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Examining The Interplay Of Diet Composition, Cardiometabolic Diseases, And Economics

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EXAMINING THE INTERPLAY OF DIET COMPOSITION, CARDIOMETABOLIC DISEASES, AND ECONOMICS

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ABSTRACT

Despite the invaluable contributions that both randomized controlled trials and longitudinal studies have made to our understanding of the relationships between diet and cardiovascular disease (CVD), a comprehensive understanding of these relationships does not yet exist from birth to death. Furthermore, the longest running of these longitudinal studies have not included a representative portion of racial minority participants. Lastly, given the financial impacts of CVD, as well as how socioeconomic status (SES) can influence diet, the interplay between these three merits consideration. Therefore, the objective of this dissertation was to evaluate the associations between diet and cardiovascular disease (CVD): 1) in diverse populations 2) over stages of the life course 3) reflexive of the etiology of CVD 4) using various methods of defining diet 5) while examining how socioeconomic status may impact diet selection, and 6) considering how diet-mediated CVD may impact healthcare costs. In the first paper we observed positive associations between added sugars in the diets of children aged 7-12 y and diastolic blood pressure and triglycerides. In the second paper, adherence to the USDA Dietary Guidelines was associated with lower risk of atherosclerosis in a middle aged population as assessed by Carotid Artery Intima-Media thickness (CIMT) and Coronary Artery Calcification (CAC) at a time point 20 years into the study; however, this finding was not statistically robust. Finally, adherence to dietary patterns (previously shown to be associated with incident CVD) was shown to be associated with socioeconomic status

and race in an older population (45+ y). These studies contribute to the broader work of nutrition sciences, as well as our corporate understanding of the manifold ways in which diet is interwoven with such themes as policy, sociology, economics, and medicine.

Keywords: cardiovascular disease, diet, economics, socioeconomic status, life course, etiology

DEDICATION

"Gratitude is not only the greatest of virtues, but the parent of all the others"

- Cicero

The completion of this dissertation, and the almost 5 years of work that it represents, would not have been possible without the invaluable support and guidance of a host of faculty, staff, classmates, friends, and family. To those of you who have helped me along this journey, I offer you my most sincere and profound thanks. At the risk of leaving anyone out, I have chosen not to list any names, but if you have had a positive impact throughout this Ph.D. process, you will certainly know it already, as I believe in expressing gratitude where it is due.

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CHAPTER 3: ADDED SUGARS IN THE DIET ARE POSITIVELY ASSOCIATED WITH DIASTOLIC BLOOD PRESSURE AND TRIGLYCERIDES IN CHILDREN

LIST OF ABBREVIATIONS

BP	Blood Pressure
BL	Blood Lipids
CAC	Coronary Artery Calcification
CI	Confidence Interval
CIMT	Carotid Intima-Media Thickness
CNPP	Center for Nutrition Policy and Promotion
CVD	Cardiovascular Disease
DGA	Dietary Guidelines for Americans
HDL-C	High-density Lipoprotein Cholesterol
HEI	Healthy Eating Index
LDL-C	Low-density Lipoprotein Cholesterol
MI	Myocardial Infarction
OR	Odds Ratio
RDA	Recommended Dietary Allowances
SES	Socioeconomic Status
TG	Triglycerides
USDA	United States Dietary Agency
WHO	World Health Organization

EXAMINING THE INTERPLAY OF DIET COMPOSITION, CARDIOMETABOLIC DISEASES, AND ECONOMICS

CHAPTER 1: INTRODUCTION

Cardiovascular disease (CVD) is the number one cause of death in the United States and contributes to 1 out of every 6 healthcare dollars spent. CVD can take decades to develop into a life-threatening event such as myocardial infarction (MI) or stroke, from risk factors such as hypertension and dyslipidemia. Research has shown that risk factors for adult CVD are present in children. Therefore, to understand CVD and identify ways to forestall its progression, it is necessary to take a lifespan perspective.

Despite the invaluable contributions that longitudinal studies have made to our understanding of the risk factors for CVD, a study from childhood to death does not yet exist. Furthermore, given the diverse racial/ethnic makeup of the US, translating findings from many of the longest-running studies is problematic, as they are comprised of a singularly or overwhelmingly non-Hispanic white population.

Limitations aside, these and other findings have demonstrated a role for diet in the primary prevention of CVD. Diet, however, is a complex subject and can be defined in multiple ways, each having its own methodological and interpretive strengths and weaknesses. In population studies, diet is typically defined as either an individual food/component, a score on a predetermined index, or as a statistically derived dietary pattern (i.e. grouping of foods).

In addition to the complexities of diet definition, diet selection does not occur in a vacuum, and it is important to consider factors such as socioeconomic status (SES) that may impact one's diet. In the words of Dr. Harvey Cushing, "A physician is obligated to

consider more than a diseased organ, more than even the whole man—he must view the man in his world." Furthermore, if diet can reduce the incidence of CVD, this will have substantial economic implications for both individuals and society at large.

Thus, the objective of this dissertation was to evaluate the associations between diet and CVD: 1) in diverse populations 2) over stages of the life course 3) reflexive of the etiology of CVD 4) using various methods of defining diet 5) while examining how socioeconomic status may impact diet selection, and 6) considering how diet-mediated CVD may impact healthcare costs. The relationships under consideration are graphically represented in Figure 1 below.

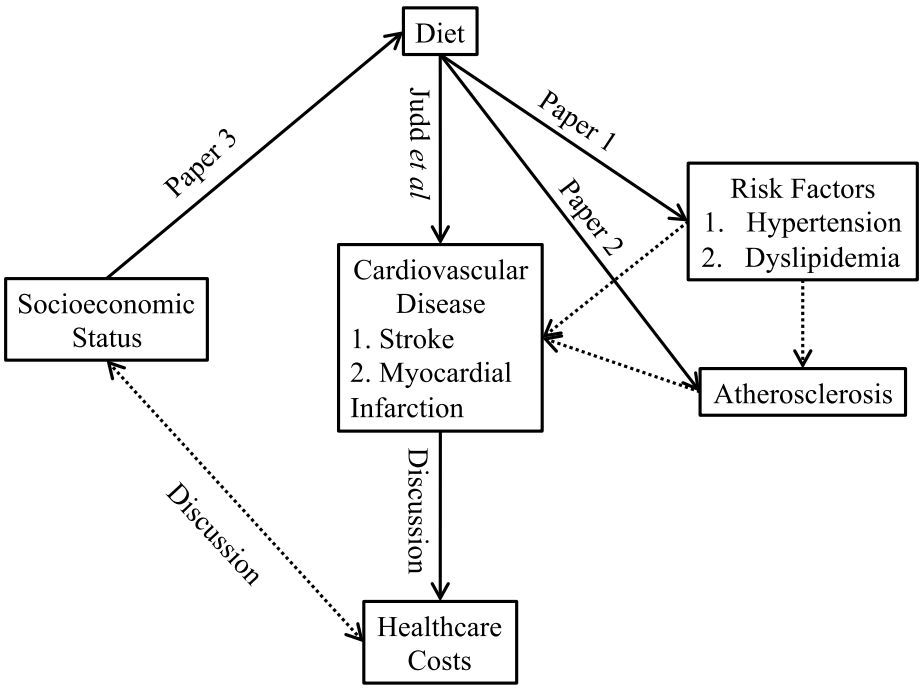

Figure 1. Theoretical framework of the interplay between diet, CVD, and economics

A graphical representation, in timeline form, of the lifespan approach used, as well as the different components of CVD etiology, diet definitions, datasets used, and papers wherein the analyses were performed and described is given in Figure 2 below.

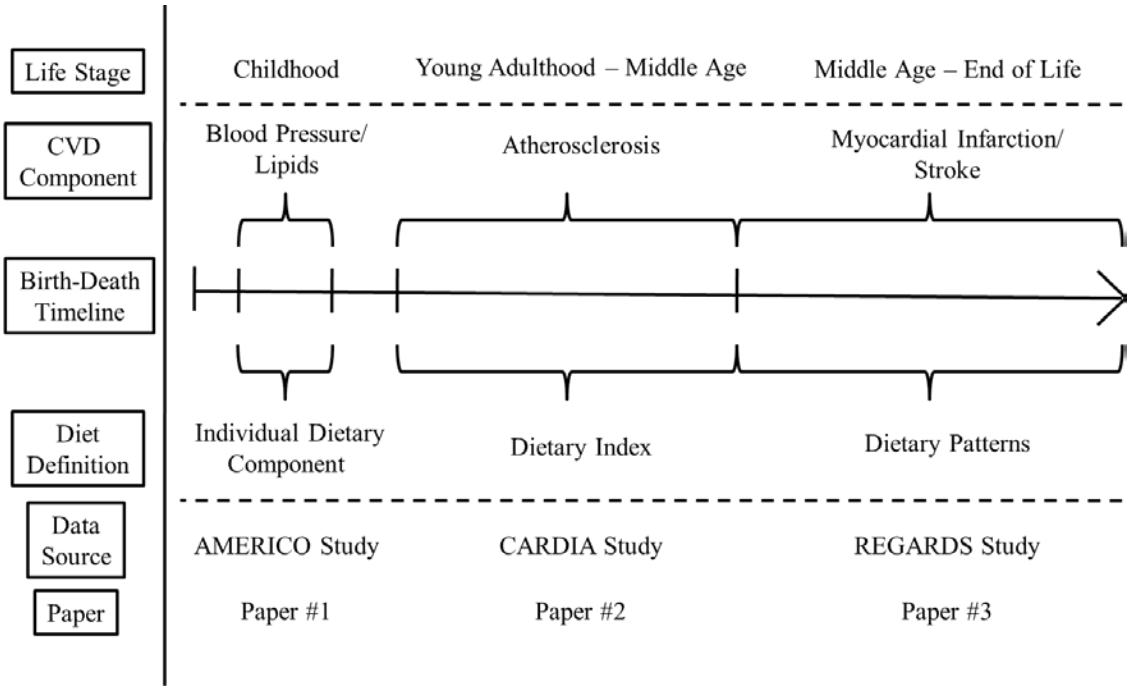

Figure 2. Lifespan perspective of the included research examining diet, CVD, and economics

Specifically, the core components of this dissertation, exploring the relationships outlined by Figures 1 and 2, are the following:

Specific Aim #1 - Chapter 3 (Paper #1): Added Sugars in the Diet are Positively Associated with Diastolic Blood Pressure and Triglycerides in Children

As CVD risk factors, and even atherosclerotic lesions, can develop as early as childhood, it is critical to examine how diet is associated with CVD risk factors. Among the most well established risk factors for CVD are hypertension and dyslipidemia. In this paper we examine the relationships between blood pressure/blood lipids and added

sugars, a dietary component that has previously been shown to be associated with hypertension and dyslipidemia in adults and adolescents. We found positive associations between added sugars in the diets of children and diastolic blood pressure, as well as plasma triglyceride levels.

Specific Aim #2 - Chapter 4 (Paper #2): Change in Adherence to USDA Guidelines (HEI) and Association with Indicators of Atherosclerosis in Adults

Venturing a little further into the lifespan, and the etiology of CVD, we examined the associations between atherosclerosis, as assessed at year 20 via coronary artery calcification (CAC) and carotid artery intima-media thickness (CIMT), and diet, as assessed via adherence to the USDA Dietary Guidelines for Americans (DGA) at baseline and year 20 (Y20). The Healthy Eating Index (HEI), developed by the USDA's Center for Nutrition Policy and Promotion, was used to evaluate the association between one's development of atherosclerosis and one's adherence to federally sanctioned dietary advice. Since the baseline dietary data preceded both the introduction of the Food Guide Pyramid, and the Nutrition Labeling and Education Act, and since Y20 HEI scores were significantly higher on average, comparing baseline to Y20 HEI score yielded a snapshot into how these campaigns may have influenced diet-mediated CAC and CIMT in this population. From our analyses we found that higher HEI scores at Y20, controlling for baseline HEI, were associated with smaller CIMT and lower odds of exhibiting CAC. These associations were not robust to the addition of CVD-related covariates. Furthermore, when assessing change in HEI score from baseline to Y20 (i.e. Y20 minus baseline), no significant associations were found with either CIMT or CAC.

Specific Aim #3 - Chapter 5a (Paper #3): Associations Between Socioeconomic Status and Dietary Patterns in US Black and White Adults

The third and final population studied included adults who were, on average, 64.7 years old. Dietary patterns were previously derived via principal components analysis in this population (REGARDS study cohort), and were shown to be associated with risk of incident stroke and MI. Given their relationships with CVD endpoints, we thought it especially pertinent to study how adherence to these dietary patterns may be impacted by individuals' socioeconomic status and race. In short, we found adherence to many of these dietary patterns to be related to one's income, education, and community SES, with some of these relationships differing significantly by race.

Specific Aim #4 - Chapter 5b: Additional thoughts and implications on healthcare costs

As previously shown in the REGARDS population, diet represents a potential opportunity to reduce the risk of developing CVD, and thereby related healthcare expenditures. This is especially true of the southern dietary pattern, since it has consistently been shown to be associated with incident stroke and MI. Taking this relationship into account, we calculated the potential healthcare cost differences related to differences in participants' adherence to the southern dietary pattern (high vs. low adherence). We found during the 5 years of follow up analyzed, on average, those participants with high adherence to the southern dietary pattern incurred $123.25 more CVD-related healthcare costs per person year, totaling over $6.5M in extra costs in this population and study period.

EXAMINING THE INTERPLAY OF DIET COMPOSITION, CARDIOMETABOLIC DISEASES, AND ECONOMICS

CHAPTER 2: LITERATURE REVIEW

Cardiovascular Disease (CVD): History, Prevalence, and Impact

History

Cardiovascular disease has been categorized as one of the major "diseases of civilization", or "diseases of affluence"[1]. Civilization, however, does not necessarily indicate modernity, since evidence of cardiovascular disease (atherosclerosis) has been noted as early as 3,500 years ago amongst the highest echelon of Egyptian society[2], and Hippocrates recognized stroke symptoms 2,400 years ago in ancient Greece[3]. Conversely, in first world countries in the current era, higher rates of CVD are seen amongst lower socioeconomic groups[4], indicating that affluence may not necessarily refer to the individual, but rather one's entire society.

In the intervening centuries between the Pharaohs, ancient Greeks, and ourselves, very little was understood about CVD. It was not until Leonardo da Vinci that the coronary arteries were studied systematically, and it took roughly four more centuries (1912) before a progressive narrowing of these same arteries was attributed to angina and "heart attack"[2]. In the mid-1600's it was discovered that people who died from stroke (then called "apoplexy") exhibited internal bleeding in the brain; however, strokes were not formally classified based upon their related vascular complications until 1928[3].

Looking further into the 20th century, the field of CVD epidemiology came upon the scene with the Minnesota Business Men Study[5], closely followed by the Framingham Study in 1948[6]. In 1949 "arteriosclerosis" was added as a disease classification, in 1950

HDL and LDL cholesterol were identified, and shortly thereafter shown to be associated with atherosclerosis. Additionally in the 1950s, Ancel Keys postulated that CVD was associated with dietary practices, echoing the initial findings of the Framingham study which indicated a relationship between diet and CVD[2].

Prevalence

CVD is the number one cause of death in the United States and worldwide[7]. This is not a recent ranking; however, as this condition has been the leading cause of death among Americans every year since 1918, shortly after World War I[8, 9]. CVD prevalence was at its height in the 1960's, with declines seen in the following decades[10], but unfortunately such declines have stalled in recent years[11]. In fact, it is anticipated that CVD prevalence will rise over the coming years, with 40.5% of Americans expected to have at least one manifestation of CVD by 2030[12]. As can be seen in the graph below, CVD prevalence is higher among older Americans, thus the increasing overall age of the population will almost certainly contribute to this escalation in rates of CVD[13].

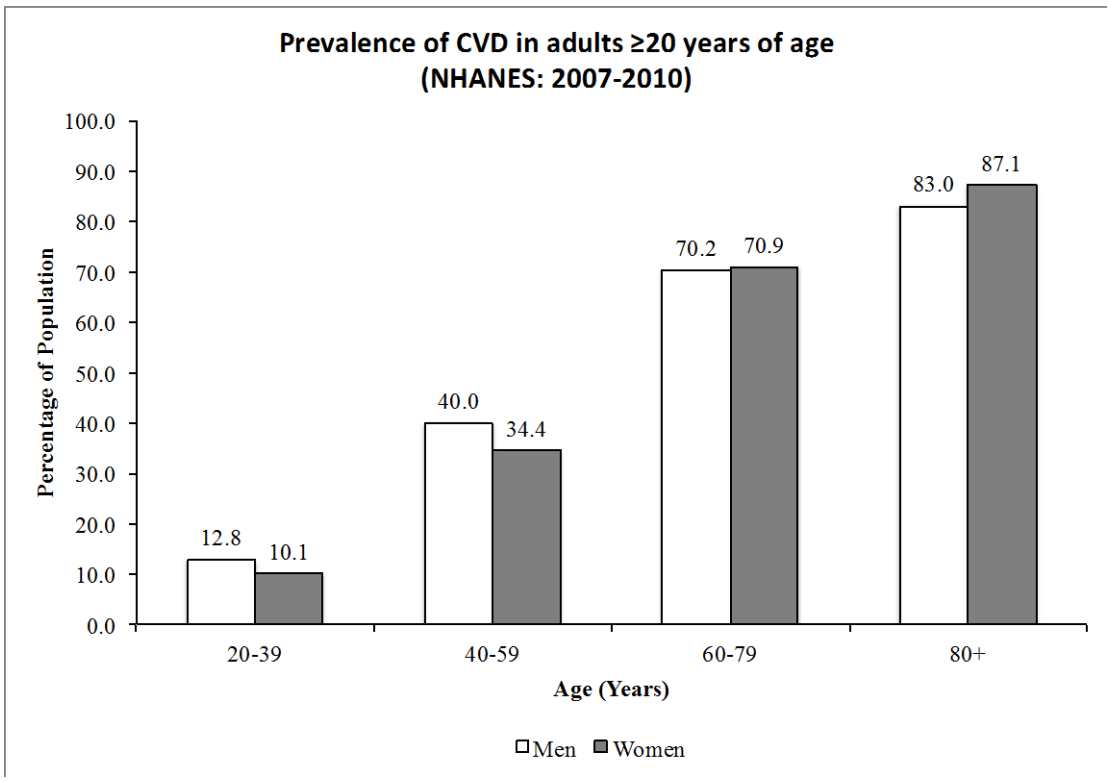

Figure 1. Source: NCHS and NHLBI. These data include CHD, HF, stroke, and hypertension[14]

Impact

Not only is CVD the nation's greatest mortality threat, it also contributes to large amounts of morbidity, diminished quality of life, lost productivity, and considerable healthcare costs[15, 16]. CVD contributes to 1 out of every 6 healthcare dollars, and in 2010 alone, cost the US over $444 billion total on CVD-related expenditures[9, 12, 17]. According to the American Heart Association, these costs are expected to surge to $818 billion in 2030 for direct medical costs alone, with an additional $276 billion incurred via lost productivity[12].

CVD: Etiology, Assessment/Risk Factors, and Treatment/Prevention

Etiology

Given the magnitude and impacts of CVD, understanding the etiology of CVD is paramount in order to identify opportunities for effective interventions. Our understanding of CVD has been an iterative process, with many presumptions being overturned as science progresses. As late as the 1950s, physicians believed severe atherosclerosis to be an inevitable result of the aging process, and factors which are now recognized as major risk factors for CVD, e.g. blood pressure and blood lipid levels, were thought to normally rise with age and/or be unmodifiable[18]. Research, however, has repeatedly shown that CVD develops across the lifespan due to these and other risk factors[19, 20].

Although CVD can be due to infections, congenital factors, or other considerations, the majority of CVD, whether coronary, cerebrovascular, or peripheral, develops over many decades due to a progressive narrowing of the arteries, i.e. atherosclerosis[21, 22]. Beginning as early as childhood, healthy vascular tissue, the endothelium in particular, is typically damaged through factors such as sustained hypertension, dyslipidemia, elevated blood glucose levels, and/or inflammation[23, 24]. As endothelial dysfunction progresses, intimal lesions form in the vasculature, thus allowing LDL to become lodged in the inner layers of the vascular tissue. (Even without intimal lesions, if LDL and/or VLDL concentrations are high enough, the particles can migrate between endothelial cells without damage to the intima being requisite). The damaged endothelial cells attract macrophages that migrate into the area to help remove the now oxidized LDL[25, 26]. However, they are unable to fully clear the area due to the persistent

onslaught of the initial damaging factors (e.g. hypertension), as well as new particles coming into the site. These macrophages continue to grow, converting into foam cells, releasing immunostimulants and other factors in an attempt to repair the area, eventually dying and releasing their accumulated lipids into this space. More and more LDL comes into the site, as well as vascular smooth muscle cells and connective tissue, now resulting in a fatty streak that is covered by a fibrous cap[27]. Although the vasculature can initially compensate for the gradual increase of the intima-media thickness via arterial remodeling, eventually the growth begins to occlude the lumen of the vasculature. Over time this fatty streak will continue to grow if the initiating and promoting factors are not properly addressed. As the occlusion gets more severe, due to factors not entirely understood, calcium often begins to be deposited in the area[28]. This may be in part to strengthen the weakened vasculature, or may be an artifact of the process itself. Eventually the bulging fatty deposit can either fully occlude the vasculature at its own site, or rupture, causing a thrombus either at the site of the occlusion, or downstream. If this occurs in a coronary artery it can result in a myocardial infarction, but if in a cerebral artery, an ischemic stroke[29].

While CVD events such as MI and stroke are typically observed later in life, as can be seen from the etiology of atherosclerosis and resultant CVD, this is a process that spans many decades. Although the earliest stages are not fully known, fibrous plaque development is thought to begin in the 20s, and fatty streaks have repeatedly been observed in children[30], even those as young as 3 years of age[31, 32].

Assessment of CVD Risk/Progression

A variety of diagnostic tests exist to determine one's risk of developing CVD, as well as the progression into atherosclerosis, and eventually cardiovascular events such as myocardial infarction (MI) and stroke. As discussed in the etiology of CVD, hypertension and dyslipidemia are among the more prominent and well-established risk factors for CVD.

Blood Pressure

In adults, blood pressure should be less than 120/80 mm HG. The top number (systolic) refers to the pressure exerted by the blood outward on the arteries when the heart is beating, i.e. blood is moving away from the heart. The bottom number (diastolic) refers to the same arterial pressure, but when the heart is at rest, i.e. filling with blood between heart beats[33]. The table below from the American Heart Association shows the value ranges for blood pressure ranging from "normal" to "hypertensive crisis".

Blood Pressure Category	**Systolic mm Hg (upper #)**		**Diastolic mm Hg (lower #)**
Normal	less than **120**	and	less than **80**
Prehypertension	**120 – 139**	or	**80 – 89**
High Blood Pressure (Hypertension) Stage 1	**140 – 159**	or	**90 – 99**
High Blood Pressure (Hypertension) Stage 2	**160** or higher	or	**100** or higher
Hypertensive Crisis (Emergency care needed)	Higher than **180**	or	Higher than **110**

Figure 2. Blood pressure categories in adults defined by the American Heart Association[34]

Unfortunately, 33% of American adults experience hypertension, but only 53% of these have their hypertension under control[14]. The prevalence of hypertension among African-Americans, in particular, is much higher than the national average, at 44% [14].

As the earliest stages of CVD have been observed in children, examining blood pressure values in the pediatric population is a critical step toward very early primary prevention. In children and adolescents, however, normative and hypertensive blood pressure values are much more complicated since this population is still growing and changing. NHANES data have been used to establish percentiles for blood pressure values by age, sex, and height percentile, where at least 3 readings have been taken. The 50th percentile is defined as the midpoint of the normal range, with the 90th percentile serving as the threshold for prehypertension, and the 95th percentile for stage 1 hypertension. Stage 2 hypertension begins at the 99th percentile plus 5 mmHG[35, 36]. Among the population between the ages of 3-18, the prevalence of prehypertension and hypertension are 3.4% and 3.6%, respectively[37]. However, among adolescents with BMI percentiles in the obese range, the combined prevalence of these conditions may be as high as 30%[38], approaching the hypertension prevalence of the general adult population[14].

Blood lipids

Blood Lipids and lipoproteins are assessed via a fasted blood test, i.e. lipid panel, that typically reports at least low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (i.e. triacylglycerol), and total cholesterol[39]. LDL-C carries cholesterol from the liver and delivers it to the rest of the body, when and where needed[40]. Since LDL-C has been implicated in the development of

atherosclerotic plaques, it is commonly referred to as “bad” cholesterol. HDL-C, on the other hand, collects excess cholesterol from the body and brings it back to the liver for processing. This function of removing cholesterol from the rest of the body, as well as positive associations between HDL-C and cardiovascular health have led to referring to HDL-C as the “good” cholesterol[41-43]. Triglycerides are the body’s storage form of lipid, and are produced by the liver in response to excess caloric intake, particularly fats and carbohydrates. Excess calories in the form of triglycerides are then sent to adipose or other tissues for storage. Elevated triglyceride levels are often observed alongside obesity and glucose dysregulation[44], both of which can increase one’s risk of CVD. Furthermore, plasma triglyceride levels have been observed to be related to CVD risk independently of HDL-C[45]. Total cholesterol is the summation of all the constituent blood lipids and lipoproteins. While some treatment guideline goals have changed recently (particularly for target LDL cholesterol when being treated with statin drugs), the following ranges for blood lipids and lipoproteins reflect the most current target values for US adults.

Category	Value	Designation
Total Cholesterol		
	< 200 mg/dL	Best
	200-239 mg/dL	Borderline High
	≥ 240 mg/dL	High
LDL-C	<70 mg/dL	Best for people with heart disease
	<100 mg/dL	Best for people at risk for heart disease
	100-129 mg/dL	Near ideal
	130-159 mg/dL	Borderline High
	160-189 mg/dL	High
	≥ 190 mg/dL	Very High
HDL-C	<40 mg/dL	Poor
	50-59 mg/dL	Better
	≥ 60 mg/dL	Best
Triglycerides	<100 mg/dL	Optimal
	< 150 mg/dL	Best
	150-199 mg/dL	Borderline High
	200-499 mg/dL	High
	≥ 500 mg/dL	Very High

Figure 3. Blood Lipid and Lipoprotein Guidelines for US Adults[39]

According to NHANES 2003-2006 data, 53% of US adults have lipid abnormalities, with the largest number of people (30%, i.e. 58.9 million citizens) experiencing fasting plasma triglyceride concentrations of ≥150 mg/dL[46]. Of the adult population, 21% have at least 2 parameters of dyslipidemia (high triglycerides, high LDL-C, and/or low HDL-C), and almost 6% experience 3 parameters of dyslipidemia simultaneously[46].

In the pediatric population, blood lipid evaluation is slightly more nuanced, as triglyceride level recommendations are broken into 2 age groups. Similar to blood pressure guidelines in children and adolescents, the cut points for elevated risk occur at the 95th percentile; however, this value is set, and does not vary due to sex, height, or age (except for triglycerides)[47]. Even within the pediatric population, dyslipidemia rates of

22.9% have been observed. Like their adult counterparts, the type of dyslipidemia most commonly seen is elevated triglycerides (13.2%)[48].

Category	**Acceptable**	**Borderline**	**High**
Total Cholesterol	< 170	170-199	≥200
LDL-C	< 110	110-129	≥130
Triglycerides			
0-9 years	< 75	75-99	≥100
10-19 years	< 90	90-129	≥130
Category	**Acceptable**	**Borderline**	**Low**
HDL-C	> 45	40-45	< 40

Figure 4. Blood Lipid and Lipoprotein Guidelines for US Children and Adolescents[47]

Atherosclerosis

Atherosclerosis, a progressive narrowing of the arteries due to plaque formation that reduces blood flow through the arterial lumen, develops over many years of hypertension, dyslipidemia, and/or other assaults to the vasculature. Although asymptomatic at first, once blockage of the artery reaches a certain threshold, pain, numbness, and/or debility can develop, the location of which depends upon the site of the blockage[29]. Diagnosis of atherosclerosis in the arteries supplying blood to the heart (coronary artery) and brain (carotid artery) utilizes imaging technology.

To assess the degree of atherosclerosis in the coronary artery, computerized tomography (CT) scans can be used to identify and calculate the degree of calcification in the artery. Calcification of the coronary artery is typically indicative of a well-established atherosclerotic plaque, and is predictive of experiencing an MI within a few years[49].

To assess atherosclerosis in the carotid artery, ultrasonography can be used to measure the carotid intima-media thickness, with a higher thickness indicating a greater degree of atherosclerosis[50].

Myocardial Infarction

One end result of atherosclerosis is a myocardial infarction (MI). MIs are typically the result of a thrombus occluding a coronary artery, thus leading to necrosis of the downstream cardiac tissue[51]. Validation that an MI has or is occurring can come through multiple means, such as ECG, blood tests, imaging, autopsy, and/or examination of symptoms[52].

Stroke

Another end result of atherosclerosis is an ischemic stroke. Similarly to an MI, a thrombus blocks the vasculature supplying blood to the brain (such as arteries downstream from the carotid artery), causing hypoxia and/or tissue necrosis. Although almost 90% of strokes are ischemic, some are the result of a ruptured blood vessel, i.e. hemorrhagic stroke, and are typically the result of uncontrolled hypertension[53].

Treatment/Prevention

A number of treatment options have been proposed and used to address CVD. These options vary in their cost, effectiveness, and risk of complications.

Medical Interventions

Surgery

Surgical interventions for CVD serve as a last resort for the treatment of severe atherosclerosis and CVD events. Such treatments oftentimes occur after the onset of symptoms such as angina, and many times are used to mitigate the risk of future events after a patient has already experienced a stroke or MI[54, 55]. Needless to say, surgery does not serve as a modality for primary prevention of atherosclerotic CVD, and comes with a substantive battery of costs and risks for complications. As such, other interventions should be exhausted for both primary and secondary prevention before this option is exercised.

Medication

Attempts to prevent the development and/or progression of CVD have typically included the use of medications aimed at addressing risk factors, (e.g. statins, antihypertensives, antiarrythmics, and antithrombotics[56-64]). These drugs, however, do not come without cost and potential complications. Furthermore, the efficacy of all of these drugs for the primary prevention of CVD has not been conclusively shown. Statins, for example, are strongly recommended for secondary prevention (i.e. prevention of another CVD event), but controversy remains whether they are able to prevent MI/stroke in otherwise low-risk people [65-68].

Lifestyle Interventions

Although some risk factors for CVD cannot be altered, e.g. age, sex, genetics, it has been estimated that up to 90% of CVD event risk may be attributable to modifiable

risk factors in some US populations, with a majority of these being diet-related[69]. On a global perspective, modifiable risk factors for CVD can be attributed to a sizeable percentage of deaths: elevated blood pressure (13%), tobacco use (9%), elevated blood glucose (6%), physical inactivity (6%), and overweight/obesity (5%) [70, 71]. It is inescapably clear that a large portion of the modifiable risk factors for CVD are influenced, at least in part, by one's diet[72]. Our understanding of the extent and manner in which diet influences these risk factors, however, leaves much to be desired.

Diet and CVD: Methods and previous findings

If demonstrated to be effective, evidence-based dietary changes may represent a lower cost alternative that can be implemented early in the etiology of CVD. Thus far, some dietary interventions have demonstrated promise in improving CVD risk factors and outcomes [73-78], and a number of association studies have shown relationships between diet and CVD [79-87]. For example, a recent randomized trial with high-CVD risk adult participants experienced great success using the Mediterranean diet in reducing the rate of major CVD events. As compared with the control diet, multivariable-adjusted hazard ratios were 0.70 (95% CI: 0.54, 0.92) for the group receiving the Mediterranean diet with olive oil, and 0.72 (95% CI: 0.54, 0.96) for the group receiving the Mediterranean diet with nuts [76]. The association between diet and CVD has also been recognized by the American College of Cardiology and American Heart Association in their 2013 guidelines, as they emphasize the use of diet to control blood pressure and lipids[72].

Diet assessment/interpretation

As has been demonstrated in previous work, the diet that one follows can have an impact on the development of CVD risk factors[72]. When examining the relationships between diet and one's health outcomes, the way in which diet is assessed and interpreted can have substantial implications on how results are construed, and to what populations they can be translated. Collecting data on one's diet has typically included instruments such as food frequency questionnaires, diet histories, 24-hour dietary recalls, and food logs[88]. Once the data collected from these instruments have been compiled and analyzed, they typically yield information pertaining to caloric content of the diet, macro/micronutrient composition, and servings of given foods, among others. Once these data points/categories are available, a number of analytical options are possible.

At the population level there are three primary ways of analyzing diet: as a single food or nutrient/component, as a score on a predetermined index, or as a unique dietary pattern of food consumption determined via statistical methods such as principal components analysis. Examples of examining diet as a single food or nutrient/component would be saturated fat or carbohydrates [89]. Dietary indices are developed by investigators *a priori*, and provide a scoring framework whereby one's diet is evaluated to see how closely it aligns with the index under consideration, e.g. Mediterranean diet index, DASH diet index, alternative Healthy Eating Index[90]. A perfect score on these indices indicates that one's typical diet is in optimal alignment with a given diet that is presumed to be healthy. Dietary patterns that are derived *a posteriori* are unique to the population under consideration, since they use statistical methodologies to analyze the dietary data at hand, looking to see where natural patterns, or groupings, of food consumption occur within the

population. Names are generally ascribed to these patterns after their derivation to describe them, based upon the top foods within a category and what these foods indicate (e.g. Plant-based, Convenience, Prudent, and Sweets/Fats)[91, 92].

Strengths and weaknesses

Each of these methods of analyzing diet has its own strengths and weaknesses, and therefore each one offers a different and informative perspective. The strength of analyzing diet as a single food/component is that it allows for the examination of direct relationships between individual diet components and health, although this may be a potentially narrow or reductionist approach. The use of diet indices may be a somewhat rigid or prescribed approach, but such indices are typically informed by scientific literature and can be used to evaluate nutrition policy (e.g. the Healthy Eating Index). Statistically determined dietary patterns can be difficult to translate to study populations other than those used to develop the dietary patterns, but these patterns allow for a more realistic assessment of participants' diets, since patterns of food consumption are allowed to emerge from the data.

Previous studies and opportunities for elucidation

Diversity of ages: A lifespan approach

Our understanding of the associations between diet and cardiovascular health is not seamless. Despite the invaluable contributions that longitudinal studies have made to our understanding of the modifiable risk factors for CVD, a lifespan perspective from childhood to death does not yet exist. One of the longest-running and most prolifically

published upon studies of lifestyle and CVD is the Framingham study [93, 94]. Its objective was "to identify the common factors or characteristics that contribute to CVD by following its development over a long period of time in a large group of participants who had not yet developed overt symptoms of CVD or suffered a heart attack or stroke." Although this remarkable study has been underway for almost 70 years, both the first (1948) and second (1971) waves of participants were enrolled as adults [6].

Taking a lifespan approach to the study of CVD is critical, since we now know that risk factors such as hypertension and dyslipidemia can silently develop quite early in the life course, and may persist for decades before noticeable symptoms develop [19, 20].

Diversity of race: A heterogeneous racial landscape

In addition to the fact that the more prominent and long-running longitudinal studies examining diet and chronic disease do not start from childhood, e.g. Framingham study, Nurses' Health Study, and Health Professionals' Follow-up Study, they were also comprised of a singularly or overwhelmingly non-Hispanic white population [82, 95, 96]. Using findings from these data to inform current and future federal nutrition policy/guidelines is problematic, since non-Hispanic whites are not projected to be the majority of the US population by 2042 [56]. Thus, it is important to use a diverse cohort when seeking to conduct studies that will be translatable to the diverse US population.

[Note: For the sake of simplicity and continuity, the term "race" is used throughout this document. The authors recognize that, from a sociological and anthropological perspective, race may be interpreted as a social construct pertaining to one's self- or other- identified place within a given society and/or culture[97], rather than a

definitive designation of one's objective geographic and/or genetic origin(s)[98]. Given that the focus of this dissertation is on the interplay amongst diet, economics, and cardiovascular disease, it is not the within the purview of this dissertation to fully expound upon the sociological implication(s) of the terms "race", "ethnicity", or other associated designations, nor would the author feel adequately versed in the field to undertake such a task. Additionally, as both the REGARDS and CARDIA grants and associated documentation use the racial designations "black" and "white", for consistency's sake these terms are used throughout this document. It is not the author's intent, in any way, to cause offense or disparage any people group. This same ethos applies to discussions of educational attainment, level of income, age, or any designation, upon the basis of which, persons have been, or continue to be, marginalized or discriminated against.]

Diversity of diet: Multiple interpretations/assessments of diet

Given that each of the methods of interpreting diet has its own unique strengths, as mentioned previously, we have chosen to take a survey approach in this dissertation. Therefore, each of our main papers uses one of each of the main methodologies for diet interpretation.

Diet and CVD: A multi-pronged evaluative approach

To evaluate the potential associations between CVD and diet in a holistic manner, we have chosen to evaluate diet in 3 ways: as a single food component, as a diet index, and as dietary patterns. Furthermore, to mirror the decades-long etiology of CVD, we

assess the associations between diet and CVD risk factors (blood pressure and blood lipids), disease progression (atherosclerosis as quantified by coronary artery calcification and carotid intima-media thickness), and final endpoints of CVD (myocardial infarction and stroke). As neither CVD nor diet selection occur in a vacuum, we also examine how socioeconomic status may impact diet selection, and how diet-mediated CVD may impact healthcare costs. These studies are all performed using data from racially diverse samples. The relationships under consideration, as well as the components and their paper designations, are graphically represented in Figures 1 and 2 below.

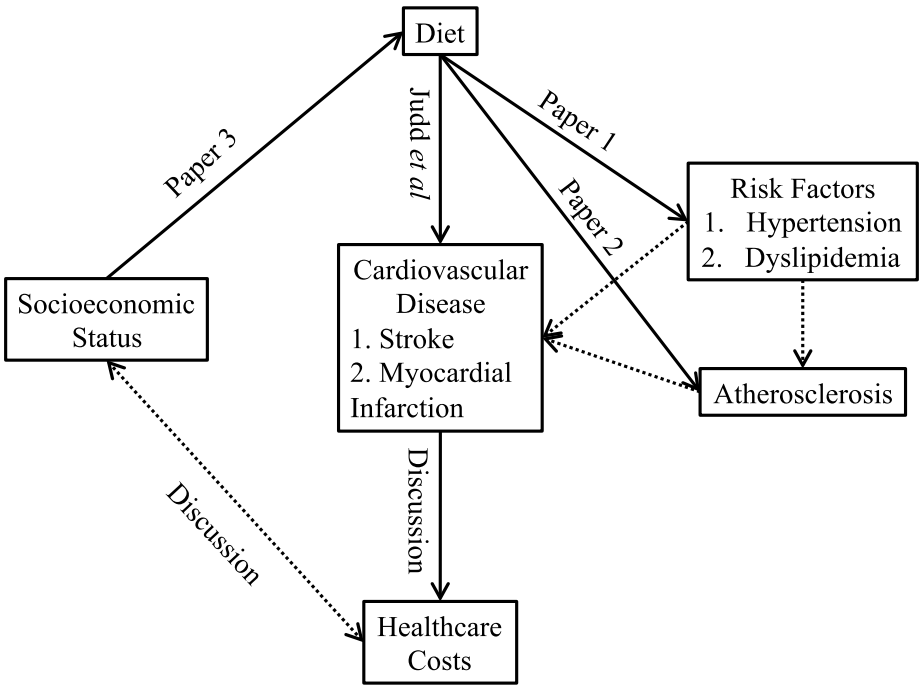

Figure 5. Theoretical framework of the interplay between diet, CVD, and economics

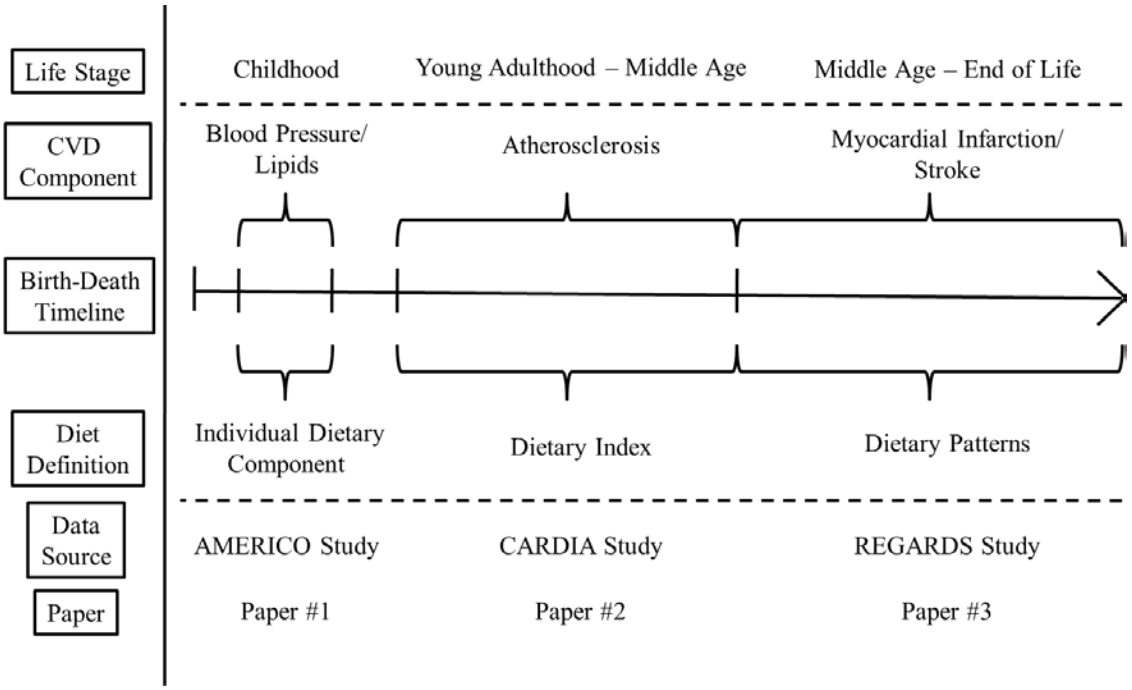

Figure 6. Lifespan perspective of the included research examining diet, CVD, and economics

Diet as a Single Food Component: Sugar as a new dietary risk factor for CVD

History of sugar consumption and recent trends

While humans have been consuming sugars in the form of fruit since time immemorial, added sugars in the form of purified sucrose have been a relatively recent introduction to the diet, especially in the quantities now consumed. This powder was originally extracted from Indian sugarcane over a millennium ago[99], and later from sugar beets, but most Europeans did not have access to this substance until the 1700s [100]. Times have changed dramatically; however, as the average American now consumes over 77 pounds of sugar annually[100], with some estimates putting that figure closer to 100 pounds[101], primarily in the form of sucrose and high fructose corn syrup. Given its

prominent place in the modern diet, interest has been drawn to the subject of added sugars and cardiovascular health.

Sugar and CVD: Previous findings

Although dietary interventions for hypertension and dyslipidemia have traditionally included decreasing one's intake of sodium and dietary fats, respectively [102, 103], more recently, added sugars in the diet, i.e. sugars and syrups added to foods or beverages during preparation or processing, have been associated with these conditions in select age groups [104-110]. In particular, positive associations have been observed between added sugars in sugar sweetened beverages (SSB) and blood pressure in both adults and older adolescents [105, 107, 109]. Furthermore, the reduction of SSB consumption has been associated with lower diastolic and systolic BP in adults [106]. Components of dyslipidemia have also been associated with SSBs and added sugars in the diet in adolescents [104, 110] and with SSB alone in children [108]. However, total added sugars (not just from SSB) have not been examined for their potential association with blood pressure and blood lipids in children.

Since almost 20% of calories in children's diets come from total added sugars [111], the potential associations between this dietary component and blood pressure/blood lipids is worth consideration. Examining added sugars is especially timely given the FDA's move to change the nutrition label to include added sugars[112], and the WHO's updated recommendations to reduce the intake of added sugars to <5% of total daily calories [113].

Overview of study design for Paper 1

In this paper we used data from a multiethnic sample of children, aged 7-12, to examine the associations between added sugars in the diet and blood pressure (diastolic and systolic, separately), as well as blood lipids (LDL-C, HDL-C, Triglycerides, and total cholesterol, separately). Multivariable logistic regression models were performed, with added sugars serving as the independent variable of interest, and either an indicator of blood pressure or blood lipids as the dependent variable of interest. Covariates included sex, race, socioeconomic status, Tanner pubertal status, percent body fat, physical activity, and total energy intake. To explore whether traditional risk factors should also be included as covariates, sodium was run as the independent variable of interest in models with blood pressure, and total dietary fat in the models with blood lipids.

Diet as an Index: Adherence to the USDA dietary guidelines and atherosclerosis

History of the USDA dietary guidelines

The United States Department of Agriculture (USDA) has been offering dietary recommendations for just over a century[114]. These first recommendations preceded the discovery of individual vitamins and minerals, and were a general guide on food group balance, as well as advice on maximizing food dollars. In general, these guides focused on adequacy of food groups, and once recommended dietary allowances (RDAs) were established, micronutrients. It was not until the 1977 Dietary Goals for the United States that the populace was encouraged to limit the excessive consumption of certain foods and food components thought to be associated with chronic diseases such as CVD[114]. Based

upon these "Dietary Goals", the USDA Dietary Guidelines for Americans were introduced in 1980 to provide information to the general population on how to maintain a healthy body weight and reduce the risk of chronic diseases, such as cardiovascular disease (CVD) [115, 116].

USDA Dietary Guideline adherence and CVD: Previous findings

Since the first guidelines were issued; however, CVD has remained the number one cause of death in adults in the United States, bringing into question the effectiveness of the guidelines, not only in garnering the public's adherence to them, but also in terms of improving health.

Adherence

In order to quantify the public's adherence to these guidelines, in the mid 1990's the USDA Center for Nutrition Policy and Promotion (CNPP) developed the Healthy Eating Index (HEI). The original HEI used a framework to which dietary data could be applied in order to calculate one's score from 0-100 [117]. Studies investigating adherence to the guidelines have noted that only about 12% of the population demonstrated "good" adherence (as defined by an HEI score >80) in the early 1990s[118], mid-1990s[119], and that very little improvement was seen in the 2000s[120].

HEI and CVD

Some studies have shown negative associations between HEI score[117, 121] and CVD risk/incidence[122-124]. However, these associations have not been examined in a

diverse population using atherosclerosis as the outcome of interest, especially as assessed by coronary artery calcification (CAC) or carotid intima-media thickness (CIMT)[125]. Furthermore, as these markers typically precede CVD events by at least a few years, examining the associations between these markers and HEI adherence will allow the development of more effective nutrition policy for preventing and/or slowing the progression of CVD, even in later stages of the etiology of CVD [49].

Overview of study design for Paper 2

The objective of this study was to examine the relationship(s) between change in adherence to the USDA Dietary Guidelines for Americans (as assessed by the Healthy Eating Index) and CAC and CIMT in the CARDIA study. Since the HEI-1995 is the HEI version closest to the midpoint of the years of diet assessment in this study (i.e. 1985 and 2005), this version of the HEI was used. HEI scores were calculated for each participant, and then a change variable was created by subtracting 1985 HEI scores from 2005 HEI scores.

Multivariable logistic regressions were used to model the associations between CAC, as well as CIMT (analyzed separately), with 1) HEI score in middle age (2005) controlling for HEI score during young adulthood (1985) and 2) change in HEI score. Clinical and demographic characteristics were included as covariates in sequential models.

Diet as Patterns: Economics of diet selection and associations with CVD events

A posteriori dietary pattern in nutrition research

In contrast to investigator-driven dietary indices, dietary patterns are derived using statistical techniques that allow the dietary data to show where patterns/clusters of food consumption exist. This method of diet assessment/interpretation is a relatively new addition to the nutritional epidemiology landscape, and represents an "alternative and complementary approach to examining the relationship between diet and the risk of chronic diseases"[126]. In the REGARDS study cohort, adherence to dietary patterns has recently been demonstrated to be associated with incident CVD events[92]. Given these associations with CVD, understanding how SES may impact individuals' adherence to such dietary patterns is of substantive interest.

Diet and SES

Differences in the content and quality of individuals' diets have been demonstrated between persons of varying levels of socioeconomic status (SES), and are thought to contribute to the disparities in CVD observed between groups. Studies investigating the associations between diet and SES have analyzed diet as individual nutrients, groupings of nutrients, and dietary indices[127-134]. However, limited research has been conducted on how SES may impact statistically derived dietary patterns, especially in older populations. Examining the association between dietary patterns and SES is particularly informative of the effects of SES on diet choice, since dietary patterns are data driven, and likely to reflect natural groupings of food in the diet according to economics, education, and social standing.

Overview of study design for Paper 3

Using data from the REGARDS study cohort, logistic regression models adjusted for age, sex, race, and geographic region were used to examine adherence to five emergent dietary patterns (convenience, plant-based, sweets/fats, southern, and alcohol/salads) according to 4 levels each of individual education, household income, and community level SES. Further models assessed adherence to these dietary patterns by race, and an overall model including both races examined if the relationships between SES and adherence to these dietary patterns differed among black and white participants.

Summary

The objective of this dissertation was to evaluate the associations between diet and CVD: 1) in diverse populations 2) over stages of the life course 3) reflexive of the etiology of CVD 4) using various methods of defining diet 5) while examining how socioeconomic status may impact diet selection, and 6) considering how diet-mediated CVD may impact healthcare costs. The following chapters outlay in great detail the studies that have been undertaken to evaluate the aforementioned associations. We feel that the studies contained herein contribute to the broader work of nutritional epidemiology, as well as our corporate understanding of the manifold ways in which diet is interwoven with such themes as policy, sociology, economics, and medicine.

CHAPTER 3: ADDED SUGARS IN THE DIET ARE POSITIVELY ASSOCIATED WITH DIASTOLIC BLOOD PRESSURE AND TRIGLYCERIDES IN CHILDREN

by

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Format adapted [and errata corrected] for dissertation

Abstract

Background: Hypertension and dyslipidemia have traditionally been associated with dietary sodium and fat intakes, respectively; however, they have recently been associated with the consumption of added sugars in adults and older adolescents, but there is no clear indication of how early in the lifespan this association manifests.

Objective: This study explored the cross-sectional association between added sugars (sugars not naturally occurring in foods) consumption in children, blood pressure (BP), and fasting blood lipids (BL: triglycerides, total, LDL, and HDL cholesterol).

Design: BP, BL, and dietary intakes were obtained in a multiethnic pediatric sample aged 7-12 of 122 European American (EA), 106 African American (AA), 84 Hispanic American (HA), and 8 mixed race (MR) children participating in the AMERICO study, a cross-sectional study conducted in the Birmingham, AL metro area investigating the impacts of racial/ethnic differences on metabolic and health outcomes. Multiple regression analyses were performed to evaluate the relationships of added sugars and sodium intakes with BP and of added sugars and dietary fat intakes with BL. Models were controlled for sex, race/ethnicity, socioeconomic status, Tanner pubertal status, percent body fat, physical activity, and total energy intake.

Results: Added sugars were positively associated with diastolic BP ($p=0.0462$, beta=0.0206) and serum triglycerides ($p=0.0206$, beta=0.1090). Sodium was not significantly associated with either measure of BP, nor dietary fat with BL. HA had higher triglycerides but lower added sugars consumption than either AA or EA children.

AA participants had higher BP and HDL, but lower triglycerides than either EA or HA children.

Conclusions: These data suggest increased consumption of added sugars may be associated with adverse cardiovascular health parameters in children, specifically elevated diastolic blood pressure and triglycerides. Identification of dietary factors influencing cardiovascular health during childhood could serve as a tool to reduce CVD risk.

Introduction

Cardiovascular disease (CVD) is the number one cause of death in adults in the United States (1), and costs an estimated $445 billion per year (2). Although incidence of CVD primarily occurs in adulthood, CVD precursors such as atherosclerotic lesions have been shown to begin as early as childhood (3). Among the major risk factors for CVD are hypertension and dyslipidemia (4), both of which have become prevalent in children in the US (5, 6). Hypertension during childhood is correlated with hypertension in adulthood (7), and elevated blood pressure in children and young adults further exacerbates the development of atherosclerotic plaques (8). Likewise, dyslipidemia during childhood is associated with dyslipidemia in adulthood and increased risk of CVD (9-11).

Due to the early nature of the development of CVD, it is imperative to identify effective lifestyle interventions for the prevention and treatment of hypertension and dyslipidemia.

Dietary interventions for blood pressure reduction have traditionally included the decreased intake of sodium, and interventions for dyslipidemia have included the decreased intake of dietary fats, with emphasis on cholesterol, saturated fat and trans fat (12, 13). More recently, however, added sugars in the diet, i.e. sugars not naturally occurring in foods, have been associated with these conditions. The main sources of added sugars in the diets of US children and adolescents are sugar-sweetened beverages (SSB), grain desserts, dairy desserts, cold cereal and candy (14). Studies have shown positive associations between SSB and blood pressure in both adults and older adolescents (15-17), furthermore, the reduction of SSB consumption has been associated with lower diastolic and systolic blood pressure in adults (18). Components of dyslipidemia have also been associated with SSB and added sugars in the diet in adolescents (19, 20), and with SSB alone in children (21).

Although the relationships between some added sugars, hypertension, and dyslipidemia have been explored in various age groups, it is not clear if, when examining added sugars from all sources, these relationships are present in children. Therefore, we investigated the relationship between added sugars, blood pressure (BP: diastolic and systolic), and blood lipids (BL: total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol) in children between the ages of 7-12, while controlling for potentially confounding lifestyle and societal factors. We hypothesized that the consumption of added sugars in children would be positively associated with blood pressure, total cholesterol and triglycerides.

Methods

Population and Data Collection.

Data were collected from October 2004 to December 2008 as part of the AMERICO study, a cross-sectional study investigating the impacts of racial/ethnic differences on metabolic and health outcomes (see Figure 1). The final sample included 320 children aged 7-12 years old, self-identified as European American (EA; n=122), African American (AA; n=106), Hispanic American (HA; n=84) and mixed race/ethnicity (MR; n=8). The children who were peripubertal (pubertal stage ≤3 as assessed by a pediatrician according to the criteria of Marshall and Tanner (22, 23), and were not taking any medications contraindicated for study participation (i.e. medication known to affect body composition, metabolism, or cardiac function) were eligible for participation in the study. Participants were recruited from the Birmingham, AL area via newspaper advertisements, community fliers and presentations at schools, churches, and health fairs. 601 children were telephone screened, 131 either self-selected out or were excluded because they did not meet the study criteria. From this stage, 470 participants came in for the study visit, but only 320 fulfilled the study criteria and completed the study. The study was approved by the University of Alabama at Birmingham (UAB) Institutional Review Board for Human Use (children and parents provided informed assent and consent, respectively, prior to participation).

Data collection occurred across two study visits, the first was outpatient and the second took place at the UAB General Clinical Research Center (GCRC). Dual-energy X-ray

absorptiometry scans and the assessment of pubertal status were conducted at the first visit and children were given an accelerometer to wear to measure physical activity (collected at second visit). The second visit occurred approximately 7 days later and included an overnight stay at the UAB GCRC, with all participants receiving the same meal and snacks, and only receiving water post 2000h until after the morning blood and blood pressure tests. 24-hour dietary recalls were conducted during both visits.

Detailed variable information below parallels the order found in Table 1 (descriptive statistics**).**

Socioeconomic Status. SES was calculated via the Hollingshead four factor index of social status (24), which includes educational level, occupational prestige, marital status, and sex. Educational level is on a 7-point scale (1= less than 7^{th} grade completed, 7= graduate degree) and is weighted by a factor of 3; occupational prestige is on a 9-point scale (1= “farm laborers/menial service workers”, 9= “Higher executives, proprietors of large businesses, and major professionals”) and is weighted by a factor of 5. Overall scores range from 8 to 66 and were determined for the participant’s working parent(s), with higher scores indicating higher SES.

Pubertal Status. Pubertal status was determined via physician assessment using the Marshall and Tanner pubertal status evaluation criteria (22, 23). The 5 stages of pubertal status are based upon pubic hair development in both sexes, breast development in females, and genital development in males. The higher value of the two developmental

criteria is used to assign the Tanner stage. In this study, only children of Tanner stages 1-3 were used.

Body Fat Percentage. Body composition was assessed via Dual-energy X-ray absorptiometry (DXA) using a GE Lunar Prodigy densitometer (DXA; GE Lunar Radiation corp., Madison, WI) with pediatric software (version 1.5e). DXA scans were conducted with participants wearing light clothing, lying flat on their back with arms at their sides. Total calculated fat mass from the scan was divided by total body weight to determine body fat percentage.

Physical Activity. Participants were given a uniaxial ActiGraph accelerometer (GT1M – Standard Model 198-0100-02; ActiGraph LLC, Pensacola, FL) to wear to capture physical activity levels and patterns (7 days of data were used). Actigraph monitors have previously demonstrated high inter-instrument reliability and the ability to distinguish between varying levels of physical activity in children (25). Epoch length was configured at 1 min and data expressed as counts/min. Data were characterized as average time (min/week) spent on moderate, hard, and very hard activities.

Dietary Recalls. Two 24-hour diet recalls were administered and analyzed by a registered dietician using the triple pass method (26). A parent/guardian was present for, and assisted with, each recall, visual aids were used to help in portion size estimation, and all 24-hour diet recalls were conducted on weekdays. Data were entered by a registered dietitian into the Nutrition Data System for Research software version 2006 (Nutrition

Coordinating Center, University of Minnesota, Minneapolis, MN). Outputs from the same participant's diet recalls were averaged and the variables of interest included the following: total calories (kcal/d), total fat (g/d), saturated fat (g/d), dietary cholesterol (mg/d), dietary sodium (mg/d), and added sugars (g/d). Added sugars were defined as those not naturally occurring in foods, but were added as a result of processing or preparation, and did not include 100% fruit juices. The Nutrition Data System for Research software derived added sugars in the diet using data from sources such as the USDA (e.g. USDA provisional tables and agricultural handbooks), scientific literature, manufacturers, calculations from recipes, and calculations from ingredient lists or similar food products (27).

Blood Pressure. During the overnight visit at the UAB GCRC, trained nurses took two BP measurements at 1800h, and two more the next day at 0700h. An automated pediatric BP cuff (Dinamap Pro 200, GE Medical Systems, Piscataway, NJ) was used for this purpose, with appropriate child-sized cuffs employed based on participant arm size. Participants were seated at rest, with feet flat on the floor, for at least 10 min before measurements were taken, and first and second measurements were separated by a 5 minute seated rest. Evening and morning measurements were not significantly different. The systolic BP and diastolic BP measurements were averaged, using a total of 4 measurements for each.

Blood Lipids & Lipoproteins. Fasted blood samples were taken at 0700h after the participants' overnight stay at the UAB GCRC. Concentrations of all serum-derived

analytes were determined at UAB in the Metabolism Core Laboratory that services the GCRC and NORC. Lipids (total cholesterol, HDL cholesterol, triglycerides) were measured using a Stanbio SIRRUS analyzer. LDL cholesterol was calculated using the method of Friedewald (28).

Statistical analysis.

Multiple variable linear regression analyses were performed, controlling for covariates, to evaluate the main associations of interest. The independent variables in our analyses were total dietary added sugars intake (g/day), total dietary sodium intake (mg/day), total dietary fat intake (g/d), total dietary saturated fat intake (g/d), and total dietary cholesterol intake (mg/d). Dependent variables included average diastolic BP (mmHg), average systolic BP (mmHg), total cholesterol (mg/dL), triglycerides (mg/dL), LDL cholesterol (mg/dL), and HDL cholesterol (mg/dL). Covariates included sex, race/ethnicity, socioeconomic status, Tanner pubertal status, percent body fat, physical activity (min/week), and total energy intake (kcal/day). All variables were continuous in nature other than sex and race/ethnicity. Race/ethnicity was entered as a dummy-coded variable as it is nominal in nature, with European-American being the reference group as they are the largest group and have the least variance for the greatest number of variables of interest.

The associations between added sugars and blood pressure (diastolic and systolic run independently) and between added sugars and blood lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol run independently) were tested using

multiple variable linear regression analyses. Identical models were also run between dietary sodium and blood pressure, and also between total dietary fat and blood lipids to evaluate their potentially confounding effects on associations between added sugars and CVD risk factors. Only those participants with values for all variables in the models were included in analyses.

Descriptive statistics were analyzed by race/ethnicity and then sex using analysis of variance (ANOVA) with Tukey's post-hoc test.

Participants with missing data were not included in the analyses. To comply with assumptions of regression, all models were evaluated for normality of residuals prior to any potential statistical transformations of the dependent variable. In all regression models, residuals exceeding three standard deviations were removed; consequently, no statistical transformations of dependent variables were necessary. All statistical analyses were performed in SAS version 9.3 (SAS, Cary, NC).

Results

Baseline characteristics of study participants are given in Table 1 for the overall sample and by sex and race/ethnicity. No statistically significant differences were observed between the sexes in terms of SES, physical activity, added sugars, dietary fat, or systolic blood pressure, and no significant differences were observed among races/ethnicities in terms of physical activity, total energy intake, total cholesterol, or LDL cholesterol.

Relative to males, females demonstrated higher tanner stage, body fat percentage and triglycerides than males but had lower total energy intake, dietary sodium, average diastolic blood pressure, and HDL cholesterol. HA participants had higher body fat percentage and triglycerides, but lower SES and added sugars consumption than either AA or EA children. AA participants had higher tanner stage, average diastolic and systolic blood pressure, and HDL cholesterol, but lower triglycerides than either EA or HA children.

A significant positive relationship was observed between added sugars and diastolic blood pressure ($p=0.0462$), as described in Table 2, with a significant contribution of sex in the model ($p=0.0259$). Sodium was not significantly associated with diastolic blood pressure, but both sex ($p=0.0301$) and total energy intake ($p=0.0436$) contributed significantly to the model. No significant relationships were observed between systolic blood pressure and either added sugars or sodium. When modeling the relationship between added sugars and systolic blood pressure, the following covariates contributed significantly to the model: sex ($p=0.0233$), tanner stage ($p=0.0127$), and body fat percentage ($p=0.0107$). When modeling the relationship between sodium and systolic blood pressure, the following covariates contributed significantly to the model: sex ($p=0.0246$), tanner stage ($p=0.0092$), and body fat percentage ($p=0.0101$). In all models of blood pressure, female sex was associated with lower values. When they contributed significantly to models of blood pressure, tanner stage, body fat percentage, and total energy intake were associated with higher values.

Added sugars were positively associated with triglycerides ($p=0.0206$), but no other blood lipids, as can be seen in Table 3. Tanner stage contributed significantly in the following models: total cholesterol ($p=0.0254$), triglycerides ($p=0.0020$) and HDL cholesterol ($p=0.0038$). Body fat percentage contributed significantly in the following models: total cholesterol ($p=0.0009$), triglycerides ($p=0.0104$), LDL cholesterol ($p<0.0001$), and HDL cholesterol ($p<0.0001$).

Total dietary fat was not significantly associated with any of the blood lipids investigated, as can be seen in Table 3. Tanner stage contributed significantly in the following models: total cholesterol ($p=0.0397$), triglycerides ($p=0.0083$), and HDL cholesterol ($p=0.0040$). Body fat percentage contributed significantly in the following models: total cholesterol ($p=0.0009$), triglycerides ($p=0.0129$), LDL cholesterol ($p<0.0001$), and HDL cholesterol ($p<0.0001$). When it contributed significantly to models of blood lipids, tanner stage was associated with higher values of triglycerides, but lower values of total cholesterol and HDL cholesterol. When it contributed significantly to models of blood lipids, body fat percentage was associated with higher values of total cholesterol, triglycerides, and LDL cholesterol, but lower values of HDL cholesterol.

Results from the aforementioned regression analyses are alternatively presented with 95% confidence intervals in supplemental Tables 1 and 2.

Discussion

This study evaluated the cross-sectional associations between added sugars in the diet, as reported via guardian-supervised children's 24-hour dietary recalls, and CVD risk factors, specifically blood pressure and blood lipids. While previous studies have shown positive cross-sectional associations between added sugars in the diet and elevated BP in adolescents and adults (15-17), and also between added sugars and triglycerides in adolescents (29), our study evaluated this relationship in children (Marshall and Tanner pubertal status ≤ 3).

In our study population, a positive statistically significant association was observed between added sugars and diastolic blood pressure, but not systolic blood pressure. This dichotomy is particularly noteworthy because of the young age of our population, given that isolated diastolic hypertension is much more common in younger than older adults (30). The relationship between added sugars and diastolic blood pressure suggested a modest increase of 0.0206 mmHg per gram of added sugars. The average daily consumption of added sugars for our participants was 308 kcal (76.9g), and for boys in the U.S. is 362 kcal (90.5g) and girls is 282 kcal (70.5g) (31), well above the range of 12-32g recommended by the American Heart Association for the age range of our study population (32) (range derivation for added sugars is available in online supplemental materials). This level of added sugars consumption by US children may parlay into an increase of 1.8643 mmHg in boys and 1.4523 mmHg in girls, which may be clinically

relevant given that a sustained increase of only 5 to 6 mmHg in diastolic blood pressure in older adults over a few years may increase risk of stroke by 67% (33).

A dietary factor traditionally thought to increase blood pressure, dietary sodium (34), did not have a statistically significant association with either measure of blood pressure in our sample. We hypothesize the lack of association in our population between dietary sodium and blood pressure may be due to the age of our population and the possibility that their vascular tone and renal function have not yet been impaired.

In terms of blood lipids, although added sugars were associated with triglycerides in our study, dietary fat did not show this association. When further examined, neither dietary cholesterol nor saturated fats were significantly associated with triglycerides (data not shown).

Data from the Framingham study show that patients with elevated blood pressure also have other metabolic conditions such as high cholesterol and triglycerides, lower HDL cholesterol, obesity and insulin resistance (30). Other studies have suggested that hypertriglyceridemia and hypertension tend to coexist in adult individuals (35). These observations suggest that metabolic diseases could respond to a common etiology, rooted in genetic and environmental factors that alter the normal functionality of the body. Our data support that the consumption of added sugars might represent a modifiable risk factor that deserves further exploration in the identification of preventive strategies for such complex diseases, particularly among the pediatric population.

Understanding how risk factors affect disease progression is critical in the development of effective interventions and treatments. Added sugars in the diet may impact blood pressure by acting on the kidneys to increase blood levels of uric acid which could, in turn, reduce the production and/or availability of nitric oxide, a powerful vasodilator, thereby raising blood pressure (36). In fact, an increased odds ratio of elevated blood pressure has been seen in those adolescents with higher serum uric acid levels (37). Alternatively, the mechanism by which added sugars may raise blood pressure could involve the renin-angiotensin pathway, as has been observed in rat studies (38, 39), or the interplay between this pathway and nitric oxide production (39). Elevation of triglycerides from added sugars, on the other hand, may have a less convoluted etiology. A likely mechanism by which added sugars may increase triglyceride levels is through stimulating hepatic de novo lipogenesis (DNL) (40, 41). While glucose alone does not appear to significantly increase DNL (42), fructose has been shown to significantly increase DNL within hours (43, 44) (both glucose and fructose are found in commonly used added sugars such as cane sugar and high fructose corn syrup).

Strengths of our study include the use of a diverse cohort in terms of race/ethnicity, and the ability to more accurately isolate the association between dietary sugars, blood pressure, and blood lipids by controlling for lifestyle (physical activity, dietary intakes) and SES, race/ethnicity, sex, tanner stage, and body fat percentage. In addition to the inclusion of these covariates, robust measures of body composition and physical activity were utilized. For instance, body fat percentage was calculated from body composition parameters and weight obtained via DXA technology instead of estimated using BMI, as

BMI has been shown to be inconsistent in classifying adiposity status across racial/ethnic groups in children, and less than one half of children in the 85^{th}-95^{th} BMI percentile (i.e. overweight) show high adiposity levels when assessed via DXA (45). Physical activity was directly measured via the use of accelerometers, as opposed to self-reported activity. Tanner status was used as a proxy for maturation status, instead of age alone, in order to better control for hormonal and developmental differences among the children.

Limitations of the study are related to the sample size (n=320), the cross-sectional nature of the study, and the inability to obtain certain data. Given that our sample was from children living in the Birmingham, AL metro area, the results may not be readily generalized to other geographic contexts. As we were not able to follow the children over time, it is not possible to determine how the observed relationships between added sugars, blood pressure, and blood lipids may change throughout the lifespan. The use of self-reported dietary assessments may bring concerns about potential underreporting of added sugars - as observed in adults (46) - that could have impacted the associations reported herein. Although 24-hour dietary recalls may introduce error due to their reliance on memory and truthfulness in reporting, a previous review has shown repeated 24-hour recalls to be the most accurate self-reported measure in children as compared to doubly labeled water (47). Despite controlling for SES (as determined via the Hollingshead index), limited parental income data were available for us to evaluate the possible effects of purchasing power constraints on diet quality and their associations with foods high in added sugars. We did not have measures of serum uric acid, nitric

oxide, or the renin-angiotensin system in our population to evaluate the potential physiological mechanisms by which added sugars may raise blood pressure.

Our results provide support to the hypothesis that increased consumption of added sugars may contribute to the development of poor cardiovascular health prior to maturity. Further research is needed in humans, especially randomized control trials and longitudinal studies, in order to verify whether the relationships between added sugars, blood pressure, blood lipids, and cardiovascular health are definitively causative or only correlative. However, in light of the current obesity epidemic, as added sugars in food products may further increase caloric load, it would be advisable to limit their consumption, especially in children

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KPK and JRF designed research analyses, KPK, MIC, MMBB, and JRF analyzed data, KPK wrote the paper, MIC, JRF and MMBB provided editing support.

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References

1. Miniño A, Murphy S, Xu J, Kochanek K. Deaths: final data for 2008. National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System 2011;59(10):1-126.
2. Heidenreich P, Trogdon J, Khavjou O, Butler J, Dracup K, Ezekowitz M, Finkelstein E, Hong Y, Johnston S, Khera A, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation 2011;123(8):933-44. doi: 10.1161/CIR.0b013e31820a55f5.
3. Stary H. Evolution and progression of atherosclerotic lesions in coronary arteries of children and young adults. Arteriosclerosis (Dallas, Tex) 1989;9(1 Suppl):32.
4. Kannel W. Hypertension as a risk factor for cardiac events-epidemiologic results of long-term studies. Journal of Cardiovascular Pharmacology 1993;21 Suppl 2:37.
5. Kit B, Carroll M, Lacher D, Sorlie P, DeJesus J, Ogden C. Trends in serum lipids among US youths aged 6 to 19 years, 1988-2010. JAMA : The Journal of the American Medical Association 2012;308(6):591-600. doi: 10.1001/jama.2012.9136.
6. Sorof J, Lai D, Turner J, Poffenbarger T, Portman R. Overweight, ethnicity, and the prevalence of hypertension in school-aged children. Pediatrics 2004;113(ff187e46-7d3e-bba6-6474-11cf9c5bdfaa):475-557.
7. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. Circulation 2008;117(25):3171-80. doi: 10.1161/circulationaha.107.730366.
8. Berenson G, Srinivasan S, Bao W, Newman W, Tracy R, Wattigney W. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. The New England Journal of Medicine 1998;338(7195c941-999f-7dd2-f662-11cf24d72df7):1650-6. doi: 10.1056/nejm199806043382302.
9. Juonala M, Järvisalo M, Mäki-Torkko N, Kähönen M, Viikari J, Raitakari O. Risk factors identified in childhood and decreased carotid artery elasticity in adulthood: the Cardiovascular Risk in Young Finns Study. Circulation 2005;112(10):1486-93. doi: 10.1161/circulationaha.104.502161.
10. Berenson G. Childhood risk factors predict adult risk associated with subclinical cardiovascular disease. The Bogalusa Heart Study. The American Journal of Cardiology 2002;90(10C).
11. Kwiterovich P, Gidding S. Universal Screening of Cholesterol in Children. Clinical Cardiology 2012. doi: 10.1002/clc.22050.
12. Appel L, Brands M, Daniels S, Karanja N, Elmer P, Sacks F, American Heart A. Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. Hypertension 2006;47(2):296-308. doi: 10.1161/01.hyp.0000202568.01167.b6.
13. Fletcher B, Berra K, Ades P, Braun L, Burke L, Durstine J, Fair J, Fletcher G, Goff D, Hayman L, et al. Managing abnormal blood lipids: a collaborative

approach. Circulation 2005;112(20):3184-209. doi: 10.1161/CIRCULATIONAHA.105.169180.
14. Reedy J, Krebs-Smith S. Dietary sources of energy, solid fats, and added sugars among children and adolescents in the United States. Journal of the American Dietetic Association 2010;110(10):1477-84. doi: 10.1016/j.jada.2010.07.010.
15. Høstmark A. The Oslo health study: soft drink intake is associated with the metabolic syndrome. Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquée, Nutrition et Métabolisme 2010;35(20b0922d-8466-3257-2133-90b59abc0be2):635-77. doi: 10.1139/h10-059.
16. Nguyen S, Choi H, Lustig R, Hsu C-y. Sugar-sweetened beverages, serum uric acid, and blood pressure in adolescents. The Journal of Pediatrics 2009;154(e6236fb2-5aa6-1d50-7b19-90b59abb9dc7):807-20. doi: 10.1016/j.jpeds.2009.01.015.
17. Brown I, Stamler J, Van Horn L, Robertson C, Chan Q, Dyer A, Huang C-C, Rodriguez B, Zhao L, Daviglus M, et al. Sugar-sweetened beverage, sugar intake of individuals, and their blood pressure: international study of macro/micronutrients and blood pressure. Hypertension 2011;57(cabba675-21a4-31b9-7020-909fc5ec66ce):695-1396. doi: 10.1161/hypertensionaha.110.165456.
18. Chen L, Caballero B, Mitchell D, Loria C, Lin P-H, Champagne C, Elmer P, Ard J, Batch B, Anderson C, et al. Reducing consumption of sugar-sweetened beverages is associated with reduced blood pressure: a prospective study among United States adults. Circulation 2010;121(d17babc3-2899-f780-e55f-90b59ac6de2d):2398-804. doi: 10.1161/circulationaha.109.911164.
19. Welsh J, Sharma A, Cunningham S, Vos M. Consumption of added sugars and indicators of cardiovascular disease risk among US adolescents. Circulation 2011;123(3):249-57. doi: 10.1161/circulationaha.110.972166.
20. Ambrosini G, Oddy W, Huang R, Mori T, Beilin L, Jebb S. Prospective associations between sugar-sweetened beverage intakes and cardiometabolic risk factors in adolescents. The American journal of clinical nutrition 2013;98(2):327-34. doi: 10.3945/ajcn.112.051383.
21. Kosova E, Auinger P, Bremer A. The relationships between sugar-sweetened beverage intake and cardiometabolic markers in young children. Journal of the Academy of Nutrition and Dietetics 2013;113(2):219-27. doi: 10.1016/j.jand.2012.10.020.
22. Marshall W, Tanner J. Variations in the pattern of pubertal changes in boys. Archives of Disease in Childhood 1970;45(239):13-23.
23. Marshall W, Tanner J. Variations in pattern of pubertal changes in girls. Archives of Disease in Childhood 1969;44(235):291-303.
24. Cirino P, Chin C, Sevcik R, Wolf M, Lovett M, Morris R. Measuring socioeconomic status: reliability and preliminary validity for different approaches. Assessment 2002;9(2):145-55.
25. Evenson KR, Catellier DJ, Gill K, Ondrak KS, McMurray RG. Calibration of two objective measures of physical activity for children. Journal of sports sciences 2008;26(14):1557-65. doi: 10.1080/02640410802334196.
26. Johnson R, Driscoll P, Goran M. Comparison of multiple-pass 24-hour recall estimates of energy intake with total energy expenditure determined by the doubly

labeled water method in young children. Journal of the American Dietetic Association 1996;96(11):1140-4. doi: 10.1016/s0002-8223(96)00293-3.
27. Nutrition Data System for Research. User Manual. Appendix 22. Sources of Food and Nutrient Data. Version current 1 March 2014. Internet: http://wwwnccumnedu/ndsrsupport/usermanualexcerpts/13appendix22_sourcesoffoodandnutrientdatapdf (accessed 1 March 2014).
28. Friedewald WT LR, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of an ultracentrifuge. Clinical Chemistry 1972;18:499-502.
29. Welsh J, Sharma A, Abramson J, Vaccarino V, Gillespie C, Vos M. Caloric sweetener consumption and dyslipidemia among US adults. JAMA : The Journal of the American Medical Association 2010;303(15):1490-7. doi: 10.1001/jama.2010.449.
30. Kannel W. Historic perspectives on the relative contributions of diastolic and systolic blood pressure elevation to cardiovascular risk profile. American Heart Journal 1999;138(3 Pt 2):205-10. doi: 10.1016/s0002-8703(99)70311-x.
31. McGuire S. Ervin RB, Kit BK, Carroll MD, Ogden CL. Consumption of added sugar among U.S. children and adolescents, 2005-2008. NCHS data brief no 87. Hyattsville, MD: National Center for Health Statistics. 2012. Advances in nutrition (Bethesda, Md) 2012;3(4):534. doi: 10.3945/an.112.002279.
32. Johnson R, Appel L, Brands M, Howard B, Lefevre M, Lustig R, Sacks F, Steffen L, Wylie-Rosett J, American Heart Association Nutrition Committee of the Council on Nutrition PA, et al. Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. Circulation 2009;120(11):1011-20. doi: 10.1161/CIRCULATIONAHA.109.192627.
33. Johnson A. NSAIDs and increased blood pressure. What is the clinical significance? Drug safety : an international journal of medical toxicology and drug experience 1997;17(5):277-89. doi: 10.2165/00002018-199717050-00001.
34. Frisoli T, Schmieder R, Grodzicki T, Messerli F. Salt and hypertension: is salt dietary reduction worth the effort? The American Journal of Medicine 2012;125(9a10fbf8-0bf2-e7b2-1b0f-306331f3a3f4):433-42. doi: 10.1016/j.amjmed.2011.10.023.
35. Karasek D, Vaverkova H, Halenka M, Jackuliakova D, Frysak Z, Orsag J, Novotny D. Prehypertension in dyslipidemic individuals; relationship to metabolic parameters and intima-media thickness. Biomedical papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia 2012. doi: 10.5507/bp.2012.046.
36. Nakagawa T, Hu H, Zharikov S, Tuttle K, Short R, Glushakova O, Ouyang X, Feig D, Block E, Herrera-Acosta J, et al. A causal role for uric acid in fructose-induced metabolic syndrome. American Journal of Physiology Renal Physiology 2006;290(ba700e1d-467d-6f6a-1aac-90b59ac3d727):31. doi: 10.1152/ajprenal.00140.2005.
37. Loeffler L, Navas-Acien A, Brady T, Miller E, Fadrowski J. Uric acid level and elevated blood pressure in US adolescents: National Health and Nutrition Examination Survey, 1999-2006. Hypertension 2012;59(ed757ade-e30c-b151-c7c7-30dbc698a05e):811-8. doi: 10.1161/hypertensionaha.111.183244.

38. Freitas R, Lopes K, Carillo B, Bergamaschi C, Carmona A, Casarini D, Furukawa L, Heimann J, Campos R, Dolnikoff M. Sympathetic and renin-angiotensin systems contribute to increased blood pressure in sucrose-fed rats. American Journal of Hypertension 2007;20(22f533f1-d02e-2ac3-6989-90b59ab2bb24):692-700. doi: 10.1016/j.amjhyper.2007.01.014.
39. Chou C-L, Pang C-Y, Lee T, Fang T-C. Direct renin inhibitor prevents and ameliorates insulin resistance, aortic endothelial dysfunction and vascular remodeling in fructose-fed hypertensive rats. Hypertension Research : Official Journal of the Japanese Society of Hypertension 2012(d145bb09-6c0a-c698-e914-4eb941c9dc1f). doi: 10.1038/hr.2012.124.
40. Parks E, Hellerstein M. Carbohydrate-induced hypertriacylglycerolemia: historical perspective and review of biological mechanisms. The American Journal of Clinical Nutrition 2000;71(2):412-33.
41. Hellerstein M. De novo lipogenesis in humans: metabolic and regulatory aspects. European Journal of Clinical Nutrition 1999;53 Suppl 1:65. doi: 10.1038/sj.ejcn.1600744.
42. Stanhope K, Havel P. Fructose consumption: recent results and their potential implications. Annals of the New York Academy of Sciences 2010;1190:15-24. doi: 10.1111/j.1749-6632.2009.05266.x.
43. Hudgins L, Parker T, Levine D, Hellerstein M. A dual sugar challenge test for lipogenic sensitivity to dietary fructose. The Journal of Clinical Endocrinology and Metabolism 2011;96(3):861-8. doi: 10.1210/jc.2010-2007.
44. Schwarz J, Neese R, Shackelton C, Hellerstein M. De novo lipogenesis (DNL) during fasting and oral fructose in lean and obese hyperinsulinemic subjects. Diabetes 1993;42(Suppl 1).
45. Flegal K, Ogden C, Yanovski J, Freedman D, Shepherd J, Graubard B, Borrud L. High adiposity and high body mass index-for-age in US children and adolescents overall and by race-ethnic group. The American journal of clinical nutrition 2010;91(4):1020-6. doi: 10.3945/ajcn.2009.28589.
46. Millen A, Tooze J, Subar A, Kahle L, Schatzkin A, Krebs-Smith S. Differences between food group reports of low-energy reporters and non-low-energy reporters on a food frequency questionnaire. Journal of the American Dietetic Association 2009;109(7):1194-203. doi: 10.1016/j.jada.2009.04.004.
47. Burrows T, Martin R, Collins C. A systematic review of the validity of dietary assessment methods in children when compared with the method of doubly labeled water. Journal of the American Dietetic Association 2010;110(10):1501-10. doi: 10.1016/j.jada.2010.07.008.

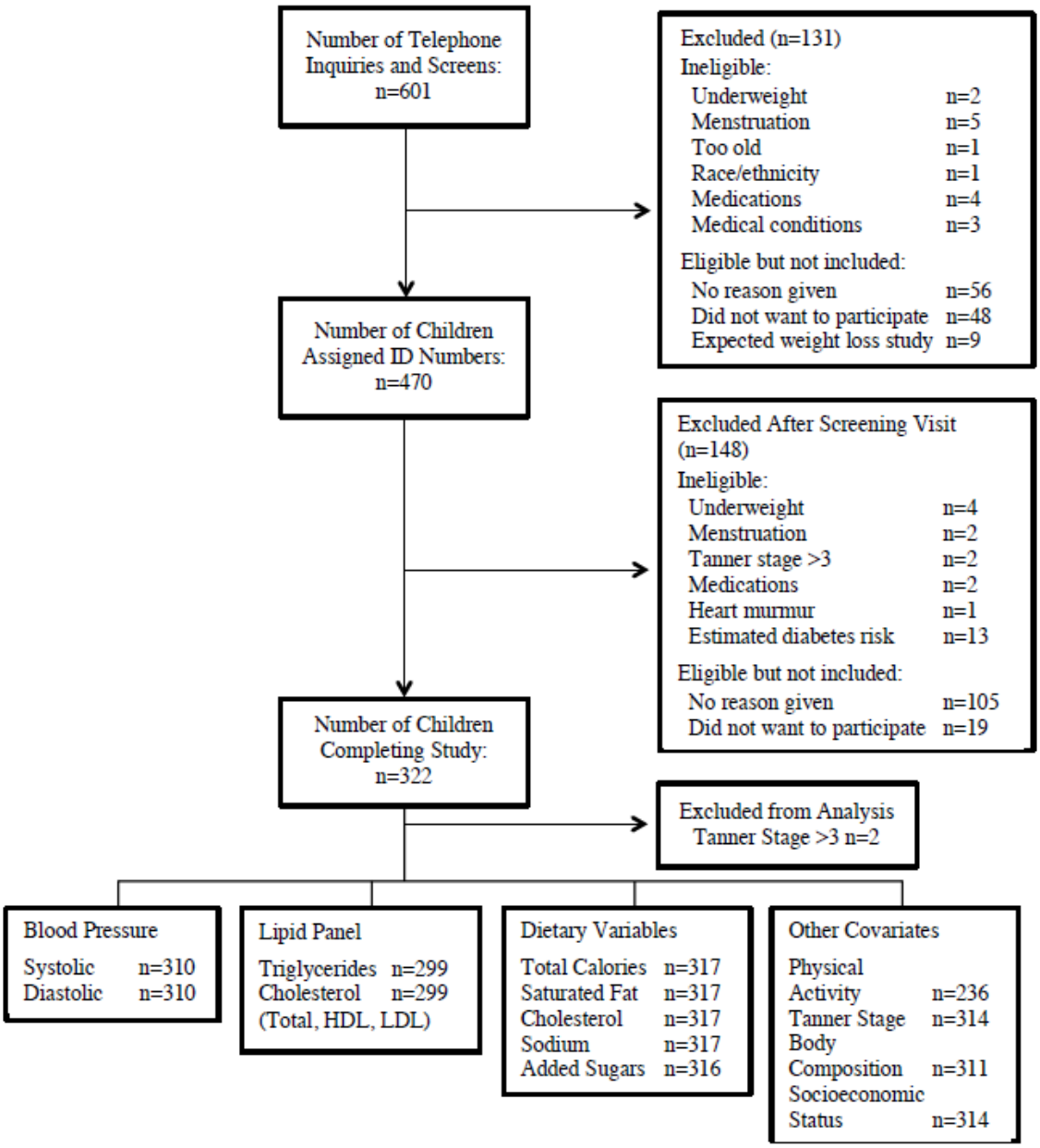

Figure 1. Recruitment and final sample size flowchart for AMERICO study*

*Reasons for participants not being included between recruitment/study stages are given to the right of the arrows denoting the transitions between stages. Final sample sizes for all variables of interest in the study are provided at the bottom of the figure.

Table 1. Descriptive statistics of AMERICO study population (Mean ± SE): Overall, by sex, and by race/ethnicity[1,2]

	Total (n=320)	Male (n=170)	Female (n=150)	EA (n=122)	AA (n=106)	HA (n=84)	MR (n=8)
Age	9.5 ± 0.1	9.7 ± 0.1[a]	9.3 ± 0.1[b]	9.7 ± 0.2	9.6 ± 0.1	9.4 ± 0.2	9.1 ± 0.7
Socioeconomic Status[3]	38.7 ± 0.8	38.7 ± 1.1	38.8 ± 1.3	49.4 ± 0.9[a]	37.0 ± 1.1[b]	25.4 ± 1.3[c]	39.4 ± 7.3[a,b]
Tanner Stage[4]	1.5 ± 0.0	1.4 ± 0.1[b]	1.6 ± 0.1[a]	1.4 ± 0.1[b]	1.7 ± 0.1[a]	1.4 ± 0.1[b]	1.3 ± 0.2[a,b]
Body Fat Percentage	23.4 ± 0.5	21.0 ± 0.8[b]	26.1 ± 0.7[a]	22.5 ± 0.8[b]	20.4 ± 1.0[b]	28.5 ± 0.9[a]	21.6 ± 2.7[a,b]
Physical Activity[5]	2012.3 ± 22.5	2015.0 ± 32.1	2009.3 ± 31.4	2016.5 ± 32.7	2036.0 ± 45.0	1965.1 ± 43.3	2201.6 ± 113.9
Total Energy Intake (kcal/day)	1894.0 ± 26.4	1950.5 ± 37.4[a]	1831.1 ± 36.7[b]	1877.3 ± 38.5	1889.6 ± 50.7	1906.0 ± 52.4	2080.3 ± 156.4
Added Sugars (g/day)	76.9 ± 2.4	79.4 ± 3.2	74.2 ± 3.7	82.9 ± 3.6[a]	84.0 ± 4.8[a]	59.5 ± 4.0[b]	77.4 ± 15.2[a.b]
Dietary Sodium (mg/day)	3207.3 ± 59.0	3299.7 ± 80.8[a]	3104.3 ± 85.7[b]	3050.1 ± 80.3	3279.8 ± 116.7	3339.6 ± 118.8	3258.9 ± 292.4
Dietary Fat (g/day)	74.4 ± 1.4	75.6 ± 2.0	73.2 ± 1.9	71.3 ± 1.9	78.2 ± 2.7	73.1 ± 2.6	86.5 ± 10.1
Diastolic Blood Pressure (mmHg)	60.1 ± 0.4	60.9 ± 0.5[a]	59.2 ± 0.6[b]	59.0 ± 0.6[b]	62.4 ± 0.7[a]	58.6 ± 0.6[b]	62.3 ± 2.4[a,b]
Systolic Blood Pressure (mmHg)	103.3 ± 0.6	104.0 ± 0.8	102.6 ± 0.9	102.4 ± 1.0[a,b]	105.8 ± 1.1[a]	101.2 ± 1.0[b]	108.2 ± 3[a,b]
Total Cholesterol (mg/dL)	154.0 ± 1.6	155.0 ± 2.2	152.8 ± 2.4	153.2 ± 2.3	153.8 ± 2.8	154.6 ± 3.6	164 ± 10.6
Triglycerides (mg/dL)	66.7 ± 2.1	63.1 ± 2.5[b]	70.8 ± 3.4[a]	66.1 ± 2.9[b]	54.3 ± 2.7[b]	83.4 ± 5.3[a]	68.2 ± 19.3[a,b]
LDL (mg/dL)	90.2 ± 1.5	90.4 ± 2.1	89.9 ± 2.3	91.6 ± 2.2	87.6 ± 2.8	91.9 ± 3.4	83.9 ± 6.1
HDL (mg/dL)	50.3 ± 0.7	52.0 ± 1.0[a]	48.3 ± 1.0[b]	48.4 ± 1.0[b]	55.5 ± 1.4[a]	46.1 ± 1.4[b]	55.2 ± 6.7[a,b]

1. EA = European American, AA = African American, HA = Hispanic American, MR = Mixed Race.
2. Means not sharing a common superscript letter ([a-c]) are significantly different at $P<0.05$ based on Tukey's post-hoc test.

3. Assessed via Hollingshead four factor index, with potential scores ranging from 8-66
4. Pubertal stage of 1-3 as assessed by a pediatrician according to the criteria of Marshall and Tanner
5. Physical activity includes total minutes per week of light, moderate, and vigorous activity

Table 2. Regression analyses of diastolic and systolic blood pressures vs. added sugars and dietary sodium, run separately[1,2,3]

	Diastolic Blood Pressure		Systolic Blood Pressure	
	b Coeff.	p-value	b Coeff.	p-value
Added Sugars (g/d)	0.0206	0.0462	0.0126	0.4827
Dietary Sodium (mg/d)	-0.0009	0.0645	-0.0001	0.8745

1. Models were linear regressions with statistically significant associations at p-value < 0.05.
2. All analyses controlled for the following covariates: sex, race/ethnicity (dummy coded), socioeconomic status, Tanner pubertal status, body fat percentage, total physical activity, and total energy intake.
3. In the above models, the sample size for which all variables were available was n=220.

Table 3. Regression analyses of blood lipids/lipoproteins vs. added sugars and dietary fat, run separately[1,2,3]

	Total Cholesterol		Triglycerides		LDL Cholesterol		HDL Cholesterol	
	b Coeff.	p-value	b Coeff.	p-value	b Coeff.	p-value	b Coeff.	p-value
Added Sugars (g/d)	0.0276	0.5995	0.1090	0.0206	0.0318	0.5259	-0.0127	0.5516
Dietary Fat (g/d)	0.1087	0.4480	-0.1351	0.2740	0.0769	0.5735	0.0496	0.3947

1. Models were linear regressions with statistically significant associations at p-value < 0.05.
2. All analyses controlled for the following covariates: sex, race/ethnicity (dummy coded), socioeconomic status, Tanner pubertal status, body fat percentage, total physical activity, and total energy intake.
3. In the above models, the sample size for which all variables were available was n=210.

CHAPTER 4: ADHERENCE TO THE USDA DIETARY GUIDELINES FOR AMERICANS AND ASSOCIATIONS WITH ATHEROSCLEROTIC DEVELOPMENT IN THE CARDIA STUDY

by

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Abstract

Adherence to the USDA Dietary Guidelines for Americans has been associated with risk factors for cardiovascular disease (CVD) and CVD events, but change in one's adherence to these guidelines over time has not been examined for its relationship with atherosclerosis, i.e. carotid intima-media thickness (CIMT) and coronary artery calcification (CAC). Using diet history data from the CARDIA study collected at baseline (1985) and year 20 (Y20; 2005), HEI-95 scores were assigned to participants for both time points (n=1,937, 56.0% female, 41.2% black, mean age at Y20 = 45.3). Assessed at Y20 only, CIMT was a continuous variable (mm), and CAC was a binary variable (Agatston score) with 1 indicating presence of calcification. Setting CIMT as the outcome of interest, linear regression models assessed its association 1) with HEI scores at Y20, controlling for baseline HEI, and separately 2) with change in HEI (Y20 minus baseline). Setting CAC as the outcome of interest, logistic regression models assessed its association 1) with HEI scores at Y20, controlling for baseline HEI, and separately 2) with change in HEI (Y20 minus baseline) with CAC. All models were first run without any covariates (unadjusted), and then adjusted to include the following covariates: age, sex, race, field center, education, family income, total energy intake, BMI, physical activity, smoking status, drinking status, and history of hypertension, dyslipidemia, or diabetes. Significant associations were observed in unadjusted models assessing HEI score at Y20, controlling for baseline HEI, with CIMT (p=0.0002, **β**coeff.=-0.0013) and CAC (OR=0.986, 95% CI=0.976,0.996). Although these associations were statistically significant, they were not robust to the addition of the aforementioned covariates. Additionally, change in HEI was not significantly associated with either CIMT or CAC.

Introduction

The USDA Dietary Guidelines for Americans (DGA) were introduced in 1980[1] to provide information to the general population on how to maintain a healthy body weight and reduce the risk of chronic diseases, such as cardiovascular disease (CVD). Since the first guidelines were issued, however, CVD has remained the number one cause of death in adults in the United States[2].

Some studies have taken a disease end-point approach and have examined the cross-sectional relationship between adherence to the DGA (assessed using the Healthy Eating Index (HEI)) and CVD incidence and mortality[3, 4]. Other prospective cohort studies have examined the cross-sectional association between HEI score and various markers of CVD risk, e.g. serum cholesterol, BMI, and waist circumference[5-7].

These studies are helpful in understanding the relationships between HEI score and CVD at the beginning and end of the etiology of CVD; however, examinations of HEI score and atherosclerosis are lacking. In order to complete the etiological spectrum, it is important to examine this dietary relationship utilizing indicators of atherosclerotic development, i.e. coronary artery calcification (CAC) and carotid intima media thickness (CIMT). Both of these measures have been shown to be independent risk factors for CVD [8-10]. Furthermore, abnormalities in CAC and CIMT can typically be detected years before a CVD event [11] through non-invasive and relatively inexpensive procedures. Therefore, examining the associations between these markers and HEI adherence can help inform effective nutrition policies for preventing and/or slowing the progression of CVD, even in the later stages of the etiology of CVD.

Effective dietary prevention measures for CVD would ideally be implemented early in the lifespan in order to maximize their potential impact. However, analyses have repeatedly shown less than ideal HEI adherence in younger populations, e.g. teenagers, young adults[12]. For example, in the population under consideration, the Coronary Artery Risk Development in Young Adults (CARDIA) study cohort, less than 10% of

participants had “good” adherence to the DGA at baseline, as indicated by an HEI-95 score >80/100. Conversely, if dietary improvements as late as middle age can reduce CVD risk, this would represent a hopeful public health message. Therefore, the focus of the present study is the association between HEI adherence over this time span and both CAC and CIMT. The hypothesis of this study is that, within the CARDIA study cohort, one’s HEI score in middle age (year 20 of the study), when controlled for HEI score during young adulthood (baseline) will be negatively associated with CAC and CIMT. Furthermore, it is hypothesized that the change in HEI score between these time points will be negatively associated with CAC and CIMT.

Methods

Study Design

The CARDIA study is a multicenter, longitudinal investigation of the evolution of coronary heart disease risk beginning in young adulthood. The CARDIA study was initiated in 1985–1986 with a baseline cohort of 5,115 adults aged 18–30 y enrolled from 4 metropolitan areas: Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. Detailed recruitment procedures and study methods, as well as information about IRB approval and informed consent, have been previously described[13, 14]. The original cohort included approximately equal numbers of blacks and whites, men and women, aged 18–24 and 25–30 y, and those with a high school education or less vs. those with more than a high school education[15, 16]. Follow-up exams for year 20 (Y20) were conducted in 2005–2006, including 71.8% of the surviving cohort. Institutional review boards at each participating institution approved the study, and all subjects provided written informed consent. Diet was assessed via the use of an interviewer-administered CARDIA diet history. Demographic, socioeconomic, lifestyle, and medical history information was obtained using standard questionnaires. Anthropometrics, blood samples and blood pressure were obtained during clinical visits. Markers of atherosclerosis included CIMT (assessed via sonography) and CAC (assessed via computed tomography (CT) scans), and were only assessed at year 20 (Y20). In order to make all covariates as chronologically matched and updated as possible with CIMT/CAC (e.g. educational

attainment at baseline would be an incomplete picture of lifetime education), their values at Y20 were used in all models. The only exception to this was medical history and history of CVD risk factors, i.e. experiencing hypertension, dyslipidemia, or diabetes at any point between baseline and Y20.

Analysis Variables

Socioeconomic Status

Information pertaining to educational attainment and family income was obtained via the use of an interviewer-administered questionnaire. Education was assessed in 20 increments as the highest grade (or year) of regular school completed, ranging from elementary through graduate school. Income was assessed in 11 increments as total combined family income for the prior 12-month period, ranging from <$5,000 up to $100,000+.

Anthropometrics

Height and weight measurements used to calculate BMI (kg/m^2) were obtained during clinical visits in accordance to standardized protocols, using calibrated instruments, and with participants wearing light clothing but no shoes[17]. Height was measured to the nearest 0.5 cm, and weight to the nearest 0.2 kg.

Health Behaviors

Information on smoking and drinking status was collected using standardized questionnaires. Smoking status was categorized as never, former, or current (smoked ≥100 cigarettes during their lifetime and smoked ≥5 cigarettes per week most weeks, for ≥3 months). Drinking status was classified as non-drinker or drinker (consumed any alcoholic beverages in past year). Physical activity for the prior year was assessed using the CARDIA physical activity questionnaire during every examination, with responses ranging from physically inactive (1) to very active (5).

Medical History and CVD Risk Factors

During medical examinations participants were asked about prior heart attacks/myocardial infarction (MI), stroke and transient ischemic attacks (TIA), as well as diagnoses of hypertension, dyslipidemia, and diabetes, and any medications taken to treat these conditions. Evidence of hypertension, dyslipidemia, or diabetes (as defined below) at any examination was used to indicate a history of these conditions (baseline, as well as years 2, 5, 7, 10, 15, and 20). Measures of blood pressure, blood lipids/lipoproteins, and glucose were obtained by trained and certified clinical staff members. Participants were asked to fast for at least 12 hours prior to the examination, as well as abstain from smoking or heavy physical activity for at least 2 hours prior.

Blood pressure measurements were taken from the right arm at 1-minute intervals after a 5-minute seated rest with a Hawksley random-zero sphygmomanometer, but with an automated device (Omron) beginning in Y20 (values were recalibrated in order to equate to random-zero values)[17]. The mean of the second and third measurements was used in analyses. Hypertension was defined as ≥140 mmHg for systolic blood pressure, ≥90 mmHg for diastolic blood pressure or use of anti-hypertensive medications[18].

Fasted blood draws were performed to ascertain lipid/lipoprotein and glucose concentrations. Total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, and glucose concentrations were directly measured; however, low-density lipoprotein (LDL) cholesterol concentration was calculated via the Friedewald equation[19]. Dyslipidemia was defined as triglycerides > 200 mg/dL, HDL < 40 mg/dL, LDL > 160 mg/dL, or the use of cholesterol-lowering medications (e.g. statins).

Fasting blood glucose and oral glucose tolerance tests were used to assess diabetes status. Diabetes was defined as exhibiting fasting blood glucose ≥126 mg/dL, 2-hour glucose ≥200 mg/dL, or the use of diabetes medications.

Carotid Intima-Media Thickness

The process for obtaining this measurement has been detailed previously[20, 21]. At the Y20 examinations only, high-resolution sonography was used to image the bilateral common carotid and internal carotid arteries. All images were obtained from the end of diastole, using the image with the lowest arterial diameter. The maximum IMT of each portion of the carotid artery was defined as the mean of the maximum IMT of the near and far wall on both sides (right and left).

Coronary Artery Calcification

The process for obtaining this measurement has been detailed previously[20, 21]. At the Y20 examinations only, each participant underwent 2 CT scans, each of which obtained 40 consecutive images from the root of the aorta to the apex of the heart[22]. A blinded reader read each participant's scan independently, identifying regions of interest for each potential focus of calcification. Calcification of the coronary artery was defined as having a positive Agatston score, averaging the 2 scans[23].

Dietary Assessment

Dietary data from years 0 (1985) and 20 (2005) were obtained via the use of an interviewer-administered CARDIA diet history. Detailed dietary assessment information has been described previously [24]. Dietary data were used to calculate the HEI (1995) scores for years 0 and 20, as this version of the HEI falls exactly in the midpoint between the years in which these diet histories were administered. The HEI-95 contains 10 components, each having a possible score of 0-10. The two main types of components are those for which adequate consumption is suggested (i.e. grains, vegetables, fruits, milk, meat, variety) and those for which limited consumption is suggested (total fat, saturated fat, cholesterol, sodium). Upper thresholds, i.e. a score of ten, for the adequacy components are unique to gender and age ranges, and are contingent upon recommended caloric ranges based on these criteria. Cholesterol, sodium, and variety are absolute ranges independent of gender or age, but total and saturated fat are calculated as percentages of total calories, and therefore contingent upon the gender-age calorie recommendations. [25]

Analytic Sample

The total sample size used in the analysis was 1,937 (Table 1). The total CARDIA study sample for which baseline and Y20 data were available was 3,549 but was reduced for our analyses by 897 due to valid data being unavailable for diet history (either missing or having implausible total energy intakes, i.e. <800 kcal/day or >5,000 kcal/day for men and <600 kcal/day or >4,000 kcal/day for women[26]), and was further reduced by 715 due to unavailable outcome or covariate information . The exclusion of people with missing covariate information from the entire analytic sample was done to ensure homogeneity of analytic samples among unadjusted and adjusted models. When compared with the full CARDIA cohort, the analytic sample was not significantly different in terms of age or sex distribution, but did have less black participants (41.2% vs. 51.6%), and a slightly different distribution among field centers (Supplemental Table 1).

Statistical Analyses

The independent variables of interest in all regression models were 1) participants' HEI-95 scores at Y20, controlling for HEI-95 at baseline, and 2) the change in HEI-95 scores between baseline and Y20 (Y20 minus baseline). The dependent variables of interest were CIMT and CAC. Due to the continuous nature of CIMT, linear regression analysis was used to assess the associations between HEI-95 at Y20 and CIMT. Conversely, the presence of CAC was defined as an Agatston score greater than 0, signifying that calcium deposits are present in the coronary artery. Due to the binary nature of CAC, logistic regression analysis was used to assess the associations between HEI-95 at Y20 and CAC, setting a score of 0 as the reference group. All models excluded participants with a history of myocardial infarction and/or stroke/transient ischemic attack.

These models were first analyzed without the inclusion of covariates (unadjusted), and were then analyzed including the following covariates: age, sex, race, field center, education, family income, total energy intake, BMI, physical activity, smoking status, drinking status, and history of hypertension, dyslipidemia, or diabetes (fully adjusted models). Additionally, sensitivity analyses were conducted to test for the robustness of

associations by adding these covariates to the unadjusted analyses in groups, namely: age, sex, race, field center (Model 2); Model 2 plus education and income (Model 3); Model 3 plus total energy intake and BMI (Model 4); Model 4 plus physical activity, smoking status, and drinking status / alcohol consumption (Model 5); Model 5 plus history of hypertension, dyslipidemia, and diabetes (Fully Adjusted Model).

The variables pertaining to history of hypertension, dyslipidemia, and diabetes were coded as 0 for no history, and 1 as having a history of these conditions, setting 0 as the reference group. Smoking and status were coded a never (0), former (1), or current (2), with never (0) set as the reference group. Drinking status was coded as either non-drinker (0) or drinker (1), with non-drinker set as the reference group (0). The reference group for sex was male, for race was black, and for field center was Oakland. All other variables were either continuous or ordinal in nature and a reference group was not assigned.

To examine whether the structure of the change in HEI variable might impact associations with CIMT or CAC (it showed very low skewness and kurtosis, but had a standard deviation approaching twice that of the mean), it was also transformed into quartiles and used in the aforementioned regression analyses.

Furthermore, the following items were assessed pertaining to baseline and Y20 HEI scores: correlation (Pearson) between scores, significant differences between the HEI scores (paired T-test), and multicollinearity (evaluated in linear regression models via variance inflation factor).

All statistical analyses were performed in SAS version 9.3 (SAS, Cary, NC).

Results

The average age of the analytic study population at the Y20 examination was 45.5 years, with 56.0% of participants being female, and 41.2% black. The average baseline HEI score was 65.5 (out of 100), and increased significantly from baseline to Y20 by an

average of 6.8 points. Female participants had significantly higher HEI scores than male participants at both baseline (68.02 vs. 62.21) and Y20 (74.22 vs. 69.65). Similarly, white participant had higher HEI scores than black participants at both baseline (67.31 vs. 62.83) and Y20 (73.89 vs. 69.82) (Table 1).

The multivariable linear regressions between HEI scores and CIMT are presented in Table 2.

When assessing participants' Y20 HEI scores, controlling for baseline HEI, a negative association was observed in the unadjusted model between Y20 HEI and CIMT ($p=0.0002$, βcoeff.$=-0.0013$). This association was not robust; however, as it did not remain significant when the all covariates were included in the fully adjusted model (age, sex, race, field center, education, family income, total energy intake, BMI, physical activity, smoking status, drinking status, and history of hypertension, dyslipidemia, or diabetes). Change in HEI, i.e. Y20 minus baseline, was not significantly associated with CIMT in either the unadjusted or fully adjusted models.

The multivariable logistic regressions between HEI scores and CAC are presented in Table 3.

When assessing participants' Y20 HEI scores, controlling for baseline HEI, a negative association was observed in the unadjusted model between Y20 HEI and CAC (OR=0.986, 95% CI=0.976, 0.996). This association was not robust; however, as it did not remain significant when the all covariates were included in the fully adjusted model. Change in HEI was not significantly associated with CAC in either the unadjusted or fully adjusted models.

For the models wherein baseline and Y20 HEI scores were run simultaneously, multicollinearity was not detected for these variables, as the variance inflation factors for each score were well below 5 in all cases.

Sensitivity analyses examining the robustness of the aforementioned models, adding covariates in a step-wise fashion, can be found in Supplemental Tables 2-5.

Discussion

Associations between CVD and adherence to USDA dietary recommendations, as assessed by the HEI, have tended to focus on disease endpoints and early risk factors[3-7]. In order to complete the etiological spectrum, however, it is important to examine this dietary relationship utilizing indicators of atherosclerosis, i.e., CAC and CIMT. Additionally, as diet is a malleable aspect of one's overall disease risk, evaluating change in HEI score may yield useful insights for public health research. Using a geographically diverse sample this study examined how HEI may relate to both CIMT and CAC, examining these relationships with HEI in middle age (controlling for HEI at baseline), and separately with change in HEI score as the independent variables of interest.

Significant cross-sectional associations were observed in unadjusted models assessing HEI score at Y20, controlling for baseline HEI, with CIMT ($p=0.0002$, **β**coeff.=-0.0013) and CAC (OR=0.986, 95% CI=0.976, 0.996). Finding significant relationships in both CIMT and CAC is reflective of research showing CIMT and CAC to be correlated with one another [27, 28] (although this relationship is not without discrepancies[29]). As pertains to CIMT, this relationship implies that every 1 point increase in Y20 HEI score, controlling for baseline HEI, is associated with a 0.0013 mm smaller CIMT. Given that the average improvement in HEI score from baseline to Y20 was just under 7, this would be associated with a 0.0091 mm smaller CIMT on average. Were this relationship causal, its clinical significance might be questionable, as the healthy range for CIMT can vary by tenths of millimeters[30], and studies examining CIMT's value in predicting CVD events assessed associations by 0.1 mm[31] and 0.03 mm/year[32] increases in CIMT.

As pertains to CAC, this relationship demonstrates that an increase in Y20 HEI score, controlling for baseline HEI, is associated with a decreased odds of experiencing CAC (OR=0.986, 95% CI=0.976, 0.996). Given the intricacies of interpreting odds ratios[33], clinical significance is difficult to infer from these findings. Furthermore, the prevalence of CAC in this population was 16%, well above the threshold of 10% prevalence wherein one may somewhat realistically, albeit perilously, interchange odds and risk ratios[34].

These caveats notwithstanding, prior work examining associations between established CVD risk factors and CAC has shown odds ratios of much greater magnitude, e.g. BMI: OR of 6.4 in men and 13.6 in women[35].

The non-robust findings of the association between Y20 HEI and CAC may be biological in nature, and related to potentially conflicting components of the USDA dietary guidelines. Prior research has shown a significant negative association between vitamin K2 intake, a fat soluble vitamin found solely in fat and cholesterol-laden animal products, and CAC[36], as well as coronary heart disease[37]. Since the USDA dietary guidelines discourage the consumption of such foods, it may be possible that a greater adherence to this component of the dietary guidelines may not be beneficial in terms of CAC. Should the diminished consumption of vitamin K2 in fact be deleterious to ones cardiovascular health, it may be mitigated, at least in part, by the other beneficial components of the dietary guidelines, e.g. fruits and vegetables[38]. Thus, if the associations between individual components of the HEI and CAC are in conflict, this could explain the small and non-robust association observed between the overall index and CAC.

Although the associations between CIMT and CAC with HEI score at Y20, controlling for baseline HEI, were statistically significant, they were not robust to the addition of the covariates in the fully adjusted model. Additionally, change in HEI was not significantly associated with either CIMT or CAC. Even when converting this variable into quartiles to account for its large variance, no significant associations were seen with either CIMT or CAC. This leads to the inference that in the CARDIA population, although HEI score at Y20 does appear to relate to CIMT and CAC (in the unadjusted model, i.e. a cross-sectional association), change in diet does not (i.e. an incomplete proxy for a longitudinal association).

The present study draws upon the rich dataset generated by the long-running CARDIA study. The CARDIA study cohort is especially suited to this endeavor because the population at the Y20 examinations were old enough (38-50 years) to have developed some CAC and increased CIMT, yet were not so advanced in age to have experienced a

large proportion of MI/stroke. The use of dietary measures obtained at such a large interval of 20 years permitted a rarely accessible vantage point from which to assess changes in diet. Furthermore, since the baseline dietary data preceded both the introduction of the Food Guide Pyramid, and the Nutrition Labeling and Education Act, and since Y20 HEI scores were significantly higher on average, comparing baseline to Y20 HEI score yielded a snapshot into how these campaigns may have influenced diet-mediated CAC and CIMT in this population. The multicenter nature of the study allows for greater generalizability of these findings, and the substantive proportion of minority participants (41.2% black) afforded the ability to identify associations between race and CIMT/CAC supportive of previous research[39-41]. Using the non-invasive and relatively inexpensive measures of CIMT and CAC offers advantages over more commonly evaluated CVD risk factors in that they are more demonstrative of actual atherosclerosis. Furthermore, these measures offer advantages over using hard disease endpoints (e.g. MI or stroke) in that they are still early enough in the CVD process that non-invasive interventions, such as lifestyle modifications, may still be effective.

Notwithstanding the strengths of this study, some limitations remain. Although the CARDIA diet histories used in this study were meticulously and rigorously obtained[24], dietary recall methods cannot flawlessly capture one's eating behaviors. Other covariates also relied on self-report, e.g., education, family income, physical activity level, and drinking status, and thus may have introduced error into the analyses. Additionally, despite the large size of the original sample (n=3,549), 25% of these did not have valid dietary information, and a similar percentage did not have available data on other variables (Supplemental Table 1). Furthermore, while every effort was made to control for confounding variables, the possibility of residual confounding of the associations of interest still remains. Lastly, as measures of CIMT and CAC were only measured at Y20, a longitudinal approach could not be utilized.

The results of this study draw attention to the importance of diet on cardiovascular health, but warrant additional investigation. Specifically, the cardiovascular clinical significance

of modifying one's diet in accordance to the DGA, as well as the utility of the HEI framework for diet assessment should be explored.

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KPK was involved in the conception and design, analysis and interpretation of data, drafting and revision of the article, and final approval of the version to be published. SEJ and JMS were involved in the conception and design, analysis and interpretation of data, revision of the article, and final approval of the version to be published. EBL was involved in the analysis and interpretation of data, revision of the article, and final approval of the version to be published. DCG was involved in the revision of the article, and final approval of the version to be published.

References

1. (2010) Report of the DGAC on the Dietary Guidelines for Americans, 2010 [U CNPP, editor].
2. Miniño A, Murphy S, Xu J, Kochanek K (2011) Deaths: final data for 2008. *National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System* **59**, 1-126.
3. Chiuve S, Fung T, Rimm E, Hu F, McCullough M, Wang M *et al.* (2012) Alternative dietary indices both strongly predict risk of chronic disease. *The Journal of nutrition* **142**, 1009-1018.
4. Rathod A, Bharadwaj A, Badheka A, Kizilbash M, Afonso L (2012) Healthy Eating Index and mortality in a nationally representative elderly cohort. *Archives of internal medicine* **172**, 275-277.
5. Nicklas T, O'Neil C, Fulgoni V (2012) Diet quality is inversely related to cardiovascular risk factors in adults. *The Journal of nutrition* **142**, 2112-2118.
6. Shah BS, Freeland-Graves JH, Cahill JM, Lu H (2010) Diet quality as measured by the healthy eating index and the association with lipid profile in low-income women in early postpartum. *Journal of the American Dietetic Association* **110**, 274-279.
7. Drewnowski A, Fiddler EC, Dauchet L (2009) Diet quality measures and cardiovascular risk factors in France: applying the Healthy Eating Index to the SU. VI. MAX study. *Journal of the American College of Nutrition* **28**, 22-29.
8. Simon A, Megnien J-L, Chironi G (2010) The value of carotid intima-media thickness for predicting cardiovascular risk. *Arteriosclerosis, thrombosis, and vascular biology* **30**, 182-185.
9. Criqui MH, Denenberg JO, Ix JH, McClelland RL, Wassel CL, Rifkin DE *et al.* (2014) Calcium density of coronary artery plaque and risk of incident cardiovascular events. *JAMA* **311**, 271-278.
10. Taylor AJ, Bindeman J, Feuerstein I (2005) Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors: mean three-year outcomes in the Prospective Army Calcium (PACC) Project. *Journal of the American College of Cardiology* **46**, 807-814.
11. Wexler L, Brundage B, Crouse J, Detrano R, Fuster V, Maddahi J *et al.* (1996) Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. A statement for health professionals from the American Heart Association. Writing Group. *Circulation* **94**, 1175-1192.
12. Kennedy EB, S.A.; Lino, M.; Gerrior, S.A.; Bsiotis, P.P. (1997) Diet Quality of Americans: Healthy Eating Index. http://www.ers.usda.gov/media/91034/aib750e_1_.pdf. *USDA/ERS*.
13. The CARDIA Coordinating Center, Coronary Artery Risk Development in (Young) Adults (CARDIA): Year 0 Exam Manual of Operations. February 1985: The CARDIA Study Coordinating Center, University of Alabama at Birmingham.
14. The CARDIA Study Steering Committee, Coronary Artery Risk Development in (Young) Adults (CARDIA): Year 0 Exam Protocol . February 1985: The CARDIA Study Coordinating Center, University of Alabama at Birmingham.
15. Friedman G, Cutter G, Donahue R, Hughes G, Hulley S, Jacobs D *et al.* (1988) CARDIA: study design, recruitment, and some characteristics of the examined subjects. *Journal of clinical epidemiology* **41**, 1105-1116.

16. Cutter GRea (1991) Cardiovascular risk factors in young adults. The CARDIA baseline monograph. *Control Clin Trials* **12(1 Suppl)**, 1S-77S.
17. Folsom AR, Burke GL, Ballew C, Jacobs DR, Jr., Haskell WL, Donahue RP *et al.* (1989) Relation of body fatness and its distribution to cardiovascular risk factors in young blacks and whites. The role of insulin. *Am J Epidemiol* **130**, 911-924.
18. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Jr JL *et al.* (2003) The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *Jama* **289**, 2560-2571.
19. Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clinical chemistry* **18**, 499-502.
20. Raynor LA, Schreiner PJ, Loria CM, Carr JJ, Pletcher MJ, Shikany JM (2013) Associations of retrospective and concurrent lipid levels with subclinical atherosclerosis prediction after 20 years of follow-up: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Ann Epidemiol* **23**, 492-497.
21. Calderon-Margalit R, Siscovick D, Merkin SS, Wang E, Daviglus ML, Schreiner PJ *et al.* (2014) Prospective association of polycystic ovary syndrome with coronary artery calcification and carotid-intima-media thickness: the Coronary Artery Risk Development in Young Adults Women's study. *Arteriosclerosis, thrombosis, and vascular biology* **34**, 2688-2694.
22. Carr JJ, Nelson JC, Wong ND, McNitt-Gray M, Arad Y, Jacobs DR, Jr. *et al.* (2005) Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. *Radiology* **234**, 35-43.
23. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr., Detrano R (1990) Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* **15**, 827-832.
24. McDonald A, Van Horn L, Slattery M, Hilner J, Bragg C, Caan B *et al.* (1991) The CARDIA dietary history: development, implementation, and evaluation. *Journal of the American Dietetic Association* **91**, 1104-1112.
25. Kennedy E, Ohls J, Carlson S, Fleming K (1995) The Healthy Eating Index: design and applications. *Journal of the American Dietetic Association* **95**, 1103-1108.
26. Willett WC (1998) *Nutritional Epidemiology*. 2 ed. New York: Oxford University Press.
27. Oei H-HSH, Vliegenthart R, Hak AE, Iglesias del Sol A, Hofman A, Oudkerk M *et al.* (2002) The association between coronary calcification assessed by electron beam computed tomography and measures of extracoronary atherosclerosis: the Rotterdam Coronary Calcification Study. *Journal of the American College of Cardiology* **39**, 1745-1751.
28. Davis PH, Dawson JD, Mahoney LT, Lauer RM (1999) Increased carotid intimal-medial thickness and coronary calcification are related in young and middle-aged adults. The Muscatine study. *Circulation* **100**, 838-842.
29. Arad Y, Spadaro LA, Roth M, Scordo J, Goodman K, Sherman S *et al.* (1997) Correlations between vascular calcification and atherosclerosis: a comparative electron

beam CT study of the coronary and carotid arteries. *Journal of computer assisted tomography* **22**, 207-211.
30. Jarauta E, Mateo-Gallego R, Bea A, Burillo E, Calmarza P, Civeira F (2010) Carotid intima-media thickness in subjects with no cardiovascular risk factors. *Revista Española de Cardiologia* **63**, 97-102.
31. Lorenz MW, von Kegler S, Steinmetz H, Markus HS, Sitzer M (2006) Carotid intima-media thickening indicates a higher vascular risk across a wide age range. *Stroke* **37**, 87-92.
32. Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH *et al.* (1998) The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Annals of Internal Medicine* **128**, 262-269.
33. Szumilas M (2010) Explaining odds ratios. *Journal of the Canadian Academy of Child and Adolescent Psychology* **19**, 227-229.
34. Tajeu GS, Sen B, Allison DB, Menachemi N (2012) Misuse of odds ratios in obesity literature: an empirical analysis of published studies. *Obesity* **20**, 1726-1731.
35. Mahoney LT, Burns TL, Stanford W (1996) Coronary risk factors measured in childhood and young adult life are associated with coronary artery calcification in young adults: the Muscatine Study. *Journal of the American College of Cardiology* **27**, 277-284.
36. Beulens JWJ, Bots ML, Atsma F, Bartelink M (2009) High dietary menaquinone intake is associated with reduced coronary calcification. *Atherosclerosis*.
37. Gast GCM, de Roos NM, Sluijs I, Bots ML (2009) A high menaquinone intake reduces the incidence of coronary heart disease. *Nutrition*.
38. Houston MC, Cooil B, Olafsson BJ (2007) Juice powder concentrate and systemic blood pressure, progression of coronary artery calcium and antioxidant status in hypertensive subjects: a pilot study. … *and Alternative Medicine*.
39. Manolio TA, Burke GL, Psaty BM, Newman AB, Haan M, Powe N *et al.* (1995) Black-white differences in subclinical cardiovascular disease among older adults: the Cardiovascular Health Study. CHS Collaborative Research Group. *Journal of clinical epidemiology* **48**, 1141-1152.
40. D'Agostino RB, Burke G, O'Leary D, Rewers M, Selby J, Savage PJ *et al.* (1996) Ethnic differences in carotid wall thickness. The Insulin Resistance Atherosclerosis Study. *Stroke; a journal of cerebral circulation* **27**, 1744-1749.
41. Newman AB, Nieto FJ, Guidry U, Lind BK, Redline S, Pickering TG *et al.* (2001) Relation of sleep-disordered breathing to cardiovascular disease risk factors: the Sleep Heart Health Study. *American journal of epidemiology* **154**, 50-59.

Table 1. Descriptive statistics of analytic CARDIA study population (1985 and 2005, n=1,937); mean ± SEs unless denoted[1]

	Whole Sample	Female	Male	Black	White
	n=1,937	n=1,085 (56.0%)	n=852	n=798 (41.2%)	n=1,139
Age at Year 20 Exam	45.34 ± 0.08	45.27 ± 0.11	45.43 ± 0.12	44.62 ± 0.13[b]	45.84 ± 0.10[a]
Baseline HEI score	65.46 ± 0.25	68.02 ± 0.33[a]	62.21 ± 0.33[b]	62.83 ± 0.36[b]	67.31 ± 0.32[a]
Year 20 HEI score[2]	72.21 ± 0.26	74.22 ± 0.35[a]	69.65 ± 0.38[b]	69.82 ± 0.40[b]	73.89 ± 0.34[a]
Year 20 - Baseline HEI	6.75 ± 0.03	6.21 ± 0.41[a]	7.44 ± 0.42[b]	6.98 ± 0.47	6.58 ± 0.38
CIMT (mm)	0.89 ± 0.00	0.86 ± 0.00[b]	0.93 ± 0.01[a]	0.90 ± 0.01[a]	0.88 ± 0.00[b]
CAC Present (% Agatston=1)	19.31	11.61[b]	29.11[a]	17.29	20.72*
Education (years)	15.31 ± 0.06	15.31 ± 0.07	15.32 ± 0.09	14.29 ± 0.08[b]	16.03 ± 0.07[a]
Income Level (% making $100k+)	34.95	29.68[b]	41.67[a]	18.05[b]	46.80[a]
Total Energy Intake (kcal)	2303.79 ± 22.59	2015.89 ± 24.29[b]	2670.42 ± 37.42[a]	2285.14 ± 39.54	2316.85 ± 26.63
BMI (kg/m^2)	29.14 ± 0.16	29.33 ± 0.22	28.89 ± 0.21	31.13 ± 0.24[a]	27.74 ± 0.19[b]
Physical Activity Level (% at level 5 of 5)	14.97	12.53[b]	18.08[a]	17.17	13.43
Smoking Status (% non-smoker)	63.96	61.66[b]	66.90[a]	66.67[a]	62.07[b]
Drinking Status (% non-drinker)	80.43	79.08	82.16	70.18[b]	87.62[a]
History of High Blood Pressure (%)	25.30	23.96	27.00	36.97[a]	17.12[b]
History of Dyslipidemia (%)	50.54	28.29[b]	78.87[a]	43.23[b]	55.66[a]
History of Diabetes (%)	8.42	8.02	8.92	12.66[a]	5.44[b]

1. All values are means ± SEs unless otherwise indicated. Means with different superscript letters are significantly different, $p< 0.05$.Chi-squared tests were performed for all categorical variables, and Student's T-test for continuous variables.

2. The Pearson correlation coefficient between year 20 and baseline HEI scores was 0.32; however, the HEI scores were significantly different from one another (paired T-test, $p<0.05$)

Table 2. Multivariable regression of HEI-1995 adherence vs. Carotid Intima-Media Thickness (mm, assessed at year 20) in the CARDIA study population (1985 and 2005, n=1,937); at year 20 controlling for baseline, as well as the difference between year 20 and baseline, run separately.

	Unadjusted Model		Fully Adjusted Model	
	β coeff.	p-value	β coeff.	p-value
HEI Values Modeled Jointly				
HEI at Year 20 controlling for Baseline*	-0.0013	0.0002	-0.0005	0.1196
Difference between HEI Values				
HEI at Year 20 - Baseline	0.0002	0.5231	0.0001	0.6541

*Unadjusted model does include Baseline HEI when modeling association between HEI at Year 20 with CIMT

Fully adjusted models include the following covariates: age, sex, race, field center, education, family income, total energy intake, BMI, physical activity, smoking status, drinking status, and history of hypertension, dyslipidemia, or diabetes.

Participants with missing data for HEI, CAC, CIMT, or any of the aforementioned covariates for were excluded from analyses

All models exclude participants with a history of myocardial infarction and/or stroke/transient ischemic attack

Table 3. Multivariable logistic regression of HEI-1995 adherence vs. Coronary Artery Calcification (Agatston score 1 vs. 0, assessed at year 20) in the CARDIA study population (1985 and 2005, n=1,937); at year 20 controlling for baseline, as well as the difference between year 20 and baseline, run separately. Odds ratios and 95% confidence intervals presented.

	Unadjusted Model		Fully Adjusted Model	
	Point Est.	95% CI	Point Est.	95% CI
HEI Values Modeled Jointly				
HEI at Year 20 controlling for Baseline*	0.986	0.976, 0.996	0.997	0.986, 1.009
Difference between HEI Values				
HEI at Year 20 - Baseline	0.996	0.987, 1.004	0.996	0.987, 1.006

*Unadjusted model does include Baseline HEI when modeling association between HEI at Year 20 with CAC

Fully adjusted models include the following covariates: age, sex, race, field center, education, family income, total energy intake, BMI, physical activity, smoking status, drinking status, and history of hypertension, dyslipidemia, or diabetes.

Participants with missing data for HEI, CAC, CIMT, or any of the aforementioned covariates for were excluded from analyses

All models exclude participants with a history of myocardial infarction and/or stroke/transient ischemic attack

CHAPTER 5: ASSOCIATIONS BETWEEN SOCIOECONOMIC STATUS AND DIETARY PATTERNS IN US BLACK AND WHITE ADULTS

by

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Abstract:

Socioeconomic status (SES) has been associated with measures of diet quality; however, such measures have not directly captured individuals' overall eating practices. Based on factor analysis of 56 food groups from food frequency questionnaires, patterns of food consumption were examined for their associations with SES in a nationwide sample of 17,062 black (34.6%) and white participants (age > 45) from the REGARDS study. Logistic regression models adjusted for age, sex, racial group, and geographic region were used to examine adherence to five emergent dietary patterns (convenience, plant-based, sweets/fats, southern, and alcohol/salads) according to 4 levels each of individual education, household income, and community level SES. Further models assessed adherence to these dietary patterns by racial group, and an overall model including both racial groups examined if the relationships between SES and adherence to these dietary patterns differed among black and white participants. For all three measures of SES, higher SES was associated with greater adherence to plant-based and alcohol/salads patterns, but lower adherence to sweets/fats and southern patterns. Statistically significant differences between black and white participants were observed in the associations between household income and adherence to alcohol/salads, individual education and adherence to plant-based and sweets/fats, and community SES and adherence to convenience patterns. As dietary pattern adherence has been shown to be associated with health outcomes in this population, e.g. stroke, this study offers valuable insight into behavioral and environmental factors that may contribute to health disparities in the diverse US population.

Introduction

Health disparities in the United States are notable among groups of differing socioeconomic status (SES) and race [1-4]. While various explanations have been given for these disparities, both biological and non-biological [5-12], a recurring and etiologically relevant theme has been differences in diet [13-20]. In order to ameliorate diet-mediated health disparities, it is necessary to identify diets that are associated with given health outcomes, e.g. cardiovascular disease (CVD), and to recognize where disparities exist in the selection and adherence to said diets.

Previous studies investigating the associations between diet, race, and SES have assessed diet in various ways. Earlier work focused on examining individual nutrients, as well as groupings of nutrients, both macro and micro [13; 14]. While scientifically and physiologically relevant, this approach does not reflect the manner in which most people select and consume foods. In order to assess dietary intake more holistically, other researchers have used hypothesis/investigator-driven (*a priori*) dietary indices in their analyses, which take into consideration patterns of foods consumed together [16; 18; 20]. More recently, data-driven/hypothesis neutral (*a posteriori*) dietary patterns have been used to analyze these relationships, with dietary patterns serving as a proxy for a variety of factors that influence how individuals consume foods, including social, cultural and financial contributors [15; 17; 19]. However, limited research has been conducted on how one's racial group and SES may impact dietary pattern adherence, especially patterns demonstrated to be related to health outcomes.

Our team of investigators have previously shown dietary pattern adherence to be associated with risk of incident stroke, contributing to excess risk in black Americans as compared with white Americans[21]. The present study seeks to advance this work by using the dietary patterns from our prior study to examine the relationships between SES and food choice and how these relationships may differ according to race. Although adherence to only some of the dietary patterns was significantly associated with risk of incident stroke (increased risk for southern, reduced for plant-based and sweets/fats

patterns), all previously derived patterns were used in the present study as our team's examinations of potential associations between dietary patterns and CVD are ongoing, and may yield further insights germane to the present study's findings. The population used for this study is especially well suited to this endeavor as it is quite large, nationwide, includes persons of varying levels of SES (both individual level and community level indicators), and includes a percentage of black participants (34.6%) large enough to explore racial differences.

Methods

Study Design

The REasons for Geographic And Racial Differences in Stroke (REGARDS) study is observational in nature and comprised of a population-based random sample (n=30,239) of men and women of black and white racial groups over the age of 45 years [(22)]. The original intent of this study was to elucidate the factors that increase one's risk of having a stroke. Recruitment occurred between January 2003 and October 2007, and the baseline data used in the current analyses were cross-sectional in nature; however, the study is ongoing. A related list from the same vendor used by the US Behavioral Risk Factor Surveillance System (BRFSS) was employed to recruit individuals. The study intentionally oversampled both blacks and residents of the stroke belt, a region of the southeastern US where people have substantially increased risk for stroke (Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, Tennessee, and South Carolina). Initial contact with participants was conducted via a mass mailing to inform participants they would be contacted via telephone to discuss participation. This call lasted approximately 45 minutes, and data were collected on self-reported race, risk factor characterization, socio-economic status (SES), and medical history. An in-home visit by a trained health professional followed the phone session, during which they obtained written consent and blood and urine samples. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Institutional Review Board at all participating institutions. Written informed consent was obtained from all participants.

Analysis Variables

Socioeconomic Status: Measurements Utilized

The present study assessed SES using education, income, and a community-level index [23]. Education is reasonably stable well into adulthood [24] (matching the composition of the REGARDS population), and has been shown to capture lifestyle/behavioral practices [24]. Income can influence access to goods such as healthful foods [24], and has been shown to impact diet independently of education [25]. The community-level index used in the present study included measures of assets, home value and occupational prestige (in addition to income and education) [23]. These additional measures are informative in that: 1) assets may help one successfully weather financial storms better than income alone [24], 2) one's home is typically the largest asset and its value has been shown to be associated with health behaviors and outcomes [26], and 3) occupational prestige can be demonstrative of one's standing in society and allostatic load independently of income [24; 27]. Including all these measures into a composite index at the community level offers an additional insight by revealing where characteristics of one's community may uniquely influence health behaviors *vis-à-vis* one's personal/family characteristics [28]; furthermore, such indices are being increasingly used in attempts to capture the polyfaceted nature of SES [29].

Assessment of Individual Education and Household Income

Level of education achieved and annual household income was self-reported during the initial phone interview session. Annual income was categorized into four groups: up to $20,000, $20,000-$34,999, $35,000-$74,999, $75,000+. The four levels of education response options were less than high school (non-high school graduate), high school graduate or GED, some college, and college graduate or above. Participants could refuse to provide both income and education.

Assessment of Community Level Socioeconomic Status

The geographical area used to assess community level SES was the US census block group (units averaging 1,000 people). Using 2000 US census data, the method developed

by Diez-Roux *et al* [23] was employed to assess community level SES through six representative measures of education, wealth/income, and occupational prestige. Two of these measures are given as dollar values: Median household income and median value of housing units. The other four measures are given as percentages: Households with interest, dividend, or rental income; adults who completed high school; adults who completed college; and residents employed in executive, managerial, or professional occupations. Z-scores were calculated for each measure and then added together to create a comprehensive score, with the lower number representing lower SES. To reflect the structure of the individual level indicators of income and education, this variable was transformed into a categorical variable with 4 quartiles.

Dietary Assessment

The Block98 food frequency questionnaire (FFQ) was given to the participants during the in-home visit with detailed directions on how to complete it and instructions to mail all forms to the REGARDS Coordinating Center at the University of Alabama at Birmingham. The Block98 FFQ (www.NutritionQuest.com) is a well-validated instrument for measuring a majority of nutrients [30], and other versions of the FFQ have been further validated in diverse populations [31]. The Block98 FFQ used in REGARDS was developed by Block Dietary Data Systems (Berkeley, CA) and distributed by NutritionQuest. The Block98 FFQ includes 150 multiple-choice questions to obtain information about the frequency and portion consumed, as well as preparation of, 107 food items. Forms were collected, scanned, and verified by at least two trained personnel at the REGARDS Coordinating Center, the results of which were sent to NutritionQuest for scoring and quantification of intake.

Dietary Pattern Derivation

Using the original 107 food items, 56 food groups were constructed based on criteria such as nutrient similarities, culinary use, and previous studies [21]. These 56 food groups were then used to derive the dietary patterns in the REGARDS cohort with FFQ data (n=21,636) via a form of exploratory factor analysis, i.e. principal components analysis (PCA) (the detailed description of the dietary pattern derivations in REGARDS has been

published [21]). A random split sample method was used to validate the patterns and ensure their ability to be replicated. The second half of the sample was used to carry out confirmatory factor analysis (CFA) to validate the PCA analyses, and only food groups with absolute value loadings exceeding 0.20 for a given factor were included in the initial CFA model. Five dietary patterns emerged from these analyses: Convenience, Plant-based, Sweets/Fats, Southern, and Alcohol/Salads (see Table 1 for the top 10 factor loadings, Supplemental Table 1 for a more comprehensive list). For each participant in the study, the factor loading of each food group was multiplied by the average consumption of each food group in order to calculate their factor scores for each dietary pattern. Dietary pattern adherence was determined by splitting individual factor scores at the median. For a given dietary pattern, participants with a factor score above the median were categorized as high adherers, whereas individuals with a factor score below the median were categorized as low adherers. The adherence of a participant to any given dietary pattern did not preclude the participant from being a high or low adherer to any other dietary pattern.

Analytic Sample

The total sample size used in the analyses was 17,062 (Table 2). The total original REGARDS study (2003-2007) sample size was 30,183 but was reduced for our analyses due to data being unavailable for FFQ (n=8,547), as well as measures of SES (n=4,574). When compared with the full REGARDS cohort, the analytic sample was not significantly different in terms of age, sex, or region. Due primarily to lower rates of return for FFQ's among black participants, there were significantly less black participants as a percentage of the sample in the analytic sample (34.6%) than in the full REGARDS cohort (41.5%), but still enough to detect racial differences, and still a percentage at least that of the general U.S. population (13.2%) [32] (see Supplemental Table 2). All results (descriptive statistics and logistic regressions) presented in the following section make use of the analytic sample.

Statistical Analyses

Logistic regression was used to assess the associations between adherence to dietary patterns and measures of individual education, household income, and community level SES. Analyses were run with only one dietary pattern per model (the dependent variable in each model), and were first run in the overall population sample, and then by racial group. In the overall model covariates included age, racial group, gender, and region (stroke belt, stroke buckle, defined as 153-counties in the coastal plains of North Carolina, South Carolina and Georgia, and non stroke belt), whereas in the models analyzed by racial group covariates included age, gender, and region. Three interaction variables were created to test for interactions between racial group and socioeconomic variables: race*individual education, race*household income, and race*community level SES. When the interaction terms were statistically significant, analyses were stratified by racial group. A significant interaction was considered to be $p < 0.05$.

All assessments of the significance of associations were taken from the Type III analysis of effects/Wald Chi-square test, and odds ratio estimates were obtained from the point estimate and 95% Wald confidence limits. SAS Version 9.3 (SAS, Cary, NC) was used for all analyses.

Results

The average age of the study sample was 64.7 years, with 54.4% being female (Table 2). In the sample, 34.6% of the population was black, 38.4% were in the highest bracket of education and 19.4% were in the highest bracket of income.

The associations between SES measures and adherence to dietary patterns for the overall sample, i.e. both black and white participants, are presented in Table 3 as odds ratios (OR) with confidence intervals. Those participants in the highest vs. lowest tiers of all SES measures - household income, individual education, and community level SES - were significantly more likely to adhere to plant-based and alcohol/salads dietary patterns

(OR>1), but less likely to adhere to either sweets/fats or southern dietary patterns (OR<1). Additionally, participants in the highest vs. lowest tiers of both individual education and community SES, but not household income, were more likely to adhere to the convenience dietary pattern.

Interactions between racial group and socioeconomic variables were tested in the overall sample using the following interaction terms in the logistic regression models: race*individual education, race*household income, and race*community level SES. As denoted by asterisks in table 3, statistically significant differences between black and white participants were observed in the associations between household income and adherence to alcohol/salads, individual education and adherence to plant-based and sweets/fats, and community SES and adherence to convenience patterns. Given the significant racial differences in the associations between measures of SES and adherence to dietary patterns, these associations were analyzed for each racial group. Although the magnitude of adherence differed significantly by racial group for some dietary patterns and measures of SES, the direction of adherence was the same for both black and white participants (Table 4).

When further including lifestyle/demographic variables such as smoking, physical inactivity, and BMI (Supplemental Tables 3 & 4), all of these associations were maintained except that those participants in the highest vs. lowest tiers of income (overall sample only) were now more likely to adhere to the convenience pattern, but no longer any more or less likely to adhere to the plant-based dietary pattern. These shifts are not surprising given the close proximity of the previous confidence intervals to 1, and the fact that health behaviors tend to be related to one another [33; 34].

Discussion

Although a number of studies have investigated the associations between diet, race, and SES, the majority of research has assessed diet either according to its component nutrients [35-37], or using prescribed, *a priori* dietary indices [16; 18; 20; 38]. These

assessments, while informative in their own right, may not entirely incorporate or reflect underlying patterns of food choice. By using *a posteriori* dietary patterns, researchers are able to see how foods group together in the diet and which foods make up a large portion of the diet [39], allowing for more effective behavioral and policy-based interventions. Using a large nationwide sample and *a posteriori* dietary patterns, some of which have previously been demonstrated to be associated with risk of incident stroke [21], this study examined how SES, both individual and community level, as well as racial group, may be associated with the dietary patterns that people choose to follow.

All measures of SES were positively associated with adherence to a plant-based dietary pattern; however, household income showed the weakest association with adherence to this pattern, leading to the conjecture that education may be a more important determinant of what could be described as a "healthy" diet than income alone. This finding is echoed by recent work in children demonstrating maternal education to be a more consistent predictor of diet than household income [40].

While both racial groups demonstrated positive associations between individual education and adherence to the plant-based dietary pattern, education in whites was more strongly associated with adherence to this pattern as compared with blacks. This finding brings to mind existing racial disparities in educational attainment, namely that the percentage of persons educated at the collegiate level and beyond is higher among whites than blacks [41; 42]. The racial disparity in plant-based diet adherence, compounded by disparities in educational attainment, may contribute to racial health disparities since the consumption of fruits, vegetables, and legumes appears similarly beneficial for both black and white Americans [43; 44]. Although initiatives to close the higher education gap are currently in place, our research evidences the importance of implementing such initiatives as a potential tool to prevent diet-mediated racial disparities in health.

A unique pattern that emerged from the factor analyses was the alcohol/salads pattern. Adherence to this pattern was positively associated with all indicators of SES. The race by household income interaction was significant in this pattern, with greater adherence

seen in whites in the highest income category than blacks in the same income category. This racial difference is not entirely surprising given the fact that the percentage of the white population who are current drinkers exceeds that of the black population by 15% [45]. Furthermore, heavy alcohol consumption such as binge drinking has been shown to increase relative to income more in whites than blacks [46; 47]. Although green salads are a positive component of the alcohol/salads pattern, the results of these analyses, taken in the aforementioned context, reveal the potential need for public health initiatives to encourage responsible consumption of alcohol among higher-earning white Americans.

Our data show that adherence to dietary patterns in both blacks and whites was in the same direction in all significant relationships, but that the magnitude of adherence between the racial groups was different in some instances. This demonstrates that while one's racial group may be an influential factor in determining food choice, stark dichotomies are not observed merely due to race.

An important message that can be gleaned from the results of this study is that SES may supersede culinary traditions in some instances. This is most clearly demonstrated when looking at the southern dietary pattern. In a previous study examining black and white older adults in the southeast, education was negatively associated with a preference for typical southern foods [48]. Our findings support this study, since in every indicator of SES used in our study, and in both racial groups (no race*SES indicator interactions were significant), SES was negatively associated with adherence to the southern dietary pattern. The ability of education, income, and/or SES to overcome the ties of cultural lifestyle observances, especially when those observances could be deleterious to one's health, may prove hopeful in public health campaigns (e.g. encouraging those persons in the lower tiers of SES who are strongly adherent to this pattern to reduce their consumption of fried and processed meats, as well as sugar-sweetened beverages). However, in order for increasing one's education to have an independent effect on diet choice, education itself must be the driving force behind this association, perhaps exerting its effect by increasing one's health literacy. This relationship, however, remains

to be conclusively known, and perhaps educational attainment may be, to some extent, a marker for familial characteristics, or even greater self-efficacy.

This study was unique due to a confluence of elements. By using dietary patterns previously shown to be associated with risk of incident stroke [21], this study was able to address how SES and/or one's racial group relate to diet selection, and sheds light on how such disparities in diet may impact disparities in health outcomes observed among such groups. The use of a nationwide dataset allows for generalizability beyond the southeastern US, a region with increased cardiometabolic risk and the original impetus for the REGARDS study. Furthermore, the population included persons of varying levels of SES (both individual level and community level indicators) as well as a substantial number of minority participants (34.6% black), especially as compared to previous studies in this arena. The large number of black participants strengthened the study by providing the power to detect significant interactions between variables within racial groups.

Despite the many strengths of the study, a number of limitations persist. While the FFQ used has been validated in a population similar to that of the present study [31], no self-reported diet measures can perfectly represent actual food consumption, especially when the recall period is an entire year. Self-report was also utilized in the collection of measures of household income and education. Since data on household size were not available, it was not possible to ensure that household income was assessed homogenously across all study participants, and this may have introduced some uncertainty in the analyses using household income. However, given that the relationships between household income and adherence to the dietary patterns mirrored the relationships between the other measures of SES and adherence to the dietary patterns (except for the convenience pattern, which approached significance), this does not appear to be of great concern. Although diet cost has been associated with diet quality in the literature [49-52], data pertaining to food purchases were not available in this sample. As a result, the putative impact of income on food accessibility, and therefore dietary pattern selection, unfortunately could not be directly assessed in this population. Although the

sample size for this study was quite large at n=17,062, almost half of the REGARDS cohort did not have sufficient SES or nutrition data for inclusion in this study (see Supplemental Table 1). Additional research needs to be conducted in order to more fully understand the underlying reasons behind the associations revealed in the present study, such as accessibility to food outlets, time constraints in food preparation, and taste preferences, among others.

This study provides insight into how groups differing by SES and/or race currently consume food, and serves as a springboard for further elucidation of diet-mediated health disparities. Given the complex nature of diet selection, intervention studies should be designed to more fully isolate the effects of specific SES components. Based upon knowledge gleaned from this study, as well as future studies, interventions can be more effectively designed to shift people's dietary patterns and practices towards ones that are healthier. Such interventions may not only ameliorate observed health disparities among groups, but also raise the overall level of health for the general population.

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KPK was involved in the conception and design, analysis and interpretation of data, drafting and revision of the article, and final approval of the version to be published. SEJ was involved in the conception and design, analysis and interpretation of data, revision of the article, and final approval of the version to be published. KEP, JMS, and JRF were involved in the interpretation of the data, revision of the article, and final approval of the version to be published.

References

1. CDC (2009) Morbidity and Mortality Weekly Report: Differences in Prevalence of Obesity Among Black, White, and Hispanic Adults - United States, 2006-2008, vol. 58, pp. 740-744.
2. CDC (2011) Health Disparities and Inequalities Report - United States. www.cdc.gov/features/healthdisparitiesreport/pdf/chdir_executivesummary.pdf (accessed June 2014).
3. NIH (2011) Strategic Plan for NIH Obesity Research. NIH Publication No. 11-5493: National Institues of Health, Department of Health and Human Services.
4. Go A, Mozaffarian D, Roger V *et al.* (2014) Executive summary: heart disease and stroke statistics-2014 update: a report from the American Heart Association. *Circulation* **129**, 399-410.
5. Baum A, Garofalo J, Yali A (1999) Socioeconomic status and chronic stress. Does stress account for SES effects on health? *Ann N Y Acad Sci* **896**, 131-144.
6. Duru O, Harawa N, Kermah D *et al.* (2012) Allostatic load burden and racial disparities in mortality. *J Natl Med Assoc* **104**, 89-95.
7. Gordon-Larsen P, Nelson M, Page P *et al.* (2006) Inequality in the built environment underlies key health disparities in physical activity and obesity. *Pediatrics* **117**, 417-424.
8. Hutch D, Bouye K, Skillen E *et al.* (2011) Potential strategies to eliminate built environment disparities for disadvantaged and vulnerable communities. *Am J Public Health* **101**, 587-595.
9. Islami F, Kahn A, Bickell N *et al.* (2013) Disentangling the effects of race/ethnicity and socioeconomic status of neighborhood in cancer stage distribution in New York City. *Cancer Cause Control* **24**, 1069-1078.
10. Mezuk B, Myers J, Kendler K (2013) Integrating Social Science and Behavioral Genetics: Testing the Origin of Socioeconomic Disparities in Depression Using a Genetically Informed Design. *Am J Public Health* **103**, S145-S151.
11. Olden K, White S (2005) Health-related disparities: influence of environmental factors. *Med Clin North Am* **89**, 721-738.
12. Snowden L (2012) Health and mental health policies' role in better understanding and closing African American-White American disparities in treatment access and quality of care. *Am Psychol* **67**, 524-531.
13. Aggarwal A, Monsivais P, Drewnowski A (2012) Nutrient intakes linked to better health outcomes are associated with higher diet costs in the US. *PloS one* **7**.
14. Bjørke-Monsen A, Roth C, Magnus P *et al.* (2012) Maternal B vitamin status in pregnancy week 18 according to reported use of folic acid supplements. *Mol Nutr Food Res* **57**, 645-652.
15. Cutler G, Flood A, Hannan P *et al.* (2011) Multiple sociodemographic and socioenvironmental characteristics are correlated with major patterns of dietary intake in adolescents. *J Am Diet Assoc* **111**, 230-240.
16. García-Arenzana N, Navarrete-Muñoz E, Peris M *et al.* (2012) Diet quality and related factors among Spanish female participants in breast cancer screening programs. *Menopause* **19**, 1121-1129.
17. Hare-Bruun H, Togo P, Andersen L *et al.* (2011) Adult food intake patterns are related to adult and childhood socioeconomic status. *J Nutr* **141**, 928-934.

18. Hiza H, Casavale K, Guenther P *et al.* (2013) Diet quality of americans differs by age, sex, race/ethnicity, income, and education level. *J Acad Nutr Diet* **113**, 297-306.
19. Nobre L, Lamounier J, Franceschini SC (2012) Preschool children dietary patterns and associated factors. *J Pediatr (Rio J)* **88**, 129-136.
20. Olmedo-Requena R, Fernández J, Prieto C *et al.* (2013) Factors associated with a low adherence to a Mediterranean diet pattern in healthy Spanish women before pregnancy. *Public Health Nutr* **17**, 648-656.
21. Judd SE, Gutiérrez OM, Newby PK *et al.* (2013) Dietary patterns are associated with incident stroke and contribute to excess risk of stroke in black Americans. *Stroke* **44**, 3305-3311.
22. Howard V, Cushman M, Pulley L *et al.* (2005) The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiology* **25**, 135-143.
23. Diez-Roux A, Kiefe C, Jacobs D *et al.* (2001) Area characteristics and individual-level socioeconomic position indicators in three population-based epidemiologic studies. *Ann Epidemiol* **11**, 395-405.
24. Shavers VL (2007) Measurement of socioeconomic status in health disparities research. *J Natl Med Assoc* **99**, 1013-1023.
25. Galobardes B, Morabia A, Bernstein MS (2001) Diet and socioeconomic position: does the use of different indicators matter? *Int J Epidemiol* **30**, 334-340.
26. Coffee NT, Lockwood T, Hugo G *et al.* (2013) Relative residential property value as a socio-economic status indicator for health research. *Int J Health Geogr* **12**, 22-22.
27. Adler NE, Stewart J (2010) Preface to the biology of disadvantage: socioeconomic status and health. *Ann N Y Acad Sci* **1186**, 1-4.
28. Robert SA (1998) Community-Level Socioeconomic Status Effects on Adult Health. *J Health Soc Behav* **39**, 18-37.
29. Oakes JM, Rossi PH (2003) The measurement of SES in health research: current practice and steps toward a new approach. *Soc Sci Med* **56**, 769-784.
30. Patterson R, Kristal A, Tinker L *et al.* (1999) Measurement characteristics of the Women's Health Initiative food frequency questionnaire. *Ann Epidemiol* **9**, 178-187.
31. Block G, Woods M, Potosky A *et al.* (1990) Validation of a self-administered diet history questionnaire using multiple diet records. *J Clin Epidemiol* **43**, 1327-1335.
32. USCB (2014) State & County QuickFacts. USA http://quickfacts.census.gov/qfd/states/00000.html (accessed October 2014).
33. Gillman MW, Pinto BM, Tennstedt S *et al.* (2001) Relationships of physical activity with dietary behaviors among adults. *Prev Med* **32**, 298-301.
34. Blair SN, Jr JDR, Powell KE (1985) Relationships between exercise or physical activity and other health behaviors. *Public Health Rep* **100**, 172-180.
35. Huffman F, Vaccaro J, Zarini G *et al.* (2012) Inadequacy of micronutrients, fat, and fiber consumption in the diets of Haitian-, African- and Cuban-Americans with and without type 2 diabetes. *Int J Vitam Nutr Res* **82**, 275-287.
36. Monsivais P, Aggarwal A, Drewnowski A (2012) Are socio-economic disparities in diet quality explained by diet cost? *J Epidemiol Commun H* **66**, 530-535.
37. Darmon N, Drewnowski A (2008) Does social class predict diet quality? *Am J Clin Nutr* **87**, 1107-1117.

38. Monsivais P, Drewnowski A (2009) Lower-energy-density diets are associated with higher monetary costs per kilocalorie and are consumed by women of higher socioeconomic status. *J Am Diet Assoc* **109**, 814-822.
39. Newby P, Tucker K (2004) Empirically derived eating patterns using factor or cluster analysis: a review. *Nutr Rev* **62**, 177-203.
40. Zarnowiecki D, Ball K, Parletta N *et al.* (2013) Describing socioeconomic gradients in children's diets - does the socioeconomic indicator used matter? *Int J Behav Nutr Phys Act* **11**, 44.
41. USCB. (2014) Educational Attainment in the United States: 2010 - Detailed Tables. Table 1. Educational Attainment of the Population 18 Years and Over, by Age, Sex, Race, and Hispanic Origin: 2010. https://www.census.gov/hhes/socdemo/education/data/cps/2010/tables.html (accessed October 2014).
42. NCES (2010) Status and Trends in the Education of Racial and Ethnic Groups. Table 26.1. http://nces.ed.gov/pubs2010/2010015.pdf (accessed October 2014).
43. Kolonel LN, Hankin JH, Whittemore AS *et al.* (2000) Vegetables, fruits, legumes and prostate cancer: a multiethnic case-control study. *Cancer Epidem Biomar* **9**, 795-804.
44. Brown LM, Swanson CA, Gridley G *et al.* (1998) Dietary factors and the risk of squamous cell esophageal cancer among black and white men in the United States. *Cancer Cause Control* **9**, 467-474.
45. SAMHSA (2007) National Survey on Drug Use and Health. Tobacco product and alcohol use. Table 2.46B. http://oas.samhsa.gov/NSDUH/2k7NSDUH/tabs/Sect2peTabs43to84.htm#Tab2.46B (accessed October 2014).
46. Spiegler D (1993) *Alcohol Use Among US Ethnic Minorities*: Diane Pub Co.
47. (2003) *Drugs, Alcohol, and Social Problems*: Rowman & Littlefield Publishers, Inc.
48. Yang Y, Buys D, Judd S *et al.* (2013) Favorite foods of older adults living in the Black Belt Region of the United States. Influences of ethnicity, gender, and education. *Appetite* **63**, 18-23.
49. Drewnowski A (2004) Obesity and the food environment: dietary energy density and diet costs. *Am J Prev Med* **27**, 154-162.
50. Drewnowski A, Darmon N (2005) Food choices and diet costs: an economic analysis. *J Nutr* **135**, 900-904.
51. Drewnowski A, Monsivais P, Maillot M (2007) Low-energy-density diets are associated with higher diet quality and higher diet costs in French adults. *J Am Diet Assoc* **107**, 1028-1032.
52. Darmon N, Briend A, Drewnowski A (2004) Energy-dense diets are associated with lower diet costs: a community study of French adults. *Public Health Nutr* **7**, 21-27.

Table 1. Principal component analysis-generated dietary patterns from the REGARDS study population (2003-2007) and their top 10 constituent food/beverage items, as ranked by factor loadings

Convenience		Plant Based		Sweets/Fats		Southern		Alcohol/Salads	
Food/Beverage Item	FL	Food/Beverage Item	FL	Food/Beverage Item	FL	Food/Beverage Item	FL	Food/Beverage Item	FL
Mixed dishes with meat	0.61	Veg. - cruciferous	0.59	Miscellaneous sugar[1]	0.54	Fried food	0.56	Salad dressing/sauces	0.55
Pasta dishes	0.59	Fruit	0.58	Dessert	0.53	Organ meat	0.47	Vegetable - green leafy	0.48
Mexican dishes	0.48	Veg. - green leafy	0.49	Bread	0.47	Processed meat	0.45	Wine	0.36
Pizza	0.45	Veg. - other	0.48	Chocolate	0.46	Eggs & egg dishes	0.42	Butter	0.32
Red meat	0.45	Veg. - dark yellow	0.41	Candy	0.40	Added fats	0.38	Liquor	0.31
Soup	0.44	Fish	0.38	Added fats[2]	0.40	SSB[4]	0.37	Coffee	0.30
Chinese dishes	0.44	Breakfast Cereal	0.38	Sweet breakfast foods	0.39	Bread	0.37	Eggs & egg dishes	0.29
French fried white potatoes	0.37	Beans/ Legumes	0.38	Margarine	0.38	Red meat	0.26	Condiments	0.29
Non-fried white potatoes	0.36	Soup	0.32	Highfat dairy[3]	0.37	Milk – Highfat[3]	0.24	Vegetable - tomato	0.27
Beans/ Legumes	0.36	Vegetable - tomato	0.32	Tea[4]	0.31	Soda[4]	0.24	Red meat	0.26

FL = Factor Loading

1. Includes items such as jelly, jam, syrup, and sugar in coffee/tea
2. Added fats includes shortening, lard, vegetable oil, olive oil, gravy, and mayonnaise
3. Highfat dairy includes dairy products made from whole fat milk, whereas Milk–Highfat only includes whole fat liquid milk
4. “Tea” includes unsweetened tea or tea sweetened with non-nutritive sweeteners, SSB (sugar-sweetened beverages) includes all beverages that use nutritive sweeteners other than 100% juice, “Soda” is a subset of SSB and includes only carbonated SSB

Table 2. Descriptive statistics of the REGARDS study population (2003-2007)*

		Whole Sample	Black	White
		n=17,062	n=5,911	n=11,151
Age (mean, std. dev.)		64.7 (9.3)	63.5 (8.9)	65.3 (9.4)
Race	Black	34.6		
Sex	Female	54.4	65.0	48.8
Region	Stroke Belt	33.9	32.4	34.7
	Buckle	21.3	18.2	22.9
	Non-Stroke Belt	44.8	49.4	42.4
Personal Education	<High school	9.1	14.8	6.0
	High school	24.9	26.8	23.8
	Some college	27.7	29.3	26.9
	College+	38.4	29.1	43.3
Personal Income	$20K	17.9	28.0	12.5
	$20K–$34K	27.1	30.3	25.5
	$35K–$74K	35.6	31.3	37.8
	$75k+	19.4	10.5	24.1
Community SES Index	Quartile 1	25.0	45.0	14.4
	Quartile 2	25.0	27.8	23.5
	Quartile 3	25.0	18.7	28.3
	Quartile 4	25.0	8.5	33.7
Current Smoker		14.0	17.5	12.2
Obese (BMI ≥ 30 kg/m^2)		37.0	48.8	30.7
Sedentary (≥4+ hours/day of screentime)		30.4	43.3	23.6

*Statistically significant differences ($p<0.05$) were observed between both races for all variables shown.
Chi-squared tests were performed for all categorical variables, and Student's T-test for continuous variables.

Unless otherwise indicated, values given are percentages

Table 3. Logistic regression of dietary patterns vs. SES indicators in the REGARDS study population (2003-2007, n=17,062)

	Convenience	Plant-based	Sweets/Fats	Southern	Alcohol/Salads
Household Income					
≤$20K	Ref	Ref	Ref	Ref	Ref
$20K–$34K	0.96 (0.87,1.06)	1.00 (0.90,1.10)	0.94 (0.86,1.04)	0.74 (0.66,0.82)	1.31 (1.19,1.45)
$35K–$74K	1.00 (0.90,1.10)	1.09 (0.99,1.20)	0.92 (0.84,1.02)	0.60 (0.53,0.66)	1.68 (1.52,1.86)
$75k+	1.09 (0.96,1.22)	1.16 (1.03,1.30)	0.65 (0.58,0.73)	0.44 (0.39,0.51)	2.35 (2.08,2.66)*
Personal Education					
<High school	Ref	Ref	Ref	Ref	Ref
High school	1.10 (0.97,1.24)	1.11 (0.99,1.26)	0.95 (0.84,1.07)	0.76 (0.66,0.87)	1.17 (1.03,1.34)
Some college	1.12 (0.99,1.27)	1.25 (1.11,1.42)	0.89 (0.79,1.01)	0.62 (0.54,0.71)	1.35 (1.19,1.54)
College+	1.23 (1.08,1.40)	1.82 (1.60,2.06)*	0.76 (0.67,0.86)*	0.43 (0.37,0.50)	1.50 (1.31,1.71)
Community SES[1]					
Quartile 1	Ref	Ref	Ref	Ref	Ref
Quartile 2	1.09 (1.00,1.20)	1.13 (1.03,1.23)	0.94 (0.86,1.03)	0.74 (0.67,0.82)	1.27 (1.16,1.39)
Quartile 3	1.19 (1.08,1.31)	1.22 (1.12,1.34)	0.83 (0.76,0.91)	0.52 (0.47,0.57)	1.46 (1.33,1.60)
Quartile 4	1.23 (1.11,1.36)*	1.56 (1.42,1.72)	0.60 (0.54,0.66)	0.35 (0.31,0.38)	2.05 (1.86,2.26)

1. Community SES z-scores were obtained using the 6-component method developed by Anna Diez-Roux, then stratified into quartiles. Components included: median household income, median value of housing units, percentage of households with interest, dividend, or rental income, percentage of adults who completed high school, percentage of adults who completed college, and percentage of residents employed in executive, managerial, or professional occupations

*Effects differ statistically by race (p-value < 0.05); see Table 4. Odds ratios and confidence intervals are given where p-values not indicated.

Covariates for income models include: age, sex, race, region, and education; Covariates for education models include: age, sex, race, region, and income; Covariates for community SES models include age, sex, race, and region

Additional thoughts and implications on healthcare costs

A large portion of the financial impacts of CVD is associated with acute CVD events that typically occur later in life, such as MI and stroke[12]. By 2030, the direct medical costs associated with stroke, coronary heart disease, and heart failure are projected to exceed $275 billion, more than triple the 2010 estimates. One of the major drivers in the increased expenditures on CVD treatment is the aging population [12]. Identifying low cost interventions, such as dietary modifications, that are effective in forestalling CVD events in older adults is paramount. While many specific diet components are related to cardiovascular health (e.g. dietary fat, dairy, eggs, and fruits/vegetables [96, 135-138]), humans do not typically consume foods in isolation. Understanding the natural groupings of foods in the diet can help inform the relationships linking diet, CVD, and CVD-related costs in a more holistic manner.

As previously shown in the REGARDS population, diet represents a potential opportunity to reduce the risk of developing CVD, and thereby related healthcare expenditures. This is especially true of the southern dietary pattern, since it has consistently been shown to be associated with incident stroke and MI[92]. Taking this relationship into account, we calculated the potential healthcare cost differences related to differences in participants' adherence to the southern dietary pattern (high vs. low adherence).

Statistical Methods

Five years of follow up data were used for all participants who had dietary pattern data and no history of CVD events at baseline. The beginning of this period was each participant's baseline (the date of the in home visit when participants were given the Block98 food frequency questionnaire), and the end of the period was either the date of an incident stroke or MI, or 5 years post-baseline for those without a CVD event. Participants without a CVD event at 5 years post-baseline were censored, and a Kaplan-Meier survival analysis was conducted to test for differences in rates of incident CVD events (MI and stroke tested separately) between those with high vs. low adherence to the southern dietary pattern.

Results

Statistically significant differences in rates of CVD events were observed between strata of adherence to the southern dietary pattern for both MI ($p<0.0001$) and stroke ($p=0.0003$). 4.8% of participants with high adherence to the southern dietary pattern experienced an MI during the 5-year follow up period (n=471 of 10,683), vs. 3.3% of those with low adherence (n=331 of 10,727). 2.9% of participants with high adherence to the southern dietary pattern experienced a stroke during the 5-year follow up period (n=309 of 10,681), vs. 2.2% of those with low adherence (n=238 of 10,724).

Cost of MI and Stroke

Due to the nature of the survivability of CVD events, and the relation of survival with cost, costs of events were weighted. In the REGARDS study, death from a CVD

event was defined as death within 1 month (28 days) of the event. Although a negligible proportion of REGARDS participants who had an incident stroke died as a result of that stroke, almost 40% of those participants who had an incident MI died as a result of the MI (Table 4). Deaths from MI were further stratified by whether the participant received treatment at the hospital before subsequently dying, or if they died from MI away from the hospital. The rationale for this place of death distinction is that since the vast majority of healthcare costs to treat MI are acute in nature, those who did not reach the hospital to receive treatment would have incurred effectively no cost. Non-fatal MI cost data were derived from Medicare Expenditure Panel Survey data by Kilgore *et al*, and reflect the incremental increase in healthcare costs due to MI for a period of 6 months post-MI. Cost data for fatal MIs among participants who died in hospital were obtained from Medicare Provider Charge Data, as these are more reflective of acute costs within 1 month of an MI. Codes included 280, 281, and 282 and were weighted by prevalence. Costs for fatal MIs among participants who died away from hospital were assumed to be a very conservative estimate of zero.

Table 4. Calculation of Weighted Cost per MI in REGARDS study population

		% of MIs in each category	Cost per MI
	Non-Fatal MI	62.4%	$38,370.00
Fatal MI	Died in Hospital	13.6%	$37,248.28
	Died away from Hospital	24.0%	$ -
Total Weighted Cost per MI			**$28,998.35**

Data for the cost of stroke came from Medicare Provider Charge Data ($37,517.60 per stroke). Codes included 064, 065, and 066 and were weighted by prevalence.

Medicare Provider Charge Data for both MI and stroke came from fiscal year 2011 (the most recent available at this time). Medicare Expenditure Panel Survey data utilized by Kilgore *et al* spanned 2000-2010.

Applying Cost-per-Event to Kaplan-Meier Analyses

Using the aforementioned weighted costs per event, the number of events in each strata of southern dietary pattern adherence was multiplied by their respective costs. The MI-related cost associated with high adherence exceeded that of the low adherence group by $4,049,768.39 over this time period in the whole population, i.e. $76.74 per person year. The stroke-related cost associated with high adherence exceeded that of the low adherence group by $2,450,769.60 over this time period in the whole population, i.e. $46.51 per person year.

When adding together the cost disparities related to southern dietary adherence for both MI and stroke, costs associated with high adherence exceeded those of the low adherence group by $6,510,517.99 over this time period in the whole population, i.e. $123.25 per person year.

Implications

In the REGARDS study population, we see that high adherence to the southern dietary pattern was associated with $123.25 in excess healthcare costs related to incident

CVD alone. Although this may seem like a small figure, given the almost 122M Americans in the same age range as the REGARDS study cohort (45 years and older)[139], the potential healthcare cost savings related to dietary improvements may be quite substantial.

In these analyses healthcare costs due to MI were weighted to account for differences in costs between fatal and non-fatal MI, as well as the significant cost differences between fatal MI in hospital vs. away from hospital. If MI deaths away from hospital partially result from disparities in access to care[140], then as such disparities are being addressed costs may be expected to increase. In the REGARDS population, for example, had all those participants who died from MI away from hospital been treated in hospital, the weighted cost per MI would have increased by 31%. In light of such considerations, as well as our findings, it may well be prudent to incorporate dietary interventions as a preventive measure to curb these costs.

CHAPTER 6: SUPPLEMENTAL MATERIALS AND EXPANDED FINDINGS

Added Sugars in the Diet are Positively Associated with Diastolic Blood Pressure and Triglycerides in Children

Supplemental tables and calculations appear on following pages

Supplemental Table 1. Regression analyses of diastolic and systolic blood pressures vs. added sugars and dietary sodium, run separately[1,2,3]

	Diastolic Blood Pressure		Systolic Blood Pressure	
	b Coeff.	95% CI	b Coeff.	95% CI
Added Sugars (g/d)	0.0206	0.0004, 0.0409	0.0126	-0.0226, 0.0478
Dietary Sodium (mg/d)	-0.0009	-0.0019, 0.0001	-0.0001	-0.0018, 0.0015

1. Models were linear regressions with statistically significant associations where 95% Confidence Intervals do not cross zero.
2. All analyses controlled for the following covariates: sex, race/ethnicity (dummy coded), socioeconomic status, Tanner pubertal status, body fat percentage, total physical activity, and total energy intake.
3. In the above models, the sample size for which all variables were available was n=220.

Supplemental Table 2. Regression analyses of blood lipids/lipoproteins vs. added sugars and dietary fat, run separately[1,2,3]

	Total Cholesterol		Triglycerides		LDL Cholesterol		HDL Cholesterol	
	b Coeff.	95% CI	b Coeff.	95% CI	b Coeff.	95% CI	b Coeff.	95% CI
Added Sugars (g/d)	0.0276	-0.0758, 0.1310	0.1090	0.0169, 0.2011	0.0318	-0.0668, 0.1304	-0.0127	-0.0546, 0.0293
Dietary Fat (g/d)	0.1087	-0.1732, 0.3906	-0.1351	-0.3781, 0.1079	0.0769	-0.1921, 0.3459	0.0496	-0.0651, 0.1642

1. Models were linear regressions with statistically significant associations where 95% Confidence Intervals do not cross zero.
2. All analyses controlled for the following covariates: sex, race/ethnicity (dummy coded), socioeconomic status, Tanner pubertal status, body fat percentage, total physical activity, and total energy intake.
3. In the above models, the sample size for which all variables were available was n=210.

Derivation of added sugars recommendations for 7-12 year old children

For the lower value, i.e. 12g added sugars/day:

In the table of discretionary calorie allowance from the American Heart Association (1), (Table 3. Discretionary Calories Allowance and Examples of How These Calories May Be Divided Between Solid Fats and Added Sugars on the Basis of the US Department of Agriculture Food Guide), 12g added sugars/day came from the 1600 calorie/day category due to the table footnote:

> The discretionary calorie allowance suggested for the 1600-calorie level is lower than the 1400-calorie pattern because it traditionally represents a calorie recommendation for young children (4 to 8 years of age). To accommodate all of the food groups to meet nutrient requirements for this age group, fewer calories are available for discretionary calorie allowance.

Given that the youngest children in our study population fell within this age range (7 years old), the 12g added sugars/day served as the lower end of the added calorie recommendation for our age range.

For the upper value, i.e. 32g added sugars/day:

The upper range of 32g added sugars/day came from the same recommendation table (1), (Table 3. Discretionary Calories Allowance and Examples of How These Calories May Be Divided Between Solid Fats and Added Sugars on the Basis of the US Department of Agriculture Food Guide), assuming a calorie consumption of 2000 calories/day for moderately active boys in the 9-13 year old age range (1800 calories/day for sedentary boys plus 200 calories/day for the upper end of moderately active). This daily calorie amount was derived from recommendations from the American Heart Association and can be found online at:

http://www.heart.org/HEARTORG/GettingHealthy/NutritionCenter/Dietary-Recommendations-for-Healthy-Children_UCM_303886_Article.jsp

1. Johnson R, Appel L, Brands M, Howard B, Lefevre M, Lustig R, Sacks F, Steffen L, Wylie-Rosett J, American Heart Association Nutrition Committee of the Council on Nutrition PA, et al. Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. Circulation 2009;120(11):1011-20. doi: 10.1161/CIRCULATIONAHA.109.192627.

Expanded Findings

In the study examining the relationships between added sugars in the diet with blood pressure and lipids/lipoproteins, positive associations were found between added sugars and diastolic blood pressure as well as triglycerides. The implications and potential explanations for these relationships were explored in some depth within the discussion section of the resultant AJCN paper; however, questions relevant to parents and policy makers alike remain as to the nature of these associations. 1) Is it reasonable to anticipate from our findings that there exists a threshold of consumption, above which, added sugars begin to associate with these CVD risk factors? 2) Are the American Heart Association recommendations for maximum added sugar intake in this age group (12-32 grams/day) and population being followed[141], and if so, what is the relationship between following these guidelines and the aforementioned CVD risk factors?

To address the first question, we scrutinized the findings of the models that showed significant associations between added sugars and CVD risk factors, i.e. diastolic blood pressure and triglycerides. Upon examining the residual plots of these models, no discernable heteroskedasticity was observed. Furthermore, when analyzing the associations between added sugars and the aforementioned risk factors, not adjusting for any covariates, there was no reason to suspect a curvilinear relationship or a regression discontinuity. From a physiological perspective, if one were to suppose that added sugars would only exert an influence on the outcomes of interest when added sugars exceed a certain percentage of calories in the diet, then total caloric intake should be significantly associated with the risk factors of interest. However, total caloric intake was not associated with diastolic blood pressure in the in the model of added sugars and diastolic

blood pressure reported previously[142]. Furthermore, although total caloric intake was significantly associated with triglycerides (as one might expect from a fat storage perspective), when an interaction term of total calories*added sugars is added to this model to elucidate any potential relationships, total calories falls out of significance. This dynamic suggests that calories from added sugars are driving the association between total calories and triglycerides. Given these reasons, there does not appear to be a threshold at which added sugars either begin or cease to be positively associated with diastolic blood pressure or triglycerides.

To address the second question, descriptive statistics were run to ascertain what percentage of the study population was meeting the AHA guidelines for added sugar consumption for this age range. Less than 13% of the study participants consumed ≤ 32g/day of added sugars, the maximum recommended amount for this population. Given the disproportionate amounts of children following vs. exceeding these guidelines, a regression analysis was untenable as the reference group would be so comparatively small. Furthermore, the average percentage of the diet comprised of added sugars in this population was just over 15%, more than 50% greater than the maximum dietary contribution recommended by the WHO, and more than three times greater than the ideal maximum contribution[113].

Adherence to the USDA Dietary Guidelines for Americans and Associations with Atherosclerotic Development in the CARDIA Study

Supplemental tables appear on following pages.

Supplemental Table 1. Descriptive statistics of the REGARDS study population (2003-2007), subset with dietary data, and subset with dietary, CAC/CIMT, and covariate data available (analytic sample)

		Entire CARDIA Cohort	Valid Dietary Data Available*	Dietary, CAC/CIMT, and Covariate Data Available (Analytic Sample)**
		n=3,549	n=2,652	n=1,937
Age (avg., SE)		45.21(0.06)	45.35(0.07)	45.34(0.08)
Race[1,2]	Black	51.56	42.91	41.20
Sex[1]	Female	54.50	56.94	56.01
Field Center[1,2]	Birmingham	23.03	24.02	23.75
	Chicago	21.67	25.49	27.83
	Minneapolis	27.41	25.08	22.25
	Oakland	27.88	25.41	26.17

Numbers are percentages of samples given, unless otherwise denoted

Chi-squared tests were performed for all categorical variables, and Student's T-test for continuous variables.

1. A significant difference ($p<0.05$) was observed between the Entire CARDIA cohort and the subsample with valid dietary data, based upon the percentage of the samples that were in the given category

2. A significant difference ($p<0.05$) was observed between the Entire CARDIA cohort and the analytic sample, based upon the percentage of the samples that were in the given category

*From the entire CARDIA cohort, 897 were either missing dietary data altogether or had implausible reported energy intakes (<800 or >8,000 kcal/d in men and <600 or >6000 kcal/d in women)

**From the subsample with valid dietary data, 715 were either missing values for CAC/CIMT or other covariates

Supplemental Table 2. Sensitivity Analysis: Multivariable regression of HEI-1995 adherence at year 20 (controlling for baseline) vs. Carotid Intima-Media Thickness (mm) in the CARDIA study population (1985 and 2005, n=1,937), showing all covariates*

	Model 2		Model 3		Model 4		Model 5		Fully Adjusted Model	
	β coeff.	p-value	β coeff.	p-value	β coeff.	p-value	β coeff.	p-value	β coeff.	p-value
HEI at Y20	-0.0008	0.0143	-0.0007	0.0249	-0.0006	0.0595	-0.0005	0.1035	-0.0005	0.1196
HEI at Baseline	-0.0011	0.0023	-0.0010	0.0059	-0.0009	0.0087	-0.0009	0.0141	-0.0008	0.0142
Age	0.0093	<.0001	0.0094	<.0001	0.0092	<.0001	0.0091	<.0001	0.0085	<.0001
Sex (Female)	-0.0650	<.0001	-0.0635	<.0001	-0.0680	<.0001	-0.0687	<.0001	-0.0611	<.0001
Race (White)	-0.0413	<.0001	-0.0354	<.0001	-0.0275	0.0007	-0.0261	0.0015	-0.0214	0.0103
Center (Birmingham)	0.0244	0.0137	0.0249	0.0122	0.0218	0.0270	0.0202	0.0415	0.0180	0.0673
Center (Chicago)	0.0135	0.1554	0.0131	0.1667	0.0146	0.1209	0.0138	0.1399	0.0148	0.1105
Center (Minneapolis)	0.0610	<.0001	0.0604	<.0001	0.0597	<.0001	0.0580	<.0001	0.0627	<.0001
Education			-0.0070	<.0001	-0.0064	<.0001	-0.0050	0.0013	-0.0041	0.0077
Family Income			0.0028	0.0427	0.0026	0.0567	0.0033	0.0155	0.0037	0.0069
Total Energy Intake					0.0000	0.2228	0.0000	0.1083	0.0000	0.1257
BMI (kg/m2)					0.0028	<.0001	0.0030	<.0001	0.0021	0.0002
Physical Activity							0.0017	0.6191	0.0026	0.4433
Former Smoker							0.0044	0.6279	0.0054	0.5502
Current Smoker							0.0435	<.0001	0.0423	<.0001
Drinker							-0.0112	0.2157	-0.0119	0.1848
History of Hypertension									0.0456	<.0001
History of Dyslipidemia									0.0095	0.2407
History of Diabetes									0.0257	0.0437

*All covariates are values at Year 20 unless otherwise indicated. History of listed conditions includes incidence of conditions anytime between baseline and Year 20. Model 1 is the unadjusted model shown in Table 2.

The reference category for sex was male, for race was black, for center was Oakland, for smoking status was non-smoker, and for drinking was non-drinker.

Supplemental Table 3. Sensitivity Analysis: Multivariable regression of HEI-1995 adherence for baseline minus year 20 vs. Carotid Intima-Media Thickness (mm) in the CARDIA study population (1985 and 2005, n=1,937), showing all covariates*

	Model 2		Model 3		Model 4		Model 5		Fully Adjusted Model	
	β coeff.	p-value	β coeff.	p-value	β coeff.	p-value	β coeff.	p-value	β coeff.	p-value
HEI at Y20 - Baseline	0.0000	0.8817	0.0000	0.8817	0.0000	0.7585	0.0001	0.6915	0.0001	0.6541
Age	0.0089	<.0001	0.0089	<.0001	0.0089	<.0001	0.0088	<.0001	0.0082	<.0001
Sex (Female)	-0.0754	<.0001	-0.0754	<.0001	-0.0766	<.0001	-0.0768	<.0001	-0.0693	<.0001
Race (White)	-0.0501	<.0001	-0.0501	<.0001	-0.0324	<.0001	-0.0309	0.0001	-0.0259	0.0017
Center (Birmingham)	0.0318	0.0012	0.0318	0.0012	0.0270	0.0058	0.0249	0.0114	0.0226	0.0207
Center (Chicago)	0.0197	0.0366	0.0197	0.0366	0.0193	0.0390	0.0180	0.0522	0.0189	0.0400
Center (Minneapolis)	0.0662	<.0001	0.0662	<.0001	0.0629	<.0001	0.0607	<.0001	0.0653	<.0001
Education			-0.0076	<.0001	-0.0069	<.0001	-0.0054	0.0005	-0.0045	0.0037
Family Income			0.0023	0.0870	0.0022	0.1048	0.0030	0.0270	0.0034	0.0125
Total Energy Intake					0.0000	0.2229	0.0000	0.1040	0.0000	0.1214
BMI (kg/m2)					0.0029	<.0001	0.0031	<.0001	0.0022	0.0001
Physical Activity							0.0010	0.7788	0.0019	0.5781
Former Smoker							0.0063	0.4848	0.0073	0.4169
Current Smoker							0.0464	<.0001	0.0452	<.0001
Drinker							-0.0117	0.1942	-0.0124	0.1657
History of Hypertension									0.0457	<.0001
History of Dyslipidemia									0.0090	0.2697
History of Diabetes									0.0270	0.0343

*All covariates are values at Year 20 unless otherwise indicated. History of listed conditions includes incidence of conditions anytime between baseline and Year 20. Model 1 is the unadjusted model shown in Table 2.

The reference category for sex was male, for race was black, for center was Oakland, for smoking status was non-smoker, and for drinking was non-drinker.

Supplemental Table 4. Sensitivity Analysis: Multivariable logistic regression of HEI-1995 adherence at year 20 (controlling for baseline) vs. Coronary Artery Calcification (Agatson 1 vs. 0) in the CARDIA study population (1985 and 2005, n=1,937), showing all covariates*. Odds ratios and 95% confidence intervals presented

	Model 2		Model 3		Model 4		Model 5		Fully Adjusted Model	
	Point Est.	95% CI	Point Est.	95% CI	Point Est.	95% CI	Point Est.	95% CI	Point Est.	95% CI
HEI at Baseline	1.00	0.99, 1.01	1.00	0.99, 1.02	1.00	0.99, 1.02	1.01	0.99, 1.02	1.01	0.99, 1.02
HEI at Y20	0.99	0.98, 1.00	0.99	0.98, 1.00	1.00	0.98, 1.01	1.00	0.99, 1.01	1.00	0.99, 1.01
Age	1.11	1.07, 1.15	1.12	1.08, 1.16	1.12	1.08, 1.16	1.12	1.07, 1.16	1.11	1.07, 1.15
Sex (Female)	0.33	0.26, 0.43	0.32	0.25, 0.41	0.30	0.23, 0.40	0.29	0.22, 0.39	0.37	0.27, 0.51
Race (White)	1.01	0.78, 1.31	1.23	0.93, 1.62	1.38	1.04, 1.83	1.38	1.03, 1.85	1.36	1.01, 1.83
Center (Birmingham)	1.07	0.75, 1.51	1.01	0.71, 1.44	0.96	0.67, 1.38	0.96	0.67, 1.38	0.93	0.64, 1.33
Center (Chicago)	1.25	0.90, 1.74	1.23	0.88, 1.71	1.25	0.89, 1.74	1.24	0.89, 1.74	1.27	0.91, 1.79
Center (Minneapolis)	1.24	0.88, 1.76	1.14	0.80, 1.62	1.11	0.78, 1.59	1.08	0.76, 1.56	1.15	0.80, 1.66
Education			0.92	0.88, 0.97	0.93	0.88, 0.98	0.95	0.90, 1.00	0.96	0.91, 1.02
Family Income			0.97	0.93, 1.02	0.97	0.93, 1.02	0.98	0.94, 1.03	0.99	0.94, 1.04
Total Energy Intake					1.00	1.00, 1.00	1.00	1.00, 1.00	1.00	1.00, 1.00
BMI (kg/m2)					1.05	1.03, 1.08	1.06	1.04, 1.08	1.04	1.02, 1.07
Physical Activity							0.97	0.86, 1.10	0.98	0.87, 1.11
Former Smoker							1.07	0.78, 1.48	1.08	0.78, 1.50
Current Smoker							2.07	1.49, 2.86	1.97	1.42, 2.73
Drinker							1.02	0.74, 1.40	1.02	0.74, 1.41
History of Hypertension									1.56	1.18, 2.06
History of Dyslipidemia									1.58	1.18, 2.13
History of Diabetes									1.24	0.82, 1.86

*All covariates are values at Year 20 unless otherwise indicated. History of listed conditions includes incidence of conditions anytime between baseline and Year 20. Model 1 is the unadjusted model shown in Table 3.

The reference category for sex was male, for race was black, for center was Oakland, for smoking status was non-smoker, and for drinking was non-drinker.

Supplemental Table 5. Sensitivity Analysis: Multivariable logistic regression of HEI-1995 adherence for baseline minus year 20 vs. Coronary Artery Calcification (Agatson 1 vs. 0) in the CARDIA study population (1985 and 2005, n=1,937), showing all covariates*. Odds ratios and 95% confidence intervals presented.

	Model 2		Model 3		Model 4		Model 5		Fully Adjusted Model	
	Point Est.	95% CI	Point Est.	95% CI	Point Est.	95% CI	Point Est.	95% CI	Point Est.	95% CI
HEI at Y20 - Baseline	0.99	0.99, 1.00	1.00	0.99, 1.00	1.00	0.99, 1.01	1.00	0.99, 1.01	1.00	0.99, 1.01
Age	1.11	1.07, 1.15	1.12	1.08, 1.16	1.12	1.08, 1.16	1.12	1.08, 1.16	1.11	1.07, 1.15
Sex (Female)	0.32	0.25, 0.40	0.31	0.24, 0.40	0.30	0.23, 0.39	0.29	0.23, 0.39	0.38	0.28, 0.51
Race (White)	0.98	0.76, 1.25	1.21	0.92, 1.59	1.38	1.04, 1.83	1.39	1.04, 1.85	1.36	1.02, 1.83
Center (Birmingham)	1.10	0.78, 1.56	1.03	0.72, 1.46	0.97	0.68, 1.37	0.95	0.66, 1.36	0.92	0.64, 1.32
Center (Chicago)	1.29	0.93, 1.79	1.25	0.90, 1.73	1.25	0.90, 1.74	1.23	0.88, 1.72	1.26	0.90, 1.77
Center (Minneapolis)	1.27	0.90, 1.79	1.15	0.81, 1.64	1.12	0.78, 1.59	1.08	0.75, 1.55	1.15	0.80, 1.65
Education			0.92	0.88, 0.97	0.93	0.88, 0.98	0.95	0.90, 1.01	0.97	0.91, 1.02
Family Income			0.97	0.93, 1.02	0.97	0.93, 1.02	0.98	0.94, 1.03	0.99	0.94, 1.04
Total Energy Intake					1.00	1.00, 1.00	1.00	1.00, 1.00	1.00	1.00, 1.00
BMI (kg/m2)					1.06	1.03, 1.08	1.06	1.04, 1.08	1.04	1.02, 1.07
Physical Activity							0.97	0.86, 1.10	0.98	0.87, 1.11
Former Smoker							1.07	0.77, 1.47	1.08	0.78, 1.49
Current Smoker							2.06	1.49, 2.84	1.96	1.41, 2.72
Drinker							1.02	0.74, 1.40	1.02	0.74, 1.41
History of Hypertension									1.56	1.18, 2.06
History of Dyslipidemia									1.58	1.18, 2.13
History of Diabetes									1.23	0.82, 1.85

*All covariates are values at Year 20 unless otherwise indicated. History of listed conditions includes incidence of conditions anytime between baseline and Year 20. Model 1 is the unadjusted model shown in Table 3.

The reference category for sex was male, for race was black, for center was Oakland, for smoking status was non-smoker, and for drinking was non-drinker.

Associations Between Socioeconomic Status and Dietary Patterns in US Black and White Adults

Supplemental tables appear on following pages.

Supplemental Table 1. Final factor loadings for food/beverage items derived in the entire REGARDS population (showing only those with absolute values > 0.15 for simplicity)

	Convenience	Plant-based	Sweets/ Fats	Southern	Alcohol/ Salads
100% fruit juice		0.2529		0.1663	-0.1716
Added fats			0.3953	0.3752	0.2533
Beans	0.3555	0.3762			
Beer		-0.1598			0.2271
Bread			0.4708	0.3656	
Bread - Whole Grain		0.3025	0.1804		
Butter			0.1721		0.3230
Candy			0.4023		
Cereal		0.3804			-0.1982
Cereal - High Fiber		0.2366		-0.2546	
Chinese food	0.4373				
Chocolate			0.4564		
Coffee			0.2171	-0.1630	0.2964
Condiments	0.2458		0.3081		0.2887
Desserts	0.1974		0.5340		-0.1666
Eggs and egg dishes				0.4161	0.2911
Fish	0.2666	0.3810			0.2099
Fried food	0.2428			0.5598	
Fried potatoes	0.3705		0.2759	0.1649	
Fruit		0.5754			
Highfat dairy	0.1777		0.3727		0.2143
Liquor					0.3104
Lowfat dairy		0.1998		-0.1865	
Margarine			0.3737		
Mexican dishes	0.4846				
Milk alternatives		0.1771			
Milk - Highfat			0.1829	0.2441	
Milk - Lowfat		0.1649		-0.4170	
Miscellaneous sugar			0.5377	0.1890	
Mixed dishes with meat	0.6136				
Organ meat	0.1736			0.4719	
Pasta dishes	0.5937		0.1660		
Pizza	0.4547	-0.1765	0.2046		
Potatoes	0.3649		0.2616		
Poultry	0.2863	0.3149			
Processed meats	0.2526		0.2575	0.4476	0.2160
Red meat	0.4476		0.1755	0.2562	0.2593
Refined grains	0.3050	0.1736	0.2044	0.2038	
Salad dressing/sauces		0.3042			0.5508
Salty snacks	0.3239		0.3040		
Seeds, nuts		0.2646	0.1907		0.1858

Shell fish	0.2755			0.2282	0.2403
Soda		-0.2265		0.2366	
Soup	0.4388	0.3172			
Sugar-sweetened beverages				0.3669	-0.1528
Sweet breakfast foods	0.1881		0.3853		
Tea			0.3105		
Vegetable - cruciferous		0.5881			
Vegetable - dark yellow		0.4068			-0.1732
Vegetable - green leafy	0.1572	0.4936		-0.2193	0.4760
Vegetable - other		0.4795			
Vegetable - tomato		0.3172			0.2674
Vegetable mixed dishes	0.3533	0.3064			-0.2530
Water		0.3168			
Wine					0.3618
Yogurt		0.3140		-0.2470	

Supplemental Table 2. Descriptive statistics of the REGARDS study population (2003-2007), subset with dietary data, and subset with dietary and SES data (analytic sample)

		Entire REGARDS Cohort	Dietary Data Available*	Dietary & SES Data Available (Analytic Sample)
		n=30,183	n=21,636	n=17,062
Age (avg., std. dev.)		64.8 (9.4)	64.9 (9.3)	64.7 (9.3)
Race[1]	Black	41.5%	33.6%	34.6%
Sex	Female	55.1%	55.9%	54.4%
	Stroke Belt	34.6%	34.4%	33.9%
Region[2]	Buckle	20.9%	21.9%	21.3%
	Non-Stroke Belt	44.5%	43.8%	44.8%

1. A significant difference ($p<0.05$) was observed in the percentage of the samples that were black between both the entire REGARDS cohort and the sample with dietary data available, and also between the entire REGARDS cohort and the sample with both dietary and SES data available.
2. A significant difference ($p<0.05$) was observed in the percentage of the samples residing in the designated regions between only the entire REGARDS cohort and the sample with dietary data available.

*From the entire REGARDS cohort, 8,546 were either missing FFQ data altogether, had more than 15% missing data on the FFQ, or had implausible reported energy intakes (<3,347 or >20,920 kJ/d in men and <2,092 or >18,828 kJ/d in women)

Chi-squared tests were performed for all categorical variables, and Student's T-test for continuous variables.

Supplemental Table 3. Logistic regression of dietary patterns vs. SES indicators in the REGARDS study population (2003-2007, n=16,666)

	Convenience	Plant-based	Sweets/Fats	Southern	Alcohol/Salads
Household Income					
≤$20K	Ref	Ref	Ref	Ref	Ref
$20K–$34K	0.97 (0.88, 1.07)	0.92 (0.83, 1.02)	0.98 (0.89, 1.08)	0.79 (0.7, 0.88)	1.38 (1.25, 1.53)
$35K–$74K	1.01 (0.92, 1.12)	0.96 (0.87, 1.07)	0.98 (0.89, 1.09)	0.66 (0.59, 0.73)	1.81 (1.63, 2.02)
$75k+	1.14 (1.01, 1.29)	0.96 (0.85, 1.08)	0.73 (0.65, 0.82)	0.52 (0.45, 0.59)	2.70 (2.38, 3.07)
Personal Education					
<High school	Ref	Ref	Ref	Ref	Ref
High school	1.12 (0.98, 1.27)	1.11 (0.98, 1.25)	0.96 (0.85, 1.08)	0.81 (0.7, 0.93)	1.25 (1.09, 1.42)
Some college	1.14 (1.00, 1.30)	1.23 (1.08, 1.39)	0.92 (0.81, 1.04)	0.66 (0.57, 0.77)	1.42 (1.24, 1.62)
College+	1.30 (1.14, 1.48)	1.67 (1.46, 1.90)	0.80 (0.71, 0.91)	0.49 (0.43, 0.57)	1.71 (1.49, 1.96)
Community SES[1]					
Quartile 1	Ref	Ref	Ref	Ref	Ref
Quartile 2	1.09 (1.00, 1.20)	1.12 (1.03, 1.23)	0.96 (0.88, 1.05)	0.76 (0.69, 0.84)	1.29 (1.17, 1.41)
Quartile 3	1.22 (1.11, 1.34)	1.16 (1.06, 1.27)	0.88 (0.8, 0.96)	0.57 (0.51, 0.63)	1.51 (1.37, 1.66)
Quartile 4	1.29 (1.17, 1.43)	1.40 (1.27, 1.55)	0.64 (0.58, 0.71)	0.40 (0.36, 0.45)	2.19 (1.98, 2.43)

1. Community SES z-scores were obtained using the 6-component method developed by Anna Diez-Roux, then stratified into quartiles. Components included: median household income, median value of housing units, percentage of households with interest, dividend, or rental income, percentage of adults who completed high school, percentage of adults who completed college, and percentage of residents employed in executive, managerial, or professional occupations

*Effects differ statistically by race (p-value < 0.05); see Table 4. Odds ratios and confidence intervals are given where p-values not indicated.

Covariates for income models include: age, sex, race, smoking status, BMI category, hours of screen time (a proxy for physical inactivity), region, and education; Covariates for education models include: age, sex, race, smoking status, BMI category, hours of screen time (a proxy for physical inactivity), region, and income; Covariates for community SES models include age, sex, race, smoking status, BMI category, hours of screen time (a proxy for physical inactivity), and region

Supplemental Table 4. Logistic regressions of dietary patterns vs. SES indicators by race: High vs. low SES indicator and adherence to dietary patterns in the REGARDS study population (2003-2007, n=16,666)

		Convenience	Plant-based	Sweets/Fats	Southern	Alcohol/Salads
Household Income	Black	1.13 (0.91, 1.42)	1.04 (0.83, 1.30)	0.82 (0.66, 1.03)	0.54 (0.42, 0.69)	2.01 (1.60, 2.53)
($75K+ vs. ≤$20K)	White	1.15 (0.98, 1.35)	0.92 (0.79, 1.08)	0.71 (0.61, 0.82)	0.52 (0.44, 0.61)	3.11 (2.65, 3.64)
($p_{interaction}$ in overall model)		0.6262	0.6083	0.3855	0.3633	0.0296*
Individual Education	Black	1.13 (0.92, 1.38)	1.35 (1.11, 1.63)	0.94 (0.78, 1.13)	0.43 (0.34, 0.55)	1.58 (1.28, 1.95)
(College+ vs. <High School)	White	1.45 (1.21, 1.74)	1.96 (1.63, 2.36)	0.72 (0.60, 0.86)	0.53 (0.44, 0.64)	1.80 (1.50, 2.16)
($p_{interaction}$ in overall model)		0.1388	0.0007*	0.0454*	0.6756	0.1012

CHAPTER 7: SUMMARY AND CONCLUSIONS

Cardiovascular Disease (CVD): History, Prevalence, and Impact

CVD is the number one cause of death both in the United States (US) and internationally[7]. This is not a recent ranking in the US, as this condition has been the leading cause of death among Americans since just after World War I[8, 9]. Mortality aside, it is anticipated that CVD prevalence will rise over the coming years, with 40.5% of Americans expected to have at least one manifestation of CVD by 2030[12]. This overwhelming morbidity associated with CVD has equally overwhelming financial implications. By 2030, the direct medical costs associated with stroke, coronary heart disease, and heart failure are projected to exceed $275 billion, more than triple the 2010 estimates[12]. Given these and other ramifications of the burden of CVD, it is of paramount importance to identify effective and low-cost methods to curb the tide of CVD.

CVD: Treatment & Prevention

Attempts to prevent the development and/or progression of CVD have typically included the use of medications aimed at addressing risk factors, (e.g. statins, antihypertensives, antiarrythmics, and antithrombotics [56-64]). These drugs, however, do not come without cost and potential complications. Furthermore, the efficacy of all of these drugs for the primary prevention of CVD has not been conclusively shown. Statins, for example, are strongly recommended for secondary prevention (i.e. prevention of another CVD event), but controversy remains whether they are able to prevent MI/stroke in otherwise low-risk people [65-68].

If pharmaceutical interventions are unable to prevent the progression of CVD, then surgical interventions for CVD can serve as a last resort for the treatment of severe atherosclerosis and CVD events. Such treatments oftentimes occur after the onset of symptoms such as angina, and many times are used to mitigate the risk of future events after a patient has already experienced a stroke or MI[54, 55]. Needless to say, surgery does not serve as a modality for primary prevention of atherosclerotic CVD, and comes with a substantive battery of costs and risks for complications.

Due to their much lower costs and risks for complications, lifestyle interventions, such as diet, could ideally be pursued as the first line of treatment. Although some risk factors for CVD cannot be altered, e.g. age, sex, genetics, it has been estimated that up to 90% of CVD event risk may be attributable to modifiable risk factors in some US populations, with a majority of these being diet-related[69]. It is inescapably clear that a large portion of the modifiable risk factors for CVD are influenced, at least in part, by one's diet[72]. Our understanding of the extent and manner in which diet influences these risk factors, however, leaves much to be desired.

If demonstrated to be effective, evidence-based dietary changes may represent a lower cost alternative that can be implemented early in the etiology of CVD. Thus far, some dietary interventions have demonstrated promise in improving CVD risk factors and outcomes [73-78], and a number of association studies have shown relationships between diet and CVD [79-87]. For example, a recent randomized controlled trial (RCT) with high-CVD risk adult participants experienced great success using the Mediterranean diet in reducing the rate of major CVD events. As compared with the control diet, multivariable-adjusted hazard ratios were 0.70 (95% CI: 0.54, 0.92) for the group

receiving the Mediterranean diet with olive oil, and 0.72 (95% CI: 0.54, 0.96) for the group receiving the Mediterranean diet with nuts [76]. The association between diet and CVD has also been recognized by the American College of Cardiology and American Heart Association in their 2013 guidelines, as they emphasize the use of diet to control blood pressure and lipids [72].

Diet and CVD: Methods and previous findings

Although RCTs are considered the gold standard for establishing causality[143], such trials have a number of limitations when it comes to the study of diet and CVD. Since CVD takes many decades to transition from the most elemental and undetectable (currently) stages to a fatal MI or debilitating stroke, a comprehensive study of diet and CVD would need to take place over the lifespan. Such as study would be infeasible to conduct using the RCT framework due to its prohibitively high cost, the difficulty of maintaining control of variables for such a long period of time, and the almost certain impossibility of obtaining IRB approval. Therefore, in order to get a lifespan perspective, researchers have historically looked to longitudinal studies of lifestyle and CVD.

Perhaps the most famous of these studies is the Framingham Heart Study[6]. This and studies like it have yielded invaluable contributions to our understanding of the risk factors for CVD; however, these studies have two main drawbacks at this point in time. First, there has yet to be a study that has followed participants from birth to death, assessing the associations between diet and CVD along the way. Second, the largest and most long-running of the longitudinal studies in the US have used either exclusively or predominantly white individuals[82, 95, 96]. Given the diverse racial landscape of the US[144],

findings generated from such racially homogenous samples cannot be readily applied to the US population at large.

Taking the limitations of the extant literature on diet and CVD into account, this dissertation has sought to augment the literature in this arena by taking a lifespan focus to the component manuscripts, using study data that were collected from racially diverse populations. Reflective of the lifespan focus, the manuscripts have looked at the relationships between diet and risk factors for CVD early in the lifespan (Paper 1), diet and atherosclerosis in middle age (Paper 2), and the associations between SES and dietary pattern adherence (previously shown to be associated with MI[92]) in older populations (Paper 3). Reflective of the unique contributions that each method of dietary evaluation adds to our understanding of the relationship between diet and CVD, diet was evaluated as a single food component (added sugars), a score on a predetermined index (Healthy Eating Index), and as a statistically derived dietary pattern.

Association of Added Sugars with Blood Pressure and Lipids/Lipoproteins

Impetus for the Study

Dietary interventions for hypertension and dyslipidemia have traditionally included decreasing one's intake of sodium and dietary fats [102, 103]; however, added sugars in the diet have recently been associated with these conditions in select age groups[104-110]. In particular, associations have been observed between added sugars in various form and blood pressure/lipids/lipoproteins in both adults and older adolescents [104-107, 109, 110]; however, added sugars as a whole (not just from SSB) have not been

examined for their potential association with blood pressure and blood lipids in children [108].

Results and Implications

In this study we found positive associations between added sugars in the diets of children and diastolic blood pressure, as well as plasma triglyceride levels. Although the beta coefficients for these relationships were not extremely large, given the very young age of this population, and the fact that CVD begins so early in the lifespan, these insights into potential dietary modifications to forestall CVD progression in children warrant attention. If the average intake of added sugar in children's diets was insignificant, or at least fell within existing federal and international recommendations, then these findings may have only been insightful for a small subset of the population. However, as it currently stands, almost 20% of calories in children's diets come from added sugars [111], almost twice the WHO's recommendation of a 10% maximum, and almost four times the ideal threshold of sugar consumption[113]. Examining added sugars is especially timely given the FDA's move to change the nutrition label to include added sugars as a subset of total sugars [49, 110].

Adherence to the USDA Dietary Guidelines for Americans and Associations with Atherosclerotic Development in the CARDIA Study

Impetus for the Study

The Healthy Eating Index (HEI) was developed by the USDA's Center for Nutrition Policy and Promotion to assess adherence to the USDA Dietary Guidelines for

Americans. Some studies have shown negative associations between HEI score [117, 121] and CVD risk/incidence [122-124]. However, these associations have not been examined in a diverse population using atherosclerosis as the outcome of interest (especially as assessed by coronary artery calcification (CAC) or carotid intima-media thickness (CIMT) [125]). Furthermore, as these markers typically precede CVD events by at least a few years, examining the associations between these markers and HEI adherence will allow the development of more effective nutrition policy for preventing and/or slowing the progression of CVD, even in later stages of the etiology of CVD [49].

Results and Implications

From our analyses we found that higher HEI scores at Y20, controlling for baseline HEI, were associated with smaller CIMT and lower odds of exhibiting CAC. These associations were not robust to the addition of CVD-related covariates. Furthermore, when assessing change in HEI score from baseline to Y20 (i.e. Y20 minus baseline), no significant associations were found with either CIMT or CAC. These results suggest that, at least in this population, at the given time points and other considerations, that neither one's adherence to the USDA dietary guidelines, nor one's improved adherence, appear to be related to atherosclerosis.

Associations Between Socioeconomic Status and Dietary Patterns in US Black and White Adults

Impetus for the Study

Studies investigating the associations between diet and SES have analyzed diet as individual nutrients, groupings of nutrients, and dietary indices [127-134]. However, limited research has been conducted on how SES may impact statistically derived dietary patterns, especially in older populations. In the REGARDS study cohort, adherence to dietary patterns has recently been demonstrated to be associated with incident CVD events[92]. Given these associations with CVD, understanding how SES may impact individuals' adherence to such dietary patterns is of substantive interest.

Results and Implications

We found adherence to many of these dietary patterns to be related to one's income, education, and community SES, with some of these relationships differing significantly by race. Although the magnitude of the association between SES and dietary pattern adherence differed among measures of SES, there were not any instances where a given measure of SES was positively associated with adherence to a pattern, but a different measure of SES was negatively associated with the same pattern. Similarly, although magnitude of the association between SES and adherence to some patterns differed between races, this association was always in the same direction for both races.

Despite the somewhat descriptive nature of these study results, the implications for these findings are noteworthy. Due to the significant associations between SES and CVD-related dietary patterns, efforts to modify individuals' eating behaviors need to take into account their SES (and race) both when designing interventions, and when

interpreting the findings of said interventions. For example, if an intervention were put in place to increase participants' consumption of vegetables, and the post-intervention results were extremely positive, yet the researchers neglected to control for the fact that the population was all high SES and already had a high consumption of vegetables at baseline, this omitted variable bias would cause an overestimation of the effect of the intervention. Conversely, if a similar intervention were carried out in a low SES population, with the results showing that participants were eating less than the recommended servings of vegetables, by neglecting to account for the low SES of the population, the effect of this intervention might be significantly underestimated.

By examining diet as a statistically derived dietary pattern, we are able to yield insights that may have gone undetected had diet been evaluated another way. When looking across dietary patterns, we may see that several patterns share certain foods in common. Identifying such foods, especially ones that are deleterious to one's health, presents the opportunity to identify "low hanging fruit" that can be targeted in dietary interventions and recommendations to maximize efforts at dietary improvements. Additionally, evaluating diet as a pattern may yield insights into the underlying reasons and motivations for diet selection. The convenience pattern, for example, includes a number of foods that typify a diet focused on quick and easy foods. This insight can enable targeted dietary interventions that are designed for individuals who strongly adhere to this pattern by offering healthier alternatives that are still convenient.

Final Thoughts

The objective of this dissertation was to evaluate the associations between diet and CVD: 1) in diverse populations 2) over stages of the life course 3) reflexive of the etiology of CVD 4) using various methods of defining diet 5) while examining how socioeconomic status may impact diet selection, and 6) considering how diet-mediated CVD may impact healthcare costs. The preceding chapters have laid out in great detail the studies that were undertaken to evaluate the aforementioned associations. We feel that the studies contained herein contribute to the broader work of nutritional epidemiology, as well as our corporate understanding of the manifold ways in which diet is interwoven with such themes as policy, sociology, economics, and medicine. Our recognition of diet's intermingling with myriad aspects of science and society is only appropriate, for when we look deeper into the past, we rediscover that diet, or *diaita*, in the original Greek, at its essence meant a "way of living".

CHAPTER 8: LITERATURE CITED

1. Burkitt DP. Some Diseases Characteristic of Modern Western Civilization. British Medical Journal. 1973;1:274-8.
2. Story C, Krucik G. The History of Heart Disease. Healthline Version current 10 April 2012 Internet: http://wwwhealthlinecom/health/heart-disease/history#2 (accessed 12 December 2014).
3. History of Stroke. Johns Hopkins Medicine. Internet: http://www.hopkinsmedicine.org/healthlibrary/conditions/nervous_system_disorders/history_of_stroke_85,P00223/ (accessed 12 December 2014).
4. Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. Circulation. 1993;88:1973-98.
5. Epstein FH. Cardiovascular Disease Epidemiology: A Journey From the Past Into the Future. Circulation. 1996;93:1755-64.
6. FHS. History of the Framingham Heart Study. Version current 2014. Internet: https://www.framinghamheartstudy.org/about-fhs/history.php (accessed 12 Dec 2014).
7. WHO. Global status report on noncommunicable diseases 2010. Geneva, World Health Organization, 2011.
8. CDC. Leading Causes of Death, 1900-1998. Internet: http://www.cdc.gov/nchs/data/dvs/lead1900_98.pdf (accessed 12 December 2014).
9. CDC. Deaths: Leading Causes for 2010. National Vital Statistics Reports 62(6). Internet: http://www.cdc.gov/nchs/data/nvsr/nvsr62/nvsr62_06.pdf (accessed 13 December 2014).
10. Reddy KS, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. Circulation. 1998.
11. Jones DS, Podolsky SH, Greene JA. The burden of disease and the changing task of medicine. The New England journal of medicine. 2012;366(25):2333-8. doi: 10.1056/NEJMp1113569.
12. Heidenreich P, Trogdon J, Khavjou O, Butler J, Dracup K, Ezekowitz M, Finkelstein E, Hong Y, Johnston S, Khera A, Lloyd-Jones D, Nelson S, Nichol G, Orenstein D, Wilson P, Woo Y, American Heart Association Advocacy Coordinating C, Stroke C, Council on Cardiovascular R, Intervention, Council on Clinical C, Council on E, Prevention, Council on A, Thrombosis, Vascular B, Council on C, Critical C, Perioperative, Resuscitation, Council on Cardiovascular N, Council on the Kidney in Cardiovascular D, Council on Cardiovascular S, Anesthesia, Interdisciplinary Council on Quality of C, Outcomes R. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation. 2011;123(8):933-44. doi: 10.1161/CIR.0b013e31820a55f5.
13. U.S. Census Bureau . U.S. Population Projections: 2010 to 2050. U.S. Department of Commerce; Washington, D.C. 2008. Internet: www.census.gov/population/www/projections/summarytables.html (accessed 18 December 2014).
14. Go AS MD, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S,, Fullerton HJ GC, Hailpern, SM, Heit, JA HV, Huffman MD, Judd SE,, Kissela, BM, Kittner, SJ, Lackland DT LJ, Lisabeth, LD MR, Magid, DJ MG, Marelli A,, Matchar, DB M, DK MEr, Moy CS,, Mussolino, ME NR, Nichol G, Pandey DK,,

Paynter, NP RM, Sorlie PD SJ, Towfighi, A TT, Virani SS, Wong ND, Woo D, Turner MB; on behalf of the American, Subcommittee. HASCaSS. Heart Disease and Stroke Statistics—2014 Update. Circulation. 2014;129:e28-e292.
15. Yazdanyar A, Newman AB. The burden of cardiovascular disease in the elderly: morbidity, mortality, and costs. Clinics in geriatric medicine. 2009;25(4):563.
16. NHLBI. Morbidity & Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases. Internet: https://www.nhlbi.nih.gov/files/docs/research/2012_ChartBook_508.pdf (accessed 14 December 2014).
17. CDC. Heart Disease and Stroke Prevention - Addressing the Nation's Leading Killers: At A Glance 2011. Version current 21 July, 2010. Internet: http://www.cdc.gov/chronicdisease/resources/publications/aag/dhdsp.htm (accessed 12 August 2014).
18. Stamler J. Low risk—and the "No more than 50%" myth/dogma. Archives of internal medicine. 2007. doi: 10.1001/archinte.167.6.537.
19. NHLBI. Coronary Heart Disease Risk Factors. Version current 1 February 2011. Internet: http://www.nhlbi.nih.gov/health/health-topics/topics/hd/atrisk.html (accessed 10 December 2014).
20. AHA. Stroke Risk Factors. Version current 23 October 2012. Internet: http://www.strokeassociation.org/STROKEORG/AboutStroke/UnderstandingRisk/Understanding-Stroke-Risk_UCM_308539_SubHomePage.jsp (accessed 12 December 2014).
21. BHF. Cardiovascular disease. Internet: http://www.bhf.org.uk/heart-health/conditions/cardiovascular-disease.aspx (accessed 13 December 2014).
22. WHO. Cardiovascular diseases. Internet: http://www.who.int/mediacentre/factsheets/fs317/en/ (accessed 8 December 2014).
23. J.Y.T. L. Atherosclerosis. The Merck Manual Professional Edition Accessed 24 Dec 2014 http://wwwmerckmanualscom/professional/cardiovascular_disorders/arteriosclerosis/atherosclerosishtml. 2012.
24. NCEP. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002 Dec 17; 106 (25): 3143–421.
25. P. CKL. Intertwining of thrombosis and inflammation in atherosclerosis. Curr Opin Hematol 2007;14(1):55–61.
26. Stocker R, Jr KJF. Role of oxidative modifications in atherosclerosis. Physiological reviews. 2004.
27. A.N. MMES. The pathophysiology of atherosclerosis. Semin Vasc Surg. 1998;11(3):134-41.
28. Wexler Lea. Inflammatory Atherosclerosis: Characteristics of the Injurious Agent. Chapter 5 - Calcification: A Physiologic Defense. RJ. F, editor. Sacramento: Heart Research Foundation; 2002.
29. Kruth HS. Lipoprotein cholesterol and atherosclerosis. Curr Mol Med 2001. 2001;1(6):633–53.

30. Strong JPM, G.T.; Newman, W.P.; Oalmann, M.C. Early lesions of atherosclerosis in childhood and youth: natural history and risk factors. J Am Coll Nutr. 1992;11:Suppl: 51S-4S.
31. Holman RLM, H.C.; Strong, J.P.; Geer, J.C. The natural history of atherosclerosis: the early aortic lesions as seen in New Orleans in the middle of the 20th century Am J Pathol. 1958;34:209.
32. Strong JPM, H.C. The natural history of atherosclerosis: Relationship to race, sex, and coronary lesions in New Orleans. Exp Mol Path. 1963;2(suppl 1): 15.
33. NHLBI. What is High Blood Pressure? Version current 2 August 2012. Internet: http://www.nhlbi.nih.gov/health/health-topics/topics/hbp (accessed 12 December 2014).
34. AHA. Understanding Blood Pressure Readings. Version current 4 August 2014. Internet: http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/AboutHighBloodPressure/Understanding-Blood-Pressure-Readings_UCM_301764_Article.jsp (accessed 13 December 2014).
35. NHLBI. Blood Pressure Tables for Children and Adolescents. Internet: http://www.nhlbi.nih.gov/health-pro/guidelines/current/hypertension-pediatric-jnc-4/blood-pressure-tables (accessed 13 December 2014).
36. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. May 2005. NIH Publication No. 05–5267. Internet: http://www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf (accessed 15 December 2014).
37. Hansen ML, Gunn PW, Kaelber DC. Underdiagnosis of hypertension in children and adolescents. Jama. 2007. doi: 10.1001/jama.298.8.874.
38. McNiece KL, Poffenbarger TS, Turner JL. Prevalence of hypertension and pre-hypertension among adolescents. The Journal of …. 2007.
39. Diseases and Conditions: High Cholesterol - Tests and Diagnosis. Version current 22 November 2014. Internet: http://www.mayoclinic.org/diseases-conditions/high-blood-cholesterol/basics/tests-diagnosis/con-20020865 (accessed 17 December 2014).
40. Tabas I. Consequences of cellular cholesterol accumulation: basic concepts and physiological implications. Journal of Clinical Investigation. 2002.
41. Link JJ, Rohatgi A, Lemos JA. HDL cholesterol: physiology, pathophysiology, and management. Current problems in cardiology. 2007;32(5):268-314.
42. Bisoendial RJ, Hovingh GK, Levels JHM, Lerch PG. Restoration of endothelial function by increasing high-density lipoprotein in subjects with isolated low high-density lipoprotein. Circulation. 2003. doi: 10.1161/01.CIR.0000070934.69310.1A.
43. Gordon T, Castelli WP, Hjortland MC. High density lipoprotein as a protective factor against coronary heart disease: the Framingham Study. The American journal of Medicine. 1977.
44. Koyama K, Chen G, Lee Y. Tissue triglycerides, insulin resistance, and insulin production: implications for hyperinsulinemia of obesity. American Journal of Physiology. 1997.
45. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a

metaanalysis of population-based prospective studies. Journal of Cardiovascular Risk. 1996. doi: 10.1177/174182679600300214.
46. Tóth PP, Potter D, Ming EE. Prevalence of lipid abnormalities in the United States: the national health and nutrition examination survey 2003–2006. Journal of clinical lipidology. 2012.
47. NHLBI. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Table 9.1. Internet: http://www.nhlbi.nih.gov/health-pro/guidelines/current/cardiovascular-health-pediatric-guidelines/summary#chap9 (accessed 13 December 2014).
48. Li J, Motsko SP, Goehring EL, Tave A. Prevalence of pediatric dyslipidemia: comparison of a population‐based claims database to national surveys. Pharmacoepidemiology and Drug Safety. 2010. doi: 10.1002/pds.1982.
49. Wexler L, Brundage B, Crouse J, Detrano R, Fuster V, Maddahi J, Rumberger J, Stanford W, White R, Taubert K. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. A statement for health professionals from the American Heart Association. Writing Group. Circulation. 1996;94(5):1175-92.
50. Stein JH, Korcarz CE, Post WS. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: summary and discussion of the American Society of Echocardiography
Carotid Intima-Media Thickness Task Force. Preventive Cardiology. 2009. doi: 10.1111/j.1751-7141.2008.00021.x.
51. Chen MA. Heart attack. Accessed 26 Dec 2014. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001246/. ADAM Medical Encyclopedia 2013.
52. Thygesen K, Alpert JS, Jaffe AS, H.D. W, Simoons ML, Chaitman BR, Katus HA, Apple FS, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ. Third Universal Definition of Myocardial Infarction. J Am Coll Cardiol. 2012;60(16):1581-98.
53. AHA. About Stroke - Types of Stroke. Accessed 26 Dec 2014. http://www.strokeassociation.org/STROKEORG/AboutStroke/TypesofStroke/Types-of-Stroke_UCM_308531_SubHomePage.jsp#2012.
54. AHA. Cardiac Procedures and Surgeries. Accessed 26 Dec 2014. http://www.heart.org/HEARTORG/Conditions/HeartAttack/PreventionTreatmentofHeartAttack/Cardiac-Procedures-and-Surgeries_UCM_303939_Article.jsp#.
55. NHLBI. Types of Heart Surgery. Accessed 26 Dec 2014. http://www.nhlbi.nih.gov/health/health-topics/topics/hs/types.
56. Ward S, Jones ML, Pandor A, Holmes M, Ara R, Ryan A, Yeo W, Payne N. A systematic review and economic evaluation of statins for the prevention of coronary events. NIHR Evaluation, Trials and Studies Coordinating Centre (UK). 2007.
57. Pignone M, Earnshaw S, Tice J, Pletcher M. Aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men: a cost-utility analysis. Annals of internal medicine. 2006;144(5):326-36.
58. McConnachie A, Walker A, Robertson M, Marchbank L, Peacock J, Packard C, Cobbe S, Ford I. Long-term impact on healthcare resource utilization of statin treatment,

and its cost effectiveness in the primary prevention of cardiovascular disease: a record linkage study. European heart journal. 2013. doi: 10.1093/eurheartj/eht232.
59. Law M, Morris J, Wald N. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ (Clinical research ed). 2009;338. doi: 10.1136/bmj.b1665.
60. Johannesson M, Jönsson B, Kjekshus J, Olsson A, Pedersen T, Wedel H. Cost effectiveness of simvastatin treatment to lower cholesterol levels in patients with coronary heart disease. Scandinavian Simvastatin Survival Study Group. The New England journal of medicine. 1997;336(5):332-6. doi: 10.1056/nejm199701303360503.
61. Gaziano T, Opie L, Weinstein M. Cardiovascular disease prevention with a multidrug regimen in the developing world: a cost-effectiveness analysis. Lancet. 2006;368(9536):679-86. doi: 10.1016/s0140-6736(06)69252-0.
62. Gaspoz J-M, Coxson PG, Goldman PA, Williams LW, Kuntz KM, Hunink MGM, Goldman L. Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease. New England Journal of Medicine. 2002;346(23):1800-6. doi: 10.1056/nejm200206063462309.
63. Bitton A, Choudhry N, Matlin O, Swanton K, Shrank W. The impact of medication adherence on coronary artery disease costs and outcomes: a systematic review. The American journal of medicine. 2013;126(4). doi: 10.1016/j.amjmed.2012.09.004.
64. Bergh M, Marais C, Miller-Jansön H, Salie F, Stander M. Economic appraisal of dabigatran as first-line therapy for stroke prevention in atrial fibrillation. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 2013;103(4):241-5.
65. Sett AK, Robinson TG, Mistri AK. Current status of statin therapy for stroke prevention. Expert review of cardiovascular therapy. 2011;9(10):1305-14. doi: 10.1586/erc.11.106.
66. Ference BA, Mahajan N. The role of early LDL lowering to prevent the onset of atherosclerotic disease. Current atherosclerosis reports. 2013;15(4):312. doi: 10.1007/s11883-013-0312-1.
67. Cimminiello C. What intervention trials don't tell us: the residual risk in primary prevention. Internal and emergency medicine. 2011;6 Suppl 1:53-60. doi: 10.1007/s11739-011-0670-z.
68. Ascunce RR, Berger JS, Weintraub HS, Schwartzbard A. The Role of Statin Therapy for Primary Prevention: What is the Evidence? Current atherosclerosis reports. 2012. doi: 10.1007/s11883-012-0229-0.
69. Hozawa A, Folsom AR. Absolute and attributable risks of cardiovascular disease incidence in relation to optimal and borderline risk factors: comparison of African American with white subjects-Atherosclerosis Risk in Communities Study. Archives of Internal Medicine. 2007. doi: 10.1001/archinte.167.6.573.
70. Mendis S, Puska P, Norrving B. Global Atlas on Cardiovascular Disease Prevention and Control. editors. World Health Organization, Geneva 2011.
71. WHO. Global Health Risks: Mortality and burden of disease attributable to selected major risks. 2009. Internet: http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf (accessed 14 Dec 2014).

72. Wenger N. Prevention of cardiovascular disease: highlights for the clinician of the 2013 American College of Cardiology/American Heart Association guidelines. Clinical cardiology. 2014;37(4):239-51. doi: 10.1002/clc.22264.
73. Saneei P, Hashemipour M, Kelishadi R, Rajaei S, Esmaillzadeh A. Effects of recommendations to follow the Dietary Approaches to Stop Hypertension (DASH) diet v. usual dietary advice on childhood metabolic syndrome: a randomised cross-over clinical trial. The British journal of nutrition. 2013;110(12):2250-9. doi: 10.1017/S0007114513001724.
74. Lima S, da Silva Nalin de Souza B, França A, Salgado Filho N, Sichieri R. Dietary approach to hypertension based on low glycaemic index and principles of DASH (Dietary Approaches to Stop Hypertension): a randomised trial in a primary care service. The British journal of nutrition. 2013;110(8):1472-9. doi: 10.1017/S0007114513000718.
75. Asemi Z, Tabassi Z, Samimi M, Fahiminejad T, Esmaillzadeh A. Favourable effects of the Dietary Approaches to Stop Hypertension diet on glucose tolerance and lipid profiles in gestational diabetes: a randomised clinical trial. The British journal of nutrition. 2013;109(11):2024-30. doi: 10.1017/S0007114512004242.
76. Estruch R, Ros E, Salas-Salvadó J, Covas M-I, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos R, Serra-Majem L, Pintó X, Basora J, Muñoz M, Sorlí J, Martínez J, Martínez-González M, Investigators PS. Primary prevention of cardiovascular disease with a Mediterranean diet. The New England journal of medicine. 2013;368(14):1279-90. doi: 10.1056/NEJMoa1200303.
77. Santos F, Esteves S, da Costa Pereira A, Yancy W, Nunes J. Systematic review and meta-analysis of clinical trials of the effects of low carbohydrate diets on cardiovascular risk factors. Obesity Reviews: An official journal of the International Association for the Study of Obesity. 2012;13(11):1048-66. doi: 10.1111/j.1467-789X.2012.01021.x.
78. Mazzaro C, Klostermann F, Erbano B, Schio N, Guarita-Souza L, Olandoski M, Faria-Neto J, Baena C. Dietary Interventions and Blood Pressure in Latin America - Systematic Review and Meta-Analysis. Arquivos brasileiros de cardiologia. 2014;102(4):345-54. doi: 10.5935/abc.20140037.
79. Yokoyama Y, Nishimura K, Barnard N, Takegami M, Watanabe M, Sekikawa A, Okamura T, Miyamoto Y. Vegetarian diets and blood pressure: a meta-analysis. JAMA internal medicine. 2014;174(4):577-87. doi: 10.1001/jamainternmed.2013.14547.
80. Williams C, Lovegrove J, Griffin B. Dietary patterns and cardiovascular disease. The Proceedings of the Nutrition Society. 2013;72(4):407-11. doi: 10.1017/S0029665113002048.
81. Tyrovolas S, Panagiotakos D. The role of Mediterranean type of diet on the development of cancer and cardiovascular disease, in the elderly: a systematic review. Maturitas. 2010;65(2):122-30. doi: 10.1016/j.maturitas.2009.07.003.
82. Sun J, Buys N, Hills A. Dietary pattern and its association with the prevalence of obesity, hypertension and other cardiovascular risk factors among Chinese older adults. International journal of environmental research and public health. 2014;11(4):3956-71. doi: 10.3390/ijerph110403956.
83. Sherzai A, Heim L, Boothby C, Sherzai A. Stroke, food groups, and dietary patterns: a systematic review. Nutrition reviews. 2012;70(8):423-35. doi: 10.1111/j.1753-4887.2012.00490.x.

84. Selem S, Castro M, César C, Marchioni D, Fisberg R. Associations between Dietary Patterns and Self-Reported Hypertension among Brazilian Adults: A Cross-Sectional Population-Based Study. Journal of the Academy of Nutrition and Dietetics. 2014. doi: 10.1016/j.jand.2014.01.007.
85. Ovbiagele B. Optimizing vascular risk reduction in the stroke patient with atherothrombotic disease. Medical principles and practice : international journal of the Kuwait University, Health Science Centre. 2010;19(1):1-12. doi: 10.1159/000252827.
86. Mente A, de Koning L, Shannon H, Anand S. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. Archives of internal medicine. 2009;169(7):659-69. doi: 10.1001/archinternmed.2009.38.
87. Grosso G, Mistretta A, Frigiola A, Gruttadauria S, Biondi A, Basile F, Vitaglione P, D'Orazio N, Galvano F. Mediterranean diet and cardiovascular risk factors: a systematic review. Critical reviews in food science and nutrition. 2014;54(5):593-610. doi: 10.1080/10408398.2011.596955.
88. USDA. Dietary Assessment Instruments for Research. Version current 2014. Internet: http://fnic.nal.usda.gov/surveys-reports-and-research/research-tools/dietary-assessment-instruments-research (accessed 26 December 2014).
89. Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Saturated fat, carbohydrate, and cardiovascular disease. The American journal of clinical nutrition. 2010;91(3):502-9. doi: 10.3945/ajcn.2008.26285.
90. Fransen HP, Ocké MC. Indices of diet quality. Current opinion in clinical nutrition and metabolic care. 2008;11(5):559-65. doi: 10.1097/MCO.0b013e32830a49db.
91. Hu FB, Rimm E, Smith-Warner SA, Feskanich D, Stampfer MJ, Ascherio A, Sampson L, Willett WC. Reproducibility and validity of dietary patterns assessed with a food-frequency questionnaire. The American journal of clinical nutrition. 1999;69(2):243-9.
92. Judd S, Gutiérrez O, Newby P, Howard G, Howard V, Locher J, Kissela B, Shikany J. Dietary patterns are associated with incident stroke and contribute to excess risk of stroke in black Americans. Stroke; a journal of cerebral circulation. 2013;44(12):3305-11. doi: 10.1161/STROKEAHA.113.002636.
93. Dawber TR, Meadors GF, Moore FE. Epidemiological approaches to heart disease: the Framingham Study. American journal of public health and the nation's health. 1951;41(3):279-81.
94. Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. Lancet. 2014;383(9921):999-1008. doi: 10.1016/S0140-6736(13)61752-3.
95. Physicians' Health Study I. Version current 17 March 2009. Internet: http://phsbwhharvardedu/phs1htm (accessed 20 December 2014).
96. Tran N, Barraj L, Heilman J, Scrafford C. Egg consumption and cardiovascular disease among diabetic individuals: a systematic review of the literature. Diabetes, metabolic syndrome and obesity: targets and therapy. 2014;7:121-37. doi: 10.2147/DMSO.S58668.
97. Omi M, Winant H. Racial Formation in the United States: From the 1960s to the 1990s: Psychology Press; 1994.
98. Duster T. Medicine. Race and reification in science. Science (New York, NY). 2005;307(5712):1050-1. doi: 10.1126/science.1110303.

99. M. A. Agricultural and Pastoral Societies in Ancient and Classical History: Temple University Press; 2001.
100. R. C. Sugar Love. National Geographic Accessed 24 Dec 2014 http://ngmnationalgeographiccom/2013/08/sugar/cohen-text. 2013.
101. Guyenet S. By 2606, the US Diet will be 100 Percent Sugar. Accessed 24 Dec 2014. http://wholehealthsource.blogspot.com/2012/02/by-2606-us-diet-will-be-100-percent.html2012.
102. Fletcher B, Berra K, Ades P, Braun L, Burke L, Durstine J, Fair J, Fletcher G, Goff D, Hayman L, Hiatt W, Miller N, Krauss R, Kris-Etherton P, Stone N, Wilterdink J, Winston M, Council on Cardiovascular N, Council on Arteriosclerosis T, Vascular B, Council on Basic Cardiovascular S, Council on Cardiovascular Disease in the Y, Council on Clinical C, Council on E, Prevention, Council on Nutrition PA, Metabolism, Council on S, Preventive Cardiovascular Nurses A. Managing abnormal blood lipids: a collaborative approach. Circulation. 2005;112(20):3184-209. doi: 10.1161/CIRCULATIONAHA.105.169180.
103. Appel L, Brands M, Daniels S, Karanja N, Elmer P, Sacks F, American Heart A. Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. Hypertension. 2006;47(2):296-308. doi: 10.1161/01.hyp.0000202568.01167.b6.
104. Ambrosini G, Oddy W, Huang R, Mori T, Beilin L, Jebb S. Prospective associations between sugar-sweetened beverage intakes and cardiometabolic risk factors in adolescents. The American journal of clinical nutrition. 2013;98(2):327-34. doi: 10.3945/ajcn.112.051383.
105. Brown I, Stamler J, Van Horn L, Robertson C, Chan Q, Dyer A, Huang C-C, Rodriguez B, Zhao L, Daviglus M, Ueshima H, Elliott P, International Study of MM, Blood Pressure Research G. Sugar-sweetened beverage, sugar intake of individuals, and their blood pressure: international study of macro/micronutrients and blood pressure. Hypertension. 2011;57(cabba675-21a4-31b9-7020-909fc5ec66ce):695-1396. doi: 10.1161/hypertensionaha.110.165456.
106. Chen L, Caballero B, Mitchell D, Loria C, Lin P-H, Champagne C, Elmer P, Ard J, Batch B, Anderson C, Appel L. Reducing consumption of sugar-sweetened beverages is associated with reduced blood pressure: a prospective study among United States adults. Circulation. 2010;121(d17babc3-2899-f780-e55f-90b59ac6de2d):2398-804. doi: 10.1161/circulationaha.109.911164.
107. Høstmark A. The Oslo health study: soft drink intake is associated with the metabolic syndrome. Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquée, Nutrition et Métabolisme. 2010;35(20b0922d-8466-3257-2133-90b59abc0be2):635-77. doi: 10.1139/h10-059.
108. Kosova E, Auinger P, Bremer A. The relationships between sugar-sweetened beverage intake and cardiometabolic markers in young children. Journal of the Academy of Nutrition and Dietetics. 2013;113(2):219-27. doi: 10.1016/j.jand.2012.10.020.
109. Nguyen S, Choi H, Lustig R, Hsu C-y. Sugar-sweetened beverages, serum uric acid, and blood pressure in adolescents. The Journal of Pediatrics. 2009;154(e6236fb2-5aa6-1d50-7b19-90b59abb9dc7):807-20. doi: 10.1016/j.jpeds.2009.01.015.

110. Welsh J, Sharma A, Cunningham S, Vos M. Consumption of added sugars and indicators of cardiovascular disease risk among US adolescents. Circulation. 2011;123(3):249-57. doi: 10.1161/circulationaha.110.972166.
111. Reedy J, Krebs-Smith S. Dietary sources of energy, solid fats, and added sugars among children and adolescents in the United States. Journal of the American Dietetic Association. 2010;110(10):1477-84. doi: 10.1016/j.jada.2010.07.010.
112. FDA. Proposed Changes to the Nutrition Facts Label. Version current 1 August 2014. Internet: http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm385663.htm (accessed 12 November 2014).
113. WHO. Guideline: Sugars intake for adults and children. Geneva: World Health Organization, 2015. Internet: http://apps.who.int/iris/bitstream/10665/149782/1/9789241549028_eng.pdf (accessed 20 December 2014).
114. Davis CSE. Dietary Recommendations and How They Have Changed Over Time. In: ERS U, editor. http://www.ers.usda.gov/media/91022/aib750b_1_.pdf.
115. Shah BS, Freeland-Graves JH, Cahill JM, Lu H, Graves GR. Diet quality as measured by the healthy eating index and the association with lipid profile in low-income women in early postpartum. Journal of the American Dietetic Association. 2010;110(2):274-9.
116. USDA. Nutrition and Your Health: Dietary Guidelines for Americans. Appendix G-5: History of the Dietary Guidelines for Americans. http://www.health.gov/dietaryguidelines/dga2005/report/html/G5_History.htm. 2005.
117. Kennedy ET, Ohls J, Carlson S, Fleming K. The Healthy Eating Index: design and applications. Journal of the American Dietetic Association. 1995;95(10):1103-8. doi: 10.1016/s0002-8223(95)00300-2.
118. USDA. The Healthy Eating Index: 1989-90. U.S. Department of Agriculture, Center for Nutrition Policy and Promotion. CNPP-1. Internet: http://www.cnpp.usda.gov/sites/default/files/healthy_eating_index/HEI89-90report.pdf (accessed 10 June 2014)1995.
119. Bowman SAL, M.; Gerrior, S.A.; Basiotis, P.P. . The Healthy Eating Index: 1994-96. U.S. Department of Agriculture, Center for Nutrition Policy and Promotion. CNPP-5. http://www.cnpp.usda.gov/sites/default/files/healthy_eating_index/HEI94-96report.pdf1998.
120. Guenther PJ, W.; Reedy, J.; Britten, P.; Lino, M.; Carlson, A.; Hiza, H.H.; Krebs-Smith S.M. USDA CNPP. Diet Quality of Americans in 1994-96 and 2001-02 as Measured by the Healthy Eating Index-2005. http://www.cnpp.usda.gov/sites/default/files/nutrition_insights_uploads/Insight37.pdf. Nutrition Insight. 2007;37.
121. Guenther P, Casavale K, Reedy J, Kirkpatrick S, Hiza H, Kuczynski K, Kahle L, Krebs-Smith S. Update of the Healthy Eating Index: HEI-2010. Journal of the Academy of Nutrition and Dietetics. 2013;113(4):569-80. doi: 10.1016/j.jand.2012.12.016.
122. Chiuve S, Fung T, Rimm E, Hu F, McCullough M, Wang M, Stampfer M, Willett W. Alternative dietary indices both strongly predict risk of chronic disease. The Journal of nutrition. 2012;142(6):1009-18. doi: 10.3945/jn.111.157222.

123. Nicklas T, O'Neil C, Fulgoni V. Diet quality is inversely related to cardiovascular risk factors in adults. The Journal of nutrition. 2012;142(12):2112-8. doi: 10.3945/jn.112.164889.
124. Rathod A, Bharadwaj A, Badheka A, Kizilbash M, Afonso L. Healthy Eating Index and mortality in a nationally representative elderly cohort. Archives of internal medicine. 2012;172(3):275-7. doi: 10.1001/archinternmed.2011.1031.
125. Imamura F, Jacques PF, Herrington DM, Dallal GE, Lichtenstein AH. Adherence to 2005 Dietary Guidelines for Americans is associated with a reduced progression of coronary artery atherosclerosis in women with established coronary artery disease. The American journal of clinical nutrition. 2009;90(1):193-201. doi: 10.3945/ajcn.2009.27576.
126. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Current opinion in lipidology. 2002;13(1):3-9.
127. Aggarwal A, Monsivais P, Drewnowski A. Nutrient intakes linked to better health outcomes are associated with higher diet costs in the US. PloS one. 2012;7(5). doi: 10.1371/journal.pone.0037533.
128. Bjørke-Monsen A, Roth C, Magnus P, Midttun O, Nilsen R, Reichborn-Kjennerud T, Stoltenberg C, Susser E, Vollset S, Ueland P. Maternal B vitamin status in pregnancy week 18 according to reported use of folic acid supplements. Molecular nutrition & food research. 2012. doi: 10.1002/mnfr.201200114.
129. Cutler G, Flood A, Hannan P, Neumark-Sztainer D. Multiple sociodemographic and socioenvironmental characteristics are correlated with major patterns of dietary intake in adolescents. Journal of the American Dietetic Association. 2011;111(2):230-40. doi: 10.1016/j.jada.2010.10.052.
130. García-Arenzana N, Navarrete-Muñoz E, Peris M, Salas D, Ascunce N, Gonzalez I, Sánchez-Contador C, Santamariña C, Moreo P, Moreno M, Carrete J, Collado-García F, Pedraz-Pingarrón C, Ederra M, Miranda-García J, Vidal C, Aragonés N, Pérez-Gómez B, Vioque J, Pollán M. Diet quality and related factors among Spanish female participants in breast cancer screening programs. Menopause (New York, NY). 2012;19(10):1121-9. doi: 10.1097/gme.0b013e3182544925.
131. Hare-Bruun H, Togo P, Andersen L, Heitmann B. Adult food intake patterns are related to adult and childhood socioeconomic status. The Journal of nutrition. 2011;141(5):928-34. doi: 10.3945/jn.110.133413.
132. Hiza H, Casavale K, Guenther P, Davis C. Diet quality of americans differs by age, sex, race/ethnicity, income, and education level. Journal of the Academy of Nutrition and Dietetics. 2013;113(2):297-306. doi: 10.1016/j.jand.2012.08.011.
133. Nobre L, Lamounier J, Franceschini SC. Preschool children dietary patterns and associated factors. Jornal de pediatria. 2012;88(2):129-36. doi: 10.2223/jped.2169.
134. Olmedo-Requena R, Fernández J, Prieto C, Moreno J, Bueno-Cavanillas A, Jiménez-Moleón J. Factors associated with a low adherence to a Mediterranean diet pattern in healthy Spanish women before pregnancy. Public health nutrition. 2013:1-9. doi: 10.1017/s1368980013000657.
135. Weaver C. How sound is the science behind the dietary recommendations for dairy? The American journal of clinical nutrition. 2014;99(5 Suppl). doi: 10.3945/ajcn.113.073007.

136. Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J. Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. Atherosclerosis. 2006;189(1):19-30. doi: 10.1016/j.atherosclerosis.2006.02.012.
137. Mor A, Omotosho P, Torquati A. Cardiovascular risk in obese diabetic patients is significantly reduced one year after gastric bypass compared to one year of diabetes support and education. Surgical endoscopy. 2014. doi: 10.1007/s00464-014-3550-6.
138. Astrup A. Yogurt and dairy product consumption to prevent cardiometabolic diseases: epidemiologic and experimental studies. The American journal of clinical nutrition. 2014;99(5 Suppl). doi: 10.3945/ajcn.113.073015.
139. U.S. Census Bureau. 2010 Census Shows Nation's Population is Aging. 2011. Internet: http://www.census.gov/2010census/news/releases/operations/cb11-cn147.html (accessed 12 Dec 2014).
140. AHRQ. Agency for Healthcare Research and Quality. Disparities in Healthcare Quality Among Racial and Ethnic Minority Groups. Fact Sheet. Version current 1 October 2014. Internet: http://www.ahrq.gov/research/findings/nhqrdr/nhqrdr10/minority.html (accessed 20 December 2014).
141. Johnson R, Appel L, Brands M, Howard B, Lefevre M, Lustig R, Sacks F, Steffen L, Wylie-Rosett J. American Heart Association Nutrition Committee of the Council on Nutrition PA, et al. Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. Circulation. 120(11):1011-20. doi: 10.1161/CIRCULATIONAHA.109.192627.2009.
142. Kell KP, Cardel M, Bohan Brown M, Fernández J. Added sugars in the diet are positively associated with diastolic blood pressure and triglycerides in children. The American journal of clinical nutrition. 2014. doi: 10.3945/ajcn.113.076505.
143. Kaptchuk TJ. The double-blind, randomized, placebo-controlled trial:Gold standard or golden calf? Journal of Clinical Epidemiology. 2001;54:541-9.
144. USCB. USA QuickFacts. People QuickFacts. Black or African American alone, percent, 2013. Internet: http://quickfacts.census.gov/qfd/states/00000.html (accessed 30 October 2014).