The Association Of Body Weight And Circumferences With Metabolic Risk Factors In Chinese Men and Women

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ABSTRACT

Eva Katz: The association of body weight and circumferences with metabolic risk factors in Chinese men and women
(Under the direction of June Stevens, PhD)

One nation facing a dramatic rise in the prevalence of adult overweight and obesity is China, where rates have increased approximately 400% in the past 20 years. This research examined issues related to the risks of adiposity in Chinese men and women including the associations between body mass index (BMI) and incident hypertension compared to American Blacks and American Whites; the interaction between BMI, age and parental history of hypertension on hypertension prevalence; and finally the influence of hip circumference on the components of the metabolic syndrome.

Data were from Chinese Asian, American Black and American White men and women from three prospective, observational studies of the natural history and risk factors for cardiovascular disease. Chinese Asians (young and middle-aged adults) were from the People’s Republic of China (PRC) study, American Black and American White young adults were from the Coronary Artery Risk Development in Young Adults (CARDIA) study and American Black and American White middle-aged adults were from the Atherosclerosis Risk in Communities (ARIC) study. Our goal was to predict risk differences and since binomial and Poisson models did not converge, we fit logistic regression models and calculated the adjusted standardized estimates using the “prvalue” command in Stata (Version 10.0).

The effects of BMI on hypertension incidence were stronger in Chinese Asians compared to American Blacks and Whites; effect modification of the BMI-hypertension
relationship by age and parental history of hypertension status was detected; and despite the relative leanness of the Chinese population, a larger hip circumference was associated with a lower risk of incident metabolic risk factors when controlling for overall adiposity. These data expand on our understanding of the impact of elevated body weight and a larger hip circumference in a Chinese population.
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LIST OF ABBREVIATIONS

AL: Alabama
ARIC: The Atherosclerosis Risk in Communities
BMI: Body mass index (kg/m²)
BP: Blood pressure
CA: California
CARDIA: The Coronary Artery Risk Development in Young Adults Study
CDC: Centers for Disease Control and Prevention
CHD: Coronary heart disease
CI: Confidence interval
CM: Centimeter
CRP: C-reactive protein
CSCC: Collaborative Studies Coordinating Center
CT: Computerized tomography
CVD: Cardiovascular disease
DASH: Dietary Approaches to Stop Hypertension
DBP: Diastolic blood pressure
DXA: Dual energy X-ray absorptiometry
HC: Hip circumference
HDL: High density lipoprotein cholesterol
HDL-C: High density lipoprotein cholesterol
Health ABC: The Dynamics of Health, Aging and Body Composition
ID: Incidence difference
IL: Illinois
IL-6: Interleukin-6

IRB: Institutional review board

LDL: Low density lipoprotein cholesterol

JNC 7: The Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure

Kg/m²: kilograms per square meter

MESA: Multiethnic Study of Atherosclerosis

mg/dl: Milligrams per deciliter

mmHg: Millimeters of mercury

mmol/l: Millimoles per liter

MN: Minnesota

MONICA: Monitoring Trends and Determinants in Cardiovascular Disease

NCEP: National Cholesterol Education Program

NEFA: Non-esterified fatty acids

NHANES: National Health and Nutrition Examination Survey

NHLBI: National Heart, Lung and Blood Institute

NIH: National Institutes of Health

OAC: Obesity in Asia Collaboration

OR: Odds ratio

PD: Prevalence difference

PRC: The People’s Republic of China

REGARDS: Reasons for Geographic and Racial Differences in Stroke

ROC: Receiver operating characteristic

RZ: Random zero mercury sphygmomanometer

SBP: Systolic blood pressure

SD: Standard deviation
SE: Standard error
SHARE: Study of Health Assessment and Risk in Ethnic groups
TG: Triglycerides
TNF-α: Tumor necrosis factor-alpha
UNC: University of North Carolina
U.S.: The United States of America
VIF: Variance inflation factor
VLDL: Very low density lipoprotein cholesterol
WC: Waist circumference
WHO: World Health Organization
WHR: Waist-to-hip ratio
LIST OF SYMBOLS

* = Significant difference (p<0.05) between groups based on Wald test
I. **INTRODUCTION**

A. **Background**

Over the past few decades, the prevalence of overweight and obesity has increased globally. One nation facing a dramatic rise in weight status is China. Along with global expansion and economic development, overweight and obesity have increased approximately 400% over the past 20 years among Chinese adults.\(^1\) This dissertation research will examine several issues related to the risks of obesity in Chinese men and women. Specifically, it will focus on the associations between body mass index (BMI) and hypertension, the interaction between BMI, age and parental history of hypertension and finally the effect of hip circumference on the components of the metabolic syndrome.

Numerous studies have shown an increase in hypertension and other metabolic risk factors with increasing BMI. The level of risk at a specific level of obesity often varies by ethnicity. Epidemiologic studies on Chinese populations have observed an increase in metabolic risk factors at a BMI of 21-24 kg/m\(^2\), values considered normal by the World Health Organizations (WHO) standards (\(>18.5\) to \(<25\) kg/m\(^2\)).\(^2\)\(^-\)\(^5\) Based on this literature a BMI of 23 or 24 kg/m\(^2\) is commonly suggested to be a more meaningful cutpoint to define overweight within China. However, much of the research in support of lower BMI cutpoints lacks a Caucasian or non-Asian comparison group.

The risk conferred by excess adiposity may be modified by genetic factors as well as age. Parental history of disease is commonly collected as a marker of heritability of hypertension in clinical and epidemiological studies. Risk scores to predict incident
hypertension in Caucasian populations incorporate measures of adiposity, parental history of hypertension and age as strong predictors in the risk score calculation. Better understanding of the interaction of parental history of hypertension, adiposity and age on hypertension risk in non-Caucasian populations may help identify individuals who present with greater disease risk and target them for disease prevention efforts.

In addition to overall adiposity, regional depots of adiposity are associated with hypertension and metabolic risk. Although greater levels of abdominal adiposity have been shown to be deleterious, adiposity in the gluteo-femoral or hip region has been shown in some cohorts to exert a protective effect. A limited body of research has examined the independent effect of hip circumference on cardiovascular risk factors. These studies have been conducted almost exclusively in Caucasian populations. Therefore, it is uncertain if regional depots of fat exert similar effects in Chinese Asian populations.

Data were from the following three cohorts:


B. Research aims

The aims of this research were as follows.

1. Primary Aim – Determine and compare the relationship of BMI with hypertension among American White, American Black and Chinese Asian adults in early and middle adulthood.
1.a. Determine the ethnic specific relationship of BMI with prevalent hypertension among American White, American Black and Chinese Asian young (24-39 years) and middle-aged (45-64 years) adults.

1.b. Determine the ethnic specific relationship of BMI with incident hypertension among American White, American Black and Chinese Asian young (24-39 years) and middle-aged (45-64 years) adults.

2. Secondary Aim – Determine the influence of parental history of hypertension on the relationship of BMI with prevalent hypertension in Chinese Asian adults; examine if this relationship differs by age.

3. Tertiary Aim – Determine the independent association of hip circumference (HC) with incident metabolic risk factors in Chinese Asian adults aged 24-71, over approximately six years of follow-up; and determine if the relationship differs by age.
II. LITERATURE REVIEW

A. Obesity in Asians

1. Overview

BMI provides a reliable indicator of body fatness. Therefore, the National Institutes of Health and the World Health Organization use BMI, (weight (kg) / height (m$^2$)), as a criterion measure to define underweight (<18.5 kg/m$^2$), normal weight (18.5 to <25.0 kg/m$^2$), overweight (25.0 to <30.0 kg/m$^2$) and obesity (>30 kg/m$^2$). Both epidemiological and randomized clinical trials have established excess adiposity to be associated with greater risks of morbidity. The overweight and obese categories are believed to confer the greatest health risks among most populations.

The prevalence of adult overweight and obesity continues to increase among adults in both China and the United States (U.S.). Within China, the prevalence of adults who fall above the overweight and obesity cutpoint is 24% and 4%, respectively, indicating approximately one in four Chinese adults are overweight or obese.$^{11}$ Compared to China, the proportion of overweight and obese adults in the United States is much higher, as the majority of adults are classified above the ‘normal weight’ category. The proportion of adults who fall above the overweight and obese cutpoints are 66% and 32%, respectively.$^{12}$ When examining the obesity prevalence by ethnicity, the African American community experiences the greatest burden of obesity (45%), an absolute greater prevalence of 13% compared to the U.S. national average.
2. **BMI cutpoints rationale**

The WHO’s most recent consensus statement, issued in 2004, suggested a range of plausible BMI cutpoints for overweight and obese exist for Asians, depending on the outcome of interest.\(^{13}\) Based on the existing scientific evidence and expert consensus, China responded by establishing country specific standards to define overweight (24.0 kg/m\(^2\) to <28 kg/m\(^2\)) and obesity (>28 kg/m\(^2\)).

The two primary reasons most often cited in support of lower BMI cutpoints to define overweight and obesity in Asians are (1) evidence of greater percent body fat at the same BMI compared to Caucasians, and (2) an observed increase in disease risk within the normal BMI range.\(^{13}\) The Chinese adult population is one of the largest in the world, close to 1 billion. Therefore, the elevated risk of cardiovascular related risk factors near the mean adult BMI (23 -24 kg/m\(^2\)) results in a substantial population risk. The excess risk of hypertension, diabetes and cardiovascular risk factors among Chinese at low BMI values, taken within the context of the population distribution of BMI, have been cited as in support for lowering cutpoints in China.

3. **Ethnic differences in body composition**

Ethnic differences in body composition may contribute to ethnic variations in disease risk associated with excess adiposity. Deurenberg et al., 2002, reported the relationship of percent body fat and BMI is ethnic-specific based on differences in trunk to leg length ratio, slenderness and muscularity as well as other physical differences.\(^{14}\) For example, Chinese men and women are usually taller and lighter with smaller waist and hip circumference then other Asian nationalities.\(^{15,16}\)
Differences in body composition are not unique to Asian populations. Ethnic differences in body composition between Asian and non-Asian ethnic groups have been well documented.\(^{14}\) Compared to Caucasians of the same BMI, age and gender, Asians typically have a 3-5\% higher body fat. Likewise, for the same body fat percent, Asians have a BMI 3-4 units lower than that observed in Caucasians.\(^{14,17}\)

Differences in body composition have also been observed between Caucasians and African Americans. African Americans have a greater bone mineral density and body protein content than do Caucasians, resulting in a greater fat-free body mass. Additionally, there are racial differences in the distribution of subcutaneous fat and the length of the limbs relative to the trunk. Generally, compared to White Americans, Black Americans have more subcutaneous fat in the trunk and less subcutaneous fat in the extremities.\(^{18}\) In addition, Black Americans have less visceral adipose tissue than Caucasians at the same BMI.\(^{19,20}\)

Therefore, at the same BMI, Blacks tend to have greater lean body mass and less fat mass and visceral fat than Caucasians. Asians have greater adiposity and a greater tendency towards central or truncal obesity, at the same BMI compared to Caucasians. Since adiposity or some aspect of its metabolism predisposes individuals to hypertension, type 2 diabetes and other cardiovascular risk factors, the logical expectation is that populations with greater adiposity at the same BMI would have a greater prevalence of obesity related disease at each BMI value of overweight on CHD are understood to occur at least partly through several physiologic risk factors.

4. **Gender differences in body composition**

Sexual dimorphism in body shape refers to the characteristically different body shapes between men and women. Typically, women exhibit a gynoid shape and males an
android shape. These characteristic shapes are hormonally driven and immerge during sexual maturation. Women tend to have a greater percent body fat compared to males at the same BMI. During menopause, it has been suggested that women are more prone to deposition of fat in the visceral or inter-abdominal region. Sexual dimorphism in body shape becomes less pronounced during this period. Most studies have attributed these gains in abdominal fat to aging and not a loss of estrogen. However, a recent longitudinal study has found effects of ovarian aging, a marker for menopause, to be associated with increased deposition of fat in the midsection.

5. **Body composition and fat distribution with age**

Typically, both males and females experience weight gain during adulthood up through ages 40–70 years, followed by decline in fat mass after age 70. Both gains in BMI and specific regions of body fat have been observed. Waist circumference has been shown to increase with age even when BMI remains stable. During young adulthood, deposition of fat in subcutaneous regions is more common. However, beginning around middle adulthood, there is a redistribution of fat. Subcutaneous depots decline, visceral fat is preserved and fat gain is typically deposited in the inter-abdominal region. Height and bone density are often lost during later adulthood. Physical activity during adulthood has been shown to protect against fat gain and muscle loss.

6. **Risk of metabolic abnormalities within the normal BMI range**

Studies in China have shown that the risk of hypertension, diabetes and other cardiovascular related metabolic risk factor increases with increasing BMI. The increase in metabolic risk factors is observed at BMI values considered normal by WHO standards (>18.5 kg/m² to <25 kg/m²). These studies, which typically lack a Caucasian comparison
group, have concluded a BMI of 23-24 kg/m² may be a better cutpoint to define overweight within China. This research presumes that a subsequent increase in metabolic risk factors within the same BMI range would not be observed within Caucasian or Western populations. However, research from the primarily Caucasian Nurses’ Health Study and the Physician Follow-up study suggest that the age-adjusted relative risk of diabetes increases above 1 beginning at a BMI of 22 kg/m² for women and 24 kg/m² for men (within the normal BMI range).

Typical analytical methods to assess the relationship of anthropometrics with adverse outcomes in Asians use receiver operating characteristic (ROC) curves or logistic regression methods. ROC curves are highly influenced by the underlying distribution of BMI within the population. The mean adult BMI is 23 kg/m² in China, much lower than that in the United States. Although the absolute risk in Chinese and other ethnic groups at a specific BMI may be very similar, because the BMI distribution of Chinese is shifted to the left of most Western populations, it is more probable that a lower country specific BMI cutpoint will have greater maximal sensitivity and specificity than the WHO recommended value based on the underlying distribution ROC analyses. Risk estimates from logistic regression analyses, another common methodologic technique, use ratios that are heavily influenced by the in the reference range. When the risk in the referent group differs between groups it is difficult to compare estimates.
B. Hypertension

1. **Overview**

   Although hypertension is defined by a blood pressure threshold, both systolic and diastolic blood pressures are associated with a continuous and graded increase in cardiovascular disease (CVD) events, even within the normal blood pressure range. Alterations in either systolic or diastolic pressure alter the circulatory system and increase the risk of cardiovascular morbidity and mortality. The presence of hypertension is associated with a doubling of cardiovascular disease risk.

   Hypertension is prevalent throughout the world. It has been suggested that mutations that produced alleles associated with hypertension occurred early in evolution and therefore, much of the gene—related variation in the prevalence of hypertension between populations is a result of differences in the prevalence of those alleles, as opposed to the action of completely novel variants. Hypertension is usually observed in post-reproductive years allowing the genetic aspect of the disease to persist in populations. The exceptions are monogenic forms – which cause a defect in blood pressure regulation that would be apparent at a young age.

   Using the standard definition of 140/90 mmHg or antihypertensive medication use, the prevalence of hypertension among the US population has increased 18%, from 24.4% in 1988-94 to 28.9% in 1999-2004.\(^{31}\) The rate of awareness is 75.7%, treatment is 65.1% and control is 36.8%.\(^{32}\) Based on NHANES 1999-2004 data, Non-Hispanic Blacks have a greater burden of hypertension compared to Non-Hispanic Whites, 40.1% and 27.4% respectively. However, estimates of awareness, treatment and control are similar.\(^{32}\)
Geographic patterns in elevated blood pressure have been noted. Hypertension prevalence is higher in the southeast than in other regions of the U.S. Contributors to this pattern include geographic patterns in obesity, physical inactivity, and salt and nutritional intake, but not different in treatment or control of hypertension. Among hypertension patients, the level of systolic blood pressure and the prevalence of severe hypertension is also higher in the South. No differences in frequency of “adding salt at the table” have been observed in North vs. South but the South has the highest overall sodium consumption and the lowest phosphorus, magnesium, copper, riboflavin, niacin, iron, and Vitamins A, C and B6. Over the past 3-4 decades there have been dramatic improvements in hypertension awareness and treatment. However, racial disparities still exist. Compared to Whites, Black participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study were more aware of their hypertension and more likely to be on treatment when aware but less likely to have their blood pressure controlled. Confounding in geography and race is well established.

Hypertension has become increasingly prevalent in developing Asian populations. In China, 19% of the adult population (18 years of age and older) are hypertensive. Regional differences in the prevalence of hypertension within China have been observed. Hypertension is less common in southern China, where diet and exercise patterns are substantially different from the north. In addition, the prevalence of hypertension is lower in rural than urban areas, which has been suggested to be related to higher levels of physical activity and lower levels of overweight.

Among Chinese adults aged 35-74 hypertension prevalence is 27.2% and rates of awareness (44.7%), treatment (28.2%) and control (8.1%) are low. A proportion of
individuals use herbal or non-traditional remedies to treat blood pressure elevations. Immigrantion of Chinese to the U.S. is associated with greater risk of hypertension. The adult prevalence of hypertension among Chinese Americans is 39%, which is comparable to Whites. After adjustment for BMI, age, sex, WC, alcohol, tobacco, diabetes, education, income and financial strain, the odds of hypertension were greater in Chinese than Whites. This suggests a potential for a rapid increase in hypertension prevalence in China as diet and physical activity patterns transition towards those observed in the U.S.

2. **Risk factors**

   a. **Genetics:**

      Typically, hypertension is a multi-genic disease in which multiple genes influence the observed phenotype. Each gene has a small effect on blood pressure and environmental factors are necessary for the development of essential hypertension. In addition, there is genetic heterogeneity in which hypertension may be phenotypically similar in different individuals but may be the result of a different combination of genes and environmental factors. Genes which encode proteins involved in the function of the kidneys, heart, brain and vascular system are some of the genes which may be related to blood pressure regulation. Chromosomal regions which may be involved in hypertension phenotypes have been identified in meta-analyses. Monogenic or single-gene forms of human hypertension are rare. These forms may be a result of mutations that result in overproduction of mineralcorticoids, or increased mineralcorticoid activity, alteration of renal ion transporters or suppression of plasma-renin activity. These forms would be apparent at birth.
b. **Age:**

Blood pressure levels and hypertension prevalence increase with age in both men and women as shown in Table 2.1. There is a gradual shift in the blood pressure risk relationship from increased diastolic pressure among young adults to increased systolic blood pressure among middle and older aged adults. An increase in vascular stiffness which occurs with aging contributes to the age-associated increase in blood pressure. Greater increase in hypertension incidence has been observed in women after age 60.

c. **Obesity**

Obesity, especially central adiposity, is strongly associated with chronic hypertension. The impact of obesity on hypertension is complex, multi-factoral and not completely understood. Hemodynamic (increased blood volume), metabolic (increased sympathetic nervous and rennin-angiotensin activity), endocrine (altered leptin and adipokine release) mechanisms and structural changes (pressure on the kidneys) may lead to obesity related hypertension.

d. **Gender**

Men have higher systolic blood pressure levels than women during early and middle adulthood. After age 60, women tend to have higher systolic blood pressure and greater hypertension incidence. Data from NHANES 2003 – 2004 reported hypertension awareness and treatment were similar among men and women.

e. **Race**

The prevalence of hypertension varies by race in the U.S. The age adjusted hypertension prevalence among adults is highest among Blacks (39.1%) compared to non-Hispanic Whites (28.5%) based on NHANES 2003-2004. Examples of hypertension
prevalence from the U.S. based Multi-Ethnic Study of Atherosclerosis (MESA) are listed in Table 2.2. This study also found Black Americans to have the greatest prevalence of hypertension compared to White and Chinese Americans. However, there is heterogeneity of hypertension prevalence within ethnic groups depending on the country of residence. Blacks in the U.S. have a high prevalence of hypertension at all ages but this trend is not observed among African and Caribbean Blacks. The age-adjusted prevalence of hypertension is low in rural Nigeria (13.5%) and intermediate among Blacks residing in Jamaica (28.6%), compared to U.S. Blacks (44.0%). Heterogeneity in hypertension rates among Caucasians has also been observed. There is a trend towards greater levels of hypertension among Caucasians residing in European countries (38.4% to 55.3%) compared to those in the U.S (26.8%).

f. **Physical Activity**

Physical activity is protective against the development and progression of hypertension. Exercise is an effective means to maintain a healthy body weight. Even in the absence of weight loss, exercise has shown to be an effective method to reduce blood pressure. Regular exercise improves the aging-induced increase in arterial stiffness which can raise blood pressure. Other possible mechanisms include reduction in norepinephrine levels and increased endothelial nitric oxide release. However, not all individuals respond to the effects of physical activity to the same extent.

g. **Diet**

Dietary modification with and without concurrent weight loss have been shown to have beneficial effects on blood pressure. Many trials, including The Dietary Approaches to Stop Hypertension (DASH) trial, lend support to the association of blood pressure with specific foods and nutrients. Dietary factors such as high sodium and alcohol and low
potassium are associated with elevated blood pressure.\textsuperscript{61, 63} The amount, rather than type of alcohol is the main determinant of blood pressure levels. Average daily intake above moderate levels (\textgreater{}1 drink for women and \textgreater{}2 drinks for men) is associated with raised blood pressure.\textsuperscript{64} Alcohol has immediate effects on vasodilation and may exert effects through neurohormonal sympathetic pathways, (rennin-angiotensin_aldosterone, insulin, cortisol) inhibition of nitric oxide, depletion of calcium and magnesium, alteration of electrolyte levels and increases in acetylaldehyde. Recommendations for lowering blood pressure include a diet that is reduced in saturated fat and cholesterol as well as alcohol, and one that emphasizes fruits, vegetables and low-fat dairy products, dietary and soluble fiber, whole grains and protein from plant sources.

h. **Smoking**

Cigarette smoking causes acute blood pressure elevation.\textsuperscript{65} Studies have shown smoking exerts effects on blood pressure via increases in arterial stiffness and increases arterial wave reflection, which leads to increased aortic systolic blood pressure.\textsuperscript{66} Epidemiologic studies have found long term smoking to be associated with lower blood pressure levels.\textsuperscript{65} These differences in blood pressure levels between smokers and non-smokers may be related to differences in body mass index.

3. **BMI-Hypertension relationship**

Studies in China and the United States have shown increasing prevalence and incidence of hypertension associated with an increase in BMI. However, few studies have examined the association in both Chinese and Caucasian populations and even fewer have studied the relationship in Chinese, Caucasian and African American populations.
The majority of analyses are cross-sectional in design which limits the ability to disentangle causation from association. Many potential confounders including diet, physical activity, smoking, drinking and education are not controlled in the analyses. Consistently, researchers conclude the association of BMI with hypertension is stronger in Chinese compared to Caucasians. Bell et al. compared the adjusted prevalence and odds of hypertension in 30–65 year old adults from the China Health and Nutrition Survey and NHANES III. Authors acknowledge, the analysis of the odds is complicated by the differences in prevalence within the reference range between ethnic groups. Lower odds at the reference value for the Chinese group enhances the potential odds of hypertension at other values. In addition, higher prevalence estimates for Blacks diminishes the potential odds of hypertension. Among men, the age-adjusted odds of hypertension was significantly greater in the Chinese, at BMI values in the upper normal, overweight and obese categories (referent range of 18.5 -22.9 kg/m²), compared to American Whites from NHANES III. Values for non-Hispanic Black men were not different from non-Hispanic White men at most BMI values. However, the age adjusted prevalence of hypertension was highest among Black men within the normal BMI range and the slope was steepest among Chinese men. Among women, the odds of hypertension were similar within the normal BMI range and for most values overall. However, the odds of hypertension was significantly lower for non-Hispanic Black Women compared to Whites within the BMI range of 23-24.9 kg/m² and 25 – 26.9 kg/m² and >31 kg/m².

Pan et al. also compared NHANES III to an Asian population, the Nutrition and Health Survey in Taiwan. Similar to the Bell’s results, the age and sex standardized prevalence of hypertension was steeper across BMI in the Taiwanese compared to Blacks
and Whites and the adjusted prevalence was higher in Taiwanese compared to Whites. However, at BMI values considered normal and underweight, Black Americans had higher (not necessarily significant) adjusted prevalence values compared to both Whites and Taiwanese. The odds ratio (95% CI) per unit change in BMI was highest in Taiwanese (1.24 (14.11, 1.39)) compared to both U.S. Whites (1.11 (1.09,1.14)) and Blacks (1.07 (1.05, 1.09)) and significantly different than Blacks. BMI cutoffs which maximize sensitivity and specificity in predicting hypertension were between 23.3 and 23.7 kg/m$^2$ for Taiwanese males and females and between 25.6 and 28.2 kg/m$^2$ for U.S. White and Black males and females.

More recent studies have employed novel approaches. Razak$^{69}$ used proportional hazard analyses and the Obesity in Asia collaborative (OAC)$^{70}$ conducted a meta-analysis. The OAC was established in 2002 to address the relationship of anthropometric measures with Cardiovascular risk factors in Asian compared to Caucasian populations by combining existing data sources from the Asia. Results from the meta-analysis did support a greater risk of hypertension and other CVD related risk factors in Asians compared to Caucasian populations. However, Asians within China, Hong Kong, India, Korea, Japan, Singapore, Thailand, and Taiwan were collectively compared to Caucasians within Australia and Iran. Deurenberg et al.$^{14}$ noted that there is much (genetic and environmental) heterogeneity in body composition within Asian populations. Additionally, environmental and cultural factors are quite distinct between regions. The effect of excess adiposity on blood pressure was assessed by examining the increase in systolic blood pressure (SBP), diastolic blood pressure (DBP) or the odds of hypertension associated with a cohort specific 0.5 SD change in each anthropometric (BMI, WC, WHR, WHtR). Because a 0.5 SD change may
encompass a very different value and range across populations, it is difficult to interpret the meaningfulness of the results.

Razak et al., 2005 & 2007 analyzed cross-sectional data on Chinese and Caucasian Canadian populations from the Study of Health Assessment and Risk in Ethnic groups (SHARE) cohort in Canada.\textsuperscript{69,71} All subjects resided in Canada for a minimum of 5 years prior to data collection. The 2005 study found an increase in median systolic pressure with increasing age and sex adjusted BMI quintile in both Caucasian and Chinese population. The increase was steeper in the Chinese compared to Europeans.\textsuperscript{71} The 2007 study employed proportional hazard analyses.\textsuperscript{69} The relationship between the blood pressure factor, which was composed of systolic and diastolic blood pressure, at a BMI of 30 in Europeans, corresponded to a BMI of 25.3kg/m\textsuperscript{2} in Chinese. The relationship between BMI and blood pressure factor was positive for both Chinese and Europeans.

4. \textit{Family history of hypertension}

Hypertension and blood pressure levels aggregate in families.\textsuperscript{72,73} It has consistently been reported that offspring of hypertensive individuals have a greater risk of hypertension than the general population.\textsuperscript{74-77} The risk increases when both parents are hypertensive.\textsuperscript{75,76,78,79} For example, compared to subjects who had a negative family history of hypertension, males and females in the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA)\textsuperscript{75} cohort who reported only one parent with a positive parental history of hypertensive had a relative risk of hypertension of 2.8 and 2.0, respectively. Within this same cohort, the relative risk of hypertension for subjects reporting a positive parental history of hypertension in both parents was 7.8 and 5.3, among males and females, respectively. The gender-specific risk of hypertension was more than double among subjects with two parents
with a positive parental history of hypertension compared to subjects with just one parent with a positive parental history of hypertension.

The strength of association between family history and incidence of hypertension is dependent on the age of onset of hypertension in the family member and the age of the individual at risk for hypertension. A history of hypertension before age 60 invokes a greater risk of hypertension in offspring.\textsuperscript{75, 78} A positive parental history of hypertension among adults 70 years or older, is associated with no greater risk than that of the general population. The mean BMI among offspring with a positive parental history of hypertension is typically higher by approximately 0.5 or more BMI units compared to individuals with a negative parental history of hypertension.\textsuperscript{77, 80, 81}

Family history of hypertension is a simple and commonly used clinical index of familial aggregation of high blood pressure which reflects the heritability of hypertension.\textsuperscript{6} Family aggregation of blood pressure reflects both the shared genetic information within a family and the shared family environment. Multiple interactions among genes and environments contribute to the prevalence of hypertension such that numerous physiologic, biochemical and environmental factors contribute to increase blood pressure. Therefore, there are many ways to become hypertensive. Studies have shown the impact of parental blood pressure is evident among offspring at an early age as well as in adulthood when environments may no longer be shared. It is estimated that between 30\% to 60\% of the interindividual variation in blood pressure is attributed to genetic factors.\textsuperscript{82, 83} Circulating levels of select biomarkers, including C-reactive protein, have been shown to be higher in normotensive offspring with a positive parental history of disease. This suggests biological
effects including inflammation may mediate the effects of blood pressure on hypertension risk.\textsuperscript{84}

The increased risk of hypertension associated with a positive family history remains after adjustment for BMI.\textsuperscript{75, 80, 81, 85} However, to our knowledge, no studies have examined the association of adiposity with incident or prevalent hypertension according to parental history of hypertension status. It is unknown whether individuals with a positive parental history may be more sensitive or resistant to the effects of excess weight.

5. \textit{Hip-hypertension (or chronic disease)}

Waist to hip ratio (WHR) is fairly common anthropometric index employed in epidemiologic studies. Although the measure may capture aspects of body shape that are undetected by BMI, it does not differentiate the independent effects of hip or waist circumference. In comparison to a large waist circumference (WC), a large hip circumference (HC) has been suggested to be less deleterious and potentially protective. Each measure reflects different depots of adiposity with potentially different lipolytic activity. WC reflects both visceral and subcutaneous adiposity around the abdomen, a more metabolically active region. HC reflects adipose and muscle mass in the thigh and buttock region (gluteofemoral). The adipose in this glutiofemoral region has been termed a “fat sink” because it may serve an important role in the removal of non-esterified fatty acids (NEFA) from the circulation.\textsuperscript{86} This hypothesized pathophysiology would protect the liver, pancreas and skeletal muscle from exposure and accumulation of NEFA and thereby limit the development of insulin resistance. Research has shown, when mutually adjusted for one another and for BMI, WC and HC have independent and opposite associations with cardiovascular risk factors.\textsuperscript{8, 87-89}
Limited epidemiologic evidence examines the independent effects of hip circumference on coronary heart disease, cardiovascular disease, cardiovascular related risk factors and total mortality. These studies have employed different methodologies to demonstrate a larger hip circumference is associated with lower mortality and more favorable lipid and glucose profiles in both men and women. Dixon, et al., used ROC curves to identify cutoff values for hip and waist circumferences in an obese female population. Based on the values generated from the ROC analysis, a small hip circumference (<115 cm) was a better predictor of the metabolic syndrome compared to a large waist circumference (>100 cm). Results from a large Danish cohort reported mortality rate ratios per 10% increase in hip circumference and per 10% smaller waist circumference. Mortality rate ratios were similar across anthropometric measures. Estimates associated with a 10% change in HC or WC were 0.52 and 0.63, respectively, in men; and 0.60 and 0.76, respectively, in women.

The evidence related to blood pressure is limited and less supportive of a protective association. Although blood pressure may be inversely associated with hip circumference, the association tends to be very weak or not statistical significance. In the Quebec Family Study, there was a slight inverse relationship of hip circumference with systolic and diastolic blood pressure in women. The beta coefficient (SE) for the association of quintiles of hip circumference with systolic and diastolic blood pressure, when adjusted for waist circumference, age and BMI, were -0.22(0.125) and -0.086(0.079), respectively. In men the association was small but positive. Beta coefficients (standard error (SE)) were 0.31 (0.23) for SBP and 0.127 (0.144) for DBP in men.

Most studies have been conducted in Caucasian populations. However, one study examined the association of hip circumference with blood pressure, serum glucose and lipid
levels in non-Caucasian populations. This study population included Melanesians, Micronesians, Indians and Creole from Mauritius, Rodrigues, Papua New Guinea and Nauru. This study evaluated the association of hip circumference with the outcome by comparing the magnitude and direction of the standardized beta coefficient for WC and HC when adjusted for each other and for age and BMI. In all ethnic groups, a larger hip circumference was associated with lower glucose and triglyceride levels in both sexes and higher high-density lipoprotein levels in women only, after adjustment for waist circumference, BMI, and age. Standardized beta coefficients associated with serum lipid and glucose levels ranged from -0.1 to -0.3 for hip circumference and 0.1 to 0.4 for waist circumference among men and women. There was an inverse trend associated with blood pressure for most ethnic groups but it was not significant.

In most studies, collinearity of anthropometric measures was evaluated. These studies have not reported a need to limit the analytic approach due to collinearity.

C. Preliminary Studies

To our knowledge, our research group published the only study, directly comparing the incidence of hypertension by BMI among Chinese Asians, American Whites and American Blacks. Our results support a stronger influence of BMI on incident hypertension among Chinese Asians compared to American Whites. However, at baseline, subjects were 45-64 years old. At this stage of life there exists a high, differential prevalence of hypertension between ethnic groups. The adjusted prevalence of hypertension among Chinese Asians, American Whites and American Blacks was 29.6, 22.5 and 44.2%, respectively. This preliminary work made us question how the prevalence of cases at baseline, which are excluded from the incidence analysis, influenced the relationship of BMI
with incident hypertension. We began to question whether a greater sensitivity to BMI may exist among certain ethnicities at younger ages. To further explore the effect of BMI on incident hypertension, we propose to examine the relationship in a younger adult population of Chinese Asians, American Whites and American Blacks, aged 24-30 years.
<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Hypertension Prevalence (%)</th>
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<tbody>
<tr>
<td>18 – 39</td>
<td>7.3</td>
</tr>
<tr>
<td>40 – 59</td>
<td>32.6</td>
</tr>
<tr>
<td>60+</td>
<td>66.6</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Race</th>
<th>Hypertension prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese American</td>
<td>39%</td>
</tr>
<tr>
<td>White American</td>
<td>38%</td>
</tr>
<tr>
<td>Black American</td>
<td>60%</td>
</tr>
</tbody>
</table>

III. METHODS

A. The People’s Republic of China (PRC) Study data

The PRC Study is a prospective, observational study of cardiovascular disease in China. This was a joint research program sponsored by the National Institutes of Health (NIH) involving the People’s Republic of China and the United States of America under the USA-PRC Cooperation in Science and Technology to conduct prospective studies on CVD and its risk factors. In 1983–1984, baseline data were collected from 13,210 Chinese men and women aged 24 – 84 years. Participants were from urban and rural regions of Beijing (Northern China) and Guangzhou (Southern China). Follow-up examinations were in 1987-88 and 1993-94. Within Guangzhou, there were 1,848 subjects between the ages of 24-35 (n=1,077 female and n=771 male) and 6,575 subjects were between the ages of 45 to 64 at baseline (n= 3,286 female and n=3,289 male). Sample sizes for follow-up visits for the full study population, aged 24-84 years, are listed in Table 3.1.

Cluster sampling of age eligible men and women was collected from 4 populations in China (Beijing urban, Beijing rural, Guangzhou urban and Guangzhou rural). Additional subjects, comprising a younger age range, were sampled in the urban and rural regions of Guangzhou. Supplementary questions and measurements were collected among subjects from Guangzhou, including parental history of hypertension and hip circumference measures. Therefore, because we are interested in these variables as well as the younger subset of Chinese aged 24-35, our analyses were limited to adults from Guangzhou. Urban participants were currently working or retired employees from eight workshops of the
Guangzhou Shipyard Company and rural participants worked in 14 of the 21 agricultural villages in the Dashi Township of Panyu County at the time of the 1981 census.

1. **Variables**

   a. **Height**

      Height without shoes was measured to the nearest centimeter by using a standard right angle device.

   b. **Weight**

      Weight was measured to the nearest kilogram by using a spring balance. The participant was in typical indoor clothing without shoes.

   c. **Hip and waist circumferences**

      Circumferences of the waist and hip were measured to the nearest 0.1 cm. Waist was measured by passing the tape measure through the midpoint between the superior iliac crest and the lowest rib. Hips were measured at their maximum protrusion.

   d. **Blood pressure**

      Trained certified technicians measured blood pressure three times at each visit using a random zero mercury sphygmomanometer on the right arm with the participant seated. The average of the last two measurements were used in the analyses.

   e. **Blood pressure medication use**

      Blood pressure medication use was self-reported on participant questionnaires at each visit.

   f. **Parental history of hypertension**

      Parental history of hypertension was assessed by self-report at baseline among the Guangzhou sample. Individuals reported whether their mother, father, both or neither
parents had high blood pressure. Subjects had the options to report unknown but this was not selected for any participants. Responses were not validated. Subjects were classified as having a parental history of hypertension if hypertension was reported by at least one parent.

g. **Lipids**

Subjects were advised to fast for 12 hours prior to clinic visit. Fasting blood specimens were obtained at each visit. Guangzhou had lipid laboratories for standardized analyses of total cholesterol (TC), high-density lipoprotein (HDL) cholesterol and triglycerides (TG) by the Lipid Standardization Program of the U.S. National Heart, Lung and Blood Institute (NHLBI) and the Centers for Disease Control and Prevention (CDC). Serum TC was measured with the Boehringer Mannheim Diagnostics high-performance enzymic reagent calibrated with precise standards on the Abbott analyzer. Serum TG was determined with use of an enzymic reagent from Abbott Laboratories. Serum HDL was measured using the same enzymatic serum cholesterol method after precipitation of other lipid fractions with dextran sulfate.

h. **Glucose**

Subjects were advised to fast for 12 hours prior to clinic visit. Fasting blood samples were drawn to assess glucose levels. All biochemical assays were performed on an Abbott autoanalyzer.

i. **Demographic characteristics**

Age, education, smoking and alcohol consumption were self reported on questionnaires.
2. **Quality Control**

Quality control of blood samples was undertaken by the CDC by analyzing a random sample.

B. **The Coronary Artery Risk Development in Young Adults (CARDIA) Study data**

The CARDIA Study, funded by the NHLBI, is an on-going, prospective, multi-site investigation examining the etiology of heart disease in young adults. In 1986-87, baseline data were collected from 5,115 Black and White American men and women aged 18-30 years. Participants were from four U.S. sites (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA) to provide approximately equal numbers within subgroups of race, gender, education (high school or less and more than high school) and age (18-24 and 25-30). Follow-up examinations occurred during 1987-1988 (Year 2), 1990-1991 (Year 5), 1992-1993 (Year 7), 1995-1996 (Year 10), 2000-2001 (Year 15), and 2005-2006 (Year 20). The retention rate at each follow-up visit is 90% (Year 2), 86% (Year 5), 81% (Year 7), 79% (Year 10), 74% (Year 15), and 72% (Year 20), respectively.

1. **Variables**

a. **Height**

Participants were standing, without shoes, when height was measured to the nearest 0.5 centimeter using a vertical ruler.

b. **Weight**

Weight was measured to the nearest 0.5 pound using a beam balance scale. Participants were dressed in a scrub suit or short sleeve shirt and shorts without shoes.
c. **Blood pressure**

Resting blood pressure was measured three times at each visit using a random zero mercury sphygmomanometer (RZ) on the right arm of a seated participant. Participants were advised to refrain from caffeine, alcohol, smoking (30 min) or heavy physical exercise for at least 2 hours prior to visit. The average of the last two measurements were used in the analyses.

d. **Blood pressure medication use**

Medication records were collected at each clinic visit by self-reported questionnaires followed by interviewer assisted follow-up as needed.

e. **Demographic characteristics**

Age, sex, race, highest education obtained, smoking status, drinking status and geographic field center were collected via interviewer administered questionnaires.

2. **Quality Control**

The CARDIA Coordinating Center, and the CARDIA Quality Control Committee monitored data collection throughout the study and all data collection technicians were centrally trained and certified. Informed consent was obtained from each participant at each examination.

C. **The Atherosclerosis Risk In Communities (ARIC) Study data**

The ARIC study is a prospective, multi-site investigation of atherosclerosis and cardiovascular disease. Baseline data were collected from 1987-1989 in 15,792 African American and White men and women, 45-64 years of age. Races other than African American or White (n=48) and African Americans in Minneapolis and Washington County (n= 55) were excluded per standard ARIC protocol because their numbers are too small to
allow ethnic and field-center specific analyses, leaving 15,689 participants. These participants were from four communities in the United States: Forsyth County, NC (12% African American; 88% White); Jackson, MS (100% African American); the northwestern suburbs of Minneapolis, MN (100% White); and Washington County, MD (100% White). A range of physiologic and behavioral risk factors were measured. Participants were measured in a maximum of four clinic visits at approximately three year intervals. We excluded visit 3 from our analysis.

1. **Variables**

   a. **Height**

      Height was measured to the nearest centimeter using a metal rule attached to a wall and a standard triangular head board.

   b. **Weight**

      Weight was measured to the nearest pound using a beam balance with subjects in a scrub suit and no shoes.

   c. **Physiologic risk factors**

      Systolic and diastolic blood pressures were measured three times after a 5-minute rest using a random zero sphygmomanometer on the right arm of the seated participant. The last two measures were averaged and recorded.

   d. **Blood pressure medication use**

      Medication records were collected at each clinic visit. Participants were reminded to bring all medications used in the previous two weeks. Names of the medications were transcribed and coded by the ARIC medication coding system, developed by a pharmacist at UNC. Subjects were classified as taking blood pressure medication if they self-reported
taking medications in general in the last two weeks, and the medications they brought included an appropriately classified medication.

e. Covariates

Age (date of birth), race/ethnicity, and gender were self-reported. Additional covariates were assessed by interviewer-administered questionnaires. We categorized education as less than a high school education, high school graduate, or at least some college. Self-reported cigarette smoking status and alcoholic beverage consumption were categorized into current use yes or no variable. The field center variable was used.

2. Quality control

ARIC field centers used a computer-assisted data collection system in which staff directly recorded the information collected from interviews and examinations. Rigorous quality control procedures were developed and implemented for all parts of the examination to ensure that data were collected uniformly at each center and over time. The Collaborative Studies Coordinating Center at the University of North Carolina at Chapel Hill served as the study coordinating center. Several papers evaluating quality control in the ARIC study have been published \(^9^4-^{10^1}\).

D. Analytic methods

Methods used in individual papers are summarized in those chapters. Additional methodological details are listed below.

1. Risk Differences

Comparisons of the effect of obesity between ethnic populations are susceptible to spurious conclusions depending on the use of multiplicative or additive risk estimates. As demonstrated by Stevens et al., conclusions regarding the relative effect of obesity in Black
vs. White adults were contradictory when employing risk ratio vs. risk difference measures.\(^{102}\) This was attributed to differences in the rate at the reference level of adiposity between ethnic groups and the impact of these differences when using a multiplicative as opposed to an additive risk assessment. This is one of the main reasons epidemiologists encourage the use of risk difference measures to estimate risk. Therefore, for each aim, we calculated the risk difference to estimate risk.

2. **“PRvalue” command**

The prvalue command by Long and Freese is a user-friendly Stata method to compute post-estimation predictions of outcomes at specific values of the independent variables.\(^{103, 104}\) After specifying the logistic regression model, values of the independent variables are specified using the “prvalue save” command which then computes the predicted value of the outcome. Difference measures or changes in the predictions at values of the independent variables were computed using the “prvalue diff” command and specifying levels of the independent variables. Confidence intervals for both predicted outcomes and discrete changes in predictions were computed using the delta method.

3. **The delta method**

The delta method was used to calculate confidence intervals for the predicted estimates in Stata with the “prvalue” command. The delta method generates confidence intervals for functions of maximum likelihood estimates by creating a linear approximation of that function and then computing the variance of the simpler linear function that can be used for large sample inference.\(^{103, 104}\) It is a technique used when functions are too complex to analytically compute the variance. This is the case for our analyses where confidence
intervals were estimated around the change (risk difference) in the predicted probabilities based on a logistic model.
Table 3.1. Sample size for 24-84 year olds in PRC

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
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</tr>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Baseline</td>
<td>13,210</td>
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</tr>
<tr>
<td>Visit 2</td>
<td>11,440</td>
<td>86.6</td>
</tr>
<tr>
<td>Visit 3</td>
<td>9,483</td>
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<tr>
<td>Completed all 3 Visits</td>
<td>8,674</td>
<td>65.7</td>
</tr>
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</table>
Table 3.2. Examination years by cohort

<table>
<thead>
<tr>
<th>Visit #</th>
<th>PRC</th>
<th>CARDIA</th>
<th>ARIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1983-84</td>
<td>1985-86</td>
<td>1987-89</td>
</tr>
<tr>
<td>2</td>
<td>1987-88</td>
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<td>3</td>
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<td>6</td>
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<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>2005-06</td>
<td></td>
</tr>
</tbody>
</table>

**Bolded** exam years indicate those used in our analyses
IV. **Impact of Body Mass Index on Incident Hypertension in American White, American Black and Chinese Asian Adults in Early and Middle Adulthood**

A. **Abstract**

Background: The impact of body mass index (BMI) on blood pressure is thought to be stronger in Asian than non-Asian populations. However, longitudinal studies with direct comparisons between ethnicities are lacking.

Objective: To compare the ethnic-specific relationship of BMI with incident hypertension in young (24-39 years) and middle-aged (45-64 years) adults.

Methods: Chinese Asians (young (n=2,896) and middle-aged (n=2,458)) adults were from the People’s Republic of China study, American Black (n=1,956 young and n=4,120 middle-aged) and American White (n=2,114 young and n=11,337 middle-aged) adults were from the Coronary Artery Risk Development in Young Adults (CARDIA) study and the Atherosclerosis Risk in Communities (ARIC) study. The incidence of hypertension and the incidence difference were calculated using a referent BMI of 21 kg/m².

Results: The incidence difference for hypertension associated with BMI was larger (p<0.05) for Chinese Asians than American Whites and American Blacks in both age groups. At a BMI of 25 kg/m² the incidence difference per 1,000 persons (95% CI) for Chinese, Blacks and Whites was 83 (36, 130), 50 (26, 74) and 30 (12, 48) among young adults and 137 (77, 198), 49 (9, 88) and 54 (38, 69) among middle-aged adults, respectively.

Conclusion: The association of BMI with the incidence difference for hypertension was greater in Chinese than in American populations during both young and middle-
adulthood. However, whether hypertension carries the same level of risk of stroke or cardiovascular disease across different national or ethnic groups remains uncertain.

B. Background

Studies in China have shown that the risk of hypertension and other cardiovascular related risk factors increase with increasing BMI within the normal BMI range considered normal\(^2-4, 13, 28, 105-109\) according to World Health Organization standards (\(<25 \text{ kg/m}^2\)). These studies\(^2-4, 13, 28, 105-109\), which typically lack a Caucasian comparison group, have concluded that a BMI of 23-24 \text{ kg/m}^2 may be a better cutpoint to define overweight in Chinese populations. The China Department of Disease Control Ministry of Health responded to the body of literature by adopting country specific BMI cutpoints which define overweight and obesity at BMI values of \(\geq 24 \text{ kg/m}^2\) and \(\geq 28 \text{ kg/m}^2\), respectively, lower thresholds than those established by the World Health Organization of \(\geq 25 \text{ kg/m}^2\) and \(\geq 30 \text{ kg/m}^2\), respectively.\(^110\)

To our knowledge, our research group published the only study\(^92\), directly comparing the incidence of hypertension by BMI among Chinese Asians, American Blacks and American Whites. Our results supported a stronger influence of BMI on incident hypertension over approximately 8 years of follow up among adults who were 45-64 years of age at baseline. Although the BMI associated incidence rate was higher in Chinese Asians, the BMI-adjusted prevalence of hypertension was similar among Chinese Asians (29.6\%) and American Whites (22.5\%), and substantially higher in American Blacks (44.2\%).

Since the prevalence was higher in 45-64 year old American Blacks, we wondered if the sensitivity of hypertension to BMI would be stronger in American Blacks at younger ages (<45 years) while Chinese Asians were more sensitive at older ages (>45 years).
Alternatively, the high prevalence of hypertension in American Blacks could be unrelated to BMI and due to other factors. We hypothesized that the American Blacks who were susceptible to developing hypertension in response to adiposity had already developed the disease by the age of 45, whereas, in Chinese Asians more years had to be accrued before they became sensitive to the effects of BMI on disease. The idea that susceptibility to the effects of BMI might differ by age in different ethnic groups led us to examine these associations in a younger cohort of Chinese Asians, American Blacks and American Whites and compare results to a middle-aged population. We speculated that the effects of BMI on hypertension incidence would be highest in American Black young adults, lowest in Chinese Asians young adults, and intermediate in American White young adults; whereas, BMI effects in middle aged adults would be highest in Chinese Asians, lowest in American Blacks and again intermediate in American Whites.

C. Methods

1. Study population

Data for this analysis were from Chinese Asian, American Black and American White men and women from three prospective, observational studies of the natural history and risk factors for cardiovascular disease (Table 4.1). In an effort to be concise, we will refer to the three ethnic groups as Chinese, White and Black throughout the remainder of the paper. Chinese (young and middle-aged adults) were from the People’s Republic of China (PRC) study, Black and White adults were from the Coronary Artery Risk Development in Young Adults (CARDIA) study (young) and the Atherosclerosis Risk in Communities (ARIC) study (middle-aged). We limited the use of data from each cohort to three examinations to result in similar lengths of follow up for Chinese, Blacks and Whites,
respectively, in young (9.5, 9.3, 9.7 years) and middle (9.0, 7.2, 7.9 years) adulthood. We also matched the ages of participants in these different cohorts by including only participants between 24-39 or 45-64 years of age.

The PRC Study data

The PRC Study included adult working men and women from urban and rural regions of Guangzhou (Southern China) and Beijing (northern China), with a "chunk" sample of at least 2,000 adults (1,000 men and 1,000 women) from each population. Subjects were limited to those from Guangzhou as data from Beijing were very limited for the young adult group. Request to participate was made to age-eligible males and females. The Guangzhou urban sample included largely employed manual workers, plus some engineers, technicians, cadres, physicians, and retired workers from eight of the 25 workshops for the Guangzhou Shipyard Company. The Guangzhou rural sample included men and women working in 14 of 21 agricultural villages near Guangzhou in the Dashi township of Panyu County at the time of the 1981 census. Baseline data were collected in 1983–1984, from 6,581 Chinese men and women. Follow-up examinations were in 1987-88 and 1993-94.

The CARDIA study data

The CARDIA Study is an on-going, multi-site investigation examining young adult Black and White men and women. In 1985-86, study baseline data were collected from participants recruited from four U.S. sites (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA) with the goal to provide approximately equal numbers within subgroups of race, gender and education. To match follow-up period and age ranges of subjects in PRC,
we used data from 1990-1991 (CARDIA study Year 5) as baseline for this analysis and data from 1995-1996 (Year 10) and 2000-2001 (Year 15) for follow-up examinations.

**The ARIC study data**

The ARIC study is an on-going investigation with baseline data collected in 1987-1989 from 15,792 White and Black men and women, aged 45-64 years. Participants were from four U.S. communities (Forsyth County, NC; Jackson, MS; the northwestern suburbs of Minneapolis, MN; and Washington County, MD). The two follow up examinations used in this analysis occurred during 1990-92 and 1996-98.

There are many similarities in the design and data collection among the three cohorts. The Collaborative Studies Coordinating Center (CSCC) at the University of North Carolina at Chapel Hill served as the coordinating center for both the PRC and ARIC studies. The coordinating center provided training manuals and protocols for data collection and was responsible for data processing and review for both studies. The Institutional Review Board (IRB) at each field center approved the study and this analysis was approved by the University of North Carolina at Chapel Hill IRB on research involving human subjects.

2. **Measurements**

For all three studies data were collected in examination centers. In each cohort, participants wore light clothing or a scrub suit without shoes during anthropometric measurements.

Trained certified technicians measured and recorded blood pressure three times at each visit using a random zero mercury sphygmomanometer on the right arm with the participant seated. For all analyses, the average of the last two blood pressure measurements
was used. Information on anti-hypertensive medication use was collected by self-reported questionnaires and followed by interviewer assisted follow-up as needed. Blood pressure thresholds were based on the National High Blood Pressure Education Program Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Participants were classified as hypertensive if 1) systolic blood pressure was greater than or equal to 140 mmHg, 2) diastolic blood pressure was greater than or equal to 90 mmHg or 3) self-report of current antihypertensive medication use.

Participants self-reported several demographic and lifestyle information including age, sex, race, current smoking status and highest education obtained. We did not have measures of diet for PRC and measures of physical activity were not comparable across studies and therefore were not included.

In young adults, participants were excluded if pregnant at baseline (n=23 Black and n=33 White), missing BMI (n=11 Chinese, n=13 Black and n=8 White), missing blood pressure (n=2 Black and n=1 White) or missing covariates (n=17 Chinese, n=8 Black and n=9 White). The analysis sample included 2,896 Chinese, 1,956 Black and 2,114 White young adults. For the incidence analysis we also excluded participants with hypertension at baseline (n=81 Chinese, n=128 Black and n=61 White), pregnant during follow-up (n=3 Chinese, n=7 Black and n=30 White) and subjects with incomplete follow-up data (n=426 Chinese, n=428 Black and n=311 White).

In middle-aged adults, we excluded 55 Blacks from Washington County, MD or Minneapolis, Minnesota, and the participants (n=48) who classified their ethnicity as other than White or Black because they were too small in number to allow ethnic and field center specific analyses. Additionally, participants were excluded if missing BMI (n=11 Chinese,
n=19 Black and n=20 White), missing blood pressure (n=2 Black and n=3 White), missing covariates (n=16 Chinese, n=15 Black and n=15 White). The analysis sample included 2,458 Chinese Asian, 4,120 Black and 11,337 White in the middle-aged adult prevalence sample. For the incidence analysis we also excluded participants with hypertension at baseline (n=355 Chinese, n=2,400 Black and n=3,721 White) and incomplete follow up data (n=508 Chinese, n=470 Black and n=1,268 White).

3. **Statistical analyses**

Interactions between gender and BMI were not significant and therefore data from men and women were combined and analyses were stratified by ethnic-specific age group and gender was included as a covariate in all models. Logistic regression models also included the covariates field center, age (years), current smoking status (smoker/non-smoker), and education level (less than high school, high school, more than high school in American populations and the best equivalent of less than secondary, secondary and greater than secondary in the Chinese population). As a large proportion of Chinese were missing education status, we created a category for unknown education for PRC. For all outcomes, the alcohol consumption was included as a covariate in preliminary models but was not included in the final models because associations of alcohol with outcomes were not statistically significant (p>0.05) and inclusion of alcohol in the models did not influence the coefficients associated with variables of interest.

We estimated risk differences using logistic regression models and calculated the adjusted prevalence and incidence and the incidence difference using the “prvalue” command in Stata (Version 10.0). To facilitate comparisons across ethnicities, standardized estimates were calculated using the mean age (32 years for young adults and 52 years for
middle-aged adults), the overall distribution of gender (44% male), for non-smokers with a high-school or secondary education and the study specific distribution of participants within field centers. Quadratic terms for BMI and age were tested and included as they were statistically significant (p<0.05). The delta method was used to calculate the standard errors and 95% confidence intervals for the prevalence, incidence and incidence difference. To summarize the ethnic-specific incidence difference results across body mass index, we constructed weighted least-squares regression models with the adjusted incidence differences as the dependent variables and the body mass index as the independent variables. The adjusted incidence differences were calculated for the body mass index range of 18-35 kg/m\(^2\). The weight was the inverse of the estimated variance of the adjusted incidence difference. Wald statistics and p values were calculated based on chi-square distribution with 1 degree of freedom (d.f.) to compare ethnic group pairs when the relationships were linear. When the relationships were quadratic, principal component analysis was used to orthogonally transform the linear and quadratic terms for BMI. Joint tests of the linear and quadratic terms to compare ethnic pairs were calculated using the Wald statistic and the p values were calculated based on chi-square distribution with 2 d.f.

D. Results

Baseline characteristics are presented in Table 4.2. Mean BMI was lowest among Chinese (20 kg/m\(^2\)) and over 90% of the Chinese were underweight (BMI <18.5 kg/m\(^2\)) or normal weight (BMI 18.5-<25 kg/m\(^2\)). Antihypertensive medication use was negligible among young-adult Chinese (0.1%) and Whites (0.7%) and slightly more common among Blacks (2.6%). Use of antihypertensive medication was low among middle-aged Chinese (1.5%), and higher among the American populations (43.7% in Blacks and 25.9% in Whites).
We also examined the mean values of systolic and diastolic blood pressure among individuals who were not using antihypertensive medications. Mean systolic and diastolic blood pressure were lower in the non-medicated sample by 0.5-2.7 mmHg and 0.3-1.3 mmHg, respectively, compared to the overall population (not shown).

The crude and adjusted, predicted prevalence and incidence of hypertension are presented in Table 4.3. As expected, prevalence estimates were lower for young adults than middle-aged adults. The adjusted incidences and prevalence tended to be highest in Blacks. The prevalence of hypertension was similar in Chinese and Whites. The incidence was also similar, but higher in the Chinese and older adults. Among young adults, the adjusted prevalence of hypertension was significantly greater for Blacks (4.4 (2.4, 6.4)) compared to Whites (1.1 (0.3, 2.0)). Ethnic specific patterns for the incidence were similar to those observed for prevalence. In young adults, the adjusted incidence of hypertension was higher in Blacks (18.5 (13.9, 23.1)) compared to Chinese (5.3 (2.9, 7.6)) and Whites (6.1 (3.5, 8.6)). Among middle-aged adults, the adjusted prevalence of hypertension was considerably higher in Blacks (40.0 (35.1, 45.0)) compared to Chinese (17.2 (9.2, 25.3)) and Whites (17.5 (15.9, 19.2)) (Table 4.3). The adjusted incidence of hypertension was higher in Blacks (35.4 (27.2, 43.7)) than Whites (20.8 (18.5, 23.2) and Chinese (30.5 (18.4, 42.6), but the difference was not significant between Blacks and Chinese.

The incidence differences for hypertension increased with increasing BMI for all ethnic groups in both young and middle adulthood. Among young adults, although there were differences in the adjusted incidence at the referent BMI of 21 kg/m² (Table 4.3), the incidence difference for hypertension associated with BMI was similar for Blacks and Whites. However, in Chinese the association of BMI with the incidence difference for
hypertension was significantly greater compared to the American populations (p=0) (Figure 4.1). Among middle-aged adults, the association of BMI with the incidence difference for hypertension was also greater among Chinese compared to Blacks and Whites (p<0.01) (Figure 4.2).

E. Discussion

We did not find support for our hypothesis that BMI associations with hypertension incidences would be greatest in Black young adults. Instead, associations between BMI and the incidence difference for hypertension were greatest in Chinese in both young and middle adulthood. In contrast, the adjusted prevalence and incidence of hypertension tended to be higher in Blacks than in Chinese and similar among Chinese and Whites in adjusted predicted estimates for slender individuals (BMI 21 kg/m$^2$). Despite these differences in the adjusted prevalence and incidence of hypertension between ethnic groups, the Chinese had a stronger association of BMI with the incidence difference for hypertension compared to Blacks and Whites as evidenced by the steeper slope of the incidence difference. Although the adjusted incidence for hypertension at the referent BMI was different between Blacks and Whites, the slope of the incidence difference was similar between these American populations but different from the Chinese. While both young and middle-aged Blacks have a high prevalence and incidence of hypertension across all BMI values, the association of BMI with the incidence difference for hypertension was not as strong as that observed for Chinese. This combination of results indicates that hypertension incidence is more strongly related to BMI in Chinese than Blacks or Whites and the higher prevalence and incidence of hypertension in Blacks compared to Chinese is likely due to factors other than BMI. Blacks may experience hypertension due to additional risk factors beyond obesity, which were
unmeasured in our study, such as dietary factors, physical activity, environmental stressors or potentially genetic differences.\textsuperscript{116-118}

Studies in China and the United States have shown increasing prevalence and incidence of hypertension associated with an increase in BMI. However, few studies have compared the association in both Chinese and Caucasian populations\textsuperscript{67-71, 92, 119} and even fewer have studied the relationship in Chinese, Caucasian and African American populations.\textsuperscript{67, 68, 92} In addition, comparisons of the effect of obesity between ethnic populations typically employ ratio measures which must be interpreted carefully. As demonstrated by Stevens et al.\textsuperscript{120} conclusions regarding the relative effect of obesity in Black versus White adults were contradictory when calculated as risk ratio versus risk difference measures. This was driven by differences in the rate at the reference level of adiposity between ethnic groups and the impact of using a multiplicative as opposed to an additive risk assessment.\textsuperscript{102, 121} Therefore, we calculated difference measures to compare estimates among ethnic groups.

In addition to the use of ratio measures, the majority of analyses which assess ethnic differences in the BMI-hypertension relationship were cross-sectional in design. This limited the ability to understand temporal sequences of associations. Bell et al.\textsuperscript{122} used cross-sectional data to compare the adjusted prevalence and odds of hypertension in 30–65 year old Chinese Asian adults from the China Health and Nutrition Survey with American Black and White adults from the Third National Health and Nutrition Examination Survey (NHANES III). At the referent range of BMI (18.5-22.9 kg/m\textsuperscript{2}), the odds of hypertension was low in Chinese and high in American Blacks. The authors found the age-adjusted odds ratio for hypertension was significantly greater in Chinese Asian men, at BMI values in the upper
normal, overweight and obese categories, when compared to American White men from NHANES III. Similarly, Chinese Asian Women had a significantly higher odds ratio for hypertension when compared to American White women within the BMI range of 27-28.9 kg/m$^2$.

Pan et al.\textsuperscript{68} compared American Whites and Blacks from NHANES III to a Taiwanese Asian population from the Nutrition and Health Survey in Taiwan. Similar to Bell’s results, the adjusted prevalence of hypertension was higher (p<0.017) in American Blacks compared to Taiwanese Asians and the age and sex standardized prevalence of hypertension was steeper across BMI levels in the Taiwanese compared to American Blacks and Whites. The odds ratio (95% CI) per unit change in BMI was highest in Taiwanese (1.24 (1.11, 1.39)) compared to both American Whites (1.11 (1.09, 1.14)) and Blacks (1.07 (1.05, 1.09)) and significantly different between Taiwanese and American Blacks. BMI cutoffs that maximized the sum of the sensitivity and specificity in predicting hypertension were between 23.3 kg/m$^2$ and 23.7 kg/m$^2$ for Taiwanese males and females, respectively, and between 25.6-28.2 kg/m$^2$ for American White and Black males and females.

The Obesity in Asia collaborative (OAC) addressed the relationship of anthropometric measures with cardiovascular risk factors in Asian compared to Caucasian populations by combining existing data sources.\textsuperscript{70} Asians within China, Hong Kong, India, Korea, Japan, Singapore, Thailand, and Taiwan were collectively compared to Caucasians within Australia and Iran. The effect of excess adiposity on blood pressure was assessed by examining the increase in systolic blood pressure, diastolic blood pressure or the odds of hypertension associated with a cohort specific 0.5 standard deviation change in BMI. Results from the meta-analyses did support a greater risk of hypertension and other CVD related risk
factors in Asians compared to Caucasian populations. However, genetic and environmental heterogeneity in body composition between Asian populations have been reported and thus information may be lost when collectively assessing various Asian ethnicities. In addition, a 0.5 standard deviation change may encompass different values and ranges across populations.

Razak et al. analyzed cross-sectional data from Canadian Chinese and Caucasians from the Study of Health Assessment and Risk in Ethnic groups (SHARE) cohort. All subjects resided in Canada for a minimum of five years prior to data collection. The 2005 study found an increase in median systolic blood pressure with increasing BMI quintile in both Caucasian and Chinese populations with adjustment for age and sex. The increase was steeper in the Chinese compared to Caucasians.

From this and other studies, the association of obesity with hypertension in Chinese populations appears stronger than that observed in non-Asian populations, even within normal BMI ranges (18.5 kg/m² < BMI < 25 kg/m²). Although the proportion of adults, who are overweight or obese in China, is less than that of the United States, the rate of increase in obesity in China is much more rapid. In the time since data was collected for this study, the prevalence of obesity has increased dramatically within Mainland China. Our population of Chinese adults was very lean in 1983-84, as less than 6% had a BMI of 25 kg/m² or higher. More recent estimates suggest 21%, or more than 1.1 billion of the mainland adult Chinese population are overweight or obese (BMI > 25 kg/m²). Despite the leanness of our sample, the association of BMI with blood pressure was significantly greater than that of American populations where the mean BMI is much higher.
The stronger association of BMI with hypertension among Chinese compared to American populations which were observed in this and other studies may be due to regional differences. Chinese Asians may have become overweight more recently, while the American populations were overweight since childhood or adolescence. Differences in the duration of excess weight may influence the association of BMI with hypertension. In addition, factors related to weight and blood pressure which affected Chinese Asians as children and adults may be quite different from those of the American samples. One of the limitations of our study was that we could not separate these regional differences from ethnic differences.

Another limitation was the lack of diet and physical activity data. Data from the CARDIA study have shown blood pressure was inversely associated with physical activity, dietary potassium and protein and these factors accounted for some of the ethnic differences in blood pressure levels. In China, diet and physical activity have also been linked to regional differences in blood pressure. Without comparable measures of diet and physical activity between populations, we cannot determine whether the stronger association of BMI with hypertension incidence in Chinese compared to U.S. populations was due to differences in diet and physical activity.

This is the first longitudinal study to examine the association of BMI with hypertension and elevated blood pressure in Chinese Asians, American Blacks and American Whites during two different stages of adulthood. Strengths of this work include the use of the CARDIA, ARIC and PRC datasets which provide some of the best data currently available, given our goals. There are many similarities between cohorts, including the study design and data collection, quality control, longitudinal design and use of measured
anthropometry. Further strengths of our study include the use of continuous BMI rather than categorical and computing estimates using difference measures rather than ratio measures to compare risks across ethnicities. This study is limited in that ethnic groups are from different countries (however, data do not exist for a large U.S. cohort of Chinese Americans), the overlay of ethnicity and social factors, geography and nationality cannot be separated, we did not have measures of diet for PRC and measures of diet and physical activity were not comparable across ethnic groups and lastly although each sample is representative of their geographical region, they are not nationally representative. There are also differences in calendar year across samples but because the PRC sample is from China and the CARDIA sample is from the U.S., we did not expect calendar time to be as relevant a criterion to match samples as duration of follow up and age range since the environment in China and the U.S. are very different for all of the years available.

Based on the results of our study and relevant literature, the association of BMI with blood pressure appears to be stronger in Chinese Asians compared to American White and American Black populations. However, it cannot be ignored that American Blacks have a disproportionately high burden of hypertension across all BMI levels. Further, it is not known whether hypertension carries the same level of risk of stroke or cardiovascular disease across different national and ethnic groups. This supports the need for tailored public health strategies to promote healthy blood pressure levels and encourage a healthy BMI among populations.
Table 4.1. Overview of study populations

<table>
<thead>
<tr>
<th></th>
<th>Young adults (24-39 years)</th>
<th>Middle-aged adults (45-64 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chinese Asian (n=2,896)</td>
<td>American Black (n=1,956)</td>
</tr>
<tr>
<td></td>
<td>Chinese Asian (n=2,458)</td>
<td>American Black (n=4,120)</td>
</tr>
<tr>
<td>Cohort</td>
<td>PRC</td>
<td>CARDIA</td>
</tr>
<tr>
<td>Country of origin</td>
<td>China</td>
<td>U.S.A.</td>
</tr>
<tr>
<td>Baseline years</td>
<td>1983-84</td>
<td>1990-91</td>
</tr>
<tr>
<td>Follow-up visits</td>
<td>4 and 10</td>
<td>5 and 10</td>
</tr>
<tr>
<td>Mean (SD) follow-up</td>
<td>9.5 (1.5)</td>
<td>9.3 (1.9)</td>
</tr>
<tr>
<td>time (years)</td>
<td></td>
<td>9.7 (1.5)</td>
</tr>
</tbody>
</table>


### Table 4.2. Baseline characteristics of young and middle-aged Chinese Asians, American Blacks and American Whites

<table>
<thead>
<tr>
<th></th>
<th>Young adults (24-39 years)</th>
<th>Middle-aged adults (45-64 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chinese Asian (n=2,896)</td>
<td>American Black (n=1,956)</td>
</tr>
<tr>
<td></td>
<td>American White (n=2,114)</td>
<td>Chinese Asian (n=2,458)</td>
</tr>
<tr>
<td></td>
<td>American White (n=4,120)</td>
<td>American White (n=11,337)</td>
</tr>
<tr>
<td>BMI (kg/m², mean (SD))</td>
<td>20.2 (2.1)</td>
<td>20.3 (2.8)</td>
</tr>
<tr>
<td></td>
<td>27.5 (6.7)</td>
<td>29.6 (6.2)</td>
</tr>
<tr>
<td></td>
<td>25.0 (4.8)</td>
<td>27.0 (4.9)</td>
</tr>
<tr>
<td>BMI categories (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5 kg/m²</td>
<td>20.1</td>
<td>27.1</td>
</tr>
<tr>
<td>18.5-&lt;25 kg/m²</td>
<td>77.1</td>
<td>66.8</td>
</tr>
<tr>
<td>25-&lt;30 kg/m²</td>
<td>2.6</td>
<td>5.7</td>
</tr>
<tr>
<td>30-&lt;35 kg/m²</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>35-&lt;40 kg/m²</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>≥40 kg/m²</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Age (years, mean (SD))</td>
<td>33.1 (4.2)</td>
<td>51.2 (4.7)</td>
</tr>
<tr>
<td>Gender (% Male)</td>
<td>43.5</td>
<td>42.8</td>
</tr>
<tr>
<td></td>
<td>43.1</td>
<td>37.8</td>
</tr>
<tr>
<td></td>
<td>48.0</td>
<td>47.3</td>
</tr>
<tr>
<td>Education, (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; high school</td>
<td>75.1</td>
<td>87.1</td>
</tr>
<tr>
<td>high school</td>
<td>15.5</td>
<td>4.0</td>
</tr>
<tr>
<td>&gt;high school</td>
<td>2.4</td>
<td>1.8</td>
</tr>
<tr>
<td>Smoke (% current)</td>
<td>33.4</td>
<td>38.7</td>
</tr>
<tr>
<td></td>
<td>34.8</td>
<td>29.8</td>
</tr>
<tr>
<td>Blood pressure (mmHg, mean (SD))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>110.5 (11.4)</td>
<td>117.0 (18.7)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>69.5 (8.9)</td>
<td>74.5 (10.8)</td>
</tr>
<tr>
<td>Anti-hypertension</td>
<td>0.1</td>
<td>1.5</td>
</tr>
<tr>
<td>medication use (%)</td>
<td>2.6</td>
<td>43.7</td>
</tr>
<tr>
<td></td>
<td>0.7</td>
<td>25.9</td>
</tr>
</tbody>
</table>
Table 4.3. Crude and adjusted baseline prevalence and incidence for hypertension by age group and race

<table>
<thead>
<tr>
<th></th>
<th>Young adults (24-39 years)</th>
<th>Middle-aged adults (45-64 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases/sample size (nos.)</td>
<td>Adjusted estimate</td>
</tr>
<tr>
<td>Hypertension Prevalence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese Asian</td>
<td>81/2,896</td>
<td>2.3</td>
</tr>
<tr>
<td>American Black</td>
<td>128/1,956</td>
<td>4.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>American White</td>
<td>61/2,114</td>
<td>1.1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypertension Incidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese Asian</td>
<td>262/2,386</td>
<td>5.3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>American Black</td>
<td>345/1,393</td>
<td>18.5&lt;sup&gt;a,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>American White</td>
<td>160/1,712</td>
<td>6.1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>= different than White; <sup>b</sup>= different than Black; <sup>c</sup>= different than Chinese based on wald test p<0.05

Adjusted estimates represent values for nonsmokers at age 32 for young adults and 52 for middle age adults with a body mass index of 21 kg/m², a high school education in Americans and a primary education in Chinese, 44% distribution of males and the distribution of field center.
Figure 4.1. Incidence difference per 1,000 persons for hypertension in young adults (24-39 years), by race

Joint tests of the linear and quadratic terms to compare ethnic pairs were calculated using the Wald statistic and the p values were calculated based on chi-square distribution with 2 d.f. *Estimates for Chinese were significantly different (p<0.05) from Whites and from Blacks.
Figure 4.2. Incidence difference per 1,000 persons for hypertension in middle-aged adults (45-64 years), by race

Joint tests of the linear and quadratic terms to compare ethnic pairs were calculated using the Wald statistic and the p values were calculated based on chi-square distribution with 2 d.f. *Estimates for Chinese were significantly different (p<0.05) from Whites and from Blacks.
V. INTERACTIONS BETWEEN OBESITY, PARENTAL HISTORY OF HYPERTENSION AND AGE ON PREVALENT HYPERTENSION, THE PEOPLE’S REPUBLIC OF CHINA STUDY

A. Abstract

Objective: To determine if the associations of body mass index (BMI) with prehypertension and hypertension vary by parental history of hypertension and by age.

Methods: Subjects included Chinese adults (n=4,104) from the People’s Republic of China Study. A positive history was indicated if hypertension was reported for either parent. Logistic models were stratified by age into 24-39 (young) and 40-71 (middle-aged) year groups, and adjusted for age, smoking, alcohol, gender and center. Prevalence differences were determined examining BMI in the continuous linear form using a referent BMI of 18.5 kg/m².

Results: In both age and parent history groups, BMI was associated with a monotonic increase in prehypertension and hypertension. Among young adults, interactions between BMI and parental history were not detected although the prevalence/1,000 persons (95% CI) was greater among subjects with a positive parental history (34.8 (15.3, 54.2)) compared to a negative parental history (6.9 (3.1, 10.8)) at the referent BMI. Among middle-aged adults, at the referent BMI, the prevalence of hypertension was similar in the two parental history groups, but the prevalence difference associated with BMI was greater among adults with a positive parental history. For example, at 25 kg/m², the prevalence difference per 1,000 persons was 375 (245, 506) compared to 97 (51, 144). Trends were similar but attenuated for prehypertension.
Conclusions: Interactions among BMI, parental history and age were found to influence hypertension risk in Chinese. The substantial size of these effects warrants further investigation.

B. Background

In China, the prevalence of hypertension among adults aged 18 and older is substantial (19%) despite low mean levels of body mass index (BMI) (23 kg/m$^2$).\textsuperscript{127} Rates of hypertension are expected to rise as levels of obesity increase in China.\textsuperscript{127} Identifying individuals who present with a greater risk for developing hypertension may help target public health prevention efforts. Risk scores used to predict incident hypertension in Caucasian populations incorporate measures of adiposity, parental history of hypertension and age.\textsuperscript{6, 128} Each of these factors contributes to hypertension onset.\textsuperscript{129} Older age and higher levels of BMI are well established risk factors for hypertension in Chinese and other populations,\textsuperscript{92, 130, 131} however, the interaction of parental history of hypertension with obesity has not been well examined and has largely been unexplored in Chinese.

Parental history of hypertension is often collected in clinical and epidemiological settings, as it captures aspects of shared genetic and environmental factors that are associated with hypertension risk. Research has shown a positive parental history of hypertension is associated with higher levels of systolic and diastolic blood pressure among offspring, as well as a greater risk of hypertension.\textsuperscript{74-77, 132-134} The correlation of blood pressure levels between parent and offspring has been observed across the life course, as early as at birth, and these associations between parent-child blood pressure levels have been shown to continue through adulthood.\textsuperscript{135, 136}
The aggregation of blood pressure within families is attributed to interactions between shared genes and environments that result in physiologic and biochemical processes that contribute to increased blood pressure.\textsuperscript{72, 73} It is estimated that 30\% to 60\% of the inter-individual variation in blood pressure is attributed to genetic factors.\textsuperscript{82, 83} Results from a Chinese sample showed that the proportion of observed variation in diastolic and systolic blood pressure that was attributed to genetic factors was 23\% and 32\%, respectively.\textsuperscript{122} In the same population, the correlation of blood pressure between either parent and child were 0.16 for both systolic and diastolic pressure.\textsuperscript{122} Genes which may be passed from parent to child, such as variants in genes encoding angiotensin-converting enzyme, alpha-adducin and aldosterone synthase have been associated with higher systolic blood pressure in Chinese populations, and these genes may predispose individuals to hypertension, especially when coupled with a high sodium diet.\textsuperscript{137}

Epidemiologic studies that examine the effect of parental history of hypertension and BMI have found mean BMI levels among offspring with a positive parental history of hypertension were typically higher, by approximately 0.5 kg/m\textsuperscript{2} or more in Whites and Blacks\textsuperscript{77, 80, 81, 138} and by 0.2 kg/m\textsuperscript{2} in Japanese\textsuperscript{76}, compared to individuals with a negative parental history of hypertension. The increased risk of hypertension associated with a positive family history in these ethnicities persists after adjustment for BMI.\textsuperscript{75, 76, 80, 81, 85} Although individuals may develop hypertension for reasons unrelated to obesity, it is important to note that hypertension and obesity may share some common genetic and environmental risk factors.\textsuperscript{139, 140} Yet it remains unclear if parental history of hypertension may modify the effect of BMI on hypertension and if the association varies by age. Are individuals with a positive parental history of hypertension more susceptible to the effects of
obesity on blood pressure; or are individuals with a positive parental history of hypertension likely to develop prehypertension or hypertension regardless of their weight status, and therefore more resistant to the effects of obesity? Also, do these relationships vary by age? The purpose of this paper is to investigate these questions in a population of Chinese adults.

C. Methods

1. Study population

Data for this cross-sectional analysis were from the People’s Republic of China (PRC) Study, which examined a community based sample of Chinese men and women from urban and rural areas of Guangzhou and Beijing, China. Only data from Guangzhou were included here as young adults were not studied in Beijing. Methods have been described previously.\textsuperscript{111} Urban participants were currently working or retired employees from eight workshops of the Guangzhou Shipyard Company and rural participants worked in 14 of the 21 agricultural villages in the Dashi Township of Panyu County at the time of the 1981 census. Data were from (n=4,445) eligible subjects collected in 1983 from men and women aged 24–71 years at the urban and rural Guangzhou examination centers. Participants were excluded if missing data on BMI (n=25), parental history of hypertension status (n=234), smoking (n=21) or alcohol (n=61). Following these exclusions, 1,939 men and 2,165 women were included in the analyses. The Institutional Review Board (IRB) at each field center approved this study, and the analysis was approved by the University of North Carolina at Chapel Hill IRB on research involving human subjects.

2. Measurements

The Collaborative Studies Coordinating Center at the University of North Carolina at Chapel Hill was responsible for protocols and training manuals for all measurements as well
as the review, processing, and analyses of all data. Data were collected by trained personnel. Participants wore light clothing without shoes during collection of height, measured to the nearest centimeter (cm), and weight, measured to the nearest kilogram (kg). Body mass index was calculated \((\text{weight (kg)} / \text{height (m)}^2)\).

Blood pressure was measured three times using a random zero mercury sphygmomanometer on the right arm with the participant seated. The average of the last two measurements was used in the analyses. Blood pressure thresholds were based on the National High Blood Pressure Education Program Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.\(^{115}\) Participants were classified as hypertensive if 1) systolic blood pressure was greater than or equal to 140 mmHg, 2) diastolic blood pressure was greater than or equal to 90 mmHg or 3) self-report of current antihypertensive medication use. Participants who were free of hypertension were classified as pre-hypertensive if 1) systolic blood pressure was 120 to 139 mmHg or 2) diastolic blood pressure was 80 to 89 mmHg.

Demographic and lifestyle factors were collected with standardized interviewer administered questionnaires. Cigarettes smoked per day (cig/day) were reported and alcohol consumed per day (grams/day) was derived from monthly alcohol consumption levels. Subjects reported highest level of education attained (less than senior middle school, senior middle school and greater than senior middle school). Parental history of hypertension was determined based on self-report of whether a participant’s mother, father, both or neither parent had high blood pressure. Subjects had the option to report “unknown” but this was not selected by any study participants. Subjects were classified as having a positive parental
history of hypertension if hypertension was reported by at least one parent and negative if hypertension was not reported in either parent.

3. **Statistical analyses**

   Our primary objective was to examine the association of BMI with prehypertension and hypertension and determine if this relationship varied by parental history of hypertension status and by age. We found a significant (p=0.02) three way interaction between BMI, parental history of hypertension status, and age using the Wald test. We also examined effect modification by sex using the Wald test with 1 degree of freedom, but this was not found (p>0.1). Therefore, logistic models were stratified into 24-39 and 40-71 year age groups and included a BMI-parental history of hypertension interaction, with BMI in the continuous form. We calculated the adjusted prevalence per 1,000 persons for BMI values 15-30 kg/m² and the prevalence difference per 1,000 persons using a BMI of 18.5 kg/m², the lowest value within the range of the normal BMI category, as the referent. The “prvalue” command in Stata (Version 10.0) was used to calculate the prevalence and prevalence difference. Estimates were adjusted to the mean age, cigarettes, alcohol and distribution of gender and field center. The delta method was used to calculate the standard errors and 95% confidence intervals for the prevalence and prevalence difference.

D. **Results**

Characteristics of the 4,104 participants varied by age and by parental history of hypertension status (Table 5.1). A positive parental history of hypertension was reported by 18.6% of the study population. In both age stratum, compared to subjects who reported a positive parental history of hypertension, subjects who reported a negative parental history of hypertension had slightly lower systolic and diastolic blood pressure, prevalence of
prehypertension and hypertension, BMI and education attainment but slightly higher consumption of alcohol and cigarettes. This sample is quite thin as approximately one-fifth of the young adults and one-quarter of the older adults had a BMI less than 18.5 kg/m$^2$. For both age groups, BMI was positively associated with the prevalence difference for prehypertension and hypertension among both parental history groups (Figures 5.1-5.4). However, age-related differences in the associations of parental history of hypertension and BMI with prehypertension and hypertension were observed.

Among young adults (24-39 years), the adjusted prevalence (95% CI) of prehypertension was similar regardless of parental history of hypertension. For example, at a BMI of 18.5 kg/m$^2$ the prevalence of prehypertension per 1,000 persons was 179 (157, 203) among subjects with a negative parental history of hypertension and 188 (140, 237) among subjects with a positive parental history of hypertension (Table 5.2). The prevalence difference associated with an increase in BMI (Figure 5.1) was also similar or almost identical between subjects, regardless of parental history status. However, when examining hypertension, parental history of hypertension was significantly associated with hypertension prevalence. The prevalence of hypertension (95% CI) at a BMI of 18.5 kg/m$^2$ was approximately four-fold greater among subjects who reported a positive parental history of hypertension (35 (15, 54) per 1,000 persons) compared to subjects who reported negative parental history (7 (3, 11) per 1,000 persons) (Table 5.2). The adjusted prevalence difference associated with an increase in BMI above 18.5 kg/m$^2$ was similar between subjects with a positive and negative parental history and almost identical within the underweight (<18.5 kg/m$^2$) and normal weight (18.5 - 24.9 kg/m$^2$) categories (Figure 5.2). This suggests, among young Chinese adults, a positive parental history of hypertension is associated with
greater hypertension risk among offspring but parental history status does not modify the prevalence difference of BMI with hypertension.

In middle-aged (40 -71 years) adults, the adjusted prevalence (95% CI) of prehypertension per 1,000 persons at the reference level of BMI (18.5 kg/m$^2$) was similar between subjects with a negative 277 (248, 307) and positive 297 (221, 374) parental history status (Table 5.2). Although not significantly different, the prevalence difference for prehypertension associated with BMI tended to be greater among subjects with a positive parental history compared to those with a negative parental history (Figure 5.3). Among the same age group, the adjusted prevalence of hypertension (95% CI) per 1,000 persons at the reference level of BMI (18.5 kg/m$^2$) was also similar by parental history status; 77 (61, 94) for subjects with a negative parental history status and 61 (27, 96) for subjects with a positive parental history status (Table 2). Although the baseline prevalence at the referent value was similar between groups, the prevalence difference for hypertension associated with BMI varied by parental history status (Figure 5.4). Across BMI, even at values within the normal BMI range (18.5 - 24.9 kg/m$^2$), the risk associated with BMI was greater among subjects with a positive parental history of hypertension. The graded and steeper slope associated with a positive parental history was more apparent for hypertension compared to prehypertension. This suggests among middle-aged adults, parental history of hypertension alone is not associated with a greater risk of hypertension, but subjects with a positive parental history of hypertension are more sensitive to the effects of obesity as observed by the greater prevalence of hypertension associated with the prevalence difference for BMI.
E. Discussion

Our goal was to determine the association of BMI with prevalent prehypertension and hypertension in Chinese adults and examine if this relationship differed by parental history of hypertension and by age. In both age groups, BMI was positively associated with prehypertension and hypertension prevalence. However, the association of parental history with prehypertension and hypertension prevalence was not consistent across age stratum. In the young adults (24-39 years), a positive parental history was associated with a four-fold greater risk of hypertension but the effects of obesity on prevalence differences were similar across parental history groups. In the middle-aged (40-71 years) group, the risk of prehypertension or hypertension was similar by parental history status, but subjects with a positive parental history of hypertension were much more susceptible to the effects of BMI as observed by the associations with the prevalence difference. The trend was similar but weaker for prehypertension.

When familial associations of blood pressure thresholds, such as hypertension are examined, studies in Caucasians have shown parental hypertension that develops before age 60 is associated with a greater risk of hypertension in offspring, whereas onset of parental hypertension at 70 years or older, was associated with no greater risk of hypertension in offspring than that of the general population. It is thought that hypertension that occurs much later in life is associated with weaker genetic and environmental factors that are less likely to be shared between parent and child. One explanation as to why parental hypertension status was not related to hypertension onset in the middle-aged adults may be related to differences in age of hypertension onset among their parents. However, we cannot
examine these associations as data related to the age of hypertension onset among subjects or their parents were not collected in this study.

Few studies have explored the interaction of parental history of hypertension status and BMI with hypertension risk. Examination of this relationship which included Caucasians and African Americans in the Atherosclerosis Risk in Communities Study (ARIC) indicated no effect modification of parental history status by BMI. A cross-sectional study of 503 Swedish middle aged adults examined the independent and combined effects of parental history and obesity (a relative BMI % of ≥120%) status on the risk of hypertension. Compared to non-obese subjects with a negative parental history of hypertension, the odds ratios (95% CI), adjusted for age, sex and physical activity, were 3.0 (1.1-8.0) for a positive parental history of hypertension, 4.8 (1.8, 13.0) for obesity and 9.1 (4.1-20.1) for the joint effects of obesity and a positive parental history of hypertension. Another cross-sectional study which examined the independent and joint effects of obesity (BMI > 26 kg/m²) and family history of hypertension (in siblings and parents) on the risk of hypertension included a large Japanese sample (n=9,914). Odds ratios, adjusted for age, sex, smoking, alcohol and exercise, were graphed without confidence intervals. The approximate values were 2.4 for obesity, 2.8 for a positive family history of hypertension and 7.0 for their joint effects. In both the Swedish and Japanese cohorts, the independent and joint effects of obesity and family history of hypertension were associated with a greater risk of hypertension compared to non-obese subjects with a negative parental history of hypertension. Although the risks of their joint effects were larger than the sum of their independent effects, interactions between these factors did not appear statistically significant.
In 1979, a nationwide screening program of 720,000 U.S. Whites and Blacks found family history was independently associated with hypertension prevalence in both 20-39 and 40-64 year old adults. When self-report weight class was also considered, the prevalence of hypertension was three to four times greater among overweight individuals with a positive parental history status compared to normal weight individuals with a negative parental history of hypertension. Excess cases of hypertension attributed to overweight among individuals with a positive parental history was 136 per 1,000 among 20-39 year olds and 262 per 1,000 among the 40-64 year olds. To our knowledge, no other studies on hypertension have reported results by weight and parental history of hypertension.

Parental hypertension status was not validated in our sample and therefore, recall and information bias may be a problem. Reports of positive parental history of disease have been linked to disease prevalence, access to care, family communication behaviors and health seeking behaviors. These factors differ within and between populations. Among Chinese adults, rates of hypertension awareness (44.7%), treatment (28.2%) and control (8.1%) are low compared to rates in the U.S. where rates of awareness (75.7%), treatment (65.1%) and control (36.8%) are much higher. If only about half of Chinese mothers and fathers who were hypertensive were aware of their hypertension, offspring reports of positive parental history status was most likely underestimated in our sample. Results from U.S. studies suggest the sensitivity and specificity of self-report parental history of hypertension are fairly high, at 76% and 84%, respectively. These rates may not apply to our population. A study of West Africans in Gambia found subjects who reported a positive family history of non-communicable disease were younger, more likely to live in a city, have higher education status and more likely to be female. This was similar to our findings in which subjects
reporting a positive parental history tended to be younger, female, have higher education, and be from the urban center. Most likely, when examining parental history status, this would bias our estimates towards the null. As hypertension awareness changes across time, older individuals may be even less aware of a positive parental history of hypertension compared to younger generations.

Although our sample was population based, subjects were from one region in southern China, Guangzhou. Regional differences in the prevalence of hypertension within China have been observed.\textsuperscript{38, 39} Hypertension is less common in southern China, where diet and exercise patterns are substantially different from the north. In addition, the prevalence of hypertension is lower in rural than urban areas, which has also been suggested to be related to higher levels of physical activity and lower levels of overweight. Diet and physical activity patterns have evolved over time and dietary and physical activity patterns of previous generations may have protected individuals from developing hypertension. The surprising lack of association between parental history of hypertension and hypertension prevalence in the 40-71 year olds may in part be due to shifts in dietary and physical activity patterns or to other factors described above such as age-related differences in parental hypertension onset and hypertension awareness.

It is important to note that health care has evolved in China. Knowledge of hypertension among the parental generation may be close to actual rates of hypertension in that generation as access to health care was fairly egalitarian from 1949 to 1978. During this time, the Chinese government operated the health system and provided equal access to health care regardless of the ability to pay.\textsuperscript{146} There was a strong emphasis on rural health, preventative medicine and community control of hypertension in many districts within
Beginning in 1978, China’s health care system gradually shifted towards a market based approach whereby the government decentralized its power over the health care system and employers became a major supplier of health insurance.\textsuperscript{146}

Surveys on blood pressure and hypertension were conducted in many areas of China as early as 1958.\textsuperscript{147} A 1991 national blood pressure survey of adults aged 15-74 years in China found the prevalence of people with blood pressure levels of greater than or equal to 140/90 mmHg were 17.1\% in urban and 11.8\% in rural areas.\textsuperscript{148} From earlier studies, hypertension prevalence rates were much higher in the older than younger age groups. A survey from 1959 found the prevalence of hypertension among Chinese aged 50-59 years was 11.3\% and among those 60-69 years the prevalence was 17.23\%.\textsuperscript{147} These prevalence estimates in older adults are similar to the prevalence of positive parental history reported by our sample. Middle-aged adults had a slightly lower prevalence of a positive parental history than young adults. Fewer cases of parental hypertension among middle-aged adults may also be due in part to previous definitions of hypertension which used higher cutpoints to define hypertension (\(\geq 160/95\) mmHg). If parental hypertension represented more severe cases of hypertension, we would expect a stronger correlation of parental hypertension with offspring hypertension.

Strengths of this work include the large population-based sample of Chinese, a group in which parental history of hypertension has largely been unexplored, use of measured anthropometrics and blood pressure and estimation using difference rather than ratio measures.\textsuperscript{120} The present study may be limited in that our analysis was cross-sectional and information regarding the age of hypertension onset among subjects were not collected. It is possible that subjects in the 40-71 year age strata may have developed hypertension during
early adulthood. Therefore, we cannot clearly separate the different findings between age strata. Additional limitations include a lack of dietary, physical activity or parental BMI data and use of self-report parental history of hypertension. The relationship between parental history status, BMI and age may be clarified with a prospective cohort begun in early adulthood and collected validated measures of parental history status. Hypertension and obesity are preventable risk factors for cardiovascular disease, which is a leading cause of death in China. The interaction of BMI and parental history of hypertension on hypertension prevalence has not been well studied and deserves further attention as this information could help inform public health efforts designed to identify individuals at risk of hypertension for prevention and early treatment.
Table 5.1. Demographic characteristics by age group and parental history of hypertension status

<table>
<thead>
<tr>
<th>Parental history of hypertension status</th>
<th>Young adults (24-39 years)</th>
<th>Middle-aged adults (40-71 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative (n=1,866)</td>
<td>Positive (n=474)</td>
</tr>
<tr>
<td></td>
<td>Positive (n=1,473)</td>
<td>Positive (n=291)</td>
</tr>
<tr>
<td>Age (years, mean (s.d.))</td>
<td>32.2 (4.0)</td>
<td>49.7 (6.7)</td>
</tr>
<tr>
<td></td>
<td>32.6 (3.9)</td>
<td>46.6 (5.4)</td>
</tr>
<tr>
<td>Gender (% women)</td>
<td>57.6</td>
<td>50.4</td>
</tr>
<tr>
<td></td>
<td>50.4</td>
<td>48.1</td>
</tr>
<tr>
<td>Body Mass Index (kg/m², mean (s.d.))</td>
<td>20.1 (2.0)</td>
<td>20.2 (2.6)</td>
</tr>
<tr>
<td></td>
<td>20.4 (2.3)</td>
<td>21.0 (2.9)</td>
</tr>
<tr>
<td>Parental history of hypertension (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>55.7</td>
<td>44.3</td>
</tr>
<tr>
<td>Mother</td>
<td>38.0</td>
<td>47.8</td>
</tr>
<tr>
<td>Both Parents</td>
<td>6.3</td>
<td>7.9</td>
</tr>
<tr>
<td>Current cigarette or leaf smokers (%)</td>
<td>33.9</td>
<td>44.7</td>
</tr>
<tr>
<td></td>
<td>32.5</td>
<td>40.2</td>
</tr>
<tr>
<td>Cigarettes or leaf smoked (cig/day, mean (s.d.))</td>
<td>5.6 (9.4)</td>
<td>8.3 (12.0)</td>
</tr>
<tr>
<td></td>
<td>5.3 (8.9)</td>
<td>8.3 (12.0)</td>
</tr>
<tr>
<td>Current drinkers (%)</td>
<td>21.9</td>
<td>26.1</td>
</tr>
<tr>
<td></td>
<td>13.9</td>
<td>18.9</td>
</tr>
<tr>
<td>Alcohol consumed (g/day, mean (s.d.))</td>
<td>10.8 (33.9)</td>
<td>17.7 (47.7)</td>
</tr>
<tr>
<td></td>
<td>6.7 (26.4)</td>
<td>11.4 (38.1)</td>
</tr>
<tr>
<td>Educational attainment (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; Senior middle school</td>
<td>77.3</td>
<td>85.4</td>
</tr>
<tr>
<td></td>
<td>56.8</td>
<td>76.3</td>
</tr>
<tr>
<td>Senior middle school</td>
<td>13.7</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>28.3</td>
<td>10.0</td>
</tr>
<tr>
<td>&gt; Senior middle school</td>
<td>1.8</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>4.6</td>
<td>4.8</td>
</tr>
<tr>
<td>Field center (% urban)</td>
<td>43.0</td>
<td>44.9</td>
</tr>
<tr>
<td></td>
<td>75.5</td>
<td>69.1</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg, mean (s.d.))</td>
<td>110.3 (11.2)</td>
<td>115.9 (17.9)</td>
</tr>
<tr>
<td></td>
<td>113.0 (11.6)</td>
<td>119.7 (20.4)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg, mean (s.d.))</td>
<td>69.0 (8.8)</td>
<td>74.2 (10.4)</td>
</tr>
<tr>
<td></td>
<td>72.0 (9.2)</td>
<td>77.8 (11.4)</td>
</tr>
<tr>
<td>Hypertension status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prehypertensive</td>
<td>22.8</td>
<td>27.7</td>
</tr>
<tr>
<td></td>
<td>25.3</td>
<td>29.2</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>2.1</td>
<td>12.0</td>
</tr>
<tr>
<td></td>
<td>6.1</td>
<td>18.6</td>
</tr>
<tr>
<td>Blood pressure medication use (%)</td>
<td>0.2</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Parental history of hypertension was positive if hypertension was reported for at least one parent and negative otherwise.

Prehypertensive was defined as non-hypertensive and systolic blood pressure of 120-139 mmHg or diastolic blood pressure of 80-89 mmHg and hypertensive defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or self-report of current anti-hypertensive medication use.
Table 5.2. Adjusted prevalence of prehypertension and hypertension per 1,000 persons (95% CI) at a BMI of 18.5 kg/m² by age group and parental history of hypertension

<table>
<thead>
<tr>
<th></th>
<th>Young adults (24-39 years)</th>
<th>Middle-aged adults (40-71 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Prehypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>179  (156, 203)</td>
<td>188  (140, 237)</td>
</tr>
<tr>
<td></td>
<td>7  (3, 11)</td>
<td>35  (15, 54)</td>
</tr>
</tbody>
</table>

Models adjusted for age, alcohol, smoking, gender and field center.

Parental history of hypertension was positive if hypertension was reported by at least one parent and negative otherwise.

Prehypertensive was defined as non-hypertensive and systolic blood pressure of 120-139 mmHg or diastolic blood pressure of 80-89 mmHg.

Hypertensive was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or self-report of current anti-hypertensive medication use.
Figure 5.1. Adjusted prevalence difference by BMI and parental history of hypertension status in Chinese young adults (24-39 years)

Prevalence differences were computed using a BMI of 18.5 kg/m$^2$ as the referent.

Adjusted to the mean age, cigarettes (smoked), alcohol consumed (g/day) and distribution of gender and field center.
Figure 5.2. Adjusted prevalence difference for hypertension by BMI and parental history of hypertension status in Chinese young adults (24-39 years)

Adjusted to the mean age, cigarettes (smoked), alcohol consumed (g/day) and distribution of gender and field center.

Prevalence differences were computed using a BMI of 18.5 kg/m$^2$ as the referent.
Figure 5.3. Adjusted prevalence difference for prehypertension by BMI and parental history of hypertension status in Chinese middle-aged adults (40-71 years)

Adjusted to the mean age, cigarettes (smoked), alcohol consumed (g/day) and distribution of gender and field center. Prevalence differences were computed using a BMI of 18.5 kg/m$^2$ as the referent.
Figure 5.4. Adjusted prevalence difference for hypertension by BMI and parental history of hypertension status in Chinese middle-aged adults (40-71 years)

Adjusted to the mean age, cigarettes (smoked), alcohol consumed (g/day) and distribution of gender and field center. Prevalence differences were computed using a BMI of 18.5 kg/m$^2$ as the referent.
VI. THE ASSOCIATION OF HIP CIRCUMFERENCE WITH INCIDENT METABOLIC RISK FACTORS IN CHINESE, THE PEOPLE’S REPUBLIC OF CHINA STUDY

A. Abstract

Studies in Caucasians have shown that after adjusting for waist circumference and body mass index (BMI), a larger hip circumference may be protective for metabolic risk factors. The associations between adiposity and metabolic risk factors have been suggested to differ between Asian and Caucasian populations, yet to our knowledge, these associations have never been examined in a Chinese population. Baseline (1987-88) and follow-up (1993-94) data were from the People’s Republic of China Study (n=1,144 men, n=1,776 women). Logistic models were stratified by sex and adjusted for age, smoking, center, and education. Incidence differences (ID) comparing the sex specific 85th percentile to the 15th percentile of hip were computed for elevated blood pressure, blood glucose and triglycerides, low HDL-C and multiple metabolic abnormalities (3 or more of the aforementioned). In models adjusted for waist and BMI, the ID (95% CI) per 1,000 persons associated with a 12 cm larger hip were -132 (-237, -26) for low HDL-C; -85 (-138, -31) for elevated triglycerides; and -49 (-83, -4) for multiple metabolic abnormalities. In males, a larger hip circumference was not associated with a reduction of incident risk factors although the ID tended to be negative. In Chinese women, greater mass in the lower trunk region was protective for incident high triglycerides, low HDL-C and multiple metabolic abnormalities when adjusted for general and central adiposity. This association was not detected in men.
Additional research is needed to better understand the mechanisms by which fat at different depots results in differential risk.

B. Background

Specific fat depots may be more closely related to metabolic risk than overall adiposity.\textsuperscript{149} Many studies have used the ratio of waist and hip circumferences as a means of capturing aspects of body shape that are poorly detected by BMI. Nevertheless, waist to hip ratio does not differentiate the independent effects of hip and waist circumferences and the ratio measure does not account for possible non-linear associations between the two anthropometrics.\textsuperscript{150, 151}

Although waist and hip are crude measures of adipose tissue distribution the circumference measures do show a high association with the size of the respective fat depots\textsuperscript{152, 153}, and they are clinically practical due to the low risk of assessments to patients, low cost and ease of collection. Waist circumference is an indicator of the amount of visceral and subcutaneous adiposity around the abdomen, while hip assesses skeletal frame size and adipose and muscle mass in the buttock and thigh regions (gluteofemoral)\textsuperscript{154, 155}. In mutually adjusted models, waist has been shown to correlate with abdominal visceral and subcutaneous adiposity and hip was inversely correlated with those depots but positively correlated with leg fat mass.\textsuperscript{155} Visceral and subcutaneous adipocytes have different lipolytic activities as visceral fat is associated with adverse cardiovascular risk factors and is more metabolically active compared with adipocytes in subcutaneous fat\textsuperscript{153}.

In contrast to a large waist circumference at a given overall body size, a large hip circumference has been suggested to be less associated with risk of disease and even potentially protective. After adjustment for one another and for BMI, waist and hip
circumferences have been shown to have independent and opposite associations with cardiovascular risk factors, coronary heart disease (CHD), cardiovascular disease (CVD) and mortality. \textsuperscript{7-10, 87-89, 91, 153, 156-162} Studies examining components of hip and waist circumferences, specifically, leg and trunk fat and leg lean mass, using dual-energy X-ray absorptiometry (DXA) or computed tomography (CT) have found positive associations of trunk fat and inverse associations of thigh or leg fat with insulin resistance, dyslipidemia, diabetes and other metabolic risk factors. These associations have been observed in Black, White and Japanese populations. \textsuperscript{155, 161, 163-166} A recent review has summarized some of the mechanistic evidence related to gluteofemoral body fat and metabolic health. \textsuperscript{167} Differential effects by BMI category and by gender have been reported. \textsuperscript{161, 166, 168} The attenuation of risk associated with proportionally greater leg fat mass is more frequently observed in overweight and obese individuals than in normal weight individuals and is more often observed in women than in men. \textsuperscript{161, 166, 168}

To our knowledge, no studies have evaluated the association of hip circumference (HC), independent of waist circumference or BMI, with cardiovascular risk factors in a Chinese population. It is well established that adiposity is associated with metabolic disease risk. As Chinese have greater adiposity at the same level of BMI compared to non-Asian populations and experience metabolic abnormalities at low levels of adiposity, \textsuperscript{92, 169} it is uncertain whether a protective effect of hip would be observed in a Chinese population. Our goal was to explore whether a larger hip circumference, when controlling for waist circumference or BMI, would be associated with a lower incidence of metabolic risk factors in a Chinese cohort from Guangzhou, China.
C. Methods

1. Study population

Data for this work are from the community-based People’s Republic of China (PRC) Study.\textsuperscript{111} Waist and hip circumferences were collected from PRC respondents who lived in the urban and rural areas of Guangzhou, China (southern). Baseline and follow-up examinations were in 1987-1988 and 1993-1994, respectively. Participants were aged 28–69 years at baseline.

Of the n=3,019 eligible subjects, participants were excluded if missing anthropometric data at baseline (n=52) or follow-up (n=15), missing education at baseline (n=1), self-report of cancer (n=13) or CHD (n=18). Following these exclusions, 1,144 men and 1,776 women were included in the analyses. For each of the incident outcomes examined, prevalent cases of the condition were excluded. This study was approved by the IRB at each field center, and the analysis was approved by the University of North Carolina at Chapel Hill Institutional Review Board on research involving human subjects.

2. Measurements

Protocols and training manuals for all measurements as well as the review, processing, and analyses of all data were administered by the Collaborative Studies Coordinating Center at the University of North Carolina at Chapel Hill. Data were collected in examination centers by trained personnel. Participants wore light clothing without shoes during collection of anthropometric data. Height was measured to the nearest centimeter (cm) and weight to the nearest kilogram (kg). Body mass index was calculated from these measures (weight (kg)/height (m)\(^2\)). Circumferences of the waist and hip were measured to the nearest 0.1 cm. Waist was measured by passing the tape measure through the midpoint
between the superior iliac crest and the lowest rib. Hips were measured at their maximum protrusion.

Subjects were instructed to fast 12 hours prior to the examination. All glucose assays were performed on an Abbott autoanalyzer. Serum glucose was measured by the hexokinase/glucose-6-phosphate dehydrogenase method. High-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were measured according to standardized protocols by the Lipid Standardization Program of the U.S. NHLBI and CDC. Serum TG was determined with use of an enzymic reagent from Abbott Laboratories. Serum HDL was measured using the Boehringer Mannheim Diagnostics high-performance enzymic reagent calibrated with precise standards on the Abbott analyzer after precipitation of other lipid fractions with dextran sulfate. To ensure quality control, random samples were analyzed by the CDC.

Blood pressure was measured three times at each visit using a random zero mercury sphygmomanometer on the right arm with the participant seated. The average of the last two measurements is used in the analyses. Participants self-reported use of hypertension medications in the previous two weeks.

Outcomes were dichotomized based on criteria from the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program for metabolic syndrome. Components of the metabolic syndrome were defined as: 1) HDL-C less than 1.03 mmol/L in males or less than 1.29 mmol/L in females, 2) triglycerides of 1.7 mmol/L or higher, 3) fasting blood glucose of 5.6 mmol/L or higher or self-reported diabetes and 4) blood pressure greater than or equal to 130/85 mmHg or self-report of current antihypertensive medication use. The fifth criterion of the metabolic syndrome is a large waist circumference. Since waist
circumference was included as a covariate in our models we did not model it as an outcome. Instead we assessed a clustering of risk factors similar to the ATP III metabolic syndrome definition but exclusive of waist circumference, which we termed “multiple metabolic abnormalities” and defined as the presence of at least three of the four aforementioned ATP III outcomes examined.

3. **Statistical analyses**

Models were stratified by gender because of the well known differences in body shape between men and women. Dichotomous outcomes were coded as 0 (no disease) or 1 (incident disease). All models include the covariates field center (urban or rural), age (years), and highest education level attained (less than senior middle school, senior middle school and greater than senior middle school). For all outcomes, the covariates for smoking, alcohol, menopausal status and physical activity were examined but were not included because associations were small, not statistically significant (p<0.05) and did not influence the coefficients associated with variables of interest.

Quadratic terms were tested to assess non-linear associations of BMI, waist, hip and age with metabolic risk factors. Most quadratic terms were not significant at p<0.05, except for age^2, which improved model fit significantly in women. Interactions between hip and age as well as hip and BMI, were assessed for each risk factor outcome using the Wald test with 1 degree of freedom and none were significant at p<0.05. The adjusted incidence at the sex specific 15\textsuperscript{th} percentile of hip and the incidence differences (ID) comparing the sex specific 85\textsuperscript{th} percentile to the 15\textsuperscript{th} percentile of hip were computed. ID estimates were obtained from logistic regression models and 95\% confidence intervals (CI) were calculated using the delta method by the prvalue command in STATA 10.0. The incidence and ID were also modeled
with adjustment for additional anthropometric measures (waist and BMI). The ID was standardized to the mean covariate values for continuous variables and to the most prevalent education level (< senior middle school) and center (rural).

D. Results

The distribution of most demographic characteristics was similar between the sexes, except for alcohol and smoking status (Table 6.1). A small percentage of women consumed alcohol (15.1%) or smoked (3.0%), whereas, men were much more likely to drink (59.4%) or smoke (66.1%). The majority of subjects were normal weight or underweight and did not have abdominal obesity according to standard WHO BMI definitions and Asian central obesity cutpoints of ≥90 cm in males and ≥80 cm in females (Table 6.1). Anthropometric measures tended to be highly correlated. In this sample, Pearson’s correlation coefficients for waist, hip and BMI were high and ranged from 0.76 to 0.83 in men and 0.79 to 0.87 in women. Despite the high correlations, collinearity of anthropometric measures, evaluated using a variance inflation factor (VIF) were all less than 5.0, well below the criterion for indication of 10.0.

The unadjusted baseline prevalence and six-year incidence for each outcome are shown in Table 6.2. In both women and men, multiple metabolic abnormalities and elevated blood glucose were the least prevalent outcomes (<10%); however, the crude prevalence and incidence levels were higher, between 10% and 34%, for elevated blood pressure, low HDL-C and elevated triglycerides. The adjusted incidences of metabolic risk factors at the 15th percentile of hip circumference are shown in Table 6.3 and the incidence difference (between the 85th and 15th percentile of hip (a difference of 11 cm in males and 12 cm in females)) per 1,000 persons are shown in Figures 6.1 and 6.2. Hip was positively associated with incident
outcomes when it was the only anthropometric measure included in the model (model 1). When adjusted for waist (model 2) or BMI (model 3), the ID tended to be null or negative, suggesting hip circumference may be neutral or inversely associated with incident metabolic risk factors when accounting for general or central adiposity. In women (Figure 6.1), with adjustment for waist circumference, a larger hip circumference was associated with a significant decrease in incidence (95% CI) per 1,000 persons for high triglycerides -74 (-120, -27) and low HDL cholesterol -114 (-207, -21); and when adjusting for BMI, hip circumference was associated with a significant decrease in incidence per 1,000 persons for high triglycerides -56 (-108, -4) and multiple metabolic abnormalities -37 (-69, -5). In males (figure 6.2), ID estimates for models 2 and 3, tended to be null or negative.

Model 4, included hip and was adjusted for both waist and BMI. In women, the ID (95% CI) per 1,000 persons was -85 (-138, -31) for incident high triglycerides, -132 (-237, -26) for low HDL-C and -49 (-83, -14) for multiple metabolic abnormalities. For blood pressure and glucose, estimates were negative but confidence intervals included zero. In men, point estimates for all the outcomes examined were negative and the confidence intervals included zero.

E. Discussion

In this prospective study, hip circumference was positively associated with incident metabolic risk factors in Chinese men and women. After adjustment for waist circumference and BMI, women with a larger hip circumference had a lower risk of incident elevated triglycerides, low HDL-C and multiple metabolic abnormalities and null associations were found for elevated blood pressure and elevated glucose. In men, after adjustment for waist or waist and BMI, the association of hip circumference with glucose, lipid levels and multiple
metabolic abnormalities was inverse but not statistically significant. Weaker protective associations in men are consistent with other studies, many of which found stronger evidence of an inverse association of hip with adverse outcomes in women.\textsuperscript{156-158, 160, 172} This differential may be due to gender differences in hip girth, body composition, and/or fat distribution. Although the gender differences in hip circumference are smaller in Chinese compared to Caucasians, gender differences in body shape and fat distribution persist.\textsuperscript{173} In this cohort, the difference in hip circumference between women and men was less than 1 centimeter, whereas, most studies in Caucasian populations have shown gender differences in hip circumference between 1 and 6 centimeters.\textsuperscript{9, 88, 155} We explored whether gender differences were related to differences in height but when height was added to the models, the estimates remained essentially unchanged.

The participants in our study were leaner than populations examined in previous studies of hip circumference, yet associations between hip and metabolic risk factors were observed. Here the mean BMI among Chinese was 20.6 kg/m\textsuperscript{2} in men and 21.0 kg/m\textsuperscript{2} in women and fewer than 6\% of men and 10\% of women had a BMI of 25 kg/m\textsuperscript{2} and above, whereas, in most studies that examined the risk factor associations with hip the mean BMI was $\geq$ 25 kg/m\textsuperscript{2}.\textsuperscript{7-10, 87-91, 172} The sex specific mean value of hip in our population was also smaller than means reported in previously published studies.\textsuperscript{7-10, 87-91, 172} For example, a recent study\textsuperscript{172} that reported an inverse association of hip circumference with incident diabetes and CHD included data from American Whites and Blacks in whom the mean value for hip circumference within the lowest quintile of hip (92.7 cm) was larger than our overall population mean for hip (87.8 cm).
We know of six studies that have used a cross-sectional design to examine the association of hip circumference with metabolic syndrome or its component risk factors (blood pressure, lipids and glucose). Two of these studies were conducted among Australians. Dixon, et al., examined obese Australian women and used receiver operating characteristic (ROC) curves to identify the values of hip and waist circumferences associated with the highest sum of sensitivity and specificity for the presence of metabolic syndrome. They then tested the odds of metabolic syndrome above versus below that cutoff. The investigators found a small hip circumference (below the cutoff of 115 cm) was associated with greater odds of the metabolic syndrome (OR (95% CI): 12.3 (3.0, 51.0)) compared to a large hip circumference (above the cutoff of 115 cm). A small hip circumference was also found to be a stronger predictor of the metabolic syndrome than a large waist circumference (above the cutoff of >100 cm) (OR (95% CI): 5.2 (1.4, 20.0)). The Australian Diabetes, Obesity and Lifestyle study, a nationally representative study among 11,247 participants aged 25 and older, found that the OR (95% CI) associated with a 1 standard deviation (SD) increase in hip (7.6 cm in men and 11.1 cm in women) was 0.55 (0.41, 0.73) in men and 0.42 (0.27, 0.65) in women for diabetes; 0.58 (0.50, 0.67) in men and 0.37 (0.30, 0.45) in women for dyslipidemia; and 0.80 (0.69, 0.93) in men and 0.88 (0.70, 1.11) in women for hypertension.

The Quebec Family Study examined the association of hip with metabolic risk factors by modeling hip as a continuous variable. Models were adjusted for age, BMI, and waist circumference. In men, a 1 centimeter increase in hip was associated with higher levels of HDL cholesterol (mean ± SD: 0.008 ± 0.004 mmol/L) and lower levels of triglycerides (-0.039 ± 0.011 mmol/L) and glucose (-0.039 ± 0.018 mmol/L). Although not significant, hip
was positively associated with systolic (0.310 ± 0.233 mmHg) and diastolic (0.127 ± 0.144 mmHg) blood pressure. In women, the association of a 1 cm increase in hip with HDL cholesterol (0.005 ± 0.003 mmol/L), triglycerides (-0.017 ± 0.006 mmol/L) and glucose (-0.002 ± 0.011 mmol/L) were similar in direction to what was observed for men, but only the association of hip with triglycerides was significant. Both systolic (-0.222 ± 0.125 mmHg) and diastolic (-0.086 ± 0.079 mmHg) blood pressure were inversely related to hip, although not significantly (p>0.05).

Two papers summarized results from a cross-sectional study of Caucasians in Tehran, Iran.\textsuperscript{156, 157} Investigators examined the association of hip circumference with components of the metabolic syndrome in 5,720 women\textsuperscript{156} and 4,040 men\textsuperscript{157} aged 18-74. Quintiles of hip circumference were used to predict the odds ratio (OR) for metabolic syndrome components as defined by the ATP III guidelines. In women, the adjusted OR (95% CI) comparing the largest versus smallest hip quintile was inversely associated with all components of the metabolic syndrome and in men this was true for all outcomes except elevated blood pressure (1.06 (0.67, 1.68)). Models were adjusted for age, smoking, physical activity, BMI, height and waist. In women, the adjusted OR (95% CI) comparing the largest (≥110 cm) versus smallest (<95 cm) hip quintile were 0.74 (0.52, 0.97) for high triglycerides, 0.56 (0.40, 0.78) for low HDL cholesterol, 0.48 (0.30, 0.78) for abnormal glucose and 0.61 (0.43, 0.90) for elevated blood pressure. In men, the adjusted OR (95% CI) comparing the largest (≥102 cm) versus smallest (<90 cm) hip quintile was 0.73 (0.47, 0.93) for high triglycerides, 0.91 (0.83, 0.96) for low HDL cholesterol, 0.36 (0.19, 0.70) for abnormal glucose and 1.06 (0.67, 1.68) for elevated blood pressure.
A cross-sectional study that examined the association of hip circumference with metabolic risk factors in non-Caucasians included Melanesians, Micronesians, Indians and Creole from Mauritius, Rodrigues, Papua New Guinea and Nauru. In all four ethnic groups studied, a 1 standard deviation larger hip circumference (6.9-11.8 cm in men and 9.7-13.6 cm in women) was associated with lower glucose and triglyceride levels in both sexes and higher HDL levels in women only, after adjustment for waist circumference, BMI, and age. Among men and women the adjusted standardized beta coefficients associated with 1 standard deviation larger hip ranged from -0.56 to -0.11 mmol/L for triglycerides, -0.01 to 0.43 mmol/L for HDL and -0.38 to 0.05 mmol/L for glucose. There was an inverse trend of hip with systolic blood pressure for all female ethnic groups and for three male ethnic groups, but none were statistically significant. An inverse association of hip with diastolic blood pressure was observed in few ethnic groups and none were significant.

To our knowledge the only other study of hip that included a large East Asian sample, used anthropometry and DXA to examine the cross-sectional association of hip circumference and depots of lean and fat mass with cardiovascular risk factors. Participants included Japanese men (n=1 249) and women (=3 007) aged 20-79 years. A 1 centimeter increase in hip circumference was associated with a decrease in the odds ((OR (95% CI) for males and for females) of hypertension (0.92 (0.87, 0.98))and (0.94 (0.91, 0.98)) low HDL-C (0.91 (0.84, 0.98)) and (0.88 (0.81, 0.95)), hypertriglyceridemia (0.91 (0.87, 0.96)) and (0.97 (0.93, 1.01)), dyslipidemia (0.92 (0.87, 0.96)) and (0.96 (0.93, 0.98)), and diabetes (0.88 (0.79, 0.97)) and (0.90 (0.84, 0.98)) when controlling for BMI and waist. Further examination of cardiovascular risk factors with measures of body composition suggested a positive association of trunk fat mass and a negative association of leg fat mass
with hypertension, hypertriglyceridemia, dyslipidemia and diabetes in men. In women, greater trunk fat mass and lower leg fat mass were significantly and positively associated with these outcomes as well as for hypercholesterolemia and low HDL-cholesterol.

The 6 cross-sectional studies presented above support the inverse association of a larger hip with metabolic risk factors when controlling for waist or BMI. The reduction in risk was generally moderate with odds ratios typically in the range of 0.9 to 0.4 for a one standard deviation increase in hip circumference or for comparison of the highest to lowest quartile or quintile of hip. Similar to our study of incidence, the majority of these studies of prevalence found weaker associations of hip with blood pressure, compared to the association with other metabolic risk factors. Hypertension is a multi-genic disease that varies in etiology; therefore, it is possible that only a subset of individuals with hypertension have elevated blood pressure as a result of mechanisms related to fat distribution.

To our knowledge, our study is the first to examine the prospective association of hip with all metabolic syndrome components. Longitudinal studies examining the associations with hip have focused on CHD, CVD, diabetes or mortality as outcome measures and none included an East Asian sample. We know of six studies that have examined longitudinal associations with hip, all of which support the protective effect of a larger hip circumference on incident CHD, CVD, diabetes and mortality when controlling for central or general adiposity. We will briefly summarize results from three of those studies that include glucose or diabetes as an outcome measure, as those results are more closely related to the present study.
A study of the Hoorn cohort from the Netherlands included 1,357 Dutch men and women aged 50-75 years over eight years of follow-up. A 1 standard deviation larger hip (5.1 cm in men and 6.9 cm in women) was associated with a lower risk of incident type 2 diabetes, independent of BMI, age, and waist circumference. The relative risk (95% CI) for incident type 2 diabetes associated with a 1 standard deviation change in hip were 0.55 (0.36, 0.85) in men and 0.63 (0.42, 0.94) in women. Further exploration of the association of a 1 standard deviation of hip at baseline with fasting glucose concentrations at follow-up were -0.178 (mmol/L) (p=0.005) in men and -0.154 (mmol/L) (p=0.008) in women after adjustment for age and BMI.

A study of 1,405 Swedish women aged 38-60 examined the association of hip with mortality and 24-year incidence of myocardial infarction, combined cardiovascular diseases and diabetes. Increasing quartiles of hip (cutpoints were 94.5, 98.5 and 103.5 cm) were associated with fewer cases of each outcome examined. The proportional hazard ratio comparing the highest to lowest quartile of hip were 0.31 (0.12, 0.80) for diabetes, 0.43 (0.23, 0.82) for cardiovascular disease, 0.34 (0.14, 0.79) for myocardial infarction and 0.59 (0.35, 0.99) for total mortality after adjustment for age, smoking, BMI and waist. When hip was modeled continuously (as residuals regressed with BMI), an inverse association for larger hip was reported for all outcomes examined.

The association of hip circumference with incident diabetes and CHD was examined in a biracial cohort of 10,767 Black and White men and women from the United States of America ARIC cohort. Successive quintiles of hip were associated with reduced hazard of diabetes (hazard ratios=1.00, 0.92, 0.77, 0.67, 0.72) when adjusted for waist, age, race, gender and study center. When models were additionally adjusted for BMI, the trend was
stronger (p<0.001) as the hazard ratios were 1.00, 0.75, 0.56, 0.41 and 0.37. Similar trends in hazard ratios across successive hip quintiles were observed for diabetes when models were stratified by gender or by race; however, the trends were statistically significant for women and for Whites only. Both of these groups had a larger sample size than the non-significant alternative. Race and sex stratified estimates were not reported for CHD. However, in models that examined CHD in the full sample, the hazard ratios associated with successive quintiles of hip were 1.00, 0.92, 0.75, 0.63 and 0.50 when adjusted for waist, age, race, sex and center and 1.00, 0.83, 0.62, 0.49 and 0.37 with additional adjustment for BMI.

Overall, results from both cross-sectional and longitudinal studies support a protective effect of a larger hip circumference with glucose, lipids and health outcomes (CHD, CVD, mortality) and perhaps a weak association with blood pressure. Although the causal mechanisms between fat depots and risk factors are not certain, it has been suggested that inflammatory markers and insulin resistance may play an intermediary role in the link between adipose tissue and metabolic risk. Adipose tissue in the gluteofemoral region may serve an important role in the removal of non-esterified fatty acids (NEFA) from the circulation. This activity could protect the liver, pancreas and skeletal muscle from exposure and accumulation of NEFA and thereby limit the development of insulin resistance. Two recent studies examined the influence of regional fat, using DXA or computerized tomography (CT), on insulin resistance and inflammatory markers in non-Asian samples. A study using DXA examined the influence of regional fat on insulin resistance in obese Norwegian Caucasians. Among subjects with a similar BMI, leg fat was inversely correlated with fasting glucose, fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR) and total cholesterol in women but neutral in men. A second study
included Black and White men and women from the U.S.A. based Dynamics of Health, Aging and Body Composition (Health ABC) study to examine the association of body composition, measured using CT scans, with the inflammatory markers C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). Differences in fat distribution were found across gender and race yet in all race and gender groups, abdominal visceral adiposity was most associated with an adverse profile of inflammatory markers, higher interleukin-6 (IL-6) and C-reactive protein (CRP) (p<0.05). Conversely, thigh subcutaneous fat was associated with a trend toward lower inflammatory marker concentrations, when adjusted for thigh intermuscular fat, BMI, age and other covariates. However, it was significantly (p<0.05) associated with lower IL-6 and TNF-α in white men only. Thigh subcutaneous fat has also been correlated with greater insulin sensitivity. More research is needed to better understand the underlying mechanisms in various populations.

This is the first longitudinal study to indicate beneficial effects of a large hip circumference on incident metabolic outcomes in a Chinese population. This population was unusually lean by Western standards, indicating that high levels of adiposity are not required in order for protective effects of hip to be detected. Strengths of this work include the quality control of the data collection and longitudinal design and use of measured anthropometry. This study is limited in that we did not have more discriminative measures of body composition such as DXA or CT scans; the sample is from one city in southern China during 1987-94 and the prevalence of obesity has increased since this time. Further examination of hip circumference with metabolic abnormalities in epidemiologic studies may help clarify the underlying pathology and differences observed across body weight categories and gender. Additional research on Chinese populations that incorporates subjects who are overweight...
and obese and includes additional measures of trunk and leg fat and leg lean mass may provide insight into the mechanistic role of regional adiposity on metabolic risk factors.
Central obesity is defined as a waist circumference > 90 cm in males and > 80 cm in females, according to the World Health Organization (WHO) guidelines for Asians.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Women (n=1776)</th>
<th>Men (n=1444)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (s.d.)</td>
<td>44.8 (8.0)</td>
<td>45.1 (8.3)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²), mean (s.d.)</td>
<td>21.0 (2.8)</td>
<td>20.6 (2.5)</td>
</tr>
<tr>
<td>Body Mass Index Category (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5 kg/m²</td>
<td>18.2</td>
<td>18.9</td>
</tr>
<tr>
<td>18.5-&lt;23.0 kg/m²</td>
<td>62.6</td>
<td>65.4</td>
</tr>
<tr>
<td>23.0-&lt;25.0 kg/m²</td>
<td>10.8</td>
<td>10.1</td>
</tr>
<tr>
<td>25.0-&lt;27.5 kg/m²</td>
<td>5.9</td>
<td>4.3</td>
</tr>
<tr>
<td>27.5-&lt;30.0 kg/m²</td>
<td>1.7</td>
<td>1.1</td>
</tr>
<tr>
<td>30.0-&lt;32.5 kg/m²</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Waist circumference (cm), mean (s.d.)</td>
<td>70.5 (7.8)</td>
<td>73.2 (7.6)</td>
</tr>
<tr>
<td>Central obesity ^ (%)</td>
<td>13.4</td>
<td>3.4</td>
</tr>
<tr>
<td>Hip circumference (cm), mean (s.d.)</td>
<td>88.1 (6.3)</td>
<td>87.4 (5.4)</td>
</tr>
<tr>
<td>Hip circumference, 15^th percentile (cm)</td>
<td>82.0</td>
<td>82.0</td>
</tr>
<tr>
<td>Hip circumference, 85^th percentile (cm)</td>
<td>94.0</td>
<td>93.0</td>
</tr>
<tr>
<td>Current cigarette or leaf smokers (%)</td>
<td>3.0</td>
<td>66.1</td>
</tr>
<tr>
<td>Current drinkers (%)</td>
<td>15.1</td>
<td>59.4</td>
</tr>
<tr>
<td>Educational attainment (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; High school</td>
<td>82.2</td>
<td>79.0</td>
</tr>
<tr>
<td>High school</td>
<td>14.6</td>
<td>17.6</td>
</tr>
<tr>
<td>Center (rural) (%)</td>
<td>56.6</td>
<td>59.7</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg), mean (s.d.)</td>
<td>112.1 (15.8)</td>
<td>113.3 (14.8)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg), mean (s.d.)</td>
<td>72.0 (9.5)</td>
<td>73.6 (9.9)</td>
</tr>
<tr>
<td>Glucose (mmol/L), mean (s.d.)</td>
<td>4.4 (1.1)</td>
<td>4.1 (0.9)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L), mean (s.d.)</td>
<td>1.4 (0.3)</td>
<td>1.4 (0.4)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L), mean (s.d.)</td>
<td>1.3 (1.0)</td>
<td>1.3 (1.1)</td>
</tr>
</tbody>
</table>

^ Central obesity is defined as a waist circumference ≥ 90 cm in males and ≥ 80 cm in females, according to the World Health Organization (WHO) guidelines for Asians.
Table 6.2. Crude baseline prevalence and 6-year incidence of metabolic abnormalities among Chinese women and men

<table>
<thead>
<tr>
<th></th>
<th>Women Prevalence</th>
<th>Women Incidence</th>
<th>Men Prevalence</th>
<th>Men Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated blood pressure (≥130/85 mmHg or medication)</td>
<td>15.2%</td>
<td>23.6%</td>
<td>17.2%</td>
<td>30.2%</td>
</tr>
<tr>
<td>Elevated glucose (≥5.6 mmol/L)</td>
<td>9.6%</td>
<td>13.1%</td>
<td>7.5%</td>
<td>8.6%</td>
</tr>
<tr>
<td>Low HDL-C (&lt;1.03 mmol/L in males; &lt;1.29 mmol/L in females)</td>
<td>34.3%</td>
<td>32.8%</td>
<td>15.0%</td>
<td>13.3%</td>
</tr>
<tr>
<td>Elevated triglycerides (≥1.7 mmol/L)</td>
<td>23.9%</td>
<td>11.1%</td>
<td>22.1%</td>
<td>15.8%</td>
</tr>
<tr>
<td>Multiple metabolic abnormalities (≥3 of the above criteria)</td>
<td>5.0%</td>
<td>8.8%</td>
<td>2.4%</td>
<td>6.1%</td>
</tr>
</tbody>
</table>
### Table 6.3. Adjusted incidence of metabolic abnormalities per 1 000 persons (95% CI) at the 15th percentile of hip circumference

<table>
<thead>
<tr>
<th>Risk at the 15th percentile of hip(^1) (95% CI)</th>
<th>Model 1(^2)</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated blood pressure (≥130/85 mmHg or medication)</td>
<td>191 (161, 220)</td>
<td>237 (194, 281)</td>
<td>233 (188, 278)</td>
<td>246 (198, 294)</td>
</tr>
<tr>
<td>Elevated glucose (≥5.6 mmol/L)</td>
<td>96 (75, 117)</td>
<td>122 (90, 155)</td>
<td>115 (82, 147)</td>
<td>123 (88, 158)</td>
</tr>
<tr>
<td>Low HDL-C (&lt;1.29 mmol/L)</td>
<td>295 (257, 334)</td>
<td>380 (323, 437)</td>
<td>366 (306, 427)</td>
<td>389 (326, 453)</td>
</tr>
<tr>
<td>Elevated triglycerides (≥1.7 mmol/L)</td>
<td>75 (56, 95)</td>
<td>128 (92, 163)</td>
<td>120 (84, 156)</td>
<td>135 (95, 176)</td>
</tr>
<tr>
<td>Multiple metabolic abnormalities (≥3 of the above criteria)</td>
<td>42 (29, 55)</td>
<td>70 (46, 93)</td>
<td>74 (49, 100)</td>
<td>81 (53, 110)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated blood pressure (≥130/85 mmHg or medication)</td>
<td>220 (183, 258)</td>
<td>274 (219, 328)</td>
<td>279 (225, 333)</td>
<td>292 (233, 350)</td>
</tr>
<tr>
<td>Elevated glucose (≥5.6 mmol/L)</td>
<td>56 (37, 75)</td>
<td>86 (51, 121)</td>
<td>84 (52, 117)</td>
<td>95 (56, 134)</td>
</tr>
<tr>
<td>Low HDL-C (&lt;1.03 mmol/L)</td>
<td>87 (63, 110)</td>
<td>138 (95, 180)</td>
<td>124 (85, 162)</td>
<td>144 (99, 190)</td>
</tr>
<tr>
<td>Elevated triglycerides (≥1.7 mmol/L)</td>
<td>112 (84, 141)</td>
<td>179 (129, 228)</td>
<td>150 (107, 193)</td>
<td>182 (130, 234)</td>
</tr>
<tr>
<td>Multiple metabolic abnormalities (≥3 of the above criteria)</td>
<td>21 (11, 31)</td>
<td>47 (24, 71)</td>
<td>40 (20, 59)</td>
<td>53 (26, 80)</td>
</tr>
</tbody>
</table>

\(^1\) The 15th percentile of hip is 82 cm in men and in women

\(^2\) Model 1 includes hip, age, smoking, center and education. For women, this model also includes age\(^2\)
Models were adjusted for baseline age, age^2, education level, smoking status and field center. Multiple metabolic abnormalities was defined as the presence of three or more metabolic abnormalities (elevated blood pressure, elevated glucose, low HDL-C and elevated triglycerides). The 15^{th} and 85^{th} percentiles of hip were 82 cm and 94 cm, respectively.
Models were adjusted for baseline age, age$^2$, education level, smoking status and field center. Multiple metabolic abnormalities was defined as the presence of three or more metabolic abnormalities (elevated blood pressure, elevated glucose, low HDL-C and elevated triglycerides). The 15$^{th}$ and 85$^{th}$ percentiles of hip were 82 cm and 94 cm, respectively.
VII. SYNTHESIS

A. Overview

The goal of this work was to better understand the association of body weight and circumference measures with metabolic risk factors in Chinese Asians. For Aim 1, we examined the ethnic-specific association of BMI with incident hypertension for Chinese Asian, American White and American Black during young and middle adulthood. For Aims 2 and 3, our analyses focused exclusively on the Chinese Asian population. We wanted to investigate associations of adiposity which have been explored in Caucasian but not Chinese populations. Since the relationship of adiposity with metabolic risk factors may vary across ethnic groups, it was important to evaluate these associations in Chinese. Specifically, our focus for Aims 2 and 3 were the influence of parental history of hypertension status and hip circumference on metabolic risk factors.

Our sample of Chinese Asians from the PRC cohort was a very lean population. Approximately 90% of subjects were normal weight or underweight and few subjects were obese by WHO (>30 kg/m²) or Chinese (>28 kg/m²) standards. However, despite the leanness of our Chinese Asian sample, we found significant associations between measures of adiposity with metabolic risk factors. For Aim 1, the association of BMI with the incidence difference for hypertension was strongest during young and middle adulthood for Chinese Asians compared to American Blacks and American Whites. This was surprising, considering American Blacks had a higher prevalence and incidence of hypertension as well as much higher mean BMI compared to Chinese Asians. Yet, despite these differences
between ethnicities, the association of BMI with hypertension was not as strong among the American Blacks as that observed for the Chinese population. In both American Blacks and Whites the association of BMI with the incidence difference for hypertension increases gradually across the BMI range for both young and middle-aged adults. However, for Chinese Asians, the association of BMI with the incidence difference for hypertension increased exponentially beginning at a BMI of 23 kg/m$^2$ in young adulthood. During middle adulthood, the association of BMI with the incidence difference for hypertension was steep across the full BMI range examined for Chinese. Based on our findings Chinese Asians appeared to be more sensitive to the effects of BMI for hypertension incidence. American Blacks may therefore experience high levels of hypertension due to additional factors beyond obesity which were unmeasured in our sample such as diet, physical activity, stress and genetic factors.

Aim 2 expanded upon the results from Aim 1, by exploring effect modification of the BMI-hypertension relationship by parental history of hypertension status and by age. Little is known about parental history of hypertension status in Chinese and few studies have examined the interaction of BMI, parental history of hypertension and age in any ethnic group. Results varied between the young and middle-aged Chinese populations. This was not surprising, considering the literature suggests age modifies the association of parental history of hypertension status with hypertension onset in offspring. We found that during young adulthood, both BMI and parental history of hypertension status influenced hypertension risk. However, interactions between BMI and parental history status were not detected. During middle adulthood, parental history status alone did not influence hypertension risk. However, effect modification of the BMI-hypertension association by
parental history status was quite strong. In the middle-aged group, a positive parental history of hypertension was associated with a greater sensitivity to BMI. The following limitations of these analyses are worth mentioning: parental history status was not validated in our sample and we did not have measures of parental hypertension onset, which has been shown to influence hypertension risk in off-spring. Therefore, it is difficult to ensure if our results are truly reflective of the underlying associations.

For Aim 3, the focus shifted from overall to regional depots of adiposity. Although greater levels of abdominal adiposity have been shown to be deleterious, adiposity in the gluteo-femoral or hip region has been shown in non-Asian cohorts to exert a protective effect on cardiovascular risk factors. Therefore, we examined the independent association of hip circumference with incident metabolic risk factors in Chinese. We found hip circumference, when adjusted for waist or BMI, attenuated the risk of incident metabolic risk factors in both men and women. A larger hip circumference was significantly associated with a lower incidence of low HDL-C, elevated triglycerides and multiple metabolic abnormalities in Women when controlling for waist and BMI. In men, none of the associations were significant. Our findings were similar to those observed in non-Asian populations. Specifically, the weaker associations of hip circumference with blood pressure and the stronger associations observed for women then for men. Adiposity in the lower trunk region has been suggested to be the component of hip responsible for the observed protective effect for metabolic risk factors. It is therefore quite noteworthy that we were able to detect protective associations of hip with metabolic risk factors in such a lean sample. It would be worthwhile to re-examine the association in a more overweight sample of Chinese.
In conclusion, Chinese tend to experience metabolic risk factors associated with adiposity, even at very low levels of BMI. This is quite concerning considering the Chinese are experiencing rapid increases in the proportion of overweight and obese adults within China. CVD, which is currently the leading cause of death in China, will most likely afflict a greater proportion of the population as obesity levels increase. This work was intended to provide a better understanding of the association of anthropometric measures with cardiovascular outcomes in multi-ethnic populations and we hope it may be used to support future research as well as initiatives designed to promote maintenance of a healthy weight, prevent the onset of excess weight and promote weight loss among those who are already overweight or obese in an effort to reduce cardiovascular risk among populations.

B. Strengths

The CARDIA, ARIC and PRC datasets provide some of the best, if not the best, data currently available, given our goals. The datasets are similar in design and provide data from diverse populations and age ranges. The Collaborative Studies Coordinating Center (CSCC) at the University of North Carolina, Chapel Hill served as the coordinating center for both the PRC and ARIC studies. They provided training manuals and protocols for data collection and were responsible for data processing and review for both studies. The University of Alabama at Birmingham served as the coordinating center for the CARDIA study. The CARDIA Coordinating Center, and the CARDIA Quality Control Committee monitored data collection throughout the study and all data collection technicians were centrally trained and certified. Many of the relevant variables for the work proposed here were collected using identical protocols in CARDIA, ARIC and PRC.
The questions evaluated by this work are novel and provide new insights into aging and obesity in ethnically diverse populations.

C. Limitations

There are limitations to this work. Namely, several factors that influence blood pressure are hard to measure (psychosocial factors); some of the variables are not equivalent across ethnic groups (education level); potential bias may be introduced by variable treatment rates across ethnic groups; the overlay of ethnicity and social factors, geography and nationality cannot be separated; populations studies are from different countries; and lastly we did not have measures of diet, parental and offspring hypertension onset, or comparable measures of physical activity across ethnic groups.

D. Conclusion

These results provide novel insights into obesity in Chinese. It would be worthy to replicate Aim 1 by using a sample of Chinese Americans. However, as this data does not currently exist, it would involve data collection which could take many years. The PRC baseline data were collected in 1983-84 and the prevalence of overweight and obesity in China during this time was lower than more recent estimates. Therefore, Aims 2 and 3, which focus exclusively on Chinese, should be replicated in more overweight populations within China and validated measures of parental hypertension status and age of parental hypertension onset should be collected. Our research provides a significant contribution to the literature and given the current availability of Chinese cohort data, these findings may be the most appropriate.
Appendix A: Incidence difference for elevated blood pressure for Chapter 4 analyses

We also examined the prevalence difference per 1,000 persons for hypertension as well as the incidence difference per 1,000 persons for elevated blood pressure (SBP/DBP >120/80 mmHg or BP meds) in both young adults (24-39 years) and middle-aged adults (45-64 years) by race.

Figure A.1. Prevalence difference per 1,000 persons for hypertension in young adults (24-39 years), by race

a=Chinese significantly different than White (p<0.05)
Figure A.2. Incidence difference per 1,000 persons for elevated blood pressure (SBP/DBP >120/80 mmHg or BP meds) in young adults (24-39 years), by race

a=Chinese significantly different than White (p<0.05)
Figure A.3. Prevalence difference per 1,000 persons for hypertension (SBP/DBP >120/80 mmHg or BP meds) in middle-aged adults (45-64 years), by race

a=Chinese significantly different than White (p<0.05)

Figure A.4. Incidence difference per 1,000 persons for elevated blood pressure (SBP/DBP >120/80 mmHg or BP meds) in middle-aged adults (45-64 years), by race
Appendix B: Additional outcomes examined for Chapter 6 analyses

The following table includes the crude prevalence and cumulative incidence for additional outcomes we explored for “The Association of Hip Circumference with Incident Metabolic Risk Factors in Chinese, the People’s Republic of China Study” (Chapter 6).
Table B.1. Crude baseline prevalence and cumulative incidence for metabolic risk factors

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<td>Baseline prevalence</td>
<td>Cumulative Incidence</td>
<td>Baseline prevalence</td>
<td>Cumulative Incidence</td>
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<td></td>
<td># cases/sample</td>
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<td>SBP &gt; 140</td>
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<td>DBP &gt; 90</td>
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<td>Elevated BP (BP &gt; 130/85)</td>
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<td>Elevated fasting glucose ≥ 110 mg/dl</td>
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<td>Diabetes</td>
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<td>Multiple metabolic abnormalities: ≥ 3 above criteria</td>
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REFERENCES


70. Is central obesity a better discriminator of the risk of hypertension than body mass index in ethnically diverse populations? J Hypertens 2008;26:169-77.


