CHANGES IN BURDEN OF CARDIOVASCULAR DISEASE FOLLOWING HYPOTHETICAL REDUCTIONS IN ADIPOSITY

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A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology in the Gillings School of Global Public Health.

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ABSTRACT

Shannon Kapuaolaokalaniākea Gellert: Changes in Burden of Cardiovascular Disease Following Hypothetical Reductions in Adiposity.
(Under the direction of Gerardo Heiss)

Cardiovascular diseases (CVD) such as peripheral artery disease (PAD) and coronary heart disease (CHD) are prominent causes of disability and death. PAD is a limb and life-threatening condition affecting 8.5 million U.S adults and CHD is the leading cause of death in the U.S. Risk factors for these CVD include hypertension and diabetes, which may lie on the causal pathway from adiposity to PAD and CHD. Therefore, adiposity may represent a modifiable upstream risk factor for PAD and CHD. Given the temporal increase in adiposity in the U.S. and the need to address the adverse health effects of adiposity at the population level, this doctoral research aimed to estimate the impact of hypothetical population reductions in adiposity on the incidence of PAD and CHD.

Our study population included over 13,000 Atherosclerosis Risk in Communities participants examined from 1987 to 2001 at 4 triennial study visits during which exposure and covariate information were ascertained. Incident PAD and CHD events were identified from cohort follow-up and active health event surveillance. The parametric g-formula was used to estimate the risk difference of PAD and CHD following a hypothetical 5% reduction in body mass index (BMI) or waist circumference (WC) relative to the natural course of the BMI or WC trajectory, to a minimum BMI of 24 kg/m² or WC of 88 cm.
Participants with incident PAD or CHD were older at baseline, and more likely to be male, of white race, have less than a high school education, smoke, have diabetes, and have hypertension compared to those without incident PAD or CHD. We estimated a small risk difference for PAD [-0.17%, 95% confidence interval (CI): -0.38, 0.13%] following a 5% reduction in BMI. The estimated risk difference for CHD was -0.56% (95% CI: -0.96, -0.14%) following a 5% reduction in BMI, and -0.96% (95% CI: -1.44, 0.48%) following a 5% reduction in WC.

If replicated in other populations, these results can inform prevention-oriented research into the health effects of dynamic population distributions of adiposity measures.
To my parents, Hank and Aloha Gellert who love and support me so I can be all that I dream.
ACKNOWLEDGMENTS

This dissertation was possible because of the love, guidance and encouragement of many people. I praise God for making this dissertation a reality and for putting the perfect people in my life to guide my doctoral training. I am thankful for my parents, Hank and Aloha Gellert who sacrificed and dedicated their lives to the success of their children. I believe that I can be all that I dream because of their love and support.

Thank you for all of my siblings – Jon, Malia, Keali`i, and Chirstian. I pray that my nieces and nephews become all that they dream. I love you Kamuela, Mehana, Paliku, and Kamakamauli`a.

I am thankful for Dr. Gerardo Heiss, my advisor and dissertation chair for his dedication to my career and personal development. Dr. Heiss was generous with his time as he met with me weekly throughout my doctoral training for a total of approximately 12,840 minutes. I consider myself to be a population scientist because of Dr. Heiss.

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Dr. Christy Avery has been a supportive dissertation committee member by encouraging me to think about approaching epidemiology and public health from a population and translation perspective.
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<th>Description</th>
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<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>ARIC</td>
<td>Atherosclerosis Risk in Communities</td>
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<tr>
<td>ASP</td>
<td>Acylation Stimulation Protein</td>
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<tr>
<td>BAT</td>
<td>Brown Adipose Tissue</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CARDIA</td>
<td>Coronary Artery Risk Development in Young Adults</td>
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<tr>
<td>CHD</td>
<td>Coronary Heart Disease</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CKD-EPI</td>
<td>Chronic Kidney Disease Epidemiology Collaboration</td>
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<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disorder</td>
</tr>
<tr>
<td>CRP</td>
<td>C-Reactive Protein</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
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<tr>
<td>DALY</td>
<td>Disability Adjusted Life Year</td>
</tr>
<tr>
<td>DXA</td>
<td>Dual energy X-ray Absorptiometry</td>
</tr>
<tr>
<td>eGFR</td>
<td>estimated Glomerular Filtration Rate</td>
</tr>
<tr>
<td>EPIETOA</td>
<td>Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults</td>
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<tr>
<td>FPG</td>
<td>Fasting Plasma Glucose</td>
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<tr>
<td>GBD</td>
<td>Global Burden of Disease</td>
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<tr>
<td>HDL-C</td>
<td>High Density Lipoprotein Cholesterol</td>
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<tr>
<td>IL-6</td>
<td>Interleukin 6</td>
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<tr>
<td>IOM</td>
<td>Institute of Medicine</td>
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<tr>
<td>LDL-C</td>
<td>Low Density Lipoprotein Cholesterol</td>
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<tr>
<td>MCP-1</td>
<td>Monocyte Chemoattractant Protein 1</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>MDCT</td>
<td>Multi-Detector Computed Tomography</td>
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<tr>
<td>MRFIT</td>
<td>Multiple Risk Factor Intervention Trial</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Examination Survey</td>
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<tr>
<td>NHLBI</td>
<td>National Heart, Lung and Blood Institute's</td>
</tr>
<tr>
<td>NIDDK</td>
<td>National Institute of Diabetes and Digestive and Kidney Diseases</td>
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<tr>
<td>PAD</td>
<td>Peripheral Artery Disease</td>
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<tr>
<td>PAI-1</td>
<td>plasminogen Activator Inhibitor 1</td>
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<tr>
<td>RAS</td>
<td>Renin Angiostensinogen System</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
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<tr>
<td>SES</td>
<td>Socioeconomic Status</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SE</td>
<td>Standard Error</td>
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<tr>
<td>SBP</td>
<td>Systolic Blood Pressure</td>
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<tr>
<td>TAIM</td>
<td>Trial of Antihypertensive Interventions and Management</td>
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<tr>
<td>TC</td>
<td>Total Cholesterol</td>
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<tr>
<td>TIA</td>
<td>Transient Ischemic Attack</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Tumor Necrosis Factor alpha</td>
</tr>
<tr>
<td>TONE</td>
<td>Trial of Nonpharmacologic Interventions in the Elderly</td>
</tr>
<tr>
<td>WAT</td>
<td>White Adipose Tissue</td>
</tr>
<tr>
<td>WC</td>
<td>Waist Circumference</td>
</tr>
<tr>
<td>WHR</td>
<td>Waist-to-hip ratio</td>
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<tr>
<td>WSR</td>
<td>Waist-Stature Ratio WSR</td>
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<tr>
<td>YPLL</td>
<td>Years of Potential Life Lost</td>
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<tr>
<td>YLL</td>
<td>Years of Life Lost</td>
</tr>
<tr>
<td>YLD</td>
<td>Years Lived with Disability</td>
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CHAPTER 1: SPECIFIC AIMS

1.1 Proposed specific aims

The initially proposed three aims of this dissertation (Appendix) were to: Aim 1) quantify the change in three specified cardio-metabolic risk factors – systolic blood pressure (SBP), fasting plasma glucose (FPG) and low density lipoprotein cholesterol (LDL-C) associated with decrements in adiposity; Aim 2) estimate the individual and joint impact of decrements in adiposity on three specified cardio-metabolic risk factors and apply these estimates to our study population; and Aim 3) estimate the change in longevity, disability and incidence of diabetes and coronary heart disease (CHD) predicted from small changes in the population distribution of adiposity.

On advice from my dissertation committee, Aim 1 was built on a systematic review developed in support of the clinical guidelines on the identification and treatment of overweight and obesity in adults\textsuperscript{1,2}, to quantify the changes in body mass index (BMI) and the changes in each of the cardio-metabolic risk factors. A further recommendation from the dissertation committee was to limit the scope of the doctoral research to two of the cardio-metabolic risk factors: SBP and FPG. This restriction still allowed us to implement the study aims as proposed given the prominent role of these two cardio-metabolic impairments in the risk for the CVD conditions selected for this study.
Aims 2 and 3 were modified to estimate the effect of a modest hypothetical yearly reduction (5%) in adiposity - BMI for Manuscript 1 (MS#1) and BMI and WC for Manuscript 2 (MS#2) on cumulative incidence of peripheral artery disease (PAD) (MS#1) and CHD (MS#2).

1.2 Specific aims after modifications:

**Aim 1.** Characterize the cross-sectional association between BMI and two specified cardio-metabolic risk factors - SBP and FPG in the ARIC cohort. Compare the effect estimates of the decrement in BMI on SBP and FPG derived from the human experimental literature to their observational equivalent in the ARIC cohort. 

**Hypotheses:** There will be a monotonic linear relationship between BMI and SBP, and between BMI and FPG. These relationships will not have evidence of a threshold over the range of the adiposity distribution included in our analysis (BMI=24-40 kg/m\(^2\)). The association between BMI and SBP and FPG will be comparable in shape and magnitude across race, sex and birth cohort. The association between BMI and SBP and FPG in the ARIC cohort will be comparable in magnitude to the association found in the human-experimental data, after adjustment for confounders.

**Aim 2.** Estimate the change in 12-year cumulative incidence of peripheral artery disease (PAD) following a hypothetical 5% yearly body mass index (BMI) reduction down to a BMI of 24 kg/m\(^2\) for all individuals under 65 years of age with a BMI> 24 kg. **Hypothesis:** Reducing BMI by 5% each year reduces the cumulative incidence of PAD.

**Aim 3.** Estimate the change in 12-year cumulative incidence of coronary heart disease (CHD) following a hypothetical 5% yearly body mass index (BMI)
reduction down to a BMI of 24 kg/m² for all individuals under 65 years of age with a BMI > 24 kg. *Hypothesis:* Reducing BMI by 5% each year reduces the cumulative incidence of CHD.

**Aim 4.** Estimate the change in 12-year cumulative incidence of coronary heart disease (CHD) following a hypothetical 5% yearly waist circumference (WC) reduction down to a WC of 88 cm for all individuals under 65 years of age with a WC > 88 cm. *Hypothesis:* Reducing WC by 5% each year reduces the cumulative incidence.
REFERENCES


CHAPTER 2: BACKGROUND AND SIGNIFICANCE

This background section summarizes the literature review conducted to address the overall goal of my doctoral work.

2.1 Burden of cardiovascular disease

2.1.1 Global mortality

Cardiovascular disease is a major global public health burden as a result of its high mortality and morbidity\(^1\). In the twenty years spanning the 1990 Global Burden of Disease study (GBD) and the 2010 GBD, ischemic heart disease and cerebrovascular disease remained the top two leading causes of death in North America and even worldwide\(^2\). In addition, a study on projections of global mortality from 2002 to 2030 predicted that total cardiovascular-related deaths would increase globally from 16.7 million in 2002 to 23.3 million in 2030\(^3\). Mortality data have traditionally been used for identifying a population’s health problems\(^4\). However, other assessments of population health that were developed in the GBD studies are more informative as the global disease burden shifts away from premature death to years lived with disability and from communicable to non-communicable diseases\(^5\).

2.1.2 DALYs

The GBD studies measured disease burden using disability adjusted life years (DALYs), which indicate the number of healthy years of life lost\(^6\). Somewhat similar to the findings reported for the leading causes of death, ischemic heart disease and cerebrovascular disease were respectively the 1\(^{st}\) and 3\(^{rd}\) leading
causes of DALYs globally. Although ischemic heart disease is ranked first as the leading cause of DALYs in North America, cerebrovascular disease is ranked 7th, preceded by other conditions such as lung cancer and chronic obstructive pulmonary disorder (COPD). Furthermore, ischemic heart disease and cerebrovascular disease are expected to remain the top two leading causes of death and the 3rd and 6th leading causes of DALYs in the world in 2030. Although CVD is a leading cause of death and DALYs among all populations, CVD disproportionately affects minority populations.

2.1.3 CVD burden in US minority populations

Chronic diseases, to a large degree CVD, are prominent causes of disability and premature death in U.S. minority populations. African Americans/Blacks had more than twice the age-adjusted death rate in 2010 than whites and more than twice the age-adjusted estimates of years of potential life lost (YPLL) from diseases of the heart compared to whites. Prevalence of risk factors associated with CVD may contribute to the health disparities seen for minorities.

Minorities, specifically African Americans are less likely than whites to have optimal cardiovascular health profiles measured by levels of cardiovascular risk factors, including body mass index (BMI), blood pressure, total cholesterol and glucose, thus emphasizing the need to address these health disparities. As with other chronic diseases, CVD represents the downstream outcome of conditions that originate early in life and are mediated by well-established behavioral, metabolic and environmental risk factors. Adiposity is one of these risk factors and has a well-documented association with several cardio-metabolic risk factors.
2.2 Associations between adiposity and cardio-metabolic risk factors

Categorical definitions of normal weight, overweight and obesity are often used to describe the associations between adiposity and cardio-metabolic risk factors and CVD. Use of these categories is common in clinical settings when establishing guidelines for diagnosis and treatment is the goal. Several studies across the world have documented that overweight and obesity are well-established risk factors for CVD and CVD risk factors.

Due to the rising prevalence of overweight and obesity, an examination of the scientific evidence on the effects of weight loss on several health factors was conducted by the Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (EPIETOA). The EPIETOA was comprised of the National Heart, Lung and Blood Institute’s (NHLBI) Obesity Education Initiative and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). This panel conducted a systematic review of the literature combining evidence from 394 randomized controlled trials (RCTs). They concluded that all overweight adults, body mass index (BMI) >25, are at risk for developing the associated morbidities and diseases such as hypertension, high blood cholesterol, type 2 diabetes, and coronary heart disease (CHD). This risk is especially high in minority groups, low socioeconomic status (SES) groups, and in those who have less education given their relatively high prevalence of overweight and obesity compared to non-minority, higher SES and higher education groups. Recommendations for the treatment of overweight and obesity were based on evidence that weight loss reduces morbidity and mortality associated with cardio-metabolic risk factors. The EPIETOA’s systematic review includes evidence for the effect of changes in adiposity (measured...
as BMI) and the three cardio-metabolic risk factors of interest for this dissertation—systolic blood pressure (SBP), fasting low-density cholesterol (LDL-C) and fasting plasma glucose (FPG). The following sections will summarize and expand this information.

2.2.1 Systolic blood pressure (SBP)

One aim of the EPIETO A’s systematic review was to evaluate the effect of weight loss on blood pressure and hypertension\textsuperscript{15}. Hypertension was defined as a SBP $> 140$ mmHg, diastolic blood pressure $> 90$ mmHg or taking hypertension medication. The panel concluded that there was strong evidence showing the association between weight loss and reductions in SBP in hypertensive and non-hypertensive adults. The inclusion criteria for the systematic review were that the study had a time frame from start to finish of at least 4 months and measured weight by study personnel and not only self-report. For this aim of the systematic review, 35 lifestyle RCT articles met their inclusion criteria with 16 articles on a hypertensive population and 19 conducted in individuals with normal or high-normal blood pressure. Prior evidence of a linear association between BMI and blood pressure that was incorporated into the EPIETO A’s systematic review came from a 1987 meta-analysis conducted by MacMahon et al\textsuperscript{30}.

This meta-analysis reported several important findings. One was that a 22 lb weight loss was associated with a 7 mmHg reduction in SBP. Another conclusion was that the evidence within and across the included RCTs was suggestive of a dose response relationship between change in weight and change in SBP. Also, the associations between change in weight and change in blood pressure were not specific to any age, race or sex group, but the association appeared to be stronger
in younger than older adults and in whites than Blacks\textsuperscript{30}. The EPIETO\textquoteright{}A\textquoteright{}s systematic review corroborated many of these findings.

The EPIETO\textquoteright{}A summarized the evidence from several studies and concluded that weight loss produced by lifestyle modification reduces blood pressure. These findings are highly relevant for the rationale of this dissertation. The following sections provide a summary of the EPIETO\textquoteright{}A\textquoteright{}s systematic review.

\textit{Trials in hypertensive participants}

The Trial of Antihypertensive Interventions and Management (TAIM) was conducted in hypertensive patients who were not taking medication for 6 months. A mean net weight reduction of 10.4 lbs reduced SBP by 2.8 mmHg, and the effects on blood pressure were equivalent to drug therapy among participants who lost 9.9 lbs or more\textsuperscript{31}. Mean net weight reduction was calculated by taking the change in weight from baseline to the end of the study in both intervention and control groups separately. Then, this value from the control group was subtracted from that in the intervention group to arrive at mean net weight reduction\textsuperscript{15}.

The Trial of Nonpharmacologic Interventions in the Elderly (TONE) was conducted with participants who were 60-80 years old. During this weight loss intervention, blood pressure medications were withdrawn. This study\textquoteright{}s investigators reported that a 9 lb weight loss reduced the occurrence of hypertension, the need for resumption of blood pressure medications and occurrence of cardiovascular clinical complication. Additionally, blood pressure control was similar among men, women, African Americans and whites.
The Multiple Risk Factor Intervention Trial (MRFIT) included men at high-risk for heart disease of which 30% were classified as hypertensive. Following an integrated weight loss intervention, a 2.2 lb weight loss after 6 years was associated with a 0.4 mmHg reduction in SBP\textsuperscript{32}.

**Trials in non-hypertensive participants**

The Trials of Hypertension Prevention (TOHP I and II) were RCTs conducted in men, women, whites and African Americans. Both TOHP I and II demonstrated that weight loss reduced blood pressure and the incidence of hypertension. A mean weight reduction of 10 kg after 18 months was associated with a 7 mmHg reduction in systolic blood pressure.

SBP is one of the cardio-metabolic risk factors associated with adiposity that was selected for consideration in this doctoral research. A continuous and graded relationship exists between SBP and CVD morbidity and mortality\textsuperscript{7,33,34}. This relationship was demonstrated using Framingham data from 1976-1998. The residual lifetime risk (lifetime cumulative incidence not adjusted for competing causes of mortality) of hypertension for middle-aged and elderly individuals was 90\%\textsuperscript{35}. In addition, the GBD 2010 study reported that elevated blood pressure was the leading global disease burden and that the largest proportion of DALYs for Ischemic heart disease is from elevated blood pressure\textsuperscript{36}. Elevated blood pressure is a major public health concern due to its frequency of occurrence and its association with disease and mortality\textsuperscript{36,37}. 
2.2.2 Low density lipoprotein cholesterol (LDL-C)

The EPIETOAs systematic review also concluded that weight loss produced by lifestyle modifications improved lipids\textsuperscript{38}. The following summary will focus on LDL-C as that was of interest for this dissertation. Eight RCTs that studied the effects of diet and/or physical activity on lipids are summarized in Table 1\textsuperscript{39-45}. For the 8 studies that reported values for LDL-C, body weight reductions ranged from a loss of 13\% for the intervention group compared to the control group to a gain of 2\%. Net percent change in LDL-C ranged from a 22\% reduction to a 2\% gain when comparing intervention to control groups.
### Table 1. Summary of RCTs included in the EPIETOAs’s systematic review of the effects of weight reduction on plasma lipids and lipoproteins

<table>
<thead>
<tr>
<th>Author, year (reference)</th>
<th>Number, sex, and group assignment</th>
<th>Duration (months)</th>
<th>Net % ∆ BMI</th>
<th>Net % ∆ LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diet only</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dengel, 1995³⁹</td>
<td>28 M (I) 14 M (C)</td>
<td>9</td>
<td>-12</td>
<td>-9</td>
</tr>
<tr>
<td>Hellenius, 1993⁴⁰</td>
<td>40 M (I) 39 M (C)</td>
<td>6</td>
<td>-2</td>
<td>-3</td>
</tr>
<tr>
<td>Simkin-Silverman, 1995⁴¹</td>
<td>253 F (I) 267 F (C)</td>
<td>6</td>
<td>-7</td>
<td>-9</td>
</tr>
<tr>
<td>Svendsen, 1994⁴²</td>
<td>50 F (I) 20 F (C)</td>
<td>12 weeks</td>
<td>-13</td>
<td>-22</td>
</tr>
<tr>
<td>Wood, 1991⁴³</td>
<td>40 M (I) 31 F (I) 39 F (C)</td>
<td>12</td>
<td>-7</td>
<td>-5</td>
</tr>
<tr>
<td></td>
<td>40 M (C)</td>
<td></td>
<td>-7</td>
<td>-8</td>
</tr>
<tr>
<td>Wood, 1988⁴⁴</td>
<td>42 M (I) 35 F (C)</td>
<td>12</td>
<td>-8</td>
<td>-3</td>
</tr>
<tr>
<td>Hellinius, 1993⁴⁰</td>
<td>39 M (I) 39 M (C)</td>
<td>6</td>
<td>-4</td>
<td>-4</td>
</tr>
<tr>
<td><strong>Diet plus physical activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>King, 1991⁴⁵</td>
<td>40 M high intensity in group 41 M (C) 42 M high intensity at home 41 M (C) 45 M low intensity 41 M (C) 34 F high intensity in group 34 F (C) 35 F high intensity home 34 F (C) 29 F low intensity 34 F (C)</td>
<td>12</td>
<td>-4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>41 M (C)</td>
<td></td>
<td>-4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>34 F (C)</td>
<td></td>
<td>2</td>
<td>-4</td>
</tr>
<tr>
<td></td>
<td>34 F (C)</td>
<td></td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>29 F low intensity</td>
<td></td>
<td>-2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>34 F (C)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from NHLBI 1998⁵⁰ to include only the results for low-density lipoprotein (LDL-C). **RCT: randomized controlled trial; EPIETOAs: Expert Panel on the Identification Evaluation and Treatment of Overweight and Obesity in Adults; (I): Intervention group, (C): control group. ***Results for LDL-C. ****net %change = difference in percent change between intervention and control groups; %change=[(value at the end of the study minus baseline)/value at baseline].
2.2.3 Glucose

Blood glucose levels were also reduced in diabetics and non-diabetics following weight loss\textsuperscript{38}. This section of the systematic review included 9 RCT reports that examined lifestyle therapy\textsuperscript{41,46-53}. Five included normoglycemic individuals, 1 included participants with impaired glucose tolerance, and 3 included patients with type 2 diabetes. The five studies among normoglycemic individuals showed that weight loss improved fasting glucose along with fasting insulin levels. The three RCTs conducted in diabetic patients showed similar results\textsuperscript{47,51,53}. One RCT in African Americans showed that a 2.4 kg weight loss decreased hemoglobin A1c (HbA1c) by 2.4 percentage units at 6 months in intervention participants compared to controls\textsuperscript{47}.

The systematic review prepared by the EPIETOA provides strong evidence of the relationship between weight reduction and the cardio-metabolic risk factors for this dissertation. Further examination of the continuous relationships between adiposity and cardio-metabolic risk factors through population studies would help to further inform programs aimed to describe CVD risk at a population level\textsuperscript{54}.

2.2.4 Summary of selected randomized controlled trial weight loss studies on changes in adiposity and cardio-metabolic risk factors

One limitation of the information provided in the systematic review prepared by the EPIETOA\textsuperscript{15} was that cardio-metabolic risk factor values were not always reported, as categorical definitions of hypertension, diabetes and dyslipidemia are sometimes reported. Therefore, we conducted a limited review of randomized controlled lifestyle and surgical weight loss interventions, most of which were conducted for 12-months and quantified the associations between small to moderate
changes in adiposity and cardio-metabolic risk factors\textsuperscript{55-58}. The observed effects of changes in adiposity on SBP, fasting LDL-C, and fasting plasma glucose (FPG) are summarized in this table. Also included are follow-up measurements made at 6-months post intervention, including calculations of amount change in cardio-metabolic risk factors per 1-unit decrease in BMI.

For SBP, the largest decreases observed per 1-unit change in BMI were noted in the commercial diet programs\textsuperscript{56} - 3.36 mmHg with the Atkins diet, 4 mmHg with Weight Watcher's, and 4.33 mmHg with the Zone diet. The Ornish diet showed a reduction in LDL-C of 8.75 mg/dL per 1-unit change in BMI, by far the largest compared to the other interventions. While the focuses of these (and similar) studies are on individuals, the translation to the population level has not been addressed to our knowledge. For this dissertation SBP and FPG were examined as cardio-metabolic risk factors influenced by adiposity.
Table 2. Summary of selected randomized controlled trial weight loss studies that examined the effect of changes in adiposity (BMI) on three cardio-metabolic risk factors (SBP, FPG, and LDL-C)

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Type of intervention</th>
<th>∆ BMI [Baseline BMI]</th>
<th>∆ SBP [Baseline SBP]</th>
<th>∆ LDL-C [Baseline LDL-C]</th>
<th>∆ FPG [Baseline FPG]</th>
<th>∆ cardio-metabolic risk factor per 1-unit decrease in BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escalona 2012</td>
<td>surgical</td>
<td>6.7 (15%) [45.1]</td>
<td>3 (2%) [134]</td>
<td>26 (21%) [121]</td>
<td>10 (10%) [104]</td>
<td>SBP=-0.45, LDL-C=-3.88, Glucose=-1.49</td>
</tr>
<tr>
<td>Goodpaster 2010</td>
<td>PA and diet</td>
<td>3.9 (9%) [43.5]</td>
<td>3.4 (3%) [135.4]</td>
<td>3.4 (4%) [93.7]</td>
<td>3.4 (4%) [93.7]</td>
<td>SBP=-0.87, Glucose=-0.92</td>
</tr>
<tr>
<td></td>
<td>PA and delayed diet</td>
<td>3.1 (7%) [43.7]</td>
<td>1.9 (1%) [134.4]</td>
<td>1.9 (2%) [93.2]</td>
<td>1.9 (2%) [93.2]</td>
<td>SBP=-0.60, Glucose=-0.81</td>
</tr>
<tr>
<td>Cooper 2012</td>
<td>Diet</td>
<td>3.3 (8%) [44]</td>
<td>1.1 (1%) [135.2]</td>
<td>0.17 (0%) [93.7]</td>
<td>0.17 (0%) [93.7]</td>
<td>SBP=-0.33, LDL-C=-0.05, Glucose=-0.93, PA=0.77</td>
</tr>
<tr>
<td></td>
<td>Diet and PA</td>
<td>3.9 (9%) [43.8]</td>
<td>3 (2%) [133.4]</td>
<td>0.09 (0%) [57.7]</td>
<td>0.09 (0%) [57.7]</td>
<td>SBP=-0.77, LDL-C=-0.42, Glucose=-1.2</td>
</tr>
<tr>
<td>Dansinger 2005</td>
<td>Atkins diet</td>
<td>1.1 (3%) [35]</td>
<td>3.7 (3%) [129]</td>
<td>2.7 (2%) [136]</td>
<td>2.7 (2%) [136]</td>
<td>SBP=-3.36, LDL-C=-2.45, Glucose=-7.09</td>
</tr>
<tr>
<td></td>
<td>Zone diet</td>
<td>0.9 (3%) [34]</td>
<td>3.9 (3%) [130]</td>
<td>6.7 (5%) [138]</td>
<td>6.7 (5%) [138]</td>
<td>SBP=-4.33, LDL-C=-7.44, Glucose=-9.11</td>
</tr>
<tr>
<td></td>
<td>Weight Watcher's</td>
<td>1.2 (3%) [35]</td>
<td>4.8 (4%) [133]</td>
<td>7 (5%) [142]</td>
<td>7 (5%) [142]</td>
<td>SBP=-4, LDL-C=-5.83, Glucose=-3.17</td>
</tr>
<tr>
<td></td>
<td>diet</td>
<td>1.2 (3%) [35]</td>
<td>0.6 (0%) [133]</td>
<td>10.5 (8%) [136]</td>
<td>10.5 (8%) [136]</td>
<td>SBP=-0.5, LDL-C=-8.75, Glucose=-4.25</td>
</tr>
</tbody>
</table>

*Note: All outcomes here are taken at 6-months from study initiation. SBP: systolic blood pressure (mmHg), FPG (mg/dL), LDL-C: low-density lipoprotein (mg/dL). Goodpaster study did not report LDL-C. PA: physical activity

2.3 Adiposity

The adipose organ is one of the largest organs in the body, constituting about 20% of total body weight\(^{54,59}\). Early work considered the adipose organ as only a storage depot for energy molecules (fatty acids) in the body. Further research into the pathophysiology of the complex structure and function of adipose tissue throughout the body, based on both murine and human models, led to the
awareness of an adipose organ with paracrine, autocrine and endocrine functions. These functions offer explanations for the associations between adiposity and cardio-metabolic risk factors, specifically SBP and FPG.

2.3.1 Depots of the adipose organ

The adipose depots have different structural organization and function. The two main depots are: 1) visceral that is found around the internal organs and 2) subcutaneous that is mostly stored in the buttocks and trunk\textsuperscript{60}. Total body fat is made up of approximately 80-90\% subcutaneous and only 6-20\% visceral adipose tissue, with variations explained by sex and individual differences in patterns of accumulation\textsuperscript{61}. Although adipose tissue is mainly found in the visceral and subcutaneous depots, other adipose depots specific to organ systems include pulmonary, perivascular, perirenal, bone marrow, and epicardial. Several epidemiologic studies have reported that accumulation of visceral adipose tissue is associated with increased cardiovascular risk and mortality\textsuperscript{62-65}. Mechanisms explaining these associations are not completely understood and possibly relate to the resistance to insulin action through increased hepatic exposure to free fatty acids leading to hyperinsulinemia, glucose intolerance, and hypertriglyceridemia\textsuperscript{66}.

2.3.2 Distribution of adipose tissue

The typical distribution of adipose tissue differs in males and females and by menopausal status. At comparable levels of adiposity, men and postmenopausal women have more visceral relative to subcutaneous adipose tissue, whereas the opposite is true for premenopausal women\textsuperscript{67-69}. Sex steroids have been implicated in the sexually dimorphic distribution of adipose tissue. In males, this distribution is likely regulated by androgens. Testosterone production in men decreases with age,
a third by age 70 years old and half by age 80 years old\textsuperscript{70}. Androgens are not as apparent in young females since they exist in much smaller quantities, except for women with androgen excess. Female sex steroids such as estrogen may promote peripheral or lower-body adipose distribution compared to males. When concentrations of estrogen decline following menopause, changes in body fat distribution from subcutaneous to visceral are observed\textsuperscript{68,71}.

\textbf{2.3.3 White and brown adipocytes}

The adipose organ has a fundamental role in the body and shows strong associations with cardio-metabolic risk factors\textsuperscript{72}. The adipose organ is primarily comprised of adipocytes, but also contains vascular elements, preadipocytes, fibroblasts, mast cells, macrophages, nervous system elements, and mesenchymal cells\textsuperscript{61}. Adipose tissue is infiltrated with macrophages at a rate that is correlated with BMI and adipocyte size. This infiltration is suggested to be associated with insulin resistance and obesity\textsuperscript{61}.

Two main types of adipose tissue are white adipose tissue (WAT) and brown adipose tissue (BAT). The main function of WAT is to store high-energy molecules (fatty acids) that can supply fuel during intervals between meals. Other more recently discovered functions include the production of adipokines (any substance released by adipose tissue) that control glucose and lipid metabolism, blood coagulation, blood pressure, and steroid hormone modulation, thereby directly influencing metabolic function\textsuperscript{73}.

BAT functions primarily to use fatty acids to produce heat through non-shivering thermogenesis, which is important for newborns and small mammals\textsuperscript{61}. The surface to volume ratio of humans is quite different from that in small mammals,
therefore human thermodispersion is much lower than that in small mammals. This results in a reduced need for BAT in adult humans. Although newborns have more BAT than adults, BAT is significantly reduced in older human adults. Therefore, the focus here will be on the function of WAT.

2.3.4 Endocrine function of the adipose organ

Adipokines have a plethora of functions that affect inflammation, blood pressure regulation, and glucose and lipid metabolism. Key adipokines that are associated with modification of the cardio-metabolic risk factors – SPG and FPG for this dissertation include leptin, interleukin 6 (IL-6), adiponectin, acylation stimulation protein (ASP), tumor necrosis factor alpha (TNF-α), monocyte chemoattractant protein 1 (MCP-1), plasminogen activator inhibitor (PAI-1), proteins of the renin angiotensinogen system (RAS), and visfatin. Many of these adipokines and their functions were discovered in the past ten years, and have not been extensively described. Table 2 provides a summary of these adipokines and their functions related to the cardio-metabolic risk factors of interest.

Leptin

There has been extensive investigation of leptin as a metabolic signal of energy sufficiency since its discovery in mice in 1994. The name leptin originates from the Greek term leptos meaning thin, because leptin decreased body weight and fat mass when injected into mice. Secretion of leptin by adipocytes is in direct proportion to adipose tissue mass as well as nutritional status. Secretion of leptin is also greater in subcutaneous compared to visceral adipose tissue with higher levels being reported in females compared to males. Leptin has endocrine, paracrine and
autocrine actions\textsuperscript{78} that have numerous functions including metabolic signaling of energy sufficiency, enhancement of insulin sensitivity, and increasing blood pressure as shown in human models\textsuperscript{67,72,75}.

\textit{II-6}

Interleukin-6 (IL-6) is a pro-inflammatory adipokine that is expressed by adipocytes and adipose tissue matrix\textsuperscript{67}. The functions of IL-6 include stimulation of C-reactive protein (CRP) expression which increases systemic inflammation, impairs glucose tolerance and promotes insulin resistance\textsuperscript{67,75}. The expression and secretion of IL-6 is two to three times greater in visceral compared to subcutaneous adipose tissue.

\textit{Adiponectin}

In contrast to the pro-inflammatory actions of leptin and IL-6, adiponectin has an anti-inflammatory action. Other actions of adiponectin include enhancing insulin sensitivity, reducing glucose synthesis and oxidation of LDL-C. Higher concentrations of adiponectin have been found in subcutaneous compared to visceral adipose tissue and in females compared to males\textsuperscript{67,72,79}.

\textit{Acylation stimulating protein (ASP)}

Studies describing the function of ASP are limited but have demonstrated that ASP promotes insulin resistance and dyslipidemia\textsuperscript{67,80}.

\textit{Tumor necrosis factor alpha (TNF-\(\alpha\))}

TNF-\(\alpha\) is a pro-inflammatory adipokine and has been shown to impair insulin signaling\textsuperscript{67}. TNF-\(\alpha\) is expressed by adipocytes and stromovascular cells with higher concentrations found in subcutaneous compared to visceral adipose tissue\textsuperscript{67,75}. 
Monocyte chemoattractant protein (MCP-1)

MCP-1 is pro-inflammatory and promotes insulin resistance. The concentrations of MCP-1 have not been clearly established for subcutaneous compared to visceral adipose tissue, and in males compared to females, but studies suggest that concentrations may not vary by site or gender\textsuperscript{67,81,82}.

Plasminogen activator inhibitor (PAI-1)

PAI-1, a protein of the hemostasis and fibrinolytic system, is secreted by adipocytes and functions to promote insulin resistance\textsuperscript{67}. Higher concentrations of PAI-1 have been reported in visceral compared to subcutaneous adipose tissue.

Proteins of the renin angiotensin system (RAS)

Adipose tissue secretes many of the RAS proteins which are involved in blood pressure regulation\textsuperscript{67}.

Visfatin

Visfatin, which was discovered in 2005, promotes hyperglycemia\textsuperscript{83,84}. Higher concentrations were found in visceral compared to subcutaneous adipose tissue\textsuperscript{83}. This description above of the various functions of the adipose organ emphasizes the importance of adiposity measurements.
Table 3. Summary of adipokines and their functions associated with adiposity and cardio-metabolic risk factors

<table>
<thead>
<tr>
<th>Name</th>
<th>Functions</th>
<th>Adipose depot concentration</th>
<th>Concentrations in males compared to females</th>
<th>Cardio-metabolic risk factor(s) of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>1. metabolic signal of energy sufficiency</td>
<td>higher in subcutaneous</td>
<td>higher in females</td>
<td>glucose</td>
</tr>
<tr>
<td></td>
<td>2. enhances insulin sensitivity</td>
<td></td>
<td></td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td></td>
<td>3. increases blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>1. pro-inflammatory</td>
<td>higher in visceral</td>
<td>not established</td>
<td>glucose</td>
</tr>
<tr>
<td></td>
<td>2. impairs glucose tolerance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. promotes insulin resistance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adiponectin</td>
<td>1. anti-inflammatory</td>
<td>higher in subcutaneous</td>
<td>higher in females</td>
<td>glucose</td>
</tr>
<tr>
<td></td>
<td>2. enhances insulin sensitivity</td>
<td></td>
<td></td>
<td>LDL-C</td>
</tr>
<tr>
<td></td>
<td>3. reduces glucose synthesis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. reduces oxidation of LDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASP</td>
<td>1. promotes insulin resistance</td>
<td>not established</td>
<td>not established</td>
<td>glucose</td>
</tr>
<tr>
<td></td>
<td>2. promotes dyslipidemia</td>
<td></td>
<td></td>
<td>LDL-C</td>
</tr>
<tr>
<td>TNFα</td>
<td>1. pro-inflammatory</td>
<td>higher in subcutaneous</td>
<td>not established</td>
<td>glucose</td>
</tr>
<tr>
<td></td>
<td>2. impairs insulin signaling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCP-1</td>
<td>1. promotes insulin resistance</td>
<td>not established</td>
<td>not established</td>
<td>glucose</td>
</tr>
<tr>
<td></td>
<td>2. pro-inflammatory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAI-1</td>
<td>promotes insulin resistance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAS proteins</td>
<td>1. blood pressure regulation</td>
<td>higher in visceral</td>
<td>not established</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td></td>
<td>2. pro-inflammatory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visfatin</td>
<td>1. promotes hyperglycemia</td>
<td>higher in visceral</td>
<td>not established</td>
<td>glucose</td>
</tr>
</tbody>
</table>

*IL-6: interleukin 6; LDL-C: low-density lipoprotein cholesterol; ASP: acylation stimulating protein; TNFα: tumor necrosis factor alpha; MCP-1: monocyte chemoattractant protein-1; PAI-1: plasminogen activator inhibitor 1; RAS: renin angiotensin system.
2.4 Measurements of adiposity

BMI is measured as weight (kg) divided by the square of height (m²), therefore BMI is an imperfect measure of body fatness as BMI does not measure fat mass directly. Yet, BMI is the most frequently used measure of an individual's weight status and is highly correlated with waist circumference (WC) and adiposity imaging methods. The Institute of Medicine (IOM) report on measuring obesity concluded that BMI is a non-invasive inexpensive surrogate marker of the degree of fat distribution that is easy to calculate and effective for showing trends in populations and subgroups. Advantages of using BMI to measure adiposity include its accuracy compared to weight alone, reliability as an indicator of total body fatness in both women and men, its ability as a marker of obesity-related cardio-metabolic risk, and its associations with morbidity and mortality. BMI also has less observer variability compared to other non-invasive anthropometric techniques, since standardized and calibrated scales can be used. For example, the use of WC in population settings to assess health risks depends on presence or absence of other risk factors (overweight, CVD, and type 2 diabetes) and could introduce measurement bias, because there is a lack of universal agreement on defining a single bone landmark to do the measurement.

Other adiposity measurement methods at the organ level that have high accuracy are imaging techniques such as computed axial tomography (CT) magnetic resonance imaging (MRI) and multi-detector computed tomography (MDCT), although these methods are associated with high costs. One of the most accurate and precise measures of total body fat is dual energy x-ray absorptiometry (DXA), but DXA requires specialized systems and x-ray exposure. The benefit of
using these higher accuracy methods over BMI in population studies does not overcome the associated cost and risks. A feasibility study comparing MDCT to other methods to evaluate visceral abdominal fat reported that MDCT measures were highly correlated with total visceral abdominal fat and with BMI.

Waist-to-hip ratio (WHR), a marker of visceral fat, is a simple and widely used method to characterize body fat distribution. Specific protocols of hip measurements taken at the widest level over the trochanters and waist measurement around the abdomen, just above the hip bone must be followed to avoid measurement error. Although WHR was found to be associated with disease risk and mortality in both males and females, WHR is partially independent of total adiposity. Since total adiposity is related to many morbid conditions including CVD, WHR may not detect total adiposity in cases where both hip and WC vary while keeping the same ratio.

WC has a closer association with CVD risk factors and with other health indicators than does WHR. WC estimates body girth at the abdomen and is a good surrogate index of visceral adiposity. Visceral fat measures obtained by imaging are highly correlated with WC. Overall, WC is a helpful index of visceral adiposity among different racial groups, but can be subject to measurement error and operator variability.

The rationale for use of BMI as a proxy for change in adiposity in this dissertation was further highlighted in a study by Flegal et al. that compared percentage body fat to BMI, WC, and Waist-Stature ratio (WSR) in the 1994-2004 NHANES populations. A high degree of correlation was seen between BMI, WC...
and WSR. These authors concluded that although BMI, WC and WSR may be inaccurate measure of body fatness, these measures are highly correlated with each other and correspond fairly well with percentage body fat within sex-age groups. BMI can be easily and accurately measured and is highly correlated with other more costly measures of adiposity. Particularly as a measure of change in adiposity, BMI has the advantage of a lower measurement error than those of WC and WSR, with the resulting reduction in opportunities for bias in the estimation of change. For the above reasons BMI and WC were chosen for characterization of change in general (BMI) and central (WC) adiposity for this doctoral research. The ARIC study examination protocol provides for standardized measurements of weight, height, and WC across study sites and repeat examinations, with documentation of measurement repeatability and of variability by technician92.

2.5 Population prevention strategies

Although persuasive work on the impact of shifts of small magnitude in the population distribution of blood pressure on the risk for CHD and stroke has been conducted93-95, little work of this kind has been reported to date to assess the population impact of modest changes in adiposity, despite the dynamic nature of adiposity distributions in the young96.

Although only a few population-based prospective studies have examined the relationship between changes in BMI (measured as a continuous variable) and changes in cardio-metabolic risk factors (measured as continuous variables)11, Droyvold et al.97 examined the association between BMI and blood pressure using data from the Nord-Trondelag Health Study (HUNT). Among this group of 29,817 participants of mean age 50 years, changes in BMI had an independent effect on
changes in SBP in both sexes. Findings from the multicenter longitudinal bi-racial Coronary Artery Risk Development in Young Adults (CARDIA) study of 3,095 participants showed that the strongest predictor of both insulin resistance and increase in glucose levels was an increase in BMI$^{11}$. Increases in adiposity, whether measured as BMI or % body fat were associated with adverse changes in blood pressure, lipids, and insulin levels regardless of initial weight, age, race or gender$^{98}$. A linear association has also been shown between weight gain and increased levels of C-reactive protein, a measure of systemic inflammation, thereby providing a mechanism to explain some of the association between adiposity and cardio-metabolic risk factors$^{13}$.

Considering the marked temporal trends of increasing adiposity$^{99}$, the evidence that the cardio-metabolic risk factors associated with the detrimental health effects of adiposity can be reversed with weight loss$^{15,100}$, and the growing burden of CVD$^{33}$, primary prevention strategies at a population level are an urgent and important need. Associations between adiposity and cardio-metabolic risk factors extend beyond categorically defined obesity to adiposity in the modal region of the population distribution$^{28,101}$. For this dissertation, we used methods already described for blood pressure and CVD outcomes. A large proportion of blood pressure-related CVD events occur in individuals within the modal region of the population distribution where blood pressure falls below the threshold for antihypertensive drug therapy. Three studies in particular highlighted the impact of small shifts in the population distribution of blood pressure on the risk of CHD events$^{93-95}$. One study using data from the Third National Health and Examination
Survey (NHANES III) examined the impact on occurrence of CHD events associated with small shifts in the population distribution of SBP that would be seen through population-wide adoption of the Dietary Approaches to Stop Hypertension (DASH) diet\textsuperscript{95}. After adjusting for race and baseline SBP, a population-wide SBP reduction of 5.5 mmHg was associated with a reduction of 416,514 CHD events. A greater relative reduction was observed for African Americans\textsuperscript{96}.

Another study used data from the Framingham study and NHANES II to estimate the impact of small reductions in the population-wide distribution of diastolic blood pressure (DBP) through population-wide lifestyle modification on CHD and stroke. These authors found that a population-wide reduction of 2 mmHg in DBP would result in a 6% reduction in risk of CHD and a 15% reduction in risk of stroke and transient ischemic attacks (TIA)\textsuperscript{93}. An overall upward shift in the population distribution of BMI over time has been described across the NHANES and Framingham data, suggesting the need to address the predictors of adverse health effects associated with adiposity at the population level and the health benefits of arresting current trends rather than focusing only on the individual\textsuperscript{99}. Similar to blood pressure, a large proportion of adiposity – related CVD events would likely occur in the modal region of the population distribution. The individuals in this region would not be classified as obese and would therefore fall below the threshold category for being classified as high-risk. For this dissertation, we hypothesized that small population-wide reductions in BMI and WC would be associated with significant reductions in CVD burden.
Further support for lifestyle modifications using population level strategies for reduction of cardio-metabolic risk factors was reported in a meta-analysis of 23 RCTs conducted between 1996 and 2011 in multiple countries. These authors examined the effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors. Reductions in body weight, WC, and other metabolic risk factors were not significantly different between the two diets. Both diet intervention types showed that lifestyle modifications achieved small reductions in weight that were associated with reductions in cardio-metabolic risk factors including total cholesterol, LDL, HDL, triglycerides, SBP and DBP, FPG and insulin.

Recommendations for achieving the goal of the American Heart Association (AHA) to improve cardiovascular health 20% by 2020 include nationwide primordial prevention efforts at the population and individual level. The paradigm of prevention strategies proposed by Rose emphasized the importance of population prevention strategies for risk factors and their associated chronic diseases since “high risk” prevention strategies that focus on the individual are limited in their ability to reduce burden of disease in the population. The individual-centered or “high-risk” strategy aims to truncate the risk distribution, whereas the population strategy aims to reduce disease outcomes by shifting the whole population distribution of a risk factor in a favorable direction. Because a large number of outcomes occur in the modal region of the distribution, a shift in the whole distribution of the risk factor would likely reduce outcomes more effectively than a truncation of the upper tail region of the distribution.
For this dissertation, we examined methods of prevention that move away from the individual-centered approach and towards a population-based approach. This would offer better measures of etiological outcome and public health importance\textsuperscript{104}.
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44. Wood PD, Stefanick ML, Dreon DM, et al. Changes in plasma lipids and lipoproteins in overweight men during weight loss through dieting as


88. Seidell JC, Kahn HS, Williamson DF, Lissner L, Valdez R. Report from a Centers for Disease Control and Prevention Workshop on use of adult


CHAPTER 3: PRELIMINARY STUDIES

Across the 4 race-gender groups in the Atherosclerosis Risk in Communities (ARIC) study, baseline mean values of BMI and SBP were the highest in African American women. Baseline mean values of LDL-C and glucose were the highest in white men and African American men respectively. White women had the lowest values for BMI, SBP, LDL-C and glucose among the 4 race gender groups (Table 4). Mean change in BMI between ARIC visits one and two varied between 0.2 to 0.5 kg/m² with the largest changes in white women and the smallest changes in white men (Table 5). Weight loss of 3% or greater of body weight over a 3-year follow-up was recorded for 1,026 ARIC participants who were overweight at baseline. The number previously overweight who showed weight loss of this magnitude over the course of 9-years is 347.
Table 4. Baseline mean (standard deviation SD) and number of observations (N) for BMI and the three cardio-metabolic risk factors by race and gender for ARIC participants

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD)</strong></td>
<td><strong>Mean (SD)</strong></td>
<td><strong>Mean (SD)</strong></td>
<td><strong>Mean (SD)</strong></td>
<td><strong>Mean (SD)</strong></td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>2629</td>
<td>1622</td>
<td>6044</td>
<td>5425</td>
</tr>
<tr>
<td><strong>BMI (kg/m(^2))</strong></td>
<td>30.8 (6.5)</td>
<td>27.6 (4.9)</td>
<td>26.6 (5.5)</td>
<td>27.5 (4.0)</td>
</tr>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td>128.0 (21.5)</td>
<td>130.4 (21.7)</td>
<td>117.0 (17.6)</td>
<td>120.2 (16.2)</td>
</tr>
<tr>
<td><strong>LDL-C (mg/dL)</strong></td>
<td>137.8 (1.1)</td>
<td>137.1 (41.9)</td>
<td>135.4 (39.5)</td>
<td>139.8 (35.7)</td>
</tr>
<tr>
<td><strong>Glucose (mg/dL)</strong></td>
<td>119.5 (3.3)</td>
<td>116.4 (51.6)</td>
<td>103.4 (32.3)</td>
<td>108.1 (31.6)</td>
</tr>
</tbody>
</table>

* BMI, body mass index; SBP, systolic blood pressure; LDL-C, low density lipoprotein cholesterol

Table 5. Mean change in BMI (standard deviation SD) between visits 1 and 2 by race and gender for ARIC participants

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD)</strong></td>
<td>0.4 (2.0)</td>
<td>0.2 (1.6)</td>
<td>0.5 (1.8)</td>
<td>0.2 (1.4)</td>
</tr>
</tbody>
</table>
REFERENCES


CHAPTER 4: INNOVATION

To our knowledge, this was the first study to estimate the association between small shifts in the population distribution of adiposity and both cardio-metabolic risk factors and their associated CVD burden. This work builds upon observational and intervention studies that focused on overweight individuals or those defined as obese, mostly without documentation of their cultural affiliation or minority status. To address these gaps in our knowledge, we calibrated the best evidence on the effect of changes in adiposity on metabolic risk factors available from the literature, to populations of African American and white men and women. These population-based effects were the basis for the estimation of the impact on CVD burden that public health scientists and policy makers can consider in the formulation of approaches to population-based prevention of chronic diseases. The quantification of the impact attributed to small changes of adiposity at a population level, of a magnitude shown to be achievable through lifestyle intervention may contribute novel information to the information base needed in the public health sciences and health policy administration.
CHAPTER 5: POTENTIAL IMPACT

Several reasons emphasize the potential high impact of this doctoral research. Deaths and disability from CVD continue to be a major public health problem, driven in part by population-wide increases in adiposity with origins early in life. The association between upstream adiposity and metabolic risk factors, and the link between cardio-metabolic risk factors and the burden of CVD have been established in observational studies and randomized clinical trials. This modern epidemic is a source of significant health disparities, derived from a high prevalence of adiposity, and a greater burden of CVD manifestations in most U.S. minority groups. The magnitude of this public health problem exceeds by far societal resources for individual-level amelioration, to which are added the known difficulties of individual behavioral changes. Primary prevention strategies at a population level to reduce risk factors for CVD are therefore crucial. Our study explored a novel approach to the study of prevention-oriented small changes in adiposity associated with cardio-metabolic risk factors and the CVD burden in the population.
CHAPTER 6: METHODS

6.1 Study population

This study utilized data from the Atherosclerosis Risk in Communities (ARIC) study, a community-based prospective cohort, designed to investigate the etiology of atherosclerosis and its clinical manifestations. The ARIC study also measures variation in cardiovascular disease (CVD)-related risk factors, medical care, prevalence and incidence by race, gender, place and time. Study participants were recruited as a probability sample of 15,792 African American and white adults aged 45-64 years, from four US communities including Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland. African American participants represent 100% of those sampled in the Jackson community. In Forsyth County, 12% of the eligible sample was African American. Washington County, MD and Minneapolis, MN sampled primarily white participants.

Demographic and health characteristics were collected during home interviews, with response rates of approximately 75% in each community. Among individuals who completed the home interview, rates of attendance at the first clinic examination varied from 63% (Jackson) to 88% in the other three communities. The follow-up rates among individuals who were alive at each visit were 93, 86 and 81% at visits two, three, and four respectively. The Institutional Review Boards at each site approved the ARIC study and all participants completed the informed consent\textsuperscript{1,2}.
6.2 ARIC study visits and follow-up

ARIC participants have completed five study visits. Our study included the first four visits, which began in 1987 and were conducted approximately three years apart. At each visit, standardized physical examinations and interviewer-administered questionnaires were conducted to gather behavioral information, medical data, contextual data, and other relevant atherosclerosis risk measurements. All measurements taken at the ARIC examinations were collected by trained technicians following a common study protocol standardized across the repeat examination visits. Participants were asked not to eat or drink anything other than water 12-hours prior to and to refrain from smoking 1-hour prior to ARIC study visits.

Annual follow-up interviews and semi-annual review of hospitalization records and death certificates were conducted (and are ongoing) to ascertain outcome information. We included a median total of 12 years of follow-up information, thereby analyzing outcome data through 2002. The overall goal of our study was to estimate the total effect of a hypothetical reduction in adiposity on disease risk.

6.3 Exposure, covariate and outcome ascertainment

Covariate information was ascertained during each of the 4 triennial study visits for BMI (kg/m²), WC (cm), cigarette smoking status (current compared to never and previous), hypertension (blood pressure>140/90 mmHg or use of anti-hypertension medication within 2 weeks), and diabetes (fasting plasma glucose (FPG) ≥126 mg/dL or non-fasting glucose ≥ 200 mg/dL or self-report of physician diagnosis or treatment with hypoglycemic agents).
6.4 Outcome assessment

The study outcomes [peripheral artery disease (PAD) and coronary heart disease (CHD)] correspond to those ascertained and classified by the ARIC investigators and released as CHD events, consistent with those published by ARIC. Participants were followed until the first occurrence of incident outcome, outcome-related death, non-outcome related death or absence from an ARIC examination visit. If participants missed a study visit they were considered at risk for incidence of the study outcome, study outcome death and non-study outcome death for three years after that missed visit. For the purposes of this study, we administratively censored individuals 3 years after the 4th visit.

6.4.1 PAD

Incident PAD events were identified using ICD-9-CM codes for PAD and CLI\textsuperscript{24} (443.1, 443.22, 443.81, 443.89, 443.9, 440.20, 440.21, 440.29, 440.30, 440.31, 440.32, 440.4, 440.8, 440.22, 440.23, 39.25, 39.29, 38.18, 38.38, and 38.48) from active surveillance of hospitalizations.

6.4.2 CHD

Ascertainment of CHD events was conducted through annual telephone interviews of health events and hospitalizations, an active surveillance of discharge lists from local hospitals and death certificates from state vital statistics offices. CHD events were validated by a morbidity and mortality classification committee. We defined incident CHD as the first occurrence of definite or probable hospitalized myocardial infarction (MI), a definite CHD death, or an unrecognized MI.
6.5 Exclusions

For the aim 1 analysis, we excluded participants with self-reported cancer at baseline, participants reporting use of heart failure medication within the two weeks prior to visit 1, and participants with an estimated Glomerular Filtration Rate (eGFR) $< 15 \text{ mL/min/1.73 m}^2$ using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. We also trimmed 1% of the lower and upper tails of the BMI distribution.

For aims 2-4, of the 15,792 ARIC participants who attended the ARIC baseline visit we excluded individuals who reported a race other than African American or white (n=48) and 55 African Americans from Minnesota or Washington county because of small site-specific numbers. Also excluded were participants who at baseline reported morbidity/chronic conditions associated with weight gain or loss, including 871 with self-reported cancer; 79 taking heart failure medication; 19 with kidney failure (eGFR$< 15 \text{ mL/min/1.73m}^2$); and 144 missing data on kidney function.

For the PAD analysis we excluded 632 individuals with prevalent PAD. Participants with missing data on baseline covariates and covariates related to exclusion criteria were excluded; 58 missing BMI, smoking, hypertension, or diabetes. After applying these exclusions, we removed outliers by trimming observations above the race-gender-specific 99th percentile of BMI (50.4 kg/m$^2$, 43.7 kg/m$^2$, 42.0 kg/m$^2$, and 39.8 kg/m$^2$ for African American women, white women, African American men and white men, respectively) or lower than the 1st percentile (18.8 kg/m$^2$, 18.1 kg/m$^2$, 18.0 kg/m$^2$, and 19.9 kg/m$^2$ for African American women, white women, African American men and white men respectively) of the baseline BMI distribution (n=282), to arrive at our analytic set of 13,604 individuals.
We excluded 667 individuals with prevalent CHD for the CHD analysis. We excluded participants with missing data on baseline covariates and covariates related to exclusion criteria. For the analysis of the effect of a hypothetical shift in BMI, we excluded 58 individuals missing BMI, smoking, hypertension, or diabetes and removed outliers by trimming observations above the race-gender-specific 99th percentile of BMI (kg/m^2) (50.3, 43.5, 42.0, and 39.6 for African American women, white women, African American men and white men, respectively) or lower than the 1st percentile (18.8, 18.1, 18.0, and 19.9 kg/m^2 for African American women, white women, African American men and white men respectively) of the baseline BMI distribution (n=241), to arrive at our analytic set of 13,610 individuals. To arrive at our analytic set of 13,301 individuals for the WC analysis, we excluded 305 individuals missing WC, smoking or BMI, and trimmed observations below the race-gender-specific 1st percentile and above the 99th percentile of the baseline distribution of WC (cm). The 99th percentile of WC was 140, 130, 127, and 124 for African American women, white women, African American men and white men, respectively and the 1st percentile of WC was 70, 68, 99, and 99 cm for African American women, white women, African American men and white men respectively.

6.6 Overview

We calculated baseline frequency and percent of selected categorical variables (race, gender, smoking status, prevalence of hypertension, diabetes, PAD and CHD, and prevalence of morbidity/chronic conditions associated with unintentional weight gain or loss) and mean and SD of BMI and age. The total effect of BMI on the specified chronic diseases occurs through multiple biological pathways. SBP and FPG are two salient cardio-metabolic risk factors along the
pathways through which BMI affects advanced PAD and CHD. Therefore, we described the cross-sectional associations between BMI and SBP and glucose in the ARIC population compared to that in the human experimental literature (Aim 1). We applied 5% hypothetical shifts to the population distribution of BMI and WC and estimated changes in the risk, for the specified CVDs - PAD (Aim 2) and CHD (Aims 3 and 4).

6.7 Statistical analysis

6.7.1 Association between BMI and SBP and BMI and glucose. [Aim 1]

All analyses were conducted using linear regression (proc reg procedure in SAS) at baseline across strata of race and gender. We examined separate analyses for SBP and FPG. SBP and FPG were included as continuous outcome variables and BMI was the main exposure variable in the model. We centered BMI to the 2000 National Health and Nutrition Examination Survey (NHANES) mean for the US population. Age was included in the model centered to 55 years old. Smoking was included as a binary variable for current versus never and former smokers. The following models are for SBP and the same methods were followed for FPG as the outcome variable.

Model 1: \( \text{SBP} = B_0 \) (intercept) + B1 (BMI) + B2 (age) + B3 (smoking status)

Model 2: \( \text{SBP} = (\text{Model 1}) + B_4 \) (BMI²)

6.7.2 Cross-sectional association in the ARIC cohort [Aim 1]

The cross-sectional association between BMI and SBP and FPG was estimated at each of the four ARIC study visits using the following linear regression model:
**Equation 1:** \( Y = \beta_0 + \beta_1(BMI) + \beta_2(\text{age}) + \beta_3(\text{smoking}) + (\varepsilon); \)

where \( Y \) was SBP in one model and FPG in a separate model, \( \beta_0 \) was the intercept, \( \beta_1 \) represented the difference in \( Y \) given a 1-unit increase in BMI controlled for the confounders - \( \beta_2(\text{age as a continuous variable}) \) and \( \beta_3(\text{dichotomous variable for current smoking}) \).

This association was stratified by birth cohort (45-54 or 55-64 years of age at baseline), race and gender. We conducted linear regression analysis to determine the association with BMI included in the model along with its polynomials to test for linearity.

**6.7.3 Comparison of the cross-sectional association in ARIC to the effect estimates in the human experimental literature [Aim 1]**

Estimates of the association between BMI and SBP and glucose have been reported in the human experimental literature. In the human experimental literature,\(^3\)\(^-\)\(^5\) for every 1-unit decrease in BMI, reductions in SBP ranged from 0.33 to 4.33 mmHg and reductions in FPG ranged from 0.81 to 9.11 mg/dL. The magnitude of the differences in SBP and glucose predicted using linear regression analysis in ARIC for a 1-unit change in BMI were compared to the estimates found in the human experimental literature\(^3\)\(^-\)\(^5\)\(^6\).

**Parametric g-formula [Aims 2-4]**

\[
\sum_{k=1}^{21} \sum_{z=10}^{10} \sum_{\cdot} \sum_{\cdot}\Pr[Dk + 1 = 1|\bar{z}k, v, \bar{D}k = \bar{C}k = \bar{N}k = 0] \\
\prod_{j=1}^{k} \left[ \Pr[Dj = \bar{N}j = 0|\bar{z}j - 1, v, \bar{D}j = \bar{C}j - 1 = \bar{N}j - 1 = 0] \right]
\]

**Equation 2:**
We used the parametric g-formula to estimate the change in incidence of PAD and CHD following hypothetical changes in the population distribution of adiposity. Briefly, the parametric g-formula draws on probability modeling, standardization and Monte Carlo sampling for an estimation of the effects of hypothetical interventions from longitudinal data. The parametric g-formula is based on several assumptions one of which is that all joint predictors of the outcome and exposure are measured at all time points for which risk predictions of the outcome are made. Since outcome information was available as date of incident PAD and CHD we classified PAD and CHD as annual incidence, thereby creating a person-year analytic set from which we estimated cumulative incidence of PAD and CHD. WC, BMI, diabetes, hypertension and smoking status were assessed at ARIC examination visits, which occurred at approximately 3-year intervals. We used a carry forward method to fill in the covariates between ARIC study visits and to create a person-year dataset.

6.7.4 Probability modeling

We describe the following sections (Probability modeling, Monte Carlo sampling, and Effect estimation) using CHD as an example and the same procedure was followed for the analysis of BMI and PAD. We constructed regression models to predict the probability of CHD, death, censoring and all of the time-varying covariates for each person-year from baseline through the end of follow-up. Baseline covariates included in each of the regression models were race, sex, and education. Age was included in all models as a time-varying covariate. Pooled logistic regression was used to predict the probability of CHD for each person-year. Binary time-varying covariates were modeled using pooled logistic regression, and BMI and
WC were included as continuous variables and modeled using pooled linear regression.

6.7.5 Monte Carlo sampling

The probability of developing CHD between baseline and end of follow-up was estimated using a Monte Carlo approximation based on the intervention-specific joint distribution of CHD, death, censoring, BMI, WC and all time-varying and time-fixed confounders. Our original datasets of 13,610 for the BMI analysis and 13,301 for the WC analysis were re-sampled with replacement for $M=1,360,000$ and $M=1,330,000$ "pseudo-participants" respectively yielding the empirical distribution of all baseline covariates. We then simulated time-varying covariate and outcome data for each of the “pseudo participants” using the conditional probabilities estimated in the probability models above, and generated a simulated population for which the joint distribution of CHD and the risk factors was approximately equal to the joint distribution implied by the parametric g-formula. No hypothetical adiposity reduction was applied to this simulated dataset, which is identified as the “natural course”.

6.7.6 Effect estimation

Using the parametric g-formula we estimated the cumulative incidence of CHD under four scenarios; natural course where no BMI change was applied for the BMI analysis, natural course where no WC change was applied for the WC analysis, a 5% annual reduction in BMI relative to the trajectory of BMI from the natural course within the population who had a BMI > 24 kg/m², and a 5% reduction in WC relative to the trajectory of WC from the natural course within the population who had a WC>88 cm. These shifts in BMI and WC relative to the natural course were applied only among those younger than 65 years of age and consistent with the usual
clinical recommendations for weight loss. The cumulative incidence of CHD was calculated using the SAS %CIF macro which estimates the cumulative incidence function while allowing for competing risks from death or censoring\textsuperscript{44}. The risk difference and 95% CI were estimated under the two scenarios mentioned using non-parametric bootstrapping. The steps described above were repeated on 200 random samples from the observed ARIC cohort with replacement, from which we estimated the standard error to calculate the 95% CI as cumulative incidence $\pm 1.96 \times$ SD (cumulative incidence) and risk difference $\pm 1.96 \times$ SD (risk difference). All analyses were conducted using SAS 9.4 (Cary, NC).
REFERENCES


CHAPTER 7: RESULTS OF AIM 1

7.1 Results for SBP (Table 6)

After adjusting for age and smoking status, the linear models (model 1) for African American women and white women had different parameter estimates for BMI as the 95% confidence intervals (CI) did not overlap (0.6, 95%CI: 0.4, 0.7 for African American women and 0.9, 95% CI: 0.8, 1.0 for white women). In comparison, the linear model for African American men and white men did have similar parameter estimates for centered BMI as these 95 % CI did overlap (0.5, 95% CI: 0.3, 0.8 for African American men and 0.8, 95% CI: 0.7, 1.0 for white women). The parameter estimates for BMI in the linear models were overlapping for African American women and men and for white women and men. The quadratic term (model 2) for BMI was not statistically significant for any of the race/sex strata.

7.2 Results for glucose (Table 7)

After adjusting for age and smoking status, all of the linear models (model 1) had similar parameter estimates for BMI with overlapping 95% CI across strata of race and sex. The quadratic term (model 2) for BMI was only statistically significant for white males.
Table 6. Results of linear regression analyses of the association between BMI systolic blood pressure at visit 1 by race and gender

<table>
<thead>
<tr>
<th>Model (1=linear model and 2=model 1 +quadratic BMI variable)</th>
<th>Population</th>
<th>Intercept</th>
<th>95%CI</th>
<th>95%CI</th>
<th>95%CI</th>
<th>95%CI</th>
<th>95%CI</th>
<th>95%CI</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 African American Women (n=2357)</td>
<td>127.8</td>
<td>126.7</td>
<td>128.8</td>
<td>0.6</td>
<td>0.4</td>
<td>0.7</td>
<td>0.8</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>1 White Women (5414)</td>
<td>120.2</td>
<td>120.0</td>
<td>121.0</td>
<td>0.9</td>
<td>0.8</td>
<td>1.0</td>
<td>0.89</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>1 African American Men (1473)</td>
<td>129.9</td>
<td>128.6</td>
<td>131.3</td>
<td>0.5</td>
<td>0.3</td>
<td>0.8</td>
<td>0.7</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>1 White Men (5013)</td>
<td>121.6</td>
<td>121.0</td>
<td>122.2</td>
<td>0.8</td>
<td>0.7</td>
<td>1.0</td>
<td>0.7</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>1 Smoking as a categorical variable (current versus former/never)</td>
<td>0.008</td>
<td>-0.009, 0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Quadratic centered BMI as a continuous variable</td>
<td>NA</td>
<td>NA</td>
<td>0.009</td>
<td>-0.004</td>
<td>0.02</td>
<td>NA</td>
<td>NA</td>
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</tbody>
</table>

(continued)
Table 7. Results of linear regression analyses of the association between BMI and fasting glucose at visit 1 by race and gender

<table>
<thead>
<tr>
<th>Model (1=linear model and 2=model 1 +quadratic BMI variable)</th>
<th>Population</th>
<th>intercept</th>
<th>95%CI</th>
<th>Centered BMI as a continuous variable</th>
<th>95%CI</th>
<th>Centered age as a continuous variable</th>
<th>95%CI</th>
<th>Smoking as a categorical variable (current versus former/never)</th>
<th>95%CI</th>
<th>Quadratic centered BMI as a continuous variable</th>
<th>95%CI</th>
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<tbody>
<tr>
<td>1</td>
<td>African American Women (n=2357)</td>
<td>117.7</td>
<td>114.7, 120.7</td>
<td>1.72, 2.1</td>
<td>1.3, 1.1</td>
<td>0.7, 1.5</td>
<td>-0.9, 4.7</td>
<td>-6.4, -4.7</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>2</td>
<td></td>
<td>119.2</td>
<td>116.1, 122.3</td>
<td>2.3, 2.8</td>
<td>1.7, 2.8</td>
<td>0.6, 1.5</td>
<td>-0.2, 5.3</td>
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<td>-0.07</td>
<td>-0.1, 0.02</td>
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<tr>
<td>1</td>
<td>White Women (5414)</td>
<td>106.5</td>
<td>105.6, 107.4</td>
<td>1.5, 1.6</td>
<td>1.3, 1.6</td>
<td>0.5, 0.7</td>
<td>0.3, 2.1</td>
<td>-1.5, -0.008</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>2</td>
<td></td>
<td>106.0</td>
<td>104.8, 107.2</td>
<td>1.4, 1.6</td>
<td>1.3, 1.6</td>
<td>0.5, 0.7</td>
<td>0.3, 2.1</td>
<td>-1.5, -0.008</td>
<td>0.02</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>African American Men (1473)</td>
<td>119.14</td>
<td>115.8, 122.5</td>
<td>1.7, 2.1</td>
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CHAPTER 8: RESULTS MANUSCRIPT 1. CHANGES IN BURDEN OF PERIPHERAL ARTERY DISEASE FOLLOWING A HYPOTHETICAL CHANGE IN THE POPULATION DISTRIBUTION OF ADIPOSITY

8.1 Introduction

Shifting the population distribution of modifiable risk factors carries a large potential to reduce the burden of chronic diseases, and sizeable reductions in myocardial infarction and stroke events are predicted from hypothetical lifestyle interventions targeting blood pressure, adiposity and other modifiable risk factors. Consideration of adiposity for population-wide interventions to reduce the burden of chronic disease is salient as 30% of the world’s population is overweight or obese, and adiposity is associated with several cardiovascular disease (CVD) risk factors and health outcomes. Furthermore, associations between adiposity, metabolic impairment and CVD extend beyond categorically-defined overweight and obesity to adiposity in the modal region of the population distribution. The feasibility of population-wide interventions on adiposity has not been fully evaluated, yet interventions and policies have been proposed to reduce obesity at a population level through healthier eating and increased physical activity. Although work has been done to estimate the reduction in disease burden following hypothetical shifts in the population distribution of various risk factors, such work has not been done for adiposity and peripheral artery disease (PAD), a costly and disabling atherosclerotic condition of the medium and large arteries.
The common clinical presentations of PAD range from intermittent claudication, or ischemic pain in the calf muscles on ambulation, to critical limb ischemia (CLI) characterized by markedly reduced blood flow to the lower extremities. The 5-year mortality associated with PAD is 15-30%, which is reported to increase to 1-year mortality of 25% once the condition progresses to CLI\textsuperscript{11}. The prevalence of PAD is related to age (~3.0% at ages 45 to 64, to 13.4% among those 65 years and older)\textsuperscript{12,13} and affects approximately 8.5 million adults in the U.S. The prevalence of PAD is thus expected to increase as the population ages\textsuperscript{14-16}.

PAD is the downstream outcome of behavioral, metabolic and environmental risk factors\textsuperscript{10}. Null or inverse associations between BMI and PAD have been reported primarily by cross-sectional epidemiological studies that employed conventional analytic models to adjust for confounders\textsuperscript{17,18}. In the setting of adiposity, elevated blood pressure, diabetes and dyslipoproteinemia are time-varying risk factors that may lie on the causal pathway between body mass index (BMI) and PAD, and are affected in turn by previous BMI. Use of conventional regression methods restricted to adjustment for confounding typically does not appropriately adjust for time-varying covariates that are affected by previous exposure\textsuperscript{17}. One method that does control for time-varying confounding by covariates that may act as both mediators and confounders, is the parametric g-formula\textsuperscript{18}, provided the availability of repeat measures of those covariates. The parametric g-formula has been used to examine the effects of hypothetical shifts in the population distribution of various risk factors on conditions such as coronary heart disease\textsuperscript{2}, diabetes\textsuperscript{19}, cancer\textsuperscript{20}, HIV\textsuperscript{17}, and asthma\textsuperscript{21}, but similar work has not
been done for adiposity and PAD to our knowledge. Therefore, the objective of our study was to apply the parametric g-formula to estimate the impact on PAD of hypothetical population shifts in BMI that are expected to primarily occur through changes in adiposity.

8.2 Methods

8.2.1 Study population

This study was conducted in the Atherosclerosis Risk in Communities (ARIC) study cohort, which is described in detail elsewhere. Briefly, ARIC includes a community-based prospective cohort, designed to investigate the etiology of atherosclerosis and its clinical manifestations. The ARIC study also conducts epidemiological surveillance to measure variation in incidence of CVD health events by race, gender, place and time.

ARIC cohort participants were first examined during 1987-1989, as a probability sample of 15,792 adults aged 45-64 years, from four US communities including Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Only African American residents were sampled in the Jackson study area.

Demographic and health characteristics were collected during home interviews with response rates of approximately 75% in each community. The completeness of follow-up among individuals who were alive at each visit were 93, 86 and 81% at visits two (1990-1992), three (1993-1995), and four (1996-1998), respectively. Institutional Review Boards at each site approved the ARIC study and all participants completed an informed consent. We limited our analysis to baseline and the three following triennial exams (1987-1998).
8.2.2 Exposure and covariate measurement

At each ARIC visit, standardized physical examinations and interviewer-administered questionnaires were used to gather behavioral information, medical data, contextual data, and other relevant atherosclerosis risk measurements. All measurements taken at the ARIC examinations were collected by trained technicians following a common study protocol standardized across the repeat examination visits. During annual follow-up interviews health outcomes and hospitalizations were ascertained.

8.2.3 Exposure, covariate and outcome ascertainment

Covariate information was ascertained during each of the 4 triennial study visits for BMI (kg/m²), cigarette smoking status (current compared to never and previous), hypertension (blood pressure>140/90 mmHg or use of anti-hypertension medication within 2 weeks), and diabetes (fasting plasma glucose (FPG) ≥126 mg/dL or or non-fasting glucose ≥ 200 mg/dL or self-report of physician diagnosis or treatment with hypoglycemic agents).

Incident PAD events were identified using ICD-9-CM codes for PAD and CLI (443.1, 443.22, 443.81, 443.89, 443.9, 440.20, 440.21, 440.29, 440.30, 440.31, 440.32, 440.4, 440.8, 440.22, 440.23, 39.25, 39.29, 38.18, 38.38, and 38.48) from active surveillance of hospitalizations. Participants were followed until the first occurrence of incident PAD, death or absence from an ARIC examination visit. If participants missed a study visit, incidence of PAD and death were considered for three years after that missed visit. The analyses were truncated to a follow-up time of 3 years post the date of visit 4; all participants were administratively censored afterwards.
Annual follow-up interviews and review of hospitalization records and death certificates were conducted to ascertain and classify study outcomes. We analyzed outcome data up to three years following the last attended ARIC visit, through a median 12 years of follow-up per participant.

8.2.4 Analysis

Exclusions

Of the 15,792 ARIC participants who attended the ARIC baseline visit, we excluded individuals who reported a race other than African American or white (n=48) and 55 African Americans from Minnesota or Washington county because of small site-specific numbers. Also excluded were participants who at baseline reported morbidity/chronic conditions associated with weight gain or loss, including 871 with self-reported cancer; 79 taking heart failure medication; 19 with kidney failure (estimated Glomerular Filtration Rate [(eGFR)<15 mL/min/1.73m$^2$]; 144 missing data on kidney function, and 632 with prevalent PAD. Participants with missing data on baseline covariates and covariates related to exclusion criteria were excluded; 58 missing BMI, smoking, hypertension, or diabetes. After applying these exclusions, we removed outliers by trimming observations above the race-gender-specific 99th percentile of BMI (50.4 kg/m$^2$, 43.7 kg/m$^2$, 42.0 kg/m$^2$, and 39.8 kg/m$^2$ for African American women, white women, African American men and white men, respectively) or lower than the 1st percentile (18.8 kg/m$^2$, 18.1 kg/m$^2$, 18.0 kg/m$^2$, and 19.9 kg/m$^2$ for African American women, white women, African American men and white men respectively) of the baseline BMI distribution (n=282), to arrive at our analytic set of 13,604 individuals.
8.2.5 Statistical analysis

*Parametric g-formula*

We used the parametric g-formula to estimate the change in risk of PAD following a hypothetical change in the population distribution of BMI. The parametric g-formula\(^2\) approach includes probability modeling, standardization and Monte Carlo sampling which enable an estimation of the effects of hypothetical interventions from longitudinal data. Key assumptions of the parametric g-formula are that there is no residual confounding and no model misspecification. A third strong assumption is treatment version irrelevance, implying that the effect of a shift in BMI applied as a hypothetical change is the same as it would have been if it had occurred naturally\(^{18,20,25,26}\).

The parametric g-formula further assumes that all joint predictors of the outcome and exposure are measured at all time points for which risk predictions of the outcome are being made. Since outcome information was available as date of incident event for PAD we classified PAD as yearly incidence, thereby creating a person-year analytic set from which we estimated yearly risk of PAD. BMI, diabetes, hypertension and smoking status were assessed at ARIC examination visits, which occurred at approximately 3-year intervals. We used a carry forward method to fill in the covariates between ARIC study visits and to create a person-year dataset.

The parametric g-formula can be described as a 3-step algorithm: 1) probability modeling; 2) Monte Carlo sampling; and 3) effect estimation\(^{20}\).
**Probability modeling**

Regression models were constructed to predict the probability of PAD, death, censoring and all of the time-varying covariates for each person-year starting at baseline through the end of follow-up. Baseline covariates included in each of the regression models were race, sex, and education. Age was included in all models as a time-varying covariate. Pooled logistic regression was used to predict the probability of PAD for each person-year. Binary time-varying covariates were modeled using pooled logistic regression and BMI was included as a continuous variable and modeled using pooled linear regression.

**Monte Carlo sampling**

Our implementation of the parametric g-formula utilized a Monte Carlo approximation of the probability of developing PAD between baseline and end of follow-up, based on the intervention-specific joint distribution of PAD, death, censoring, BMI, and all time-varying and time-fixed confounders. Our original dataset of 13,604 was re-sampled with replacement for M=1,360,400 “pseudo-participants” yielding the empirical distribution of all baseline covariates. We then simulated time-varying covariate and outcome data for each of the “pseudo participants” using the conditional probabilities estimated in the probability models above, and generated a simulated population for which the joint distribution of PAD and the risk factors was approximately equal to the joint distribution implied by the parametric g-formula. A hypothetical BMI reduction is not applied to this simulated dataset, which is identified as the “natural course”.
**Effect estimation**

Using the parametric g-formula we estimated the cumulative incidence under two scenarios; natural course where no BMI change was applied, and a 5% annual reduction in BMI relative to the trajectory of BMI from the natural course. These shifts in BMI relative to the natural course were applied only among those younger than 65 years of age who had a BMI > 24 kg/m$^2$, to avoid applying a hypothetical population shift outside of the usual clinical recommendations for weight loss. The cumulative incidence of PAD was calculated using the SAS %CIF macro which estimates the cumulative incidence function while allowing for competing risks from death or censoring$^{27}$. The risk difference and 95% CI were estimated under the two scenarios using non-parametric bootstrapping. The steps described above were repeated on 500 random samples from the observed ARIC cohort (N=13,604) with replacement, from which we estimated the standard error to calculate the 95% CI as cumulative incidence + 1.96 X SD (cumulative incidence) and risk difference + 1.96 X SD (risk difference). All analyses were conducted using SAS 9.4 (Cary, NC).

8.3 Results

8.3.1 Characteristics of study participants

At baseline, study participants had a median age of 54 years (IQR: 48, 59), were more likely to be female (54%), of white race (73%), and to have at least a high school education (77%). Cigarette smoking (27%) and diabetes (20%) were less common than hypertension (58%) among baseline participants. Study participants at baseline had a median BMI (kg/m$^2$) of 26.9 (IQR: 24.1, 30.4) (Supplemental Table1).
During a median 11.8 (IQR: 9.0, 11.8) years of follow-up, 231 incident PAD events were identified. Participants with incident PAD were more likely to be male (69%), of white race (83%), and have less than a high school education (34%) compared to those without incident PAD. Smoking (51%), diabetes (45%) and hypertension (77%) were more frequent among those who developed incident PAD compared to those without incident PAD (Table 1). Participants who did not develop incident PAD had a more favorable cardio-metabolic risk profile compared to those who developed incident PAD. Specifically, among those who developed incident PAD: systolic blood pressure (SBP) was 127 mmHg (IQR: 113, 142); fasting plasma glucose (FPG) was 106 mg/dL (IQR: 98.2, 141.6); total cholesterol (TC) was 216 mmHg (IQR: 194, 246); and high density lipoprotein (HDL) was 38.3 mmHg IQR: 31.8, 49.1. Conversely, among those who did not develop incident PAD, SBP was 118 mmHg (IQR: 108, 131), FPG was 99 mg/dL (IQR: 93, 107), TC was 212 mmHg (IQR: 186, 239) and HDL was 49.1 mmHg (IQR: 39.5, 61) (Table 1).

The probability models used to create our natural course scenario included a cubic term for follow-up time and a restricted quadratic spline for BMI with knots at 21.1 kg/m$^2$, 25.8 kg/m$^2$, and 29.4 kg/m$^2$ (Figure 1). The cumulative incidence of PAD under the natural course was 1.89% (95%CI: 1.62, 2.17%) and 1.72% (95%CI: 1.46, 2.08%) following the hypothetical BMI change (Figure 2). The risk difference was -0.17% (95% CI: -0.38, 0.13%) comparing no BMI change to the hypothetical BMI change (Table 2).
8.4 Conclusions and discussion

We estimated the effects of a hypothetical change in the population distribution of BMI on the incidence of PAD. This shift of 5% in a population distribution of BMI, which is slightly above what may be considered weight maintenance (<3% change) is therefore considered feasible\textsuperscript{28} and may be achieved through population-wide interventions that reduce caloric intake such as taxes on sugary-beverages\textsuperscript{9} or subsidies on healthier foods\textsuperscript{7}. Body weight reductions as low as 5% are associated with reduced incidence of cardio-metabolic risk factors\textsuperscript{29}. We implemented a BMI shift that was consistent with the observed temporal variability in BMI, by reducing BMI annually by 5% relative to the natural course in individuals who were younger than 65 years of age and had a BMI >24 kg/m\textsuperscript{2}. For example, if the natural course of an individual’s BMI (kg/m) at baseline, year 1, year 2 and year 3 was 25.4, 24.3, 25.2, and 26.0 respectively, then after the 5% BMI intervention this individual’s BMI (kg/m\textsuperscript{2}) at baseline, year 1, year 2 and year 3 was 24.1, 24, 24, and 24.7 respectively. The predicted result from this hypothetical intervention was a small reduction in the risk of PAD to follow this population-wide reduction in BMI.

Several cross-sectional epidemiological studies have reported the absence of, or an inverse association between BMI and PAD\textsuperscript{14,30-35} using standard regression methods, although these studies may not have appropriately adjusted for time-varying confounding that is affected by previous exposure. These studies were also limited in their ability to examine the longitudinal association between BMI and PAD following implementation of a BMI reduction at multiple time points. To overcome the limitations of standard analytic methods and to allow for application of our hypothetical BMI reduction at multiple time points, we used the parametric g-formula
as an approach that combines parametric regression modeling to obtain conditional probabilities and Monte Carlo sampling to approximate standardization and to estimate measures of effect\textsuperscript{18,20}.

As a result, we were able to consider feedback loops in the form of time-varying confounders affected by prior exposure, and other dynamic systems for realistic modeling of the processes hypothesized to be associated with PAD as the study outcome\textsuperscript{36}. Prior reports have applied the parametric g-formula to estimate the effects of different lifestyle interventions (and their combination) on complex chronic conditions such as coronary heart disease\textsuperscript{2}, diabetes\textsuperscript{19}, cancer\textsuperscript{20} and asthma\textsuperscript{21}, and to estimate the effects of therapeutic interventions among individuals in treatment for HIV\textsuperscript{17}. To our knowledge, such work has not been applied to PAD.

A population-wide reduction in BMI of 5% over a median 11.8 years in a middle-aged, bi-racial cohort predicted a small (0.17%) reduction in the risk of PAD. The small magnitude of this estimated reduction in the risk of PAD attributed to a shift in the population distribution of BMI likely reflects the larger effects of PAD risk factors that are not influenced by BMI, such as cigarette smoking and age. Although impaired glucose metabolism and elevated blood pressure/hypertension may lie in part on the causal path between BMI and PAD, the effects of a 5% reduction in BMI are considered to be quite small in magnitude in this population-based cohort of men and women who were middle-aged at study enrollment.

Conditional on several assumptions, observational study data can be used to mimic randomized experiments of pre-specified interventions, to compare the distribution of the outcome of interest among the hypothetical intervention groups\textsuperscript{37}. 
The main assumption on which our results rely is the absence of unmeasured confounding to be approximately true, in order to mimic a randomized experiment in an observational setting, in which populations are contrasted as a counterfactual. We focused on adiposity at the level of the population and its potential impact on an outcome (PAD) that demonstrably is influenced by a number of antecedent risk factors. Changes in adiposity, indexed in this instance by changes in BMI, have well established effects on the risk factors for PAD in the population, such as elevated blood pressure, insulin resistance, diabetes and impaired lipid metabolism. This provides a plausible basis for a reduction in BMI as a hypothetical intervention aimed at reducing the risk of an atherosclerotic sequela such as PAD. Cigarette smoking in contrast, the main risk factor for PAD other than age, is inversely associated with BMI and a reduction in BMI is not expected to lead to changes in the acute effects of smoking on the vasculature, nor to influence the effect of cumulative exposure to smoking on the risk of PAD. The role of cigarette smoking as a cofounding factor has been incorporated in our model, and we did not observe qualitative differences in the association between BMI and the risk of PAD among those who smoked cigarettes or those who had diabetes.

Adiposity is a complex trait, influenced by factors ranging from behaviors to social norms, education, ethnicity, economic factors and food marketing practices, and reductions in adiposity may be achieved through various means. While targeted interventions at the population level can be desirable and feasible, such as the reduction of salt content in processed foods, single interventions on complex traits such as adiposity are likely to be less relevant for population-based policy. Further,
different methods to change adiposity in populations may influence the risk of PAD through mechanisms that do not involve BMI, even if they were to achieve the same value of BMI. Single interventions involving BMI reduction are thus sensitive to the treatment version irrelevance assumption, which states that the method by which BMI reduction occurs should not affect the outcome, that is, whether the reduction occurs due to dietary, exercise, or other lifestyle changes should not affect our results. In our data, this effect is identified through natural reductions (or increases) in BMI, so our hypothetical intervention approximates what would occur if individuals were motivated to reduce BMI through their own means, or structural or contextual changes occurred that affected the energy balance throughout the population.

The results presented in this paper predict that 9% of PAD cases occurring in this study population-based cohort over the course of 9 to 12 years of follow-up could have been prevented by a 5% shift in the population distribution of BMI. This observation does not imply a causal inference, which would require a well-defined intervention, and preferably the manipulation of such an intervention. Instead, a shift in the population distribution of BMI may result from different types of intervention, some of which may affect the risk of PAD in ways that are not mediated through adiposity, and may differ across populations and over time.

Consistent with previous reports, our hypothetical shift of 5% from the natural trajectory of BMI can be considered of modest magnitude, and corresponds to changes that are actually observed in the population. We therefore submit that the intervention can be considered well-defined in the sense that it is observed in the data, even though a single mechanism is not specified through which reductions in
BMI occur in all individuals. We are sensitive to the unmeasured confounding that may occur if our analytic approach failed to adjust for PAD risk factors that influence one or more of the routes by which individuals reduce their BMI. By adjusting for population predictors of BMI that may also be independently associated with PAD, we have reduced the potential for such residual confounding.

In this study we considered arguably realistic reductions in the population distribution of BMI, as sustained shifts in the dynamic factors that affect BMI in a population setting through unspecified combinations of behavioral, environmental, social and economic factors. To translate our findings to population interventions, modifiable behaviors and lifestyle factors would have to be identified and tested. Such efforts are not warranted at this point, given that our results predicted only small benefits on PAD from a modest reduction in the population distribution of BMI.

Our study had limitations, such as the truncation of our follow-up time to a median length of follow-up of 11.8 years, as required to meet the assumption of the parametric-g formula to have exposure and outcome information at all time periods. Applying the parametric g-formula methodology to PAD ascertained over a longer period of follow-up would provide a more meaningful estimate of the effect of a population-wide impact in the distribution of BMI on PAD, but a long interval between examination visits 4 and 5 in ARIC prevented us from using information beyond 2002. A strength of our study is the use of the parametric g-formula to estimate the change in risk of PAD following a hypothetical intervention on an upstream PAD risk factor (BMI), considering that such work on BMI and PAD has not been reported in the literature.
Although we predict only a small effect on the risk of PAD following a modest population-wide shift in adiposity, our results may inform the need for further investigation in other populations or to older ages when PAD risk is highest. Investigation of this question in birth cohorts with a lower prevalence of smoking is similarly warranted to address the potential benefits of a population shift of adiposity on cardiovascular disease outcomes.

Future analyses stratified by race may be warranted as the frequency of occurrence of PAD, like that of other cardiovascular diseases, is higher among African Americans\textsuperscript{15}, whose cardiovascular risk profiles and burden of adverse health outcomes are higher than those of other population groups in the U.S.\textsuperscript{39,40}.
Table 8. Characteristics of the study population at baseline by incidence of PAD status between 1987 and end of follow-up in 2011. The ARIC Study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Incident PAD (n=231) Number (%)</th>
<th>Without Incident PAD (n=13,373) Number (%)</th>
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<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>71 (31)</td>
<td>7296 (55)</td>
</tr>
<tr>
<td>Race</td>
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<tr>
<td>African American</td>
<td>39 (17)</td>
<td>3587 (27)</td>
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<td>Education</td>
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</tr>
<tr>
<td>&lt; High school graduate</td>
<td>78 (34)</td>
<td>3057 (23)</td>
</tr>
<tr>
<td>High school graduate or vocational school</td>
<td>81 (35)</td>
<td>5456 (41)</td>
</tr>
<tr>
<td>Some college or college graduate</td>
<td>72 (31)</td>
<td>4860 (36)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
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<td></td>
</tr>
<tr>
<td>Current</td>
<td>118 (51)</td>
<td>3614 (25)</td>
</tr>
<tr>
<td>Diabetes</td>
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</tr>
<tr>
<td>FPG &gt;126 mg/dL or self-report physician diagnosis</td>
<td>102 (45)</td>
<td>2660 (20)</td>
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<tr>
<td>Hypertension</td>
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<td></td>
</tr>
<tr>
<td>Blood pressure&gt;140/90 mmHg or use of anti-hypertension medication within 2 weeks</td>
<td>178 (77)</td>
<td>7732 (58)</td>
</tr>
<tr>
<td>Follow-up time</td>
<td>6.8 (3.9, 8.9)</td>
<td>11.8 (9.0, 11.9)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59 (55,62)</td>
<td>54 (49, 59)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.5 (25.4, 31.5)</td>
<td>26.9 (24.1, 30.3)</td>
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<tr>
<td>SBP (mmHg)</td>
<td>127 (113,142)(^a)</td>
<td>118 (108, 131)(^b)</td>
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<tr>
<td>FPG (mg/dL)</td>
<td>106 (98.2, 141.6)</td>
<td>99 (93, 107)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>216 (194, 246)(^a)</td>
<td>212 (186, 239)(^*)</td>
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<tr>
<td>High density lipoprotein (HDL)</td>
<td>38.3 (31.8, 49.1)(^a)</td>
<td>49.1 (39.5, 61)(^**)</td>
</tr>
</tbody>
</table>

\(^a\)N=230, \(^b\)N=13,353, \(^*\)N=13,277, \(^**\)N=13,279
Figure 1. Manuscript 1 Figure 1. Cumulative 12-year incidence of PAD comparing the natural course to the observed
Figure 2. Manuscript 1 Figure 2. Cumulative 12-year incidence of PAD comparing the natural course to a hypothetical 5% shift in the population distribution of BMI

Table 9. Manuscript 1 Table 2. Cumulative 12-year incidence and risk difference (95% confidence interval) for the natural course cohort compared to the cohort subjected to a hypothetical 5% shift in the population distribution of BMI

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Effect measure&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Estimate (%)</th>
<th>95% CI&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>Natural Course</td>
<td>Incidence</td>
<td>1.89</td>
<td>1.62, 2.17</td>
</tr>
<tr>
<td>Hypothetical BMI lifestyle intervention</td>
<td>Incidence</td>
<td>1.72</td>
<td>1.46, 2.08</td>
</tr>
<tr>
<td>Natural course vs. hypothetical BMI lifestyle intervention</td>
<td>Risk difference</td>
<td>-0.17</td>
<td>-0.38, 0.13</td>
</tr>
</tbody>
</table>

<sup>a</sup>Confidence Interval (CI)

<sup>b</sup>Baseline covariates include age, sex, race, and education. Time varying covariates include years at risk for PAD, diabetes, hypertension, smoking, and BMI.
Table 10. Manuscript 1 Supplemental Table 1. Baseline demographics and covariates of 13,604 ARIC participants

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Number (%)</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td>Female 7367 (54)</td>
</tr>
<tr>
<td>Race</td>
<td>African American 3626 (27)</td>
</tr>
<tr>
<td>Education</td>
<td>&lt; high school graduate 3131 (23)</td>
</tr>
<tr>
<td></td>
<td>High school graduate or vocational school 5540 (41)</td>
</tr>
<tr>
<td></td>
<td>Some college or college graduate 4933 (36)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>Current 3732 (27)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Fasting glucose ≥126 mg/dL or self-report physician diagnosis 2777 (20)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Blood pressure &gt;140/90 mmHg or use of anti-hypertension medication within 2 weeks 7910 (58)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Continuous variables</th>
<th>Median</th>
<th>Interquartile interval</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>54</td>
<td>48, 5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.9</td>
<td>24.1, 30.4</td>
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<tr>
<td>Follow-up time in years</td>
<td>11.8</td>
<td>9.0, 11.8</td>
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REFERENCES


CHAPTER 9: MANUSCRIPT 2. CHANGES IN BURDEN OF CORONARY HEART DISEASE FOLLOWING HYPOTHETICAL REDUCTIONS IN GENERAL AND VISCERAL ADIPOSITY

9.1 Introduction

Coronary heart disease (CHD) is the leading cause of death in the world with 7.4 million deaths in 2012\(^1\). Although death attributable to CHD declined overall in the U.S. from 186.8 per 100,000 population in 2003 to 102.6 per 100,000 population in 2013, these declines were disparate across different race-gender subgroups and slower in certain groups such as African American women\(^2,3\).

The incidence of CHD, which includes first myocardial infarction (MI) and fatal CHD also declined significantly from 1987 to 2011 and was differential by race-gender groups\(^4\). These age-adjusted incidence rates per 1,000 population among were 3.7 in white men, 6.2 in African American men, 2.1 in white women, and 4.1 in African American women who were 35 to 84 year old participants in the Atherosclerosis Risk in Communities (ARIC) study\(^3\). While the mean predicted 10-year risk for CHD among adults aged 30 to 74 years decreased from 7.2% during 1999 to 2000 to 6.5% during 2009 to 2010, this risk increased non-significantly among African American women\(^2\).

The public health burden of CHD is emphasized by the high health care costs of CHD, which are expected to double between 2013 and 2030\(^3\), and the high mortality from CHD of which a large component includes sudden cardiac death (SCD)\(^5,6\). Continued progress in reducing mortality, incidence, and case-fatality...
related to CHD requires sustained and expanded public health efforts aimed at prevention of CHD at the population level. Modifiable risk factors for CHD are well established, such as hypertension and diabetes, while most of the CHD risk associated with overweight/obesity is mediated by the metabolic dysregulation associated with excess adiposity, with manifestations such as hypertension and diabetes. The causal role of excess adiposity on hypertension and diabetes is also well documented. Risk of CHD including SCD increases with increasing overweight and obesity. The strength of the association between general (BMI) and central (WC) adiposity with CHD is of similar magnitude: a 1 standard deviation increment in BMI or WC is associated with a 25-30% higher risk of CVD including CHD.

Although excess adiposity is associated with CHD, the effect of adiposity reduction on CHD risk is unclear, and to our knowledge no randomized, controlled clinical trial has put this question to a test. Several observational studies have found increased adiposity to be predictive of increased risk of CHD while others have reported increased risk of CHD following weight loss, and other studies reported no association. Since the effect of adiposity on CHD risk likely occurs through the well documented, adverse effects of excess adiposity on cardiometabolic intermediates in the path to CHD, adiposity represents a modifiable, upstream risk factor for CHD.

In 2015 an estimated 30.6% of U.S. adults were obese (BMI >30 kg/m²), which is slightly higher than the 29.9% prevalence estimate of adult obesity in 2014. The prevalence of excess adiposity is even higher (69%) when including...
those who are overweight (BMI=25-29.9 kg/m\(^2\)) or obese. The national prevalence of elevated abdominal adiposity, defined using sex-specific cut points of WC, i.e. >88 cm for women and >102 cm for men\(^\text{15}\), also has increased over time, differentially by sex and race\(^\text{34}\). The increases in the prevalence of excess abdominal adiposity from 1999 to 2000 and 2010 to 2011 were greater than expected based on increases in BMI\(^\text{3}\).

While previous reports examined the effect on CHD of hypothetical BMI interventions\(^\text{25,35}\), we considered both BMI and WC as measures of adiposity in our analysis, to estimate the effects on the incidence of CHD predicted from hypothetical interventions on general, as well as on central adiposity. As a surrogate measure for visceral fat, the more metabolically active adipose depot associated with production of adipokines and metabolic dysregulation\(^\text{36,37}\), WC has a potential but understudied role in the assessment and modification of CHD risk, since few studies have examined population-based reductions in general and/or central adiposity to reduce the public health burden for CHD\(^\text{24,25}\). WC may also convey a simpler and more compelling public health message than BMI. The purpose of this study was to examine the effect of small hypothetical changes (5%) in two commonly used measures of general (BMI) and central adiposity (WC) on the incidence of CHD.

9.2 Methods

9.2.1 Study population

This study was conducted in the community-based prospective Atherosclerosis Risk in Communities (ARIC) study cohort\(^\text{38}\), which was designed to investigate the etiology of atherosclerosis and its clinical manifestations. The ARIC
study also conducts epidemiological surveillance to measure variation in incidence of CVD health events by race, gender, place and time.

ARIC cohort participants were first examined during 1987-1989, as a probability sample of 15,792 adults aged 45-64 years, from four US communities including Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Only African American residents were sampled in the Jackson study area.

Demographic and health characteristics were collected during home interviews with response rates of approximately 75% in each community. Follow-up interviews were carried out for 93, 86 and 81% of living individuals at visits two (1990-1992), three (1993-1995), and four (1996-1998), respectively. Institutional Review Boards at each site approved the ARIC study and all participants completed an informed consent\textsuperscript{38,39}. We limited our analysis to baseline and the three following triennial exams (1987-1998).

**9.2.2 Exposure and covariate measurement**

At each ARIC visit, standardized physical examinations and interviewer-administered questionnaires were used to gather behavioral information, medical data, contextual data, and other relevant atherosclerosis risk measurements. All measurements taken at the ARIC examinations were collected by trained technicians following a common study protocol standardized across the repeat examination visits\textsuperscript{38}. Annual follow-up telephone interviews ascertained health outcomes and hospitalizations.
9.2.3 Exposure, covariate and outcome ascertainment

Covariate information was ascertained during each of the 4 triennial study visits for BMI (kg/m$^2$), WC (cm), cigarette smoking status (current compared to never and previous), hypertension (blood pressure > 140/90 mmHg or use of anti-hypertension medication within 2 weeks), and diabetes (fasting plasma glucose (FPG) $\geq$ 126 mg/dL or non-fasting glucose $\geq$ 200 mg/dL or self-report of physician diagnosis or treatment with hypoglycemic agents).

Ascertainment of CHD events was conducted through annual telephone interviews of health events and hospitalizations, an active surveillance of discharge lists from local hospitals and death certificates from state vital statistics offices. CHD events were validated by a morbidity and mortality classification committee. We defined incident CHD as the first occurrence of definite or probable hospitalized myocardial infarction (MI), a definite CHD death, or an unrecognized MI.

Participants were followed until the first occurrence of incident CHD, CHD death, non-CHD death or absence from an ARIC examination visit. If participants missed a study visit they were considered at risk for incidence of CHD, CHD death and non-CHD death for three years after that missed visit. For the purposes of this study, we administratively censored individuals 3 years after the 4$^{th}$ visit.

9.2.4 Analysis

Exclusions

Among the 15,792 ARIC participants who attended the ARIC baseline visit we excluded individuals who reported a race other than African American or white ($n$=48) and 55 African Americans from Minnesota or Washington county because of small site-specific numbers. Also excluded were participants who at baseline
reported morbidity/chronic conditions associated with weight gain or loss, including 871 with self-reported cancer; 79 taking heart failure medication; 19 with kidney failure; 144 missing data on kidney function; and 667 with prevalent CHD. We excluded participants with missing data on baseline covariates and covariates related to exclusion criteria. For the analysis of the effect of a hypothetical shift in BMI, we excluded 58 individuals missing BMI, smoking, hypertension, or diabetes and removed outliers by trimming observations above the race-gender-specific 99th percentile of BMI (kg/m²) (50.3, 43.5, 42.0, and 39.6 for African American women, white women, African American men and white men, respectively) or lower than the 1st percentile (18.8, 18.1, 18.0, and 19.9 kg/m² for African American women, white women, African American men and white men respectively) of the baseline BMI distribution (n=241), to arrive at our analytic set of 13,610 individuals. To arrive at our analytic set of 13,301 individuals for the WC analysis, we excluded 305 individuals missing WC, smoking or BMI, and trimmed observations below the race-gender-specific 1st percentile and above the 99th percentile of the baseline distribution of WC (cm). The 99th percentile of WC was 140, 130, 127, and 124 for African American women, white women, African American men and white men, respectively and the 1st percentile of WC was 70, 68, 99, and 99 cm for African American women, white women, African American men and white men respectively.

9.2.5 Statistical analysis

*Parametric g-formula*

We used the parametric g-formula to estimate the change in incidence of CHD following hypothetical changes in the population distribution of adiposity. Briefly, the parametric g-formula draws on probability modeling, standardization...
and Monte Carlo sampling for an estimation of the effects of hypothetical interventions from longitudinal data\textsuperscript{40-43}. The parametric g-formula is based on several assumptions one of which is that all joint predictors of the outcome and exposure are measured at all time points for which risk predictions of the outcome are made. Since outcome information was available as date of incident CHD we classified CHD as annual incidence, thereby creating a person-year analytic set from which we estimated cumulative incidence of CHD. WC, BMI, diabetes, hypertension and smoking status were assessed at ARIC examination visits, which occurred at approximately 3-year intervals. We used a carry forward method to fill in the covariates between ARIC study visits and to create a person-year dataset.

**Probability modeling**

We constructed regression models to predict the probability of CHD, death, censoring and all of the time-varying covariates for each person-year from baseline through the end of follow-up. Baseline covariates included in each of the regression models were race, sex, and education. Age was included in all models as a time-varying covariate. Pooled logistic regression was used to predict the probability of CHD for each person-year. Binary time-varying covariates were modeled using pooled logistic regression, and BMI and WC were included as continuous variables and modeled using pooled linear regression.

**Monte Carlo sampling**

The probability of developing CHD between baseline and end of follow-up was estimated using a Monte Carlo approximation based on the intervention-specific joint distribution of CHD, death, censoring, BMI, WC and all time-varying and time-
fixed confounders. Our original datasets of 13,610 for the BMI analysis and 13,301 for the WC analysis were re-sampled with replacement for $M=1,360,000$ and $M=1,330,000$ “pseudo-participants” respectively yielding the empirical distribution of all baseline covariates. We then simulated time-varying covariate and outcome data for each of the “pseudo participants” using the conditional probabilities estimated in the probability models above, and generated a simulated population for which the joint distribution of CHD and the risk factors was approximately equal to the joint distribution implied by the parametric g-formula. No hypothetical adiposity reduction was applied to this simulated dataset, which is identified as the “natural course”.

**Effect estimation**

Using the parametric g-formula we estimated the cumulative incidence of CHD under four scenarios; natural course where no BMI change was applied for the BMI analysis, natural course where no WC change was applied for the WC analysis, a 5% annual reduction in BMI relative to the trajectory of BMI from the natural course within the population who had a BMI $> 24$ kg/m$^2$, a 5% reduction in WC relative to the trajectory of WC from the natural course within the population who had a WC$>88$. These shifts in BMI and WC relative to the natural course were applied only among those younger than 65 years of age and consistent with the usual clinical recommendations for weight loss. The cumulative incidence of CHD was calculated using the SAS %CIF macro which estimates the cumulative incidence function while allowing for competing risks from death or censoring$^{44}$. The risk difference and 95% CI were estimated under the two scenarios mentioned using non-parametric bootstrapping. The steps described above were repeated on 200 random samples
from the observed ARIC cohort (N=13,301) with replacement, from which we estimated the standard error to calculate the 95% CI as cumulative incidence $\pm 1.96$ X SD (cumulative incidence) and risk difference $\pm 1.96$ X SD (risk difference). All analyses were conducted using SAS 9.4 (Cary, NC).

9.3 Results

9.3.1 Characteristics of study participants

During a median 12 years of follow-up, 763 and 712 incident CHD events were identified among the 13,610 (BMI analysis) and 13,301 (WC analysis) middle-aged men and women in this cohort. Participants who experienced incident CHD were older at baseline (median age=62 years), more likely to be male (67%), of white race (73%), and have less than a high school education (30%) compared to those without incident CHD. Smoking (29%), diabetes (28%) and hypertension (59%) were more frequent at baseline among those who developed incident CHD compared to those without incident CHD (Table 1). Participants who did not develop incident CHD had a more favorable cardio-metabolic risk profile compared to those who developed incident CHD. Specifically, baseline values among those who developed incident CHD were: 126 mmHg median systolic blood pressure (SBP); 104 mg/dL median fasting plasma glucose (FPG); 221 mg/dL total cholesterol (TC) and 44 mg/dL high density lipoprotein (HDL) (Table 1).

The probability models used to create the natural course scenario included a cubic term for follow-up time and a restricted quadratic spline for BMI with knots at 21.1 kg/m$^2$, 25.8 kg/m$^2$, and 29.4 kg/m$^2$ (Figure 1). The difference in CHD incidence between the natural course and the hypothetical shift increased with follow-up time for both the BMI and WC analyses (Figure 2 and 3). The median BMI (kg/m$^2$) was
between 26.9 and 28.18 in the natural course and between 24.7 and 25.6 in the
population where a hypothetical 5% shift in BMI was applied (Figure 4). The median
WC (cm) was between 95.9 and 100.6 in the natural course and between 88.6 and
93.8 in the population exposed to a hypothetical 5% shift in WC (Figure 5). For the
BMI analysis, the cumulative incidence of CHD under the natural course was 6.34%
(95%CI: 5.90, 6.78%) and 5.78% (95%CI: 5.22, 6.35%) following the hypothetical
BMI change. The risk difference was -0.56% (95% CI: -0.96, -0.14%) comparing no
BMI change to the hypothetical BMI change (Table 2). For the waist circumference
analysis, the cumulative incidence of CHD under the natural course was 6.21%
(95%CI: 5.75, 6.67%) and 5.24% (95%CI: 4.60, 5.88%) following the hypothetical
WC change. The risk difference was -0.96% (95% CI: -1.44, -0.48%) comparing no
WC change to the hypothetical WC change (Table 2).

9.4 Discussion/conclusions

We estimated the effects of a hypothetical change in the population
distribution of general (BMI) and central (WC) adiposity on the cumulative incidence
of CHD in the ARIC study cohort. Moderate weight loss of 5-10% is recommended
for people who are overweight45, although the mechanisms by which weight loss
influences cardio-metabolic outcomes has been unclear. A recent randomized
controlled trial (RCT) examined the effects of moderate weight loss (5-10%) on
cardio-metabolic outcomes46 reporting that moderate weight loss improves metabolic
function in several organs, including improvements in multi-organ insulin sensitivity,
β cell function, and multiple risk factors for cardio-metabolic disease such as
glucose, triglycerides, alanine transaminase, and leptin. A monotonic (‘dose-
response’) relationship between weight loss and key adipose tissue biological
pathways was observed. The results of this RCT lend plausibility to our results that 9% and 16% of CHD events occurring in the ARIC study population over 12 years could have been prevented by a 5% shift in BMI and WC, respectively.

The risk reduction in CHD was larger following a hypothetical 5% WC reduction compared to a hypothetical 5% BMI reduction, which may suggest a stronger metabolic impact of WC modifications and the associated risk of CHD. Other reasons for this difference to be considered are residual confounding if preclinical disease is present, although we adjusted for baseline morbidity/chronic conditions related to weight change, and model misspecification. While correct model specification under the hypothetical reduction in adiposity cannot be demonstrated, the models in the natural course were not substantially misspecified when comparing the natural course to the observed models to predict CHD.

The effect of modest hypothetical shifts in the population distribution of BMI on incidence of CHD was previously examined using data from the Nurse’s Health Study. The authors modeled several hypothetical lifestyle interventions, one of which targeted maintenance of a BMI<25 kg/m². This hypothetical intervention was not predicted to have an effect on the incidence of CHD. The authors further stated that this particular hypothetical intervention on BMI was unrealistic since it would require that an individual at a BMI of 35 kg/m² reduce her BMI to 25 kg/m² in a 2-year time period. Instead, the authors proposed, but did not test, a more realistic intervention to be one that reduces BMI by a small percentage (i.e. 5%).

Although the effects on incidence of CHD following hypothetical modifications of BMI have been examined, other measures of adiposity have not been addressed,
to our knowledge. We therefore examined the effects on incidence of CHD following hypothetical modifications of two measures of adiposity – BMI and WC. BMI is the most frequently used measure of excess adiposity and is highly correlated with accurate yet expensive measures of adiposity such as multi-detector computed axial tomography (MDCT) and dual energy x-ray absorptiometry (DXA). Advantages of using BMI as a measure of adiposity include its ease of use and reliability as an indicator of total body fatness in women and men, its relationship with adiposity-related cardio-metabolic risk, and its association with health outcomes. While BMI is an index of general adiposity, WC is a surrogate index of visceral adiposity and thus more closely associated with cardio-metabolic impairments on the pathway to CHD, including diabetes and hypertension. The hypothetical WC reduction we applied at the 24th percentile of the WC distribution (WC> 88cm) predicted a larger risk reduction compared to a WC threshold at the gender-specific clinical guidelines that recommend a WC<88 cm for women and <102 cm for men. In our study population, the percentile values that correspond to these gender-specific guidelines (<88 cm for women and <102 cm for men) are the 25th and 40th percentile for African American and white women respectively and the 73rd and 70th percentile for African American and white men respectively.

The choice of adiposity measure in the formulation of population interventions and the development of public health messages aimed to reduce the risk of CHD deserve attention. Public health strategies to reduce excess adiposity typically consider the potential benefits and cost of interventions, which may favor a focus on central adiposity if the results presented here stand the test of replication. A focus on
central adiposity also opens opportunities for public health messages that address modification in WC or perhaps clothing size, as more tangible measures than a ratio formulation such as BMI. Although restricted in this case to CHD, the benefits we estimated would follow hypothetical shifts of small magnitude in the population distribution of adiposity suggesting that central adiposity should have a more prominent place in the public health efforts to modify the burden of excess adiposity in U.S. adults.

Population-based programs to achieve sustained effects of modest magnitude but wide penetration are needed to complement clinical efforts that target excess adiposity, and to influence norms and trends that shift adiposity levels in populations\textsuperscript{23,58-61}. Waist girth and central adiposity tap into cultural norms and popular perceptions different from those surrounding BMI and general adiposity\textsuperscript{3,62,63}, as reflected in messages in the media and health product outlets. The work reported here estimated the potential benefit on the risk of incident CHD of hypothetical shifts in the population distribution of WC, comparing to that estimated for an equivalent hypothetical shift in the population distribution of general adiposity, indexed by BMI. Our results suggest that central adiposity, approximated by a simple measure of WC is a population intervention target potentially superior to BMI. These results warrant replication in other population-based longitudinal studies with access to cultural, race/ethnic, and socioeconomic diversity. These results also call for assessments of the relative merit of hypothetical shifts in the distributions of WC and BMI on other health outcomes influenced by adiposity, more closely linked causally and in time lag to adiposity than is the case for CHD.
Several weaknesses of this study should be highlighted. To meet the assumptions built into the analytic model these analyses were limited to the initial three, consecutive re-examination visits of the ARIC cohort. As a result, the length of our follow-up is unlikely to fully capture the long term impact of adiposity at midlife on the risk of CHD during the life epochs when the incidence of CHD is highest. Since the use of WC as a measure of adiposity is reportedly not accurate in individuals with a BMI over 40 kg/m$^2$ we excluded participants at the upper and lower 1% of the baseline population distribution of WC, which was also done for the analysis of BMI. Our estimates are therefore not generalizable to the segment of the population that exceeds this BMI threshold value. Strengths of our study derive from the estimation of the effect of a hypothetical reduction in BMI and of WC on the incidence of CHD in a bi-racial cohort of men and women, to our knowledge for the first time. We applied a hypothetical shift to the population distribution of adiposity at a threshold that was established to be near the clinical guidelines for excess adiposity$^{15}$, which for our population was at the 24th percentile of the baseline distribution of BMI and WC.

This report adds new information to the literature on the effects of hypothetical shifts in general and central adiposity on the incidence of CHD in a middle aged, bi-racial cohort. In the setting of a high population burden of overweight and obesity$^{15,33,34}$ clinical as well public health efforts are needed to curb the epidemic of adiposity and control its societal impact on morbidity, survival, and cost of health care. Declines in mortality and incidence of CHD have been reported over the last decade and ongoing primary prevention of risk factors for CHD would be
required to continue the trajectory of these declines. This report speaks to the important area of modest shifts in the population distribution of adiposity to influence an upstream condition that exerts a profound impact on health and longevity through metabolic dysregulation and its abnormalities. Estimation of the impact that can be achieved from small shifts in the population distribution of general and central adiposity indicated that a meaningful impact can be predicted on the risk of CHD, more so from a shift in central than in general adiposity. The population distribution of adiposity is dynamic, and subject to diverse influences and temporal trends. Desirable shifts in population distributions of adiposity are the focus of public health policies aimed at serving sizes, limits on sugar-sweetened beverages, subsidies for healthier food choices, and increased accessibility for physical activity, among others. Using CHD as a sentinel condition, our results predict a modest effect on the incidence of CHD following small, population-wide shifts in central adiposity, and to a lesser degree in general adiposity. If replicated, these results can inform research into the effects of dynamic population distributions of various measures of adiposity toward public health efforts to reduce the population impact of adiposity.
Table 11. Manuscript 2 Table 1. Characteristics of the study population at baseline by incidence of CHD between 1987 and end of follow-up in 2011. The ARIC Study. (BMI analysis: N=13,610; WC analysis: N=13,301)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Incident CHD Number (%)</th>
<th>Without Incident CHD (n=12,847) Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMI analysis N=763</td>
<td>WC analysis N=712</td>
</tr>
<tr>
<td>Female</td>
<td>254 (33)</td>
<td>230 (32)</td>
</tr>
<tr>
<td>African American</td>
<td>207 (27)</td>
<td>190 (27)</td>
</tr>
<tr>
<td>&lt; HS graduate</td>
<td>230 (30)</td>
<td>211 (30)</td>
</tr>
<tr>
<td>HS graduate or vocational school</td>
<td>291 (38)</td>
<td>270 (38)</td>
</tr>
<tr>
<td>Some college or college graduate</td>
<td>241 (32)</td>
<td>230 (32)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>221 (29)</td>
<td>285 (40)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>213 (28)</td>
<td>242 (34)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>450 (59)</td>
<td>487 (68)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (Interquartile interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMI analysis</td>
</tr>
<tr>
<td>Follow-up time (years)</td>
<td>6.0 (3.0, 8.8)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62 (57,66)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.8 (25.1, 31.0)</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>NA</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>126 (115, 140)</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>104.0 (95, 122.3)</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>221 (195, 248)</td>
</tr>
<tr>
<td>HDL</td>
<td>41.4 (34.7, 51.0)</td>
</tr>
</tbody>
</table>

High school: HS. Diabetes was defined as a fasting plasma glucose (FPG) ≥126 mg/dL or self-report physician diagnosis of diabetes. We defined hypertension as a blood pressure>140/90 mmHg or use of anti-hypertension medication within 2 weeks. Systolic blood pressure: SBP. Total cholesterol: TC. High density lipoprotein (HDL).

*N=762  bN=758, cN=757  *N=12,842, **N=12,757  ***N=12,756
Figure 3. Manuscript 2 Figure 1. Cumulative 12-year incidence of CHD comparing the natural course to the observed
Figure 4. Manuscript 2 Figure 2. Cumulative 12-year incidence of CHD comparing the natural course to a hypothetical 5% shift in the population distribution of BMI.
Figure 5. Manuscript 2 Figure 3. Cumulative 12-year incidence of CHD comparing the natural course to a hypothetical 5% shift in the population distribution of WC.
Figure 6. Manuscript 2 Figure 4. Median BMI (kg/m²) across increasing years of follow-up in the natural course and following the hypothetical 5% BMI reduction
Figure 7. Median waist circumference (WC) across increasing years of follow-up in the natural course and following the hypothetical 5% WC reduction.
Table 12. Manuscript 2 Table 2. Cumulative 12-year incidence and risk difference (95% confidence interval) of CHD for the natural course cohort compared to the cohort subjected to a hypothetical 5% shift in the population distribution of adiposity

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Estimand</th>
<th>Estimate (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural Course for BMI</td>
<td>Incidence</td>
<td>6.34</td>
<td>5.90, 6.78</td>
</tr>
<tr>
<td>Hypothetical 5% BMI reduction</td>
<td>Incidence</td>
<td>5.78</td>
<td>5.22, 6.35</td>
</tr>
<tr>
<td>Natural course vs. hypothetical reduction</td>
<td>Risk difference</td>
<td>-0.56</td>
<td>-0.96, -0.14</td>
</tr>
<tr>
<td>Natural course for WC</td>
<td>Incidence</td>
<td>6.21</td>
<td>5.75, 6.67</td>
</tr>
<tr>
<td>Hypothetical 5% reduction in WC if WC&gt;88 cm</td>
<td>Incidence</td>
<td>5.24</td>
<td>4.60, 5.88</td>
</tr>
<tr>
<td>Natural course vs. hypothetical WC reduction</td>
<td>Risk difference</td>
<td>-0.96</td>
<td>-1.44, -0.48</td>
</tr>
</tbody>
</table>

*aBaseline covariates include in the models were age, sex, race, and education

Time-varying covariates included in the models were years at risk for CHD, diabetes, hypertension, smoking, and the measure of adiposity specific to each analysis of a hypothetical 5% reduction in general (BMI) or central (WC) adiposity.

bConfidence Interval (CI)
REFERENCES


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cardiovascular disease: collaborative analysis of 58 prospective studies. 


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CHAPTER 10: CONCLUSIONS

10.1 Dissertation goal

The overall goal of this doctoral research was to contribute to the understanding of the potential impact of moderate population-level changes in adiposity on specified cardiovascular diseases (CVD). Although the overall goal remained the same throughout this dissertation process, we sharpened the scope of the specific aims while meeting the overall dissertation goals within a reasonable time frame.

10.2 Discussion of results

We predicted a small but non-statistically significant reduction in the cumulative 12-year incidence of PAD [risk difference (RD): -0.17%, 95% confidence interval (CI): -0.38, 0.13] following a 5% population-wide reduction in BMI down to a BMI of 24 kg/m\(^2\) in adults younger than 65 years of age (MS#1). The small magnitude of this estimated reduction in the risk of PAD attributed to a shift in the population distribution of BMI likely reflects the larger effects of PAD risk factors that are not influenced by BMI, such as cigarette smoking and age. Although impaired glucose metabolism and elevated blood pressure/hypertension may lie in part on the causal path between BMI and PAD, the effects of a 5% reduction in BMI are considered to be quite small in magnitude in this population-based cohort of men and women who were middle-aged at study enrollment.
For MS#2, we estimated a -0.56% (95% CI: -0.96, -0.14%) reduction in the 12-year cumulative incidence of CHD following a 5% shift in BMI down to a BMI of 24 kg/m² in adults younger than 65 years of age with a BMI greater than 24 kg/m². We also estimated a -0.96% (95% CI: -1.44, 0.48%) reduction in 12-year cumulative incidence of CHD following a 5% reduction in WC down to a WC of 88 cm in adults under 65 years of age. We estimated that 9% and 16% of CHD events occurring in this study population over 12 years could have been prevented by a 5% shift in BMI and WC, respectively.

The risk reduction in CHD was larger following a hypothetical 5% WC reduction compared to a hypothetical 5% BMI reduction, which may suggest a stronger metabolic impact of WC modifications on the associated risk of CHD. Other reasons for this difference to be considered are residual confounding if preclinical disease is present¹, although we adjusted for baseline morbidity/chronic conditions related to weight change, and model misspecification. While correct model specification under the hypothetical reduction in adiposity cannot be demonstrated², we saw no indications of model misspecification in reference to the natural course models.

### 10.3 Strengths and weaknesses

Several weaknesses of this study should be highlighted. To meet the assumptions built into the analytic model these analyses were limited to the initial three, consecutive re-examination visits of the ARIC cohort. As a result, the length of our follow-up is unlikely to fully capture the long term impact of adiposity at midlife on the risk of PAD and CHD during the life epochs when the incidence of PAD and CHD is highest. Since the use of WC as a measure of adiposity is reportedly not
accurate in individuals with a BMI over 40 kg/m$^2$ we excluded participants at the upper and lower 1% of the baseline population distribution of WC, which was also done for the analysis of BMI. Our estimates are therefore not generalizable to the segment of the population that exceeds this BMI threshold value.

Adiposity is a complex trait, influenced by factors ranging from behaviors to social norms, education, ethnicity, economic factors and food marketing practices, and reductions in adiposity may be achieved through various means. While targeted interventions at the population level can be desirable and feasible, such as the reduction of salt content in processed foods, single interventions on complex traits such as adiposity are likely to be less relevant for population-based policy. Further, different methods to change adiposity in populations may influence the risk of PAD and CHD through mechanisms that do not involve adiposity, even if they were to achieve the same value of BMI or WC. Single interventions involving adiposity reduction are thus sensitive to the treatment version irrelevance assumption, which states that the method by which adiposity reduction occurs should not affect the outcome\textsuperscript{4}, that is, whether the reduction occurs due to dietary, exercise, or other lifestyle changes should not affect our results. In our data, this effect is identified through natural reductions (or increases) in BMI and WC, so our hypothetical intervention approximates what would occur if individuals were motivated to reduce adiposity through their own means, or structural or contextual changes occurred that affected the energy balance throughout the population.

Strengths of our study derive from the estimation of the effect of a hypothetical reduction in adiposity on the incidence of PAD and CHD in a bi-racial
cohort of men and women, to our knowledge for the first time. We applied a hypothetical shift to the population distribution of adiposity at a threshold that was established to be near the clinical guidelines for excess adiposity, which for our population was at the 24th percentile of the baseline distribution of BMI and WC.

10.4 Dissertation process

In approaching the aims of this dissertation, we overcame challenges mostly related to the methodologic complexity and computational requirements of using the parametric g-formula. In approaching the methods for Aims 2 and 3, we learned that traditional regression methods would not allow for inclusion of time-varying confounders such as diabetes and hypertension in the estimation of these associations. Furthermore, diabetes and hypertension are time-varying covariates that are posited to lie on the causal pathway between BMI and the two specified CVD – PAD and CHD, and are in turn affected by previous BMI. To overcome the limitations of standard analytic methods and to allow for application of our hypothetical adiposity reduction at multiple time points, we chose to use the parametric g-formula, an approach that combines parametric regression modeling to obtain conditional probabilities and Monte Carlo sampling to approximate standardization and to estimate measures of effect. Although the parametric g-formula has been implemented to examine the effects of hypothetical shifts in the population distribution of various risk factors on conditions such as CHD, diabetes, cancer, HIV, and asthma, such an approach has not been applied to our knowledge for adiposity and PAD. Furthermore, this approach has not been conducted in a bi-racial cohort nor has it been conducted using measures of adiposity other than BMI.
To implement the parametric g-formula, we collaborated with faculty (Drs. Cole and Westreich), a post-doctoral fellow (Alex Keil) and a student (Catherine Lesko) at the University of North Carolina (UNC) who focus on epidemiologic methods. No uniform way to run these estimations was available so the UNC Odum institute and others at UNC who focus on epidemiologic methods helped to write an efficient statistical program in SAS to run these analyses. The UNC Information Technology Services department created a state of the art virtual desktop environment with the computation requirements needed to run our analyses.

10.5 Future directions

Replication of these results in other populations is a desirable next step to assure the generalizability of the results emerging from this research. Analyses stratified by race also are warranted as the frequency of occurrence of PAD and CHD, like that of other cardiovascular diseases, is higher among African Americans\(^{11}\), whose cardiovascular risk profiles and burden of adverse health outcomes are higher than those of other race groups. There also is need for characterization of the effect of reducing mid-life adiposity on PAD and CHD with an extended follow-up time, and to older ages when PAD and CHD risk is highest. This work also warrants application to other cohorts with diversity to enrich the information base, especially in multi-ethnic cohorts where the distribution of adiposity may be different than what is observed in the ARIC cohort. Declines in mortality and incidence of CHD have been reported over the last two decades\(^ {12}\) and ongoing primary prevention of risk factors for CVD likely are required to continue the trajectory of these declines\(^ {13}\).
If replicated, these results can inform research into the effects of dynamic population distributions of various measures of adiposity toward public health efforts to reduce the population impact of adiposity.
REFERENCES


APPENDIX

Proposed Specific Aims

Aim 1. Quantify the change in three specified cardio-metabolic factors associated with decrements in adiposity, of the kind achieved with lifestyle behavior modification programs, in the range of the temporal trends documented for young and middle-aged adults in the U.S. **Hypothesis:** Effects of reduction in adiposity (BMI) on SBP, FPG and fasting LDL-C estimated in a meta-analysis of weight reduction interventions will be linear, without evidence of a threshold. **Methods:** Effect measures from changes in adiposity metrics on three cardio-metabolic risk factors will be quantified individually and simultaneously from a meta-analysis of diet, physical activity and surgical weight loss interventions.

Aim 2. Estimate the individual and joint impact of decrements in adiposity on three cardio-metabolic risk factors and apply these estimates to population-based samples of African Americans and whites from the ARIC cohort. **Hypothesis:** (a) The effect of a reduction in adiposity on SBP, FPG and fasting LDL-C in a prospective, bi-racial observational cohort will be best fit as linear, without evidence of a threshold over the range of the adiposity distributions. (b) Pre-specified reductions of small magnitude in adiposity informed by the literature will shift the cardio-metabolic profile of the population in an additive fashion, as predicted from the literature on weight reduction interventions and the empirical estimates from these cohorts. **Methods:** Empirical effect measures of change in adiposity on three cardio-metabolic factors will be estimated from longitudinal data on African Americans and whites in the ARIC cohort and calibrated against the summary estimates from the meta-analysis of lifestyle modification programs. Multivariate regression modeling will be employed to
examine individual and joint impacts of changes in BMI on the three cardio-
metabolic risk factors. **Aim 3. Estimate the change in longevity, disability and the incidence of diabetes and coronary heart disease (CHD) predicted from small changes in the population distribution of adiposity, in a sample of African Americans and whites.**  

**Hypothesis:** Small reductions in adiposity will be associated with detectable (beneficial) differences in years of life lost (YLL), years lived with disability (YLD), risk of diabetes, fatal and non-fatal CHD, and cerebrovascular disease predicted from the ARIC cohort data.  

**Methods:** Population burden will be estimated as YLL, YLD, and its composite measure of disability adjusted life years (DALYs). Incidence rate differences and 95% confidence intervals (1) will be estimated for diabetes and CHD. The population burden of disability, morbidity and premature death will be estimated directly for BMI and for the cardio-metabolic risk factors based on the change in cardio-metabolic factor predicted from the pre-specified change in adiposity metrics.

The estimation of the health impact of small changes in adiposity shown to be feasible through lifestyle behavior modification in population-based cohorts of African Americans and whites will provide a sound empirical base for the planning of population intervention strategies directly relevant to the primary and secondary prevention of the conditions that most severely impact the burden of disease in U.S. adults.