models and photo books for portion-size estimates were used for the recalls. This type of dietary assessment is widely used in international epidemiological studies[31,32,33]. Macronutrients (protein, fat, and carbohydrate), fibre, minerals (such as calcium, magnesium, sodium, potassium, and phosphorus), vitamins (such as A, B_6, B_{12}, C, D, E, and biotin) and cholesterol were calculated in the appropriate units, using a computer programme based on the South African food composition tables[34].

Statistical analysis

All processed data were transferred to Excel and further statistically analysed by means of the software computer package STATISTICA[35]. Due to skewed distributions all dietary variables were logarithmically transformed. Multivariate analyses and forward stepwise regression analyses were used to assess the association between SBP, DBP, SV, PP and C as dependent variables and the following (log-transformed) independent variables: dietary macronutrients (total protein, plant protein, animal protein, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, total carbohydrates, added sugar, energy), dietary fibre, dietary cholesterol, dietary minerals (calcium, magnesium, potassium, sodium, zinc, iron, phosphorus, copper) and dietary vitamins (vitamin A, thiamine, riboflavin, nicotinic acid, biotin, pantothenic acid, vitamin B_6, folic acid, vitamin B_{12}, ascorbic acid, vitamin E). Stepwise regression analyses were done to determine the most significant ($p \leq 0.05$) determinants of SBP, DBP, SV, TPR, PP and C in the four subject groups, namely normotensive males, hypertensive males, normotensive females and hypertensive females. Independent t-tests were used to determine if significant differences existed between two groups.

Results

The age, cardiovascular characteristics of participants at baseline and dietary intake values for biotin and total protein of the four subjects groups are shown in Table 1. The hypertensive and normotensive male groups showed significant differences between SBP ($p \leq 0.001$), DBP ($p \leq 0.001$), PP ($p \leq 0.05$) and TPR ($p \leq 0.05$). The hypertensive and normotensive female groups showed significant differences between SBP ($p \leq 0.001$), DBP ($p \leq 0.001$), C ($p \leq 0.05$) and PP ($p \leq 0.05$). Biotin intake and protein intake showed no significant differences between the groups. The mean biotin intake of all the groups was well below the adequate intake level of 20 µg/d prescribed for children aged 9-13 years[16]. The mean protein intake, however, was higher than the RDA values of 45-46 g/d for children aged 11-15 years[36].

Table 1. Characteristics of subjects: age, cardiovascular parameters and dietary intakes.

Variable	Males			
	N	Normotensive†	N	Hypertensive‡
Age (years)	281	12.5 ± 1.7	40	12.4 ± 1.5
SBP (mmHg)	281	96 ± 12**	40	120 ± 11**
DBP (mmHg)	281	61 ± 8**	40	81 ± 8**
C (ml/mmHg)	263	1.09 ± 0.40	33	0.98 ± 0.31
PP (mmHg)	263	34.1 ± 7.5*	33	38.1 ± 11.3*
TPR (mmHg.s/ml)	263	2.1 ± 1.2*	33	2.8 ± 1.4*
SV (ml)	263	34.14 ± 13.3	33	33.2 ± 11.3
Biotin intake (μg/d)	281	16.1 ± 15.8	40	15.4 ± 12.0
Total protein (g/d)	281	62.8 ± 27.8	40	60.9 ± 25.9
	Females			
	N	Normotensive	N	Hypertensive
Age (years)	294	12.6 ± 1.7	79	12.0 ± 1.9
SBP (mmHg)	294	96 ± 11**	79	123 ± 9**
DBP (mmHg)	294	63 ± 8**	79	78 ± 8**
C (ml/mmHg)	270	1.04 ± 0.36*	65	0.93 ± 0.38*
PP (mmHg)	270	36.5 ± 7.8**	65	45.7 ± 9.1**
TPR (mmHg.s/ml)	270	2.0 ± 0.8	65	2.2 ± 0.8
SV (ml)	270	34.2 ± 13.2	65	36.8 ± 14.5
Biotin intake (μg/d)	294	16.8 ± 16.3	79	15.9 ± 13.4
Total protein (g/d)	294	58.6 ± 23.4	79	59.2 ± 23.0

Values are mean ± SD

† Normotensive defined by blood pressure lower than the 90th percentile. Adjusted for age, sex and height.

‡ Hypertensive defined by blood pressure in the upper 10th percentile. Adjusted for age, sex and height.

* Significant $p \leq 0.05$; ** Highly significant $p \leq 0.001$

In the stepwise regression model (Table 2), with SBP, DBP, SV, C, PP and TPR as the dependent variable and all the dietary factors used as independent variables, biotin (β = 0.44) together with folic acid (β = -0.35), magnesium (β = 0.43) and added sugar (β = -0.29) accounted for 27.5 % of the variance in SBP (R^2 = 0.275) in hypertensive males. Biotin (β = 0.80) together with pantothenic acid (β = -0.53), added sugar (β = -0.24), zinc (β = 0.40) and energy (β = -0.27) explained 28.9 % of the variance in DBP in hypertensive males. Biotin (β = 0.31) with vitamin E (β = -0.18), nicotinic acid (β = 0.30), carbohydrates (β = -0.46), calcium (β = 0.33) and manganese (β = -0.21) accounted for 34.4 % of the variance in C in hypertensive males and biotin was the only independent variable that showed a significant ($p \leq 0.05$) relationship with C. In hypertensive females biotin (β = 0.24) together with vitamin A (β = -0.28), energy (β = 0.44), iron (β = -0.58) and folic acid (β = 0.30) accounted for 22.3 % of the variance in DBP.

Table 2. Stepwise regression of SBP, DBP, SV, C, PP and TPR as dependent variables with all dietary factors as independent variables, but only biotin results are indicated. Regression coefficients beta (β) and level of significance, *p* are shown.

	SBP	DBP	SV	C	PP	TPR
Males						
Normotensive	NS	NS	NS	NS	NS	NS
Hypertensive	$\beta = 0.44$, $p = 0.003$	$\beta = 0.79$, $p = 0.001$	$\beta = 0.30$ $p = 0.04$	$\beta = 0.31$ $p = 0.04$	NS	NS
Females						
Normotensive	NS	NS	NS	NS	NS	NS
Hypertensive	NS	$\beta = 0.24$, $p = 0.02$	NS	NS	NS	NS

NS indicates not significant ($p > 0.05$). Biotin intake is regarded as a significant marker when $p \leq 0.05$.

No significant dietary markers were indicated for any of the normotensive groups.

Discussion

The effects of a combination of dietary factors on blood pressure have recently been recognised as most important and specific attention to this matter is urgently needed[32]. To determine the associations of biotin with the cardiovascular parameters, it was necessary to include all the other dietary factors for the regression analysis to be valid, since the impact of an individual nutrient on blood pressure is modified by the intake of other nutrients[33].

The dataset of the biotin content of foods in the South African Food Composition Tables is not complete[34]. But all of the richest sources of biotin are included and the food sources that were left out, were food sources not normally ingested by children in these parts of South Africa, for example goat milk, cheese, roast duck, venison, rye bread and some ready-to-eat breakfast cereals. There were, however, also some missing data for some chicken dishes and soup powder.

Because reduced blood concentrations of biotin have been observed in children with severe protein-energy malnutrition[12], it was necessary to determine the protein intake of the subjects. According to the results in Table 1 none of the groups showed deficient protein intakes, but low biotin intakes were observed in all of the groups. It is, however, well known that the quality of the protein ingested by children from the low income group may be inferior[26].

Biotin showed strong positive associations with SBP, DBP, SV and C of the hypertensive groups, but no significant differences were indicated between the biotin intakes of the normotensive and hypertensive groups. It might be explained by a genetic predisposition of the hypertensive group, but since information about the determinants of bioavailability of biotin remains unknown[6], the origin for the positive relationships in hypertensives is unclear.

The positive associations of biotin with both C and SV are reflected in the equation: $C = SV/PP$ [21]. Biotin was the only dietary factor that was positively associated with arterial compliance and it seems as if biotin intake could possibly play a preventative role in the aetiology of hypertension in black children.

Low biotin intakes were observed in both normotensive and hypertensive groups, but it only showed strong relationships with cardiovascular parameters of the hypertensive group. This could mean that a suboptimal biotin status might accelerate or initiate the development of hypertension in a person who is genetically predisposed to be hypertensive.

The physiological meaning of the positive relationship between blood pressure and biotin intake may be explained by the following mechanism. A specific threshold for biotin intake is proposed and could cause an inversion of the cardiovascular effect of biotin. This means that insufficient intake of biotin could cause an increase in cardiovascular risk for hypertension. Due to the coenzymatic activity of biotin in the holocarboxylase complexes, insufficient amounts of exogenous biotin could affect elongation and desaturation of essential fatty acids, contributing to endothelial cell dysfunction[1]. A gradual increase in biotin intake could result in a higher risk until a threshold value is reached. From this point, which could also be a sufficient biotin intake, the cardiovascular risk could be lowered.

Conclusion

Current knowledge regarding the biotin content and bioavailability of biotin in common foods is limited[6]. Because biotin is produced by the microflora in the colon[5], dietary biotin intake is often regarded as unimportant and little thought is given to the possible effects of biotin on the development of cardiovascular diseases.

This study is the first to show that biotin might be regarded as a possible risk marker for the aetiology of hypertension in black children. Diets, however, are made up of multiple nutrients, and one needs to take into account combinations of nutrients to estimate the effects of dietary patterns. Since dietary habits are potentially modifiable, the manipulation of diet could have a significant impact not only on blood pressure levels, but also on the rise in blood pressure with age. This means that there is a need for further research concerning the effect of biotin on adults.

Since the impact of an individual nutrient on blood pressure is modified by the intake of other nutrients, it is important to assess the overall diet rather than any single nutrient in isolation when measuring the impact of diet on blood pressure[33]. A diet rich in fruits, vegetables, and non-fat dairy foods and low in saturated fat and total fat is proposed. Such a diet has been calculated to have a biotin content of about 25-30 μg per day. According to the DASH (Dietary Approaches to Stop Hypertension) study such a diet will decrease systolic blood pressure and it would be effective in the prevention and control of high blood pressure[37], in some cases as an adjunct to antihypertensive medication.

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6

Factor analysis of possible risks for hypertension in a black South African population

AE Schutte, JM van Rooyen, HW Huisman, HS Kruger, JH de Ridder

ABSTRACT

Objective: To examine the interrelationship of main hypertension risks by using factor analysis in order to detect underlying risk patterns.

Design: Two cross-sectional epidemiological studies.

Setting: North West Province, South Africa.

Participants: Apparently healthy subjects aged 16-70 years (N=1203) were recruited from 37 randomly selected sites throughout the North West Province during 1996-1998. Exclusion criteria were pregnancy, lactation, casual visitors, drunkenness, and treatment for chronic diseases, such as hypertension. Subjects with blood pressures exceeding 140/90 mmHg were classified as hypertensive.
Children aged 10-15 years were recruited from 30 randomly selected schools during 2000-2001 (N=694). Children were classified as hypertensive when an average systolic or diastolic blood pressure greater than or equal to the 90th percentile for age and sex were encountered, while correcting for height.

Main outcome measures: Hypertension risk factors: urbanisation, obesity, plasma fibrinogen, lipids, and insulin, serum gamma glutamyl-transferase, dietary intake, smoking, alcohol consumption.

Results: From twenty three risks the factor analysis disclosed five factors that explained 56.2% of the variance in the male and 43.5% of the variance in the female group: an urban malnutritional phenomenon, the metabolic syndrome X, a hypercholesterolaemic and obesity complex, an alcoholic hypertriglyceridaemia, and central and peripheral cardiovascular hypertensive effects.

Conclusions: South Africans migrating from rural to urban areas adapt to a new lifestyle with numerous risks resulting in conditions like malnutrition, the metabolic syndrome X, dyslipidaemia, alcoholism, obesity and increased peripheral vascular resistance. For successful prevention of hypertension in a population in transition, a whole risk pattern should be corrected, rather than an individual risk factor by implementing lifestyle modification programmes.

Key words: South African black population; hypertension; factor analysis; risk factors; metabolic syndrome X; malnutrition; dyslipidaemia; obesity; peripheral vascular resistance.

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- Tables: each table must have a title and should be assigned an Arabic numeral, e.g. (Table 3). Vertical rules should not be used. Tables should not duplicate the content of the text. Each table should consist of at least two columns. Table footnotes - information should be listed in the following order: abbreviations and symbols should be defined in the order in which they appear in the table; spell out all abbreviations and symbols used in the table, even if they have already been listed in previous tables or the text itself – when giving a key, use a comma rather than =, e.g. H, hypertensive and not H= hypertensive.

Introduction

It is known that age [1], gender [2], urbanisation [3], obesity [4] and certain dietary factors [5] could strongly influence the occurrence of essential hypertension. But to date, only a small number of studies investigated the pattern of associations within a set of hypertension risk factors.

A similar idea came from the work of Maruši [6] and Wright, Carbonari and Voyles [7] who examined interrelationship of standard coronary heart disease risk factors. Maruši [6] obtained a four-factor solution that involved dyslipidaemic and haemostatic complex, pure hypercholesterolaemia, metabolic syndrome X and family and medical histories.

Since hypertension is multifactorial [8] – as coronary heart disease – the factor analysis would be an ideal instrument to identify a small number of underlying risk patterns or to see whether specific risk factors tend to form patterns. No previous attempts have been made to detect underlying structure and patterns of hypertension risk factors by means of factor analysis. Since many of the risks for coronary heart disease overlap with hypertension risks, it is expected that some hypertension patterns will also overlap with the results of Maruši [6].

Since there is very little direct evidence about the determinants of common cardiovascular diseases in populations of sub-Saharan Africa according to the World Health Organisation [1], this study was done on primarily Tswana-speaking black South Africans. The effects of different population groups, when compared to the results of Maruši [6], will be evaluated.

The THUSA study (Transition and Health during Urbanisation in South Africa) was designed to assess the relationships between the level of urbanisation (strata) and measures of health status, such as blood pressure in the black adult population (aged 16 – 70 years) of the North West Province in South Africa [3]. Some of the objectives were: to assess the rate of hypertension in apparently healthy black subjects in the North West Province and to assess the relationship between dietary and anthropometric risk factors for cardiovascular disease and blood pressure. Two years after finishing this project a follow-up study in children (aged 10 – 15 years), namely the THUSA BANA study (Transition and Health during Urbanisation in South Africa in Children; Bana = Children) was done in the same province. This study was designed to assess the relationship between the level of urbanisation and health status of children of the North West Province.

The main aim of the present study was to examine the interrelationship of main hypertension risk factors: urbanisation [3], age [2], smoking [9], alcohol consumption [10], four measurements of lipid profile [11, 12], obesity [13], cardiovascular variables [14], certain dietary factors [15,16,17,18,19,20], plasma fibrinogen [21] and fasting insulin [22] in a black South African population by combining the results of the THUSA and THUSA BANA studies.

Methods

The detail of the methods used in the THUSA and THUSA BANA study are published elsewhere [3,23]. However, the methods used during the THUSA and THUSA BANA study are summarized here in short.

Study design

THUSA subjects were recruited from 37 randomly selected sites throughout the North West Province from 1996 to 1998. Visits were made to these sites during the weeks preceding the collection of data, in order to get permission from government officials and tribal chiefs to work in the area and to notify the local community of the visit of the research team [3].

For the THUSA BANA study thirty black schools were randomly selected from a list of schools in the five regions of the North West Province from 2000 to 2001. These schools were visited during the weeks preceding the collection of data, in order to obtain permission from the relevant school principals as well as from the parents of the children. Children within the schools were also randomly selected from class lists. Data collection took place during normal school hours. Both studies were cross-sectional.

Local organisers assisted in the recruitment of subjects and had to ensure that the subjects fasted overnight (adults) prior to the day of the study.

In the THUSA study, besides two rural strata (people living in tribal areas, stratum 1 and people living on farms, stratum 2), three different strata of urbanisation were distinguished for urban subjects, namely stratum 3 for the subjects living in informal settlements, stratum 4 for subjects living in established townships with full access to water and electricity and stratum 5 for fully westernised subjects living in western-type houses in upper-class suburbs [3].

In the THUSA BANA study (children) three strata were identified, namely people living in rural areas, stratum 1, people living in informal settlements, stratum 2, and stratum 3 for people living in established urban areas.

Subjects

During the THUSA study all volunteers were recruited during a period of 5 days at each site. Inclusion criteria were apparently healthy men and women 15-70 years of age. Exclusion criteria were pregnancy, lactation, casual visitors, drunkenness, and treatment for chronic diseases, for example hypertension and diabetes mellitus. A total of 963 male and female subjects were used. Subjects who had systolic and/or diastolic blood pressures greater than 140 and 90 mmHg, according to the WHO cut-off points (WHO, 1999), were classified as hypertensive.

In the THUSA BANA study apparently healthy children between 10 and 15 years of age were recruited from each of the 30 schools. A total of 694 black male and female subjects were used. Children were classified as hypertensive when an average systolic or diastolic blood pressure greater than or equal to the 90th percentile for age and sex were encountered [24]. Height percentiles were also taken into consideration since body size is the most important determinant of blood pressure in childhood and adolescence [24].

Subjects from the above-mentioned studies were classified into three age groups to investigate the different risks of the age groups. Group A consisted of children aged 10 to 15 years (n=694), group B consisted of adolescents and adults aged 16 to 40 years (n=583) and group C consisted of adults aged 41 to 70 years (n=380).

Both studies have been approved by the Ethics Committee of the Potchefstroom University and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. All THUSA subjects and all parents of the THUSA BANA subjects gave informed consent.

Data collection and Measurements

The subjects were all introduced to the experimental setup, after which each one was separately subjected to the following procedures:

Blood pressure

The subjects were connected to a Finapres (finger-arterial pressure) apparatus [25,26] and blood pressure was recorded continuously. After a period of rest of at least 10 minutes, resting blood pressure values were obtained. Blood pressure was regarded as resting when the systolic blood pressure did not change with more than 10 mmHg during the last minute of this period, otherwise the resting period was extended. The resting blood pressure was then recorded continuously for 1 minute. The data was stored on magnetic tape by means of a Kyowa RTP-50A four-channel data recorder and digitised for further analysis by means of the Fast Modelflo software program [27]. In this way the systolic (SBP), and diastolic blood pressure (DBP), cardiac output (CO) total peripheral resistance (TPR) and arterial compliance (C) were obtained.

Anthropometric measurements

Anthropometric measurements were done by qualified anthropometrists under guidance of a level III anthropometrist, according to standard methods as described by Norton and Olds [28]. Maximum height was measured to the nearest 0.1 cm by means of a stadiometer with the head in the Frankfort plane. Weight was measured to the nearest 0.1 kg by means of a calibrated electronic scale (Precision Health scale) with the subject wearing the minimum clothing. The waist and hip girths of the subjects were measured with a flexible Lufkin steel anthropometric tape to the nearest 0.1 cm. During these measurements the subject had to stand erect with the feet together and without volitionally contracting the gluteal muscles.

The following equations were used to determine body mass index and waist-to-hip ratio [28]: BMI = body mass (kg)/stature^2 (m); WHR = waist girth (cm)/hip girth (cm).

Skinfolds were taken using a Harpenden skinfold caliper with a jaw pressure of 10 g/mm^2 and were taken to the nearest 0.2 mm by using the standard methods as described by Norton and Olds [28]. Percentage body fat was calculated according to the equation of Boileau [29].

Dietary intake

Dietary intake data were collected face-to-face by fieldworkers trained by registered dieticians. The data collection interview method and nutrient coding were the same for all questionnaires. Food models and photo books for portion-size estimates were used.

A validated quantitative food frequency questionnaire (QFFQ) [30] was used during the THUSA study. The QFFQ is adapted specifically for the black community of the North West province and the repeatability and validity were satisfactory [31].

A 24-hour dietary recall questionnaire was used during the THUSA BANA study. This type of dietary assessment is widely used in international epidemiological studies [32,33,34].

The results obtained with the above-mentioned questionnaires are basically the same. Different questionnaires were used because the subjects of the THUSA BANA study (aged 10 to 15 years) were too young to fully understand and answer the QFFQ meaningfully.

Macronutrients (plant protein, animal protein, saturated fat) dietary fibre, dietary micronutrients (sodium), and dietary vitamins (vitamin A, vitamin B_6, vitamin E) were calculated in the appropriate units, using a computer programme based on the South African food composition tables [35].

Plasma fibrinogen, serum lipids, serum gamma glutamyl-transferase (s-GGT) and insulin

Blood samples were drawn from the vena cephalica or medial cubital vein of the THUSA subjects only. The plasma and serum were prepared according to standard methods. Biochemical analyses were done in independent laboratories, using standardised methods [3].

Smoking

Smoking habit was assessed by means of a questionnaire specifically developed for the THUSA study population.

The main variable of the study was the *presence or absence of hypertension.* Subjects were classified as hypertensive according to WHO guidelines [1] and guidelines of the Task Force Report on High Blood Pressure in Children and Adolescents [24]. Twenty three exploratory variables were identified and constituted of main hypertension risk factors:

- *level of urbanisation* as presented by the strata;
- *smoking and utilisation of alcohol;* smoking habit was coded as 1 or 0 and alcohol consumption was presented by s-GGT values;

- *total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride* as four measurements of lipid profile;
- *obesity;* presented by *body mass index (BMI)* and *percentage body fat (%BF),* and central obesity presented by *waist-to-hip ratio (WHR)*;
- *cardiovascular parameters*; *cardiac output (CO), total peripheral resistance (TPR), arterial compliance (C), and pulse pressure (PP)* were calculated;
- *dietary intake*; intake of saturated fat, plant protein, animal protein, fibre, sodium, iron, vitamin A, vitamin B_6 and vitamin E;
- *plasma fibrinogen*;
- *fasting insulin values.*

Statistical analysis

The software computer package STATISTICA [36] was used. Due to skewed distributions all dietary variables, insulin and fibrinogen values were logarithmically transformed. Independent t-tests were done on all parameters to determine whether significant differences existed between the normotensive and hypertensive subjects. Obtained data were subjected to factor analyses. The main applications of factor analytic techniques are to reduce the number of variables and to detect structure in the relationships between variables. Therefore, factor analysis is applied as a data reduction or structure detection method [36]. Factor analysis could thus be successfully used to identify a small number of underlying hypertension risk patterns which explain most of the variance observed in a much larger number of risks [37]. The varimax raw rotation method was chosen.

Results

Figure 1 indicates the rate of hypertension in both sexes of the three age groups. It is evident that the females showed an overall higher hypertension rate than the males. In the youngest group A the females showed a significant higher rate of 21.4% than the 12.5% of the male group. The oldest group C showed the highest rate of hypertension.

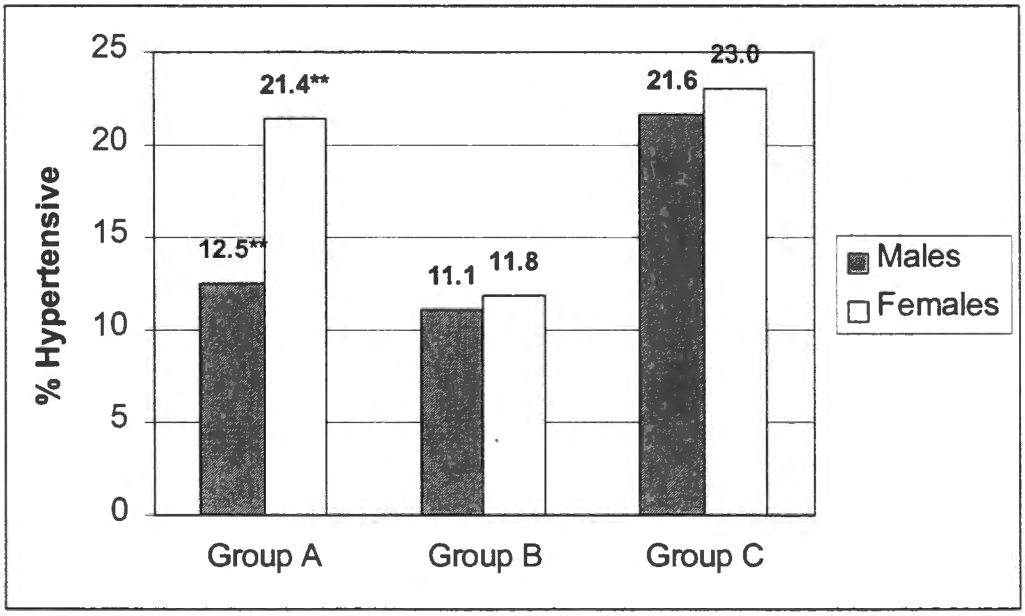

Figure 1. Rate of hypertension in the three age groups
Group A: aged 10-15 years (N=695); Group B: aged 16-40 years (N=760); Group C: aged 41-70 years (N=443); **$p < 0.001$; Hypertensive children defined by blood pressure greater than the 90th percentile - adjusted for age, sex and height. Hypertensive adults who have SBP and DBP greater than 140/90 mmHg.

In Table 1 the following basic characteristics of the different age groups are indicated: number of subjects (N), age, body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP). The significant differences ($p \leq 0.05$) between the normotensive and hypertensive groups are also indicated. Highly significant differences ($p \leq 0.001$) between SBP and DBP of the normotensive and hypertensive groups are an indication of a successful classification of normotensive and hypertensive subjects.

Table 1. Subject characteristics of the different age groups

	Men		Women	
	NT[†]	HT[‡]	NT	HT
Group A (10-15 years)				
N	281	40	294	80
Age (years)	12.5 (1.75)	12.4 (1.5)	12.6 (1.7)*	12.0 (1.9)*
Body mass index (kg/m^2)	16.6 (2.5)	17.3 (3.4)	18.1 (3.8)	18.9 (4.3)
SBP (mmHg)	95.8 (11.5)**	120.1 (11.4)**	99.6 (11.0)**	122.0 (10.4)**
DBP (mmHg)	61.4 (7.8)**	81.1 (7.7)**	62.9 (7.6)**	77.5 (9.4)**
Group B (16-40 years)				
N	283	53	377	47
Age (years)	26.2 (6.8)*	29.2 (6.6)*	27.3 (6.8)*	30.3 (6.5)*
Body mass index (kg/m^2)	20.9 (3.3)	21.4 (6.9)	25.7 (6.1)	26.0 (5.8)
SBP (mmHg)	110.6 (13.7)**	141.5 (12.9)**	110.5 (14.5)**	146.7 (15.3)**
DBP (mmHg)	71.4 (10.2)**	94.2 (11.7)**	68.8 (10.4)**	95.6 (10.8)**
Group C (41-70 years)				
N	139	62	184	58
Age	54.8 (9.9)	52.2 (7.1)	52.5 (8.3)	51.5 (7.9)
Body mass index (kg/m^2)	21.9 (4.2)	22.4 (4.4)	28.3 (6.8)	26.5 (6.8)
SBP (mmHg)	113.7 (14.9)**	142.8 (14.9)**	111.6 (15.7)**	149.3 (16.2)**
DBP (mmHg)	70.9 (11.6)**	94.7 (10.2)**	67.8 (11.1)**	92.1 (15.1)**

Values in parentheses are standard deviations. NT, normotensive; HT, hypertensive; N, number of subjects, SBP, systolic blood pressure; DBP, diastolic blood pressure; significant difference: $*p \leq 0.05$; highly significant difference $**p \leq 0.001$; [†] Normotensive children defined by blood pressure lower than the 90th percentile. Adjusted for age, sex and height. Normotensive adults who have SBP and DBP lower than 140/90 mmHg. [‡] Hypertensive children defined by blood pressure higher than the 90th percentile. Adjusted for age, sex and height. Hypertensive adults who have SBP and DBP greater than 140/90 mmHg.

Significant differences ($p \leq 0.05$) between other variables are indicated in Table 2. Again, significant differences were indicated for most cardiovascular parameters in all three groups, as suspected. A higher percentage body fat, higher levels of urbanisation (strata), serum cholesterol, triglycerides, fibrinogen, dietary saturated fat and animal protein were detected in the hypertensives groups, while the hypertensives also had significantly lower levels of dietary plant protein and vitamin E intake.

Table 2. Significant differences (p ≤ 0.05) encountered between all variables of normotensive and hypertensive subjects in the three age groups

	Men		Women	
	NT†	HT‡	NT	HT
Group A				
N	280	39	292	80
CO (L/min)	2.64 (1.02)	2.64 (0.86)	2.83 (1.03)*	3.19 (1.27)*
TPR (mmHg.s/ml)	2.13 (1.21)*	2.80 (1.35)*	2.01 (0.80)	2.19 (0.75)
C (ml/mmHg)	1.09 (0.40)	0.98 (0.31)	1.04 (0.36)*	0.92 (0.38)*
PP (mmHg)	34.1 (7.5)*	38.1 (11.3)*	36.4 (7.8)**	45.7 (9.0)**
% BF	13.5 (5.5)*	15.9 (6.9)*	22.4 (7.0)	22.6 (7.3)
Group B				
N	283	53	377	47
Stratum	2.95 (1.43)**	3.69 (1.01)**	2.73 (1.37)*	3.36 (1.15)*
TPR (mmHg.s/ml)	1.72 (0.61)**	2.44 (1.14)**	1.86 (0.64)**	2.74 (1.13)**
C (ml/mmHg)	1.73 (0.28)**	1.38 (0.22)**	1.19 (0.20)*	1.02 (0.79)*
PP (mmHg)	39.1 (11.2)**	47.3 (14.9)**	41.6 (10.8)**	51.1 (15.4)**
TC (mmol/L)	3.71 (0.93)*	4.10 (0.94)*	3.86 (0.91)	4.12 (1.03)
HDLC (mmol/L)	1.11 (0.37)*	1.37 (0.55)*	1.08 (0.28)	1.15 (0.37)
Triglycerides (mmol/L)	1.04 (0.83)	1.09 (0.73)	0.93 (0.48)**	1.25 (0.97)**
Dietary saturated fat (g/d)	20.3 (9.8)	20.3 (7.8)	17.4 (8.6)*	20.7 (10.7)*
Dietary animal protein (g/d)	31.1 (17.3)	34.7 (17.4)	26.5 (14.4)*	31.89 (17.2)*
Dietary plant protein (g/d)	40.0 (18.8)*	33.5 (14.3)*	31.2 (13.1)	30.4 (10.9)
Plasma fibrinogen (g/L)	2.98 (0.96)*	3.30 (1.26)*	3.46 (1.18)*	3.90 (1.46)*
Group C				
N	139	62	184	58
Stratum	2.40 (1.44)*	2.98 (1.23)*	2.33 (1.37)*	2.77 (1.35)*
CO (L/min)	3.85 (1.29)*	3.23 (1.45)*	3.38 (0.99)**	3.06 (1.20)**
TPR (mmHg.s/ml)	1.63 (0.79)**	2.78 (1.58)**	1.74 (0.72)**	2.69 (1.38)**
C (ml/mmHg)	1.69 (0.35)**	1.17 (0.26)**	1.23 (0.28)**	0.85 (0.22)**
PP (mmHg)	42.8 (11.9)*	48.0 (17.5)*	43.8 (10.9)**	57.1 (21.2)**
Dietary vitamin B_6 (mg/d)	1.01 (0.59)	0.93 (0.63)	0.82 (0.40)*	0.95 (0.57)*
Dietary vitamin E (mg α-TE/d)	11.40 (7.04)*	9.35 (4.27)*	9.72 (4.93)	9.62 (6.07)

NT, normotensive; HT, hypertensive; N, number of subjects; CO, cardiac output; TPR, total peripheral resistance; C, arterial compliance; PP, pulse pressure; %BF, percentage body fat; TC, total cholesterol; HDLC, high density lipoprotein cholesterol; significant difference: *p ≤ 0.05; highly significant difference **p ≤ 0.001; † Normotensive children defined by blood pressure lower than the 90th percentile. Adjusted for age, sex and height. Hypertensive adults who have SBP and DBP lower than 140/90 mmHg. ‡ Hypertensive children defined by blood pressure higher than the 90th percentile. Adjusted for age, sex and height. Hypertensive adults who have SBP and DBP greater than 140/90 mmHg.

With the factor analysis (see Tables 3, 4 and 5) it was possible to investigate the number of various subgroups or factors and to identify what these subgroups represent conceptually.

The factor analysis of the two oldest male groups B and C provided eight factors with eigenvalues greater than 1.00 (4.31, 2.83, 2.44, 3.01, 2.04, 1.63, 1.41, 1.27), but the first factor was a simple combination of all dietary factors. The remaining seven factors explained 56.2% of total variance of hypertension risk. Table 3 displays the structure matrix of the seven-factor solution.

Table 3. Structure matrix of the factor analysis of risk factors for hypertension in male subjects aged 16 and older

Risk factors for hypertension	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6	Factor 7
Urbanisation	**0.63**						
Age	**-0.42**	**0.41**	**0.50**				
Dietary saturated fat	**0.70**						
Dietary animal protein	**0.80**						
Dietary sodium	**0.45**						
Dietary vitamin A	**0.59**						
Dietary vitamin B_6	**0.57**						
Central obesity (WHR)	**-0.35**	**0.37**	**0.57**				
Smoking		**0.65**					
Plasma fibrinogen		**0.40**			**0.56**		
Insulin		**-0.53**					
Serum cholesterol			**0.84**				
LDLC			**0.86**				
Triglyceride			**0.41**	**0.80**			
Body mass index			**0.68**		**0.31**		
s-GGT				**0.90**			
HDLC					**-0.86**		
Incidence of hypertension						**0.86**	
Peripheral resistance						**0.55**	**-0.73**
Arterial compliance						**-0.81**	**0.34**
Pulse pressure							**0.87**
Cardiac output							**0.91**
Dietary plant protein							
Dietary fibre							
Dietary iron							
Dietary vitamin E							
% variance explained	11.6	4.9	10.9	6.2	5.4	7.8	9.4

LDLC, low density lipoprotein cholesterol; s-GGT, serum gamma glutamyl transferase; HDLC, high density lipoprotein cholesterol

The factor analysis of the two oldest female groups B and C also provided eight factors with eigenvalues greater than 1.00 (4.89, 2.43, 2.08, 2.61, 1.55, 1.84. 1.42, 1.49). The first and third factors were left out. The first was again a simple combination of all dietary factors and the third a combination of all cardiovascular parameters. The remaining seven factors explained 43.5% of total variance of hypertension risk. Table 4 displays the structure matrix of the six-factor solution.

Quite similar results were found when factor analysis was applied to groups B and C separately. Those results are not tabulated but will be incorporated into the discussion.

Table 4. Structure matrix of the factor analysis of risk factors for hypertension in female subjects aged 16 and older

Risk factors for hypertension	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
Urbanisation	**0.65**					
Dietary saturated fat	**0.55**					
Dietary plant protein	**-0.31**					
Dietary animal protein	**0.74**					
Dietary sodium	**0.37**					
Dietary vitamin A	**0.61**					
Dietary vitamin B_6	**0.49**					
Insulin	**0.44**	**0.54**				
Body mass index		**0.55**	**0.31**			
HDLC		**-0.74**				
Plasma fibrinogen		**0.40**			**0.45**	
Smoking		**-0.31**		**0.50**	**0.31**	
Age			**0.41**	**0.46**		
Triglyceride			**0.45**	**0.55**		
Serum cholesterol			**0.96**			
LDLC			**0.94**			
s-GGT				**0.70**		
Central obesity (WHR)				**0.69**	**0.71**	
Incidence of hypertension					**0.75**	**-0.43**
Pulse pressure						**0.44**
Peripheral resistance						**-0.90**
Cardiac output						
Arterial compliance						
Dietary fibre						
Dietary iron						
Dietary vitamin E						
% variance explained	10.1	5.9	9.3	7.1	5.7	5.4

s-GGT, serum gamma glutamyl transferase; LDLC, low density lipoprotein cholesterol; HDLC, high density lipoprotein cholesterol

Those cardiovascular risk factors obtained through a blood sample analysis could not be performed in the THUSA BANA study because rural black children were not so willing to donate a blood sample. Therefore, factor analysis for this age group was done separately. Table 5 displays the structure matrix for both males and females of the youngest group A. The two factors for the male group explained 22.0% of total variance (eigenvalues: 3.06, 1.11) and the three factors of the female group explained 36.4% of total variance of hypertension risk (eigenvalues: 3.71, 1.61, 1.61).

Table 5. Structure matrix of the factor analysis of risk factors for hypertension in subjects aged 10 to 15 years

Risk factors for hypertension	Males		Females		
	Factor 1	Factor 2	Factor 1	Factor 2	Factor 3
Urbanisation	**0.46**				**0.30**
Age	**0.94**		**0.88**		
Body mass index	**0.35**		**0.39**		**0.77**
Central obesity (WHR)	**-0.30**		**-0.60**		
% Body fat			**0.37**		**0.78**
Cardiac output	**0.78**		**0.84**	**0.38**	
Peripheral resistance	**-0.42**		**-0.81**		
Arterial compliance	**0.95**		**0.89**		
Incidence of hypertension		**0.81**		**0.76**	
Pulse pressure				**0.88**	
Dietary vitamin E		**-0.53**			**0.33**
Dietary saturated fat					
Dietary plant protein					
Dietary animal protein					
Dietary fibre					
Dietary sodium					
Dietary iron					
Dietary vitamin A					
Dietary vitamin B_6					
% variance explained	16.1	5.9	19.5	8.5	8.4

Factor analysis extracted seven factors, each consisting of clusters of risks for hypertension as seen for the groups in Table 3 and 4. Five patterns are extracted from these results:

The first factor (Factor 1) is characterised by high intakes of saturated fat, animal protein, sodium, vitamin A and B_6 and a high level of urbanisation. These variables correlated negatively with age and central obesity. This factor is also characterised by a low intake of plant protein and a high insulin level in female subjects. In the female subjects of group B (aged 16-40) low intakes of plant protein, fibre, iron and vitamin E, as well as high values for insulin and urbanisation level were clustered together. In the females of the youngest group A (Table 5) factor 3 also indicates a combination of BMI, % body fat, urbanisation level and vitamin E intake. This factor forms the first pattern, named *urban malnutritional phenomenon.*

Since some of the variables of the second and fifth factors overlap and both are characterised by approximately the same risks, they are combined to form the *metabolic syndrome X*. These elements include: an increased body mass index and waist-to-hip ratio (central obesity), hypertension, insulin resistance, a high triglyceride value (indicated for male subjects of group C), and a low HDLC value. Except for these major features of the metabolic syndrome X, the following syndrome X associated factors are also positively indicated [38,39]: smoking, hyperfibrinogenaemia and age.

The third factor is *hypercholesterolaemic and obesity complex* associated with increased aging (total serum cholesterol, LDLC, triglycerides, BMI, central obesity and age).

The fourth factor is named *alcoholic hypertriglyceridaemia* (serum gamma glutamyl-transferase and triglycerides) associated with old age, smoking habit and central obesity.

The sixth and seventh factors of Tables 3 and 4 are combined and named *central and peripheral hypertensive effects.* This pattern is also evident in factors 1 and 2 of the young subjects indicated in Table 5.

Discussion

The genesis of hypertension is complex and cannot readily be simplified. In any given patient one factor may be more important than others, but often hypertension is multifactorial [8].

The exploratory factor analysis was performed to see whether the given risks tend to form patterns in the different groups. This study was based on the work of Maruši [6], who examined interrelationship of coronary heart disease risk factors. All of these factors are, however, not confirmed by the present study. In this study of African subjects factor analysis extracted five basic patterns of risk factors for hypertension as seen for the groups in Tables 3, 4 and 5.

The first pattern was named *urban malnutritional phenomenon* as it was characterised by high dietary intakes of nutrients such as saturated fat, animal protein and sodium known to increase blood pressure [15,17,18] (Table 3 and 4). Although plant proteins have been shown to have a hypocholesterolaemic effect, the subject is still a matter of debate [40]. No blood pressure fall was reported in trials with specific nutrient change from animal to vegetable protein at a fixed level of total protein [41,42]. In the present study, however, plant protein was distinguished from other nutrients in not contributing to the effects of the others on urbanisation. In the young female group B plant protein was associated with fibre, iron and vitamin E while correlating negatively with urbanisation. It seems as if plant protein plays a protective role in the urbanisation process and lowers blood pressure [43]. It has also been suggested that a high saturated fat intake could induce insulin resistance independently of obesity [44]. A high intake of saturated fat in these urbanised communities might contribute to the development of insulin resistance.

Several elements constituting the *metabolic syndrome X* [39] – a severely atherogenic state – were investigated in this series, including hypertension, insulin resistance, dyslipidaemia (hypertriglyceridaemia and decreased HDL cholesterol) and central obesity type, characterised by localisation of fat on the upper body. Other associated factors, namely smoking habit, hyperfibrinogenaemia and age, also became evident. All these were included in the second pattern, which should be, without any reservations, named the metabolic syndrome X [38,39,45]. A more complete pattern of this syndrome were found in the present study when compared to the results of Maruši [6] who found hypertension, dyslipidaemia, central obesity and glucose metabolism disorders to form the pattern *metabolic syndrome X.* Whereas the present study in black subjects also identified smoking habit, hyperfibrinogenaemia and age, together with the suspected insulin resistance.

The third pattern, *hypercholesterolaemic and obesity complex*, that was associated with increased aging, was almost a simple combination of total cholesterol and LDL, the latter being the major carrier of cholesterol to the cells of the peripheral tissues. Not surprisingly, the association between LDL and total cholesterol was very strong. They also correlated with triglyceride, which forms a core of LDL with cholesterol [6]. Aside from the lipids correlating with one another, strong associations were also found with obesity and aging. This is in concordance with a study in children which suggests that hypercholesterolaemic children have greater body fat, the expression of the hypercholesterolaemia precedes the expression of increased body fat, and body fat increases with age [46].

Alcoholic hypertriglyceridaemia, the fourth factor, was not a surprising pattern, but its positive association with age, smoking habit and central obesity in the females (table 4) are a clustering of factors associated with an increase in plasma plasminogen activator inhibitor-1 (PAI-1) [47], thus linked to the risk of ischaemic heart disease. According to Lakshman *et al.* [48] chronic moderate alcohol consumption correlated with a favourable plasma lipid and lipoprotein profile in normal, but not in obese, men. But obesity, as indicated in the results of the present study, is associated with an adverse plasma lipid and lipoprotein profile and race, alcohol intake, and obesity may be important modifiers of coronary artery disease in hypertensives [48].

The last pattern encountered, namely *central and peripheral hypertensive effects*, is a replica of the results observed in black South Africans of different age groups in a study of Van Rooyen *et al.* [49]. They indicated that urbanised males older than 45 years had an increased total peripheral resistance (peripheral effect) when compared to a rural group younger than 25 years with an increased cardiac output (central effect). Therefore, urbanisation caused the change from a central to peripheral effect.

The results of De Champlain *et al.* [50] in a study of hypertensive patients, also support the present results. Hypertensive subjects showed a smaller increase in cardiac output and a greater increase in peripheral resistance when compared to normotensive subjects. In the present study the youngest group A (table 5) showed a strong positive association between urbanisation and cardiac output, together with arterial compliance, while correlating negatively with total peripheral resistance. However, in the adult groups (tables 3 and 4) it was evident that the incidence of hypertension and total peripheral resistance correlated positively, while hypertension correlated negatively with cardiac output and arterial compliance. There was a shift from a centrally acting mechanism (high CO), probably of β-adrenergic origin, in the 10-15 year olds to a more peripheral mechanism (high TPR), presumably α-adrenergic in origin, in the subjects 40 years and older.

This condition may be triggered initially by sympathoadrenal hyperactivity, which would result in attenuation of beta-adrenergic receptors, while alpha-adrenergic functions are potentiated in cardiovascular tissues of hypertensive patients [51]. Structural changes and adaptation in the intima of the blood vessels could also contribute to the higher total peripheral resistance in the older subjects. Factors, associated with aging, such as smoking, alcohol consumption, low physical fitness and obesity, are causes of elevated haemostatic factors like fibrinogen and plasma plasminogen activator inhibitor-1 [19,47].

Conclusions

Hypertension, a complex combination of genetic and environmental influences, requires exploration of all risks simultaneously to detect underlying structure and pattern. Obviously, all five extracted biological risk patterns fit well into recent medical theories about risk of developing hypertension. Few studies have, however, proposed specific underlying structures that indicate the risks of hypertension in relation to one another and possibilities of interactions between different risk patterns. It is when studying a combination of risk factors that specific observations, such as the protective effect of plant protein intake on the consequences of the urbanisation process, like high blood pressure and insulin resistance (Table 4), could be seen clearly.

Results of the THUSA and THUSA BANA studies in South Africa sketch a picture of a mainly Setswana-speaking black population migrating from traditional rural to urban areas while adapting a new lifestyle to which their ancestors were not accustomed to. This new lifestyle includes numerous risks such as malnutrition because of unavailability of healthy food sources, abundant availability of tobacco and alcohol as well as social and psychological stresses like no running water and electricity in informal settlements and extremely high crime rates. For a successful therapeutic intervention study it is necessary to focus on and change a whole pattern, rather than individual risk factor correction to improve the prevention of hypertension. The latter should be coupled with educational programmes, lifestyle modification and some psychological treatment to increase probabilities of smoking cessation and weight reduction, which would in turn have positive impact on at least two broader risk patterns presented in this study.

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7

General Findings and Conclusions

1 Introduction

In this chapter, a summary of the main findings from the four papers reported in this thesis will be given. The results from each paper will be discussed, interpreted, elucidated and compared to the relevant literature in the separate chapters. Recommendations to health professionals will be made from these findings. The general discussion in this chapter will therefore focus on the compatibility of the main findings and recommendations following from each paper in order to provide risk markers and dietary guidelines for the management of hypertension in black people of South Africa.

2 Summary of the main findings

The salient findings of the four papers reported in this thesis were:

1. **Dietary risk markers for hypertension (Chapter 3)**

   In complying to the aim of this paper, the following dietary factors were identified as risk markers in hypertensive black children: total energy, biotin, folic acid, pantothenic acid, zinc, iron, magnesium and vitamin A intakes. These dietary factors were the strongest markers for systolic, diastolic and mean blood pressure.

   The most profound results were those found with dietary biotin, where strong positive associations were observed throughout with systolic and diastolic blood pressure of hypertensive children. It was evident that, amongst other nutrients, biotin intake was well below the Adequate Intakes for 10 to 15 year old children. Despite this low intake, biotin showed a strong positive association with blood pressure. Folic acid, on the other hand, indicated negative relationships with blood pressure – although intakes were also deficient – and was significantly associated with lower blood pressure.

   These dietary factors are identified as risk markers that could be associated with the development of hypertension in black children.

2. **Dietary markers of hypertension associated with pulse pressure and arterial compliance (Chapter 4)**

   As a follow-up on the first paper, the aim of this paper was to focus mainly on the association of dietary nutrients with cardiovascular parameters of the peripheral vasculature, such as arterial compliance and peripheral vascular resistance, but also on pulse pressure and stroke volume. Especially macronutrient intakes, such as carbohydrates, protein, saturated fat, and monounsaturated fat, but also magnesium, iron and manganese, were associated with higher pulse pressure and decreased arterial compliance.

   Dietary biotin intake showed somewhat contradictory results, namely associated with increased stroke volume, but also with increased arterial compliance of hypertensive black children – being the only nutrient to be associated with increased arterial compliance.

   When placing the emphasis on the overall dietary intake of these black children, it was quite clear that most had low micronutrient intakes. Although vitamin C and E intakes did not comply to Recommended Dietary Allowances, both were associated with lower pulse pressure. An imbalance between the intake of micro and macronutrients results in malnutrition, which might be reflected in a warped profile of the cardiovascular health of these children.

3. Role of biotin as dietary risk marker for hypertension (Chapter 5)

Results of the first two papers forced further investigations concerning the associations and possible mechanism of action of biotin on the cardiovascular system. Biotin intake again showed strong positive associations with systolic and diastolic blood pressure, stroke volume and arterial compliance of hypertensive children. The positive association of biotin with arterial compliance could indicate that biotin intake might possibly play a protective role in the development of hypertension in children. It was also clear that dietary intake of biotin were insufficient in normotensive and hypertensive subjects, with the mean intake being well below the Adequate Intakes for 10 to 15 year old children.

There is still a contradiction that exists: biotin intake is associated with increasing systolic blood pressure, diastolic blood pressure, and stroke volume, but it also has the beneficial association with arterial compliance. Whether the insufficient biotin intakes of these children are the cause of this phenomenon is uncertain, but it could be possible that a suboptimal biotin status might accelerate or initiate the development of hypertension in a person who is genetically predisposed to be hypertensive.

4. Five hypertension risk patterns identified in a black African population (Chapter 6)

By placing dietary intake, as a modifiable environmental factor, in relation to other known risks for hypertension, the contribution of diet becomes more clearly evident. By complying to the objectives of this paper, five basic patterns of risk factors for hypertension in children (THUSA BANA) and adult South African subjects (THUSA) were extracted by means of factor analysis:

i) *Urban malnutritional phenomenon*, characterised by a high level of urbanisation and high dietary intakes of nutrients such as saturated fat, animal protein and sodium. Plant protein, fibre, iron and vitamin E correlated negatively with urbanisation.

ii) *Metabolic syndrome X*, characterised by a higher age, insulin resistance, central obesity, dyslipidaemia (hypertriglyceridaemia and decreased HDL cholesterol), hypertension, smoking habit, and hyperfibrinogenaemia.

iii) *Hypercholesterolaemia and obesity complex*, was associated with increased aging, obesity, and a combination of total cholesterol and LDL.

iv) *Alcoholic hypertriglyceridaemia*, showed positive associations with age, gamma glutamyl-transferase, plasma triglycerides, smoking habit and central obesity in the females. A clustering of these factors are associated with an increase in plasma plasminogen activator inhibitor-1, thus linked to the risk of ischaemic heart disease.

v) *Central and peripheral hypertensive effects*, indicated that hypertension in children is positively associated with cardiac output and negatively with peripheral vascular resistance, while in hypertensive adults the incidence of hypertension and peripheral vascular resistance correlated positively, while hypertension correlated negatively with cardiac output and arterial compliance. Therefore a shift from a centrally acting mechanism (high cardiac output) to a more peripheral mechanism (high peripheral resistance) in subjects 40 years and older. A typical volume-loading type of hypertension in the population group studied (Guyton & Hall, 2000; Opie, 1998).

It was evident from the results that certain risk factors of the children were intensified in the adult subjects. Especially anthropometrical parameters of obesity, such as body mass index and waist-to-hip ratio, but no nutrients, were intensified when compared to the adults.

A compact summary of the main findings from the results of the first three papers (Chapter, 3, 4 and 5) are summarised in Table 7.1.

When the results from this study (Table 7.1) are compared to results found in the literature (as presented in Table 2.2, Chapter 2), it is evident that certain findings confirmed those found in the literature. Examples are the associations with lowered blood pressure of folic acid (Prasad, 1999), ascorbic acid (Das, 2001), pantothenic acid (Schwabedal *et al.*, 1985), vitamin B_{12} (Chait *et al.*, 1999), vitamin E (Pezeshk & Dalhouse, 2000), and fibre intake (He & Whelton, 1999), as well as associations with increased blood pressure of monounsaturated fat (Simons-Morton *et al.*, 1997). But there are also findings that are in contrast with the literature, including the positive association of magnesium intake with blood pressure (Das, 2001) (especially pulse pressure), the positive associations of blood pressure with zinc (Bergomi *et al.*, 1997) and nicotinic acid (Kelly *et al*, 2000), the positive association of pulse pressure with iron (Hatton *et al.*, 1991), while pulse pressure is also associated with lower diastolic blood pressure. Also the negative association of diastolic pressure with vitamin A intake (Jacobson *et al.*, 1999), the negative association of pulse pressure with polyunsaturated fats, and while saturated fat intake is associated with lower pulse pressure of females (Simons-Morton *et al.*, 1997), it seems to be associated with higher stroke volume of male subjects.

Discrepancies exist in the literature regarding the effects of carbohydrate and protein intake (Stamler *et al.*, 1996; Hajjar *et al.*, 2001), and it is clear from results of this study that both are associated with higher blood pressure of this population group.

Certain results from the literature are not evident in this study, such as the association of sodium chloride on blood pressure. Attention given to the association of sodium chloride with blood pressure in this study was restricted because it was difficult to measure sodium chloride intake accurately with the questionnaires used. The subjects could not report the volume or weight of table salt used in cooking or at the table.

However, other results were evident in this study, but not in the literature. These included the positive association of diastolic blood pressure with high total energy intake in females, the positive association of pulse pressure with manganese intake in the males, the negative association of phosphorus intake with pulse pressure and total peripheral resistance in the male subjects, and last but not least, the positive associations of systolic and diastolic blood pressure, as well as stroke volume and arterial compliance with low biotin intake. It is therefore urgent to investigate these results further, not only on systolic and diastolic blood pressure level, but by focusing on other cardiovascular parameters such as endothelial function, arterial compliance and pulse pressure.

Discrepancies between the results of this study and the literature might be explained by racial differences, since the main focus of the literature is on Caucasian populations, while this study focused on black subjects. Another difference is that children were used as subjects in this study compared to adults in most studies in the literature. Intake of quite a number of dietary factors were deficient, which might also exert an influence on the results. The study method used, namely 24-hour recall questionnaires, cannot provide accurate data on the habitual intakes of all nutrients (Hammond, 2000).

Table 7.1 Summary of the associations of dietary factors with cardiovascular parameters of hypertensive black children

Dietary factor	Cardiovascular parameters						
	SBP	DBP	BP	PP	C	SV	TPR
MALE SUBJECTS:							
Saturated fat						↑	
Polyunsaturated fat				↓			
Total carbohydrate					↓	↓	
Vitamins							
Water-soluble							
Nicotinic acid						↑	
Folic acid	↓		↓				
Ascorbic acid				↓		↓	
Pantothenic acid		↓					
Biotin	↑	↑	↑		↑	↑	
Minerals							
Macrominerals							
Magnesium	↑			↑			
Phosphorus				↓			↓
Microminerals/Trace elements							
Zinc		↑					
Manganese				↑			
FEMALE SUBJECTS:							
Energy		↑					
Total protein						↑	
Total fat						↓	
Saturated fat				↓			
Monounsaturated fat				↑			
Fibre				↓		↓	
Vitamins							
Fat-soluble							
Vitamin A		↓				↑	
Vitamin E				↓			
Water-soluble							
Vitamin B_{12}						↓	
Ascorbic acid				↓			
Biotin		↑					
Minerals							
Macrominerals							
Magnesium				↑			
Microminerals/Trace elements							
Iron		↓		↑			

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BP: Blood pressure; PP: Pulse pressure; C: Arterial compliance; SV: Stroke volume; TPR: Total peripheral resistance; ↑: Increase; ↓: Decrease

The results of the fourth paper (Chapter 6) placed the role of dietary intake in relation to the roles of urbanisation, blood lipids, age, insulin resistance, plasma fibrinogen, obesity, smoking habit, alcohol consumption and cardiovascular parameters. By extracting the pattern, *urban malnutritional complex*, it became evident that dietary factors like saturated fat, animal protein and dietary sodium, known to increase blood pressure, are associated with the urbanisation process, which is also known to be associated with a higher prevalence of hypertension in black South Africans (Van Rooyen *et al.*, 2000). Plant protein, fibre, iron and vitamin E intake, on the other hand, were negatively associated with urbanisation. These results confirmed the results of the first three papers and forms part of the objective of this study, namely to identify dietary risk markers for hypertension and to examine the interrelationship of these risk factors observed in the pattern, *urban and malnutritional complex*.

3 Discussion of main findings

Chance, Bias and Confounding

Before the main findings of this epidemiological study could be discussed, it is important to reflect critically on some important factors that might have affected the results. There are some methodological issues that could have caused weaknesses in this study, and therefore, might have influenced the outcomes.

At first, the number of subjects, especially those classified as hypertensive, could be questioned. The THUSA BANA project consisted of a total of 1257 subjects, which means that a limited number of subjects were available for hypertension classification. A forced availability sample of subjects were used as subject groups. If larger subject groups were available, it could have lead to more plausible and reliable results. This could therefore definitely be stated as a weakness of this study. Another possible weakness is the method of classification of hypertensives. Although the proposed and standardised method was used (National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents, 1996), the classification could be criticised in the same way as using pure statistics in biological sciences, namely leaving no room for individual and physiological differences.

Although the 24-hour dietary recall method was used to acquire dietary data from the children, results could be queried because of individual differences in presenting or recalling their dietary intake. Although trained field workers were used to overcome the language barrier, the strange and unknown situation might have exerted an effect on especially the young children from rural areas. Because of the magnitude of the THUSA BANA project, different field workers had to be used and it was therefore not possible to use the same person throughout. This measurement of dietary intake might therefore have been imprecise. The dietary data was skewed, even after being logarithmically transformed, which might be a result of the method used. The means of nutrient data had a wide spread, indicated by a high standard deviation, and was also a factor indicating that more subjects should have been used and that the measures were not that accurate.

Concerning biotin results, the possibility of **chance** should be taken into account. With 31 nutrients used in the forward stepwise regression analysis, statistics have indicated that one out of twenty significant correlations may be because of chance. With relation to the significant results found with biotin, the possibility therefore does exist that it might be explained by chance, but the results might also be plausible. This does not only account for biotin, but also for all other nutrient associations found in this thesis. The correlations of biotin with other nutrients should also have been more closely investigated, since certain nutrients act together in fulfilling their function.

A focus on the dietary patterns of this population could have resulted in a better indication of the dietary needs of this group, than the current focus on specific dietary nutrients. The results are therefore more focused on individual nutrients and their possible mechanisms, than on a dietary pattern and its consequences.

Information bias. The possibility that hypertensive subjects represented their dietary data in a different manner than the normotensive subjects, without knowing that they were hypertensive is unlikely, and this possibility is dismissed. Another possibility is that certain subjects were more restless or afraid because of the strange procedures – despite the fact that they were informed about the procedures – while their blood pressure measurements were taken, which could lead to a false high blood pressure.

Selection bias. Although it was attempted to draw representative samples from the population in the North West Province, it is possible that the subjects did not represent the population from which they were selected. Schools were randomly selected from the province. Children were then randomly selected from class lists obtained from the Department of Education before the days of measurement. On the day that a school was visited, some children were absent from school which meant that a substitute had to be used. This could have influenced the results of the study. Another possibility is that there are unknown factors that differentiate the hypertensive children from the normotensive children, other than being hypertensive. Although this is possible, it is unlikely.

Confounders. The association between an exposure and its health outcome (as described on page 4 in Chapter 1), could strongly be affected by confounders. The confounder, as an extraneous factor, could lead to over- or under-estimation of the association between the dietary factor (exposure) and hypertension (health outcome). Sex, as possible confounder in this study, was addressed by the classifications of male and female groups. Although the ages of the subjects in chapters 3-5 were all between 10 and 15 years, it is possible that it could have influenced the classification of normotensive and hypertensive subjects, because age is known to be one of the strongest predictors of hypertension. Body size and the level of development of the children, which are also known predictors of hypertension in children, could have had the same effect. Environmental factors, such as social relationships, living conditions, AIDS, stunted growth and poverty might all be regarded as possible confounders. Although Tswana-speaking field workers were used as translators, the understanding of the procedures by the subjects could not be guaranteed and could therefore have had confounding effects on the outcome of the study.

Confounders can also mask a real association, such as the strong associations between most nutrients that can mask the effect that a specific nutrient might have on blood pressure.

In the interpretation of the results in this thesis it was attempted to interpret statistical results from a physiological standpoint at all times, while keeping in mind that a statistical significance does not necessarily mean physiological significance, and vice versa.

When comparing the findings of this study (Table 7.1) to results found in the literature (Table 2.2), it is especially the contribution of the following group of nutrients that is highlighted: biotin, folic acid, ascorbic acid, vitamin E and magnesium.

Biotin intake

Biotin is often referred to as the *forgotten vitamin* (Said, 2002), possibly because considerable basic information concerning biotin bioavailability and nutritional status remains unknown (Said, 1999). Despite controversies concerning whether biotin deficiencies could occur (Mock, 1999; Said, 1999) – which is confirmed in this study – little is known about the effects of biotin on the cardiovascular system.

Ho and Cordain (2000) were the first to indicate that there may be a substantial link between cereal grain intakes and cardiovascular disease stemming from both biotin and essential fatty acid insufficiencies. Although biotin content in cereal grains appear to be high, digestibility and absorption are commonly very low. Poor digestion of cereal grains stems from the presence of unabsorbable biotin complexes (Ho & Cordain, 2000). With the black South African population ingesting cooked maize porridge in large quantities, coupled to a low intake of fruits, vegetables, legumes and milk (Vorster *et al.*, 1997), it is possible that this might link them to biotin and essential fatty insufficiencies.

The physiological meaning of the positive relationship between blood pressure and biotin intake observed in this study, may be explained by the following mechanism: a specific threshold for biotin intake is proposed and could cause an inversion of the cardiovascular effect of biotin. This means that insufficient intake of biotin could cause an increase in cardiovascular risk for hypertension. Due to the coenzymatic activity of biotin in the holocarboxylase complexes, insufficient amounts of exogenous biotin could affect elongation and desaturation of essential fatty acids, contributing to endothelial dysfunction (Ho & Cordain, 2000) (see Table 7.1 – biotin is positively associated with arterial compliance). A gradual increase in biotin intake could result in a higher risk until a threshold value is reached. From this point, which could also be a sufficient biotin intake, the cardiovascular risk could be lowered.

With this study being the first to show that biotin might be regarded as a possible risk marker for hypertension in black children, the urgent necessity for further research arise. A prospective study would be the comparison of hypertensive white children with black children, as well as adults in the North West Province of South Africa. By focusing on the level of endothelial cells and arterial compliance the effects of biotin could also be closely investigated.

Folic acid

It is well documented that folic acid supplementation can lower homocysteine levels in subjects with hyperhomocysteinaemia. By reducing this risk factor for cardiovascular disease, folic acid intake contributes to the lowering of blood pressure (Chait *et al.*, 1999). The literature is confirmed by the results of the present study, namely the significant reduction in blood pressure of hypertensive black children by folic acid intake. Woo *et al.* (1999) indicated that folic acid supplementation improves arterial endothelial function in adults with relative hyperhomocysteinaemia, with potentially beneficial effects on the arteriosclerotic process. The same mechanism could also be prevalent in the children of the present study.

The active form of folic acid, 5-methyltetrahydrofolate (MTHF), has also been reported to restore nitric-oxide status in hypercholesterolaemic patients (Stroes *et al.*, 2000). Stroes and co-workers (2000) indicated direct effects of MTHF on the enzymatic activity of nitric-oxide synthase in endothelial cells. By improving arterial compliance via this mechanism, the blood pressure levels could therefore be lowered.

Ascorbic acid

Ascorbic acid intake has shown to be significantly associated with reduced pulse pressure in hypertensives of both gender groups. Pulse pressure, a powerful predictor of cardiovascular disease, could be lowered by increasing arterial compliance (Dart & Kingwell, 2001). It has also been shown in other studies that treatment of hypertensive patients with ascorbic acid lowered blood pressure (Duffy *et al.*, 1999). A hypothesis for this mechanism is that ascorbic acid may reduce blood pressure through a nitric-oxide mediated mechanism. Ascorbic acid has also been shown to improve endothelium-dependent vasodilation in essential hypertension (Taddei *et al.*, 1998) and in patients with hypercholesterolaemia (Ting *et al.*, 1997), and to restore nitric-oxide mediated flow-dependent dilation in patients with heart failure (Hornig *et al.*, 1998). By exerting these beneficial effects on the endothelium, supplemental ascorbic acid could improve the effects of hypertension in children to prevent the occurrence of hypertension in adult life.

Vitamin E

Results for vitamin E intake were similar to that of ascorbic acid, namely being associated with lower pulse pressure of hypertensive children. These results are confirmed by the literature. Vitamin E treatment has also shown to lower blood pressure, and increase membrane fluidity in rats (Pezeshk & Dalhouse, 2000). It has been reported that vitamin E inhibit progression of hypertension and improve endothelial function and antioxidant status. Vitamin E also correct vascular remodelling. These beneficial effects of vitamin E, as antioxidant in vascular damage associated with hypertension, are related to alteration in vessel redox state (Touyz *et al.*, 2000).

Magnesium

Results of the present study showed that magnesium is positively associated with pulse pressure of hypertensive male and female children. The results also indicated that magnesium intake of the subjects were insufficient, whereas hypertensives of both sexes showed a lower magnesium intake than the normotensives, although not a significant difference. The literature, on the other hand, indicates a negative association between magnesium and pulse pressure (Hajjar *et al.*, 2001), implying that magnesium intake has a beneficial effect on hypertension.

This apparent contradiction could be explained by the deficient magnesium intakes of the subjects, because it is well known that magnesium deficiency could induce hypertension (Johnson, 2001; Miyagawa *et al.*, 2000).

Attention is growing for a potential role of magnesium in the patho-aetiology of cardiovascular disease. Magnesium modulates mechanical, electrical and structural functions of cardiac and vascular cells, and small changes in extracellular magnesium levels and intracellular free magnesium concentration may have significant effects on cardiac excitability and on vascular tone, contractility and reactivity (Laurant & Touyz, 2000). But the therapeutic value of magnesium in the management of essential hypertension is unclear, so is the role of magnesium on the endothelium unclear. A study by Miyagawa and co-workers (2000) indicated that magnesium removal impairs the inhibitory function of the endothelium against contraction induced by norepinephrine, without affecting endothelium-dependent relaxation in response to acetylcholine. This possible mechanism might therefore account for the positive association between the low magnesium intakes of the THUSA BANA subjects with pulse pressure.

At all times it must be kept in mind that the impact of one dietary or non-dietary factor on blood pressure is modified by the effect of another dietary or non-dietary factor. It is therefore necessary to have a focus regarding blood pressure control that is not too narrow, but wide enough to include the possibility that a combination of any of these factors could have a potentiating effect and coupled with genetic predisposition could lead to a higher prevalence of hypertension.

4 Conclusions

The results of this study complied to the aims and objectives set in Chapter 1.

- Dietary factors were identified as risk markers that could be associated with hypertension in black children. Amongst others, the following dietary markers could be singled out: biotin, folic acid, ascorbic acid, vitamin E and magnesium. The associations of dietary factors were investigated in depth by using a range of cardiovascular parameters, including systolic and diastolic blood pressure, arterial compliance, pulse pressure, cardiac output, peripheral vascular resistance, and stroke volume.
- As a follow-up on the first papers biotin or low biotin intakes were recognised as contributing to the prevalence of hypertension in black children. Specific mechanisms were proposed for this finding.
- The interrelationships of risk factors for hypertension in black South Africans were described in terms of risk patterns, suggesting that these risk patterns be addressed in future hypertension intervention trials, rather than correcting a single known risk factor.

The major contributions of this study probably lie in the results of biotin intake as marker for hypertension, but also in the results found with specific cardiovascular parameters, such as arterial compliance, stroke volume, peripheral vascular resistance and pulse pressure. It has been shown in previous studies, for example, that pulse pressure is a powerful predictor of cardiovascular disease, but the association of pulse pressure with diet has not been well studied (Hajjar & Grim, 2000). Since a recent review of publications stated that there is a paucity of studies examining the effects of multiple nutrients and/or macronutrients in children (Simons-Morton & Obarzanek, 1997), manuscripts in this thesis have also contributed. Lacking evidence regarding the determinants of hypertension in large populations such as in sub-Saharan Africa (WHO, 1999) is addressed by proposing five patterns of hypertension risks that occur in a black South African population.

There are abundant literature regarding hypertension research of westernised Caucasian populations, but literature concerning the black population of South Africa, are lacking to a great extent. Not only has this black population unique characteristics, living conditions and religious beliefs – which make extrapolation from Caucasian populations difficult and impede the task of the researcher – but to obtain research funds is another obstacle a researcher in South Africa has to overcome.

The results of this study are therefore valuable in contributing to the current knowledge regarding the black South African population, and since only associations of nutrients and cardiovascular parameters were investigated it could also give direction for future clinical research concerning cause and effect relationships that could be used for recommendations to health professionals (see Recommendations).

5 Recommendations

Results from the four papers reported in this thesis led to the formulation of additional recommendations that can be used by policy makers and health departments of government, the food industry and health professionals for prevention of cardiovascular diseases. Although this study was not designed to determine nutrient needs, the recommendations could possibly prevent the development of hypertension.

For a successful therapeutic intervention study it is strongly recommended to focus on and change a whole pattern of risk factors, rather than individual risk factor correction, for example adjusting a person's whole diet, and not only restricting sodium chloride consumption. Since it is suspected that black children from the THUSA BANA study suffer from malnutrition, a diet that is rich in protein, fibre, vitamin A, vitamin C, vitamin E, nicotinic acid, folic acid, vitamin B_{12}, biotin and phosphorus is recommended, because it could possibly prevent the development of hypertension in black children. A balanced intake of polyunsaturated, saturated and monounsaturated fatty acids is also needed.

A diet consisting of above-mentioned nutrients, namely rich in fruits, vegetables, non-fat dairy foods and low in saturated fat and total fat (Appel *et al.*, 1997) is therefore proposed. Since deficient biotin intake is associated with the occurrence of hypertension in children, such a diet will be ideal to supply an adequate biotin content of about 25-30 μg per day, compared to the dietary reference intake of 20-25 μg per day (Combs, 2000). The results of this study also indicated that there is a need for further research concerning the effect of biotin in the development of hypertension, such as the effect of biotin on endothelium function and arterial compliance.

The recurrence of results in the literature and this study that low dietary intakes of essential micronutrients exist in black children, forces the author to strongly recommend that the government implement fortification programmes, nutritional and health educational programmes, not only for children, but also for rural adults of the black population. For example, children in schools need education on how to choose healthy foods and in some remote rural areas a total school meal programme is a necessity. These programmes should be coupled with lifestyle modification and psychological support to increase probabilities of smoking cessation, moderate alcohol consumption, weight reduction and elevated physical fitness levels.

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