THE ASSOCIATIONS OF ETHNICITY, CARDIOVASCULAR RISK FACTORS, AND SOCIOECONOMIC STATUS WITH SUBCLINICAL CARDIOVASCULAR DISEASE

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Cardiovascular disease (CVD) is the leading cause of mortality among American women, and event rates are particularly high among African Americans. Recent technologies have facilitated early detection of subclinical vascular changes that precede clinical events. This research project examined the interrelationships of ethnicity, CVD risk factors, socioeconomic status (SES), and psychosocial health with these subclinical CVD changes among women.

We examined data from the Study of Women's Health Across the Nation (SWAN) Heart Study (n's=303-536), a prospective epidemiological study of middle-aged African Americans and Caucasians. Coronary artery calcification (CAC), aortic calcification (AC), carotid artery intima-media thickness (IMT), and aortic pulse-wave velocity (PWV) were assessed at two visits, an average of 2.3 years apart.

We examined ethnic differences in the associations of traditional CVD risk factors on PWV progression, or arterial stiffening. Systolic blood pressure (SBP) and waist circumference were associated with accelerated PWV progression. The effect of SBP was stronger among African Americans than among Caucasians, and LDL-C, diastolic blood pressure (DBP) and glucose levels were associated with PWV progression only among African Americans.

African American women have poorer CVD outcomes but do not consistently have higher subclinical CVD in the literature. We speculated that SES partly explains relationships between ethnicity and subclinical CVD. Our findings indicated that low education was related to

AC, after adjustment for ethnicity. African American ethnicity was associated with IMT and PWV after adjustment for education, but not income. A significant interaction between ethnicity and income suggested that low-income African American women were at greatest risk of presenting with high PWV.

Finally, we observed that low educational attainment was associated with greater CAC progression among Caucasians but not African Americans. Financial strain partly mediated this relationship.

Our findings suggest that certain CVD risk factors are more strongly related to progression among African Americans than among Caucasians. Furthermore, SES may explain some ethnic differences in the extent of subclinical CVD. Lastly, psychosocial indicators explain higher CAC progression among low-SES Caucasian women.

This project has public health significance. Clarifying how biological and psychosocial factors contribute to subclinical CVD may reveal targets for prevention of clinical disease.

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1.0 DISSERTATION OVERVIEW AND OBJECTIVES

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among women in the United States. While African American women have greater prevalence of clinical events, including coronary heart disease (CHD) and stroke, autopsy and angiography studies reveal that they are unexpectedly less likely than are Caucasian women to show lesions or stenoses in their coronary vessels.

This paradox also extends to subclinical measures of cardiovascular disease, which represent early stages of adverse vascular change and may precede clinical outcomes and symptoms. African American women have less coronary artery calcification (CAC) than do Caucasian women, but greater prevalence or extent of aortic calcification (AC), carotid artery intima-media thickness (IMT) and aortic pulse wave velocity (PWV). Ethnic discrepancies between subclinical CVD and clinical outcomes underscore the fact that relatively little is known about why certain women develop subclinical disease or what risk factors contribute to the progression of these early stages of disease.

The objective of this dissertation was to examine the interrelationships of ethnicity and biologic, physiologic, and psychosocial risk factors with regard to subclinical CVD changes among women. Research questions were investigated in the Study of Women's Health Across the Nation (SWAN) Heart study, a prospective study of CHD-free, middle-aged African American and Caucasian women.

Research questions were addressed in a series of three research articles:

1. What are the associations of traditional CVD risk factors with the progression of arterial stiffness? Do these relationships vary by ethnicity?

2. What are the independent and combined associations of ethnicity and socioeconomic status (SES) with cross-sectional measures of CAC, AC, IMT, and PWV?

3. What are the combined relationships of ethnicity and SES with respect to progression of CAC? Are these relationships explained by psychosocial factors?

In order to prevent these early cardiovascular changes from progressing into clinical events among women, it is important to identify and understand the effects of pertinent risk factors that promote subclinical CVD onset and progression.

2.0 BACKGROUND

2.1 CARDIOVASCULAR DISEASE BURDEN IN WOMEN

Cardiovascular disease (CVD) is the leading cause of death and disability in the United States. In 2007, the American Heart Association reported that cardiovascular diseases were responsible for 869,700 deaths, or approximately 1 of every 2.8 deaths in the United States. An estimated 80,000,000 living Americans are burdened with at least one form of CVD, including hypertension, coronary heart disease (CHD), stroke, or heart failure.[1]

CVD was traditionally considered to be a disease of men, since CVD symptoms and events present approximately ten years earlier in men than in women.[2] Estrogen is a cardioprotective hormone and is postulated to ameliorate the inflammatory cascade that contributes to vascular disease.[3] After estrogen levels decline during the menopause transition, CVD mortality rates in women rapidly equalize to those of men—indeed, 52.8% of total CVD deaths in 2004 occurred among women. The most recent statistics from the American Heart Association indicate that between 2004 and 2005, 217,800 women died from CHD, 7.3 million women developed clinical CHD, 4.6 million women developed angina pectoris, and 3.0 million women endured myocardial infarctions.[1]

Despite these sobering statistics, the earlier-mentioned gender bias in CVD assessment has contributed to a deficiency of studies that focus on CVD in women. Findings from studies of men are typically generalized to women-- an approach that may be inappropriate due to differences in hormones, distributions of adipose tissue, CVD risk factor profiles, lifestyle and psychosocial factors between the genders.[4] This underscores the need to better understand risk

factors that contribute to CVD in women, particularly at the earliest and potentially reversible stages of adverse vascular change.

Indeed, there is still much to learn about why certain women are at higher risk of developing CVD. Notably, CVD incidence and prevalence are particularly burdensome for African American women. Compared to Caucasian women, African American women have higher estimated rates of CVD mortality (333.8/100,000 versus 238.0/100,000), and prevalence of myocardial infarction (3.3% versus 2.5%), CHD (7.8% versus 6.0%) and stroke (4.1% versus 2.7%). This disproportionate burden in part reflects a higher proportion of adverse CVD risk factors among African American women: compared to Caucasian women, African American women are more likely to be overweight or obese (79.6% versus 57.6%), hypertensive (44.6% versus 33.6%), and diabetic (13.2% versus 5.6%).[1]

Paradoxically, while the CVD risk factor burden, prevalence and incidence of CVD events are higher among African American women, the extent of clinically-detectable vascular disease appears to be greater among Caucasians. Two angiography studies found that Caucasian women had more extensive coronary artery disease than did African American women, and were also more likely to present with coronary obstructions or stenoses. [5, 6] These results are consistent with studies of men, which are more numerous; autopsy or angiography studies of individuals with MI/unstable angina indicate that African American men are less likely to have coronary obstructions, and more likely to have normal angiography findings than are Caucasian men.[7-9] This paradox is still largely unexplained.

2.2 SUBCLINICAL CARDIOVASCULAR DISEASE

The paradoxical finding that higher detectable vascular disease among Caucasians is not associated with higher clinical outcomes has also been observed in a variety of subclinical CVD measures. Subclinical CVD measures represent aspects of arteriosclerosis and atherosclerosis--two distinct yet related processes that may culminate in clinical outcomes. Both processes share common mechanistic progenitors, including inflammation and dyslipidemia; they also share common clinical risk factors. According to the American Society of Hematology, "proven risk factors…are hypercholesterolemia, hypertension, cigarette smoking, obesity, physical inactivity, age, family history, diabetes and male sex."[10] However, these known risk factors explain only part of the variation in clinical CVD outcomes.[11] Identification and modification of reversible risk factors among women may help to prevent the progression of atherosclerosis and arteriosclerosis into clinical CVD events.

The following sections will describe the overall pathogenesis of atherosclerosis and arteriosclerosis, and then describe the subclinical CVD measures that represent various aspects of these processes.

2.2.1 Pathogenesis of Atherosclerosis

Atherosclerosis is characterized by fatty degeneration of the vasculature, plaque formation and localized arterial stiffening. Vascular endothelial cells may over-express adhesion molecules when injured or exposed to an inflammatory milieu. VCAM-1, a well-characterized adhesion molecule, attracts immune cells and lipids to a weakened or damaged vessel. Circulating lipids begin to accumulate underneath the damaged endothelium. Macrophages engulf the lipids, developing into large foam cells that are trapped in the intima layer.

Histologically, this is described as the "fatty streak," and represents one of the earliest detectable lesions of atherosclerosis. The foam cells are also a major component of the atheroma, or the lipid-laden core of the developing plaque. Foam cells express cytokines that attract inflammatory molecules. As foam cells die, they expel their contents into the sub-intimal space; this attracts additional macrophages and inflammatory cytokines. Smooth muscle cells from the neighboring media layer also migrate into the area of vascular injury, contributing to arterial stiffening around the damaged area. Advanced lesions may become calcified. A fibrous cap, or connective tissue scar, forms as a result of the inflammatory process and may initially stabilize the plaque.

Atherosclerotic plaque formation results in vessel narrowing, which reduces blood flow and oxygenation of tissues distal to the stenosis. This general process is observed in myocardial infarction, peripheral arterial disease, and/or cerebrovascular disease; consequences may be fatal. Plaque rupture or thrombosis may lead to complete or partial vessel occlusion further along the cardiac artery. High shear stress at areas of stenosis may cause subsequent plaque instability and rupture. Thrombi may also form on the surface of the tethered plaque due to variations in shear stress across the lesion. If a ruptured clot or plaque fragment partially obstructs a coronary vessel distal to the original lesion, it may cause angina pectoris; if it completely occludes the vessel, it may cause myocardial infarction and tissue death. [12]

2.2.2 Pathogenesis of Arteriosclerosis

Arteriosclerosis is marked by generalized vascular stiffening, resulting from reduced elasticity of large- and medium-sized arteries, including the aorta. A normal, healthy artery must be sufficiently compliant, durable, and stable to withstand a range of hemodynamic forces. The extracellular matrix of the vascular wall is composed primarily of four proteins: collagen, elastin, glycoprotein and proteoglycan. Collagen is needed for structural integrity and tensile strength, while elastin provides flexibility needed for the normal dilation and constriction of the vessel. Reduction of elasticity in the large arteries commonly occurs with age, and is coupled with

increases in collagen content and accumulation of vascular smooth muscle cells. These processes are often evidenced by systolic hypertension and widened pulse pressures in the elderly. Natural, age-related processes in women, such as estrogen decline through menopause, may also be accompanied by decreases in aortic compliance. [13, 14]

Stiffening may be abnormally accelerated in response to certain disease processes. Diabetes mellitus, the metabolic syndrome, excess adiposity, and hypertension are each associated with measurable increases in inflammatory molecules. Inflammatory molecules may initiate a cascade of additional abnormal processes, culminating in overproduction of dysfunctional collagen, disordered endothelial cells, broken elastin molecules, leukocyte infiltration into the arterial wall, vascular smooth muscle cell accumulation, and a thicker arterial wall.[15, 16] Endothelial dysfunction may be a secondary effect of hypertension or inflammation, and result in reduced synthesis and/or release of nitric oxide, a potent vasodilator.[16, 17] Hyperglycemia, in addition to its association with inflammation, may further stimulate collagenation in the vascular wall.[18] In relation, hyperinsulinemia has been shown to activate an adrenergic response, leading to vascular wall hypertrophy.[19] Tachycardia, a physiologic response to sympathetic nervous system activation, has been associated with increased vascular smooth muscle tone.[20] These processes independently or cumulatively may result in a stiffer artery.

A stiffer artery has a lower reserve for injury, and is more susceptible to damage from factors such as hypertension, tobacco use, and elevated plasma homocysteine.[13] Once an artery is damaged, the process of atherosclerosis may commence as described in the preceding section (2.2.1.). In addition, arterial stiffening results in increased blood pressure, which leads to greater arterial damage and stiffening; this reinforcing feedback cycle is linked to clinical events such as stroke and cerebrovascular incidents.[21]

2.2.3 Measures of Subclinical Cardiovascular Disease (CVD)

Clinical cardiovascular event and mortality rates are higher among African American than among Caucasian women. However, among women with clinical symptoms, African American women may have similar levels or less angiographically-detectable CHD than do Caucasian women. As noted earlier, the apparent contradiction of these observations can be observed even in the subclinical phase of disease, prior to the advent of clinical symptoms and events.

Subclinical CVD measures are surrogate indicators of atherosclerosis or arteriosclerosis. These measures have been developed in order to detect adverse vascular changes prior to clinical symptoms or events. Unlike angiography, these measures may be used prior to the onset of clinical symptoms and are noninvasive. The measures that will be assessed in this project include: coronary artery calcification (CAC) and aortic calcification (AC), carotid artery intima-media thickness (IMT), and carotid-femoral (aortic) pulse wave velocity (PWV). Although no studies have examined the associations of all of these measures within a single cohort, various studies have found correlations between CAC, AC, IMT, and PWV. [22-27]

It is important to understand what factors contribute to subclinical CVD in order to appreciate how and why some women develop adverse clinical cardiovascular outcomes. Among women who have already developed clinical disease, clarifying the cardiovascular risk factors that contributed to their CVD may be difficult, given possible confounding by current medication usage or alterations in lifestyle or behaviors—therefore, it is advantageous to examine risk factors before the onset of clinical disease. In addition, much work has already been dedicated to understanding how traditional CVD risk factors, such as excess body weight, hyperglycemia, and hypertension, relate to clinical events. However, there is incremental value in examining subclinical CVD measures rather than CVD risk factors alone in studies of ethnicity, atherosclerosis or clinical outcomes. Many middle-aged or older women present with more than one CVD risk factor,[28, 29] and the complex interactions between multiple risk factors may obscure their independent contributions to atherosclerosis, arteriosclerosis, or to CVD events. Subclinical CVD measures are a reflection of the vascular changes that are promoted by

the presence and extent of adverse CVD risk factors. Therefore, it may be optimal to directly assess representative measures of the atherosclerotic or arteriosclerotic processes—*i.e,* subclinical CVD-- rather than to examine CVD risk factors alone or the vasculature after clinical outcomes have occurred.

A woman's genetic background, environment and behaviors over the life course—from infancy to adulthood-- may be reflected in a cross-sectional measure of subclinical CVD. Assessments of subclinical CVD progression over a specified period of time may provide additional insight, by revealing risk factors that are most important in promoting short-term increases in subclinical disease. This project will present findings from cross-sectional and longitudinal assessments of subclinical CVD among women.

The subsequent sections will describe CAC, AC, IMT, and PWV in greater detail. Sections will include for each subclinical CVD measure: 1) descriptions and measurement, 2) associations with known CVD risk factors, 3) predictive value of future clinical events, and 4) variations in extent or prevalence by ethnicity. Studies of women will be highlighted in the following review.

2.2.3.1 Coronary Artery and Aortic Calcification (CAC, AC)

Coronary artery calcification (CAC) and aortic calcification (AC) represent calcified atherosclerotic plaque in the coronary arteries and aorta. Circulating calcium phosphate particles precipitate onto debris from dead immune cells and smooth muscle cells that were involved with formation of the atherosclerotic lesion. Greater extent of calcification is directly correlated with a greater burden of atherosclerotic vessel disease, and worse prognosis for future clinical events.[30] For undetermined reasons, AC presents earlier than does CAC among women, and women tend to have more AC than do men at the same age.[31]

Electron-beam computed tomography (EBCT) is the gold-standard method of detecting calcified atherosclerotic plaque. The amount of detectable calcification in all of the coronary

vessels or aorta can be summed and scored, with higher scores representing a larger burden of calcified plaque. Most calcium scores are calculated using the gold-standard Agatston method, in which a lesion is defined as 2 to 4 adjacent pixels (area greater than 0.51mm^2) with a signal density greater than 130 Houndsfield Units (HU). The lesion area is multiplied by a constant representing the signal density. This calculation generates a score that corresponds to the size, density and quantity of calcium in the lesion. If multiple calcified lesions are detected, the calcium scores from each lesion are summed to yield a total calcium score. Calcium scores from the coronary arteries are summed separately from those of the aorta.

The most important risk factors for cross-sectional and longitudinal CAC measures include age and male gender.[32] Hypercholesterolemia, higher body mass index (BMI), systolic blood pressure (SBP), and triglycerides, current smoking status, and diabetes mellitus have also been identified as risk factors for cross-sectional and longitudinal measures of CAC.[32-34] The Multi-Ethnic Study of Atherosclerosis (MESA) reported that AC is associated with most traditional CVD risk factors, and most strongly associated with hypertension and current smoking status.[31] Consistent with these findings, the Healthy Women Study (HWS) reported that among postmenopausal women, high AC scores were associated with higher low-density lipoprotein cholesterol (LDL-C) levels, current smoking status, and SBP.[35]

Higher CAC scores are associated with greater incidence of CVD events and mortality in studies of men and women. [36-40] MESA also reported that among women who were at low risk for clinical CVD based on the Framingham score 10-year CHD risk score, those who had detectable CAC as compared to women with no CAC were over 5 times more likely to have CHD or CVD events over a 4-year follow-up period.[38] AC, although less studied than CAC, has also been associated with CVD events and mortality. [41-43] In the Framingham study, middle-aged women with detectable AC were at approximately twice the risk of developing CVD than were women with no AC during a 12-year follow-up, and after adjustments for multiple CVD risk factors.[42]

Healthy African American women have similar or less CAC than do Caucasian women in a majority of studies. Four large prospective studies—the Prospective Army Coronary Calcium

study (PACC), MESA, a study by UCLA investigators, and the Cardiovascular Health Study (CHS)—found that African American women had less extensive CAC than did Caucasian women.[36, 44-47] Three studies—the Coronary Artery Risk Development in Young Adults (CARDIA), Women's Health Initiative Observational Study (WHI-OS), and Dallas Heart Study (DHS)—found that African American and Caucasian women had similar levels of CAC.[48-50] One study conducted by a separate group of UCLA investigators, found that African American women had higher CAC levels than did Caucasians, although participants had an excess of CVD risk factors as compared to Caucasians.[51] Only one study has examined CAC progression in a multi-ethnic cohort, and reported that while Caucasian women on average had higher cross-sectional CAC scores, levels of CAC progression were similar between African American and Caucasian women.[33] These findings cumulatively suggest that African American women have less calcified atherosclerotic plaque in the coronary arteries than do Caucasians despite having a larger burden of clinical cardiovascular disease.

The Study of Women's Health Across the Nation (SWAN) Heart Study observed that AC was significantly more prevalent among middle-aged African American women than Caucasian women (76.8% vs. 64.0%). The extent of AC was not reported in this sample. To our knowledge, this is the only study with sufficient enrollment of African Americans to examine biracial differences in AC.[52]

It is important to note that the findings of each of these studies were statistically adjusted for a number of CVD risk factors, including age. In addition, these data are also consistent with observations in African American and Caucasian men. In fact, because men tend to have greater CAC than women at the same ages, the higher CAC gradient among Caucasian men as compared to African American men is even more pronounced than that observed among women.[44]

2.2.3.2. Carotid Artery Intima-Media Thickness (IMT)

Abnormal thickening of the intima and media layers of the carotid wall occurs due to atherosclerotic plaque and/or in response to hypertension or other physiologic stressors.

Increased IMT may thereby reflect a combination of arteriosclerotic and atherosclerotic processes. First, the arterial wall may thicken in response to changing tensile and shear stresses related to hypertension.[53] In addition, sub-intimal atherosclerotic plaque in segments of the carotid artery may increase the apparent thickness of the intima and media layers. Therefore, an abnormally thickened carotid artery may reflect compensatory arterial remodeling and/or detectable atherosclerotic plaque.

Thickening of the vascular wall may be detected by B-mode ultrasound. In carotid artery IMT protocols, an ultrasound probe is placed on an individual's skin surface perpendicular to the carotid artery. This yields a series of images of the intima, media, and adventitial layers of the artery. A trained reader digitally traces the thickness of the combined intima and media layers, which are quantified via computer software. The clearest images are typically obtained from the common carotid artery due to its linear anatomy, although the carotid bifurcation, internal and external carotid segments are other common imaging sites. Normal mean IMT levels range from 0.36 mm to 0.90 mm.[54]

Carotid artery IMT is associated with most traditional CVD risk factors. The HWS reported that pre-menopausal levels of triglycerides, pulse rate, and a history of smoking were related to mean IMT after controlling for participant age.[55] Age, pulse pressure, LDL-C levels, SBP, BMI, triglycerides, smoking status, and the metabolic syndrome have also been associated with higher IMT.[56-59]

Higher IMT is an independent risk factor for CHD and stroke.[30, 60] The Atherosclerosis Risk in Communities (ARIC) study observed that women with mean IMT levels ≥ 1 mm were over 5 times more likely to have CHD than women with lower IMT over a 4 to7 year follow-up period (95% confidence interval [CI]=3.08-8.36).[61] Indeed, each 0.1 mm increase in IMT is associated with greater incidence of CVD events and mortality in studies of men and women. [62]

African Americans appear to have higher IMT than do Caucasians across a variety of age groups. This is particularly noted in the common carotid segment (CCA-IMT) or using a mean thickness score averaged across multiple carotid sites (Mean Average IMT).[63-67] Several studies

also indicate that African American women have greater IMT progression than do Caucasian women. The Bogalusa study of young adults reported that African American women as compared to Caucasian women had significantly greater mean average IMT progression and CCA-IMT progression; these results mirror those from the ARIC study, which found that of 6797 middle-aged and older adults, African American women had greater CCA-IMT progression than did Caucasian women.[68]

2.2.3.3. Carotid-Femoral (Aortic) Pulse Wave Velocity (PWV)

Arterial stiffness reflects arteriosclerosis, atherosclerosis and aberrant vascular remodeling. As described in sections 2.2.1. and 2.2.2., inflammation, endothelial damage, adrenergic activation, and hyperglycemia may contribute to arterial stiffening and vascular damage.

Aortic stiffness is assessed by the gold standard method, carotid-to-femoral PWV. In PWV protocols, arterial flow waves are simultaneously and non-invasively recorded at the carotid and femoral arteries of supine participants, using unidirectional transcutaneous Doppler flow probes. Aortic PWV is calculated as distance between the probes divided by the transit time of the pulse wave (cm/seconds). The transit time of the pulse wave is calculated as the foot-to-foot delay between the averaged carotid and femoral waveforms. The distance traveled by the pulse waveform is estimated by measurement over the participant's torso. The distance from the carotid to aortic site is subtracted from the sum of the aortic to umbilicus and umbilicus to femoral site to adjust for the opposite direction of the blood flow in that arterial branch. A higher PWV indicates a stiffer vessel. This measure has been demonstrated to have good reproducibility, with an overall laboratory intraclass correlation of 0.77. [69]

Traditional CVD risk factors, including SBP, pulse rate, elevated leukocytes, elevated blood glucose, and family history of diabetes, have been associated with higher PWV in studies of women.[20, 70] Indicators of obesity and hyperglycemia, including higher BMI, type 2 diabetes and/or poor glucose control, have also been associated with higher PWV in a study of older and

younger adults by Wildman and colleagues[71], in addition to two studies of older Americans.[72, 73] Increased PWV progression over time has been associated with higher BMI, hypertension, and the metabolic syndrome. [74-76]

Higher PWV is associated with increased risk of CVD events.[77-80] In a study of middle-aged and older women, participants with high PWV were 2.45 times more likely to develop CVD during the four-year follow-up period.[81] Among postmenopausal Dutch women, increase in PWV of 1 m/s was associated with a 2.2% increased risk of death over an 10-12 year follow-up, a 1.4% increased risk of CHD, and a 0.9% elevated risk of stroke.[20]

Only two studies have examined carotid-femoral PWV differences between healthy African American and Caucasian women—this represents a substantial gap in the literature. One study reported that young African Americans had higher PWV increases over 2 years than did Caucasians; this finding persisted after adjustments for BMI and BMI change,[74] and the second study reported that African American adolescents had higher PWV than did Caucasian adolescents;[82] neither study reported findings by gender, and no studies have yet examined ethnic differences in PWV among middle-aged women. Several additional studies suggest that people of African heritage may alsop have higher PWV than do Caucasians. One study reported that Afro-Brazilians had higher PWV than did Caucasians; after adjusting for hypertension, Afro-Brazilians had lower PWV than did Caucasians.[83] Two European studies reported that Afro-Caribbeans had higher PWV than did Caucasians.[84, 85]

2.3 ETHNICITY IS INCONSISTENTLY ASSOCIATED WITH SUBCLINICAL CARDIOVASCULAR DISEASE

To summarize briefly, African American women experience a disproportionate burden of clinical cardiovascular events as compared to Caucasian women. However, African American women do not consistently present with greater extent of all subclinical CVD measures. African American ethnicity appears to be most strongly associated with higher IMT, while Caucasians have higher or similar levels of CAC as compared to African Americans. African and African American ethnicities may be related to higher PWV levels, although the scope of the literature is limited. Ethnic differences in AC are also understudied, although African American women appear to have more prevalent AC as compared to Caucasians. The origins of ethnic differences in clinical outcomes and subclinical disease are unclear.

Ethnic differences in subclinical CVD may partly reflect genetic variations.[86] For example, while high CAC represents a greater extent of atherosclerotic plaque, a higher amount of calcium in a particular coronary lesion may stabilize the plaque, preventing rupture and subsequent myocardial infarction. Several studies indicate that Caucasians have higher levels of calcium in their individual plaques, which may reflect genetic polymorphisms in calcium metabolism,[87] and may protect Caucasians against myocardial infarction. Caucasian women also have been observed to have a greater propensity for developing osteoporosis than do African American women. Bone density appears to be inversely associated with vascular calcification, which has led some researchers to hypothesize that bone remodeling among Caucasians may lead to more deposition of calcium in the coronary arteries.[30, 86]

Ethnic differences may also originate from different cardiovascular risk factor distributions. For example, African American women have a higher prevalence of hypertension and diabetes than do Caucasian women[1], which are independently associated with arterial

stiffening and atherosclerosis. While many of the studies of subclinical CVD make statistical adjustments for known CVD risk factors, it is also possible that not all pertinent risk factors have been identified or tested.

In addition, the consequences of certain CVD risk factors in subclinical CVD development may differ by ethnicity. For example, hypertension or hyperglycemia may play a larger role in the adverse remodeling of arteries in African Americans than among Caucasians. This hypothesis is understudied, and greater emphasis on identifying CVD risk factors related to ethnicity may better clarify the pathogenesis of cardiovascular disease in certain groups. Indeed, certain CVD risk factors may require more aggressive management among African American women or Caucasian women in order to prevent adverse clinical sequelae. This project examined the independent and combined associations of traditional CVD risk factors with progression of arterial stiffening, as measured by PWV, and examined whether these associations vary by ethnicity [**Research Article 1 (Chapter 3)**].

Socioeconomic status (SES) is another important risk factor that may help to further explain the inconsistent associations between ethnicity and subclinical CVD measures. In a 2003 U.S. telephone survey of 256,155 Americans, nearly half of all African Americans reported having at least two CVD risk factors; African Americans had the highest prevalence of CVD risk factors as compared to all other ethnic groups. Low educational attainment and low household income were also associated with higher prevalence of multiple CVD risk factors among respondents.[88] The study did not assess the combined associations of SES and ethnicity with respect to CVD risk factor prevalence in this sample. However, from childhood through adulthood, African Americans are more likely to be poor, less-educated, and more disenfranchised from the health care system than are Caucasians.[89, 90] Given that low SES is independently associated with higher prevalence of CVD risk factors, and that African Americans disproportionately report indicators of low SES, it is conceivable that low SES may explain some of the associations between African American ethnicity and subclinical CVD. Differences in SES distributions by ethnicity across different study samples may also contribute to varying associations between ethnicity and subclinical CVD measures. Understanding the role of SES may better clarify the associations between African American ethnicity and the

extent of subclinical CVD. This project examined the combined associations of ethnicity and SES with regard to cross-sectional and longitudinal measures of subclinical CVD [**Research Articles 2 and 3 (Chapters 4, 5)**].

The relationships between ethnicity and CVD risk factors with respect to PWV progression, and the relationships between socioeconomic status, ethnicity, and subclinical CVD measures, will be discussed further in the following sections.

2.3.1 Relationships Between Ethnicity and Cardiovascular Risk Factors May Explain Differences in Progression of Arterial Stiffness

Accelerated arterial stiffening is associated with adverse clinical cardiovascular outcomes. [77-80] As an artery stiffens, it becomes more vulnerable to endothelial injury, hypertension and atherosclerosis.[91] These changes increase the risk of stroke and CHD. Carotid-femoral, or aortic, PWV is a measure of aortic stiffening that has been associated with higher BMI, SBP, type 2 diabetes mellitus, and the metabolic syndrome. [70, 75, 92, 93] An individual with multiple CVD risk factors has a greater risk of developing aggressive PWV progression; in one study, people with three or more CVD risk factors had significantly higher PWV progression than did people with fewer risk factors.[92]

As noted earlier, African Americans appear to have higher PWV than do Caucasians. [74] African American women also have a greater prevalence of traditional CVD risk factors than do Caucasian women, particularly with respect to excess body weight and waist circumference, the metabolic syndrome, hypertension, and diabetes mellitus.[1] Furthermore, at younger ages, the risk of developing hypertension is higher among African Americans than among other ethnic groups.[94] The preponderance of risk factors in addition to cumulative lifetime exposure to risk factors among African American women may culminate in premature or accelerated arterial stiffening in this group. This pathway may also help to explain the excess burden of CHD and stroke among African American women.

A related but understudied question is whether the magnitude of the influence of certain CVD risk factors on arterial stiffness also varies by ethnicity. For example, hypertension among African Americans is associated with a CVD mortality rate that is 3 to 5 times that of Caucasians.[95] In the ARIC study, hypertension was an especially robust predictor of CHD among African American women as compared to Caucasian women.[96] Therefore, it is possible that African American women who have certain CVD risk factors such as hypertension are at greater risk of developing clinical or subclinical CVD than are Caucasian women.

Several proposed pathways support the hypothesis that the effects of certain risk factors on arterial stiffness may be stronger among African Americans. A study of adult males observed that Afro-Brazilians experienced a greater SBP-dependent increase in cross-sectional PWV measurements than did Caucasians, resulting in substantially higher PWV among Afro-Brazilians with hypertension as compared to Caucasians with hypertension.[97] The Bogalusa Study of young adults reported that luminal enlargement associated with early atherosclerosis was more strongly related to mean arterial pressures and vascular wall thickness among African Americans than among Caucasians. In a milieu of atherosclerotic or pressure-related risk factors, the vasculature of African Americans may be more inclined to undergo compensatory remodeling processes.[98] This protective mechanism initially may preserve perfusion, but the reserve capacity of the vessels is limited; after this capacity is exhausted, centralized stiffening of the central arteries may ensue. In a separate pathway, endothelial injury is thought to enhance PWV progression by limiting the endogenous nitric oxide supply needed for normal vasodilation. African Americans generally have less of a vasodilatory response to nitric oxide than do Caucasians;[99] if atherosclerotic or hypertensive damage to the endothelium occurs, even less endogenous nitric oxide is available to facilitate vasodilation and arterial relaxation for African Americans. This may lead to increased blood pressures and additional endothelial damage, in a positive, re-enforcing feedback loop.

To summarize, the effects of hypertension, mean arterial pressures, or atherogenic risk factors might lead to more extensive arterial remodeling among African Americans as compared to Caucasians. While some studies have examined the associations of CVD risk factors with

accelerated PWV progression, no study to our knowledge has examined whether the strength of these associations varies by ethnicity.

Because higher PWV is associated with greater risk of clinical cardiovascular disease events,[1, 77-80] part of the excess burden of clinical disease among African American women may be attributed to accelerated arterial stiffening in this group. Examining the relative importance of various CVD risk factors on PWV progression by ethnicity may lead to better understanding of why African Americans appear to have stiffer arteries, more accelerated arterial stiffening and more clinical outcomes than do Caucasians. Few studies have examined PWV progression among African American women, and this question has clear clinical significance for this group. Aggressive management of certain CVD risk factors that promote PWV progression may thereby reduce the risk of accelerated arterial stiffening and prevent clinical sequelae.

2.3.2 Socioeconomic Status May Explain Inconsistencies Between Ethnicity and Subclinical CVD

2.3.2.1 Definitions of Socioeconomic Status

As defined by Krieger and colleagues, socioeconomic status (SES) is "an aggregate concept that includes both resource-based and prestige-based measures as linked to both childhood and adult social class position. Resource-based measures refer to material and social resources and assets, including income, wealth, educational credentials… prestige-based measures refer to an individual's rank or status in a social hierarchy, typically evaluated with reference to people's access to and consumption of goods, services, and knowledge, as linked to their occupational prestige, income, and educational level."[100]

Strong and inverse associations between SES and health outcomes have been observed in a substantial body of literature. This project will focus primarily on the associations of adulthood educational attainment, income, and financial strain with subclinical CVD.

Educational attainment is the most frequently-used surrogate measure of SES, and is found in approximately 45% of epidemiologic studies on SES.[101] Advanced education may facilitate higher social status, enhance an individual's ability to navigate through the health system, and provide access to better employment, higher wages, and occupational prestige. Education is a widely-used SES indicator in part because of its stability: generally, education is maximally attained in early adulthood and remains unchanged through adulthood. Furthermore, there is less variability over time in years of education or educational degrees than is observed with other SES indicators, such as income or occupation. Finally, a majority of adults in the U.S. have some educational attainment, and response rates to education questions typically are high.[102]

Income is another widely-used SES indicator, and is typically assessed by total combined household income over a designated period.[102] Higher incomes may facilitate direct access to material resources and access to health-promoting activities, and may contribute to social power and prestige.[103] Without adequate finances, people may be subject to substandard housing conditions, may be unable to afford health care or medications, or may not have access to healthy nutrition or opportunities for physical activity. Interestingly, while income and education are related, the associations between income and health outcomes do not fully overlap with those of education.[104] This suggests that income and education indicators may each provide important information with regard to health.

Studies relating SES with health outcomes have traditionally examined those individuals who report the lowest levels of education and income. The assumption has been that poverty and inadequate educational attainment—*i.e.,* severe deprivation and social disenfranchisement—are the true origins of adverse health outcomes. In actuality, there is a consistent, graded and inverse association between health outcomes and SES across a wide span of SES levels, including higher income and educational degree categories.[104] This finding was observed in the Whitehall study, which examined cardiovascular health outcomes among 17,530 male British civil servants over 10 years. Among skilled, professional levels in the cohort, top administrators had lower CHD mortality risk than did executives who were ranked slightly lower; both grades also had lower

CHD mortality than did unskilled grades in the cohort.[105] As reported by Gallo and Matthews, "the impact of SES is not only at the poverty line. Rather, health discrepancies have a monotonic relationship with SES, so that even relatively affluent groups exhibit worse health than their higher SES counterparts."[106] In certain social groupings, the association between low SES and health may be better conceptualized as an association between relatively low versus relatively high levels of SES. Studies of these groups may help to clarify the effects of comparative social status and prestige on health.[107]

SES is a multifaceted construct, and education and income indicators merely approximate an individual's true economic and social position. Indeed, prior research findings have suggested that the social and financial returns of higher education differ by gender, age, and ethnicity.[108] Furthermore, the quality of the institution granting the educational degree, or the social connections that may be gained through attendance at a particular institution, are difficult to quantify, but may have substantial effects on power, social status, and material resources.[102]

Income must be also considered with some caution, particularly among women: 1) income may be affected by reverse causation, where the effects of poor health may influence material resources or employment; [106] 2) income may vary considerably over the life course; 3) only 59% of all women are in the labor force, and 39% of married women do not earn their own salaries, so personal income versus combined household income measurement is not recommended; [109] 4) non-response to income-related questions is high, averaging between 9 and 10%;[103] 5) if combined household income is not adjusted by the number of people in the household, it is challenging to approximate economic status; 6) most income measurements do not account for regional differences in living costs.

Several studies advocate the usage of financial strain assessment in conjunction with or in lieu of income in order to assess an individual's economic well-being.[110, 111] Typically, participants are asked either if they have experienced difficulty paying for basic goods and services, or if they have been unable to pay their monthly bills more than once over a designated period. Financial strain is a subjective evaluation, and in some cases, may better reflect an individual's true financial status than objective reports of income. For example, an individual

may report a low income but receive financial help from an outside source, or a family may report a large combined income, but carry a sizeable burden of debt. In these cases, the ability to pay for basics or pay monthly bills may be influenced by factors that are not directly related to income, and would not otherwise be captured if using income as a single indicator of SES. However, there are limitations to assessments of financial strain. Because perceived financial strain is subjective and often undefined, definitions of "basic" goods and services may vary substantially between respondents. Furthermore, this measure typically does not differentiate between persistent or temporary strain; short-term financial strain associated with purchasing a home may convey different information than does long-term financial stress due to chronic illness.

By assessing more than one SES indicator in studies of SES, it may be possible to avoid some of the limitations that are associated with independent evaluations of education, income, or financial strain. However, despite these shortfalls, education and income in particular have each been associated with greater CVD mortality in an exceptionally large body of literature. This attests to the robustness of these measures, and the strength of the relationships between low SES and CVD.

2.3.2.2 Associations Between Socioeconomic Status and Subclinical Cardiovascular Disease

Research studies over the past fifty years have consistently found inverse relationships between SES and CVD events and mortality.[4, 112] A component of this excess risk may be that low SES women carry an excess burden of CVD risk factors, such as LDL-C, SBP, total cholesterol, triglycerides, BMI, and fasting glucose levels.[113]

Inverse associations have also been observed between SES and certain measures of subclinical CVD. Lower educational attainment was associated with higher CAC and AC in the Healthy Women Study, [114] and low education was associated with higher CAC prevalence

among young African Americans and Caucasians.[115] The ARIC study reported that lower education and income were associated with higher IMT among both African American and Caucasian adults.[68] A study of African American and Caucasian adolescents reported that lower income categories and low neighborhood SES were associated with higher PWV, and that fewer household assets (e.g., number of cars, loans, home ownership) were related to higher IMT.[82] Low job status and educational attainment, [116-118] economically disadvantaged neighborhood status,[119] and low SES at birth have each been associated with greater degree of carotid stenosis, [120] higher cross-sectional levels of IMT, or accelerated IMT progression.

This evidence suggests that low SES is a potent predictor of adverse atherosclerotic and arteriosclerotic changes. Currently, it is difficult to assess the relative importance of SES across the different subclinical CVD indicators among women because no studies have examined all four measures in a single cohort; it is possible that certain measures of subclinical CVD are more strongly associated with certain indicators of SES than with others.

2.3.2.3 Combined Associations Between Ethnicity and Socioeconomic Status Towards Subclinical CVD

Although African American ethnicity and low SES are consistently and independently related to certain measures of subclinical disease, it is conceivable that they have a combined association. African American ethnicity and low SES are highly correlated in the United States. It is possible that SES effects may actually be misclassified in extant literature as effects of African American ethnicity, and vice versa.

In addition to any undefined genetic factors or CVD risk factors that may render African Americans particularly vulnerable to subclinical and clinical CVD,[86] behavioral and environmental risk factors could confer greater risks to this group. Lifetime effects of low SES, including adverse health behaviors and inadequate access to health care, may disproportionately

impact African Americans. Furthermore, certain social stressors related both to ethnicity and subclinical CVD may affect African Americans specifically;[121] for example, African American women who experienced recurrent episodes of discrimination had higher levels of CAC in one study. [122] In sum, African American women with low SES may be at even greater risk than Caucasian women with low SES of developing subclinical CVD—and ultimately, clinical outcomes. Given the preponderance of low SES in the African American community, low SES may partly confound the relationship of African American ethnicity towards subclinical and clinical CVD outcomes.

2.3.2.4 Epidemiologic Link

Given the substantial overlap between African American ethnicity and low SES, it is important to examine both simultaneously in order to clarify their independent roles in subclinical CVD development. This type of analysis may be achieved through basic statistical methods. However, while hundreds of studies have examined ethnicity *or* SES with respect to CVD, only nineteen studies in one literature review had examined ethnicity *and* SES with respect to CVD.[123] Even fewer prospective cohort studies—five to our knowledge, from four different cohorts-- have examined ethnicity and SES in combination with respect to measures of subclinical CVD.[68, 82, 115, 124, 125]

One study of 214 U.S. adolescents examined the independent and combined associations between ethnicity and SES with respect to PWV and IMT. Among African Americans only, low and medium household income categories were related to higher PWV, and lower neighborhood SES was associated with higher IMT. Low education was related to higher PWV among Caucasians only. Results were not reported by gender.[82]

The CARDIA study of 2913 young adults (ages 33-45) examined associations between education, 15-year CVD risk factor progression, and cross-sectional measures of CAC. While the interaction between ethnicity and education was not directly tested, both variables were included in logistic regression models predicting CAC. Individuals who were Caucasian or had

less than a high school degree had higher CAC levels, with or without simultaneous adjustment for various CVD risk factors. Indeed, people with less than a high school education had 2.5 to 4.1 times the risk of having prevalent CAC as compared to postgraduate education; African Americans had around half the risk of having prevalent CAC than did Caucasians. These trends were not assessed by gender specifically.[115]

The MESA study of 6814 middle-aged adults examined associations between ethnicity and SES as main effects in an analysis of subclinical disease.[124] Caucasians with high as compared to low educational attainment had lower prevalence of carotid plaque and lower IMT levels in the internal carotid arteries. Among African Americans, a weak, inverse association between household income and carotid plaque was observed. Across African American and Caucasian ethnicities, the strength of the associations between different SES indicators and carotid IMT and plaque may vary. The study did not stratify by gender, so it is not clear how robust these associations are for women.

The ARIC study also has examined the combined associations of ethnicity and SES with regard to IMT.[68] ARIC reported that income, education, neighborhood SES, and a composite SES score were all inversely associated with baseline CCA-IMT among both Caucasians and African Americans. CCA-IMT progression was also assessed over 5 years. For Caucasians, low income and low composite SES scores were associated with highest rates of IMT progression. However, higher income, education, and neighborhood SES were associated with greater IMT progression among African Americans. These results remained either significant or marginally significant after adjustments for baseline CVD risk factors. The authors noted that these unexpected findings probably did not result from selective attrition among African Americans. While low SES African Americans presented with higher baseline IMT levels than did high SES African Americans, the authors refute that a "ceiling effect" explained the slower progression in this group; earlier published studies in the cohort showed that baseline IMT levels were not associated with the rate of change IMT. The ARIC data suggest that assessing ethnicity and SES interactions in studies of subclinical CVD progression may give us different insights about risk factors than do cross-sectional measures. However, this study also reveals the limits of our knowledge about the origins of ethnicity and SES interactions in subclinical CVD literature. It is

unknown why middle-aged, high SES African Americans are at highest risk of adverse IMT progression. Like MESA, ARIC reported aggregate findings of men and women; it is unclear whether these results are consistent when stratified by gender.

2.3.2.5 Psychosocial Factors May Explain Associations Between Ethnicity, Socioeconomic Status, and Subclinical CVD

The authors of the ARIC study were unable to clarify reasons why they observed that among African Americans, 1) low SES predicted greater baseline IMT, and 2) high SES participants experienced significantly greater IMT progression than did low SES participants.[68] One explanation may be that emotional and affective factors may mediate some relationships between ethnicity, SES and subclinical CVD.

Baron and Kenny proposed that a mediator variable explains how another variable, or a "predictor," affects an outcome; the predictor must be correlated with the candidate mediator, the mediator must be associated with the outcome, and the predictor must be associated with the outcome variable.[126] As was noted earlier, low SES may be associated with subclinical CVD progression—specifically measures of AC, CAC, and IMT. African American ethnicity is associated with higher levels of some, but not all, subclinical CVD measures. The following sections will provide evidence linking low SES with negative emotions and attitudes, examine the relationships between negative emotions, attitudes and subclinical CVD progression, and describe how these relationships may vary by ethnicity. We propose that negative emotions and attitudes should be tested in a mediational framework in order to clarify the associations between ethnicity, SES and subclinical CVD progression.

2.3.2.6 Emotions, Affect and Subclinical CVD Progression

An emerging body of literature has examined the associations of affect and adverse health behaviors with regard to subclinical CVD progression among women. The majority of these associations have been observed in studies of IMT. Higher IMT progression has been observed among women with high versus low trait anger scores, women who reacted angrily to adverse situations, and women with sustained anxiety over a 2-year period as compared to women without anxiety.[127, 128] These studies suggest that negative affect or emotions predict accelerated progression of one measure of subclinical CVD.

2.3.2.7 Emotions, Affect, SES and Ethnicity

Low SES is associated with negative affect and emotions in a substantial body of literature. A review by Gallo and Matthews proposed that low-SES individuals may be exposed to adverse situations where interpersonal, intrapersonal or tangible resources are required. However, their environments may not facilitate maintenance or renewal of these resources, and their "reserve capacity" to overcome life challenges may be limited. Resultant stress may lead to negative or fatalistic attitudes and emotions, and potentially, riskier or adverse health behaviors.[106] For example, compared to women with higher educational attainment, women with low education in one U.S. study were more likely to report feelings of anger and depression, and indicate low levels of social support. These women were also more likely to smoke, consume alcohol, and were more often physically inactive than were women with higher education.[129] As Gallo and Matthews summarized, "an association between SES and negative emotions and attitudes is likely. The evidence is particularly strong for an association between low SES and depressive, hopeless, anxious, and hostile symptoms… our review points to an a number of areas for further research, including additional studies examining the association between SES and anxiety symptoms."[106] It is important to underscore that anxiety, hopelessness, and hostility have also been independently associated with IMT progression, as noted in Section 2.3.3.1.

Only one study has examined whether negative affect mediates the associations between low SES and CHD. Thurston and colleagues reported that the lowest levels of education as compared to college education were associated with increased CHD risk among men and women in the NHANES cohort.[130] Higher versus lower levels of depressive and anxious symptoms were also associated with increased CHD risk among men and women. However, depression and anxiety did not appear to explain the relationship between low educational attainment and CHD. It is possible that the effects of depression and anxiety are most pronounced during the subclinical phase of disease, as they may predispose an individual to incident CHD. Results were not presented by ethnicity or gender to low representation of African Americans in the sample, and it is unclear whether the mediational framework was tested in all subgroups.

The inverse associations between SES and negative mood or affect have been examined in predominately Caucasian samples, but a limitation of the existing literature is that few studies have examined these associations among African American women. Early evidence in the SWAN cohort suggests that middle-aged African American women have better psychological coping strategies to financial strain and adversity than do Caucasian women,[110] although these preliminary findings have not been replicated in other samples.

2.3.2.8 Additional Considerations

Baron and Kenny infer that a predictor variable precedes the mediator, which then exerts its effects on the outcome.[126] However, as Kraemer and colleagues have observed in the field of mental health research, it is challenging to establish a temporal association between a predictor and a mediator in most study designs.[131] While negative emotions and attitudes may indeed result from the difficulties associated with low SES, the potential for reverse causation should also be considered; negative or antagonistic attitudes may predispose individuals to low SES.[106] Therefore, any examination of negative emotions and attitudes as mediators of SES must consider results with caution.

2.4 LIMITATIONS OF EXISTING EPIDEMIOLOGIC LITERATURE

African American women have a greater incidence of clinical cardiovascular events than do Caucasian women.[1] It is likely that this excess CVD risk is partly due to excess CVD risk factors among African American women. However, some evidence suggests that ethnic variation in the magnitude of the influence of certain CVD risk factors may result in different susceptibilities towards subclinical or clinical outcomes.[95, 96] No studies have examined this question with respect to PWV progression, a marker of arteriosclerosis. While it is possible that certain CVD risk factors may aggravate adverse PWV progression among African American women as compared to Caucasian women, it is unclear which traditional CVD risk factors might be particularly detrimental to African Americans. Most epidemiologic studies of PWV progression have involved only European cohorts;[92, 132] one study included African Americans, but adjusted for ethnicity rather than presenting these data separately.[93] Understanding the role of CVD risk factors in PWV progression may better help to explain why African Americans have more pronounced and accelerated arterial stiffening over time, and may reveal candidate areas for intervention.

Furthermore, while African American ethnicity is associated with higher levels of clinical outcomes, the associations between African American ethnicity and various measures of subclinical CVD are inconsistent across studies. It is possible that part of this inconsistency is explained by the effects of SES. SES has been examined with respect to certain measures of subclinical CVD, and particularly with CAC and IMT measures. However, most epidemiologic studies that examine ethnicity and subclinical CVD do not adjust for SES, or vice versa. Given the strong correlations between low SES and African American ethnicity in the United States, SES and ethnicity should be considered jointly in studies of subclinical CVD.

2.5 SPECIFIC AIMS

The three studies presented in this project utilized data from the Study of Women's Health Across the Nation (SWAN) Heart Study, a cohort study examining the cardiovascular changes of African American and Caucasian women during middle age.

The aim of **Research Article 1** (Chapter 3) was to examine whether the associations between CVD risk factors and PWV progression varied by African American or Caucasian ethnicity. Traditional CVD risk factors assessed in this study included age, SBP, DBP, LDL-cholesterol, HDL-cholesterol, fasting glucose levels, triglyceride levels, and waist circumference.

The aim of **Research Article 2** (Chapter 4) was to examine the independent and combined associations of ethnicity and SES with respect to four subclinical CVD measures—CAC, AC, IMT, and PWV. Also investigated were the effects of blood pressure on these relationships.

The aim of **Research Article 3** (Chapter 5) was to examine the independent and combined associations of ethnicity and SES with respect to CAC progression. Also assessed was whether psychosocial factors—including reported feelings of financial strain, trait anxiety, or cynical hostility—explained the hypothesized relationships.

3.0 AFRICAN AMERICAN ETHNICITY AND CARDIOVASCULAR RISK FACTORS ARE RELATED TO AORTIC PULSE WAVE VELOCITY PROGRESSION

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3.1 ABSTRACT

Accelerated central arterial stiffening as represented by progression of aortic pulse-wave velocity (PWV) may be influenced by cardiovascular disease (CVD) risk factors. Little is known about the relationships between CVD risk factors and PWV progression among women transitioning through the menopause, or whether these relationships vary by ethnicity. To address this knowledge gap, we conducted a subgroup analysis of 303 African American and Caucasian participants in the Study of Women's Health Across the Nation (SWAN) Heart Study received PWV scans at baseline examination and at a follow-up examination an average of 2.3 years later. CVD risk factors were also assessed at baseline.

Systolic blood pressure (SBP) and waist circumference were the strongest predictors of PWV progression, after adjustment for age, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), diastolic blood pressure (DBP), glucose, and triglyceride levels. The magnitude of the influence of SBP, DBP, LDL-C, and glucose on PWV progression varied by ethnicity (difference in slopes: $p=0.03$ for SBP, $p=0.001$ for DBP, $p=0.01$ for LDL-C, and $p=0.06$ for glucose). The positive relationship between SBP and PWV progression was significant among women of both ethnicities, but stronger among African Americans. LDL-C, DBP, and, to a lesser extent, glucose levels were positively associated with PWV progression only among African Americans.

Arterial stiffening is associated with clinical cardiovascular events and mortality. Blood pressure, LDL-C, glucose, and excess body size may be important targets for improving vascular health and preventing clinical outcomes, particularly among African American women.

3.2 INTRODUCTION

Arterial stiffening, as measured by aortic pulse-wave velocity (PWV), is an age-related process associated with clinical cardiovascular disease (CVD) events and mortality.[77-80] However, premature arterial stiffening may occur as a response to risk factors such as excess body weight, hypertension, type 2 diabetes mellitus, and the metabolic syndrome. These risk factors may also predict the progression of aortic PWV over time.[70, 75, 92, 93]

African American women have greater incidence of and mortality from clinical cardiovascular events,[1] and appear to have higher PWV than do Caucasians.[74, 133] In addition, African American women have a greater prevalence of CVD risk factors, including obesity, hypertension, and type 2 diabetes mellitus.[1] This disproportionate CVD risk factor burden may contribute to higher PWV progression among African American women.

The effect of certain CVD risk factors on arterial stiffness may also vary by ethnicity. Hypertensive African Americans have a cardiovascular mortality rate 3 to 5 times higher than that of hypertensive Caucasians,[95] and hypertension is an especially robust predictor of coronary heart disease (CHD) among African American women.[96] African Americans also develop higher systolic blood pressures (SBP) than do Caucasians beginning in early adulthood;[134] greater arterial stiffness among African Americans may reflect the greater cumulative lifetime exposure to high SBP and hypertension. Several studies also suggest that African Americans may be particularly susceptible to vascular remodeling after exposure to hypertension, high mean arterial pressures, or to cytokines and growth factors related to atherosclerosis.[97, 98, 135] Therefore, it is conceivable that African American women with hypertension or atherogenic risk factors may develop more accelerated arterial stiffening than do Caucasian women with the same risk factors. This question has not been assessed in relation to PWV progression, and may identify a potential pathway by which African American women develop more prevalent clinical disease.

Identification and modification of risk factors that contribute to early arterial stiffening among women transitioning through the menopause may help to advance preventative care and improve clinical outcomes. In this study of CHD-free, middle-aged women, we assessed: 1) the relationships of baseline levels of SBP, DBP, waist circumference, LDL-C, HDL-C, glucose, and triglycerides with PWV progression, and 2) whether associations between PWV progression and these individual CVD risk factors varied by ethnicity. We hypothesized that risk factors related to blood pressure would be most strongly associated with accelerated PWV progression among African American women.

3.3 METHODS

3.3.1 Study Population

The SWAN study examines the changing biological and psychological health of women across the menopause transition. Descriptions of the study design and methods have been reported elsewhere. [136] Between 1996 and 1997, 3302 pre-menopausal or peri-menopausal women were recruited to one of seven research centers: Detroit, MI; Boston, MA; Chicago, IL; Oakland, CA; Los Angeles, CA; Newark, NJ; and Pittsburgh, PA. Eligibility criteria for the SWAN were as follows: aged 42-52 at enrollment, intact uterus and at least one ovary, menstrual bleeding within the prior three months, no current pregnancy or breast-feeding, no usage of reproductive hormones within the prior three months, and self-identification as a member of 1 of 5 ethnic groups depending on the research site: Caucasian (all sites), African American (Boston, Chicago, Detroit, Pittsburgh), Chinese/Chinese American (Oakland), Hispanic (Newark) or Japanese/Japanese American (Los Angeles).

SWAN Heart is an ancillary study designed to assess subclinical CVD in mid-life African American and Caucasian women. SWAN participants from the Chicago and Pittsburgh sites (n=608) were recruited to the SWAN Heart cohort between 2001 and 2003 if they met the following criteria: no history of coronary heart disease, stroke, hysterectomy, or postmenopausal status, and no usage of diabetes medications or hormone therapy.

Participants who met study criteria received their initial PWV measurements at SWAN Heart baseline (n=554). Of the original cohort, 316 participants returned for a follow-up PWV measurement an average of 2.3 years later (range: 1.1 - 4.3 years). Those who did not return were more likely to be African American, enrolled at the Chicago study site, and had marginally higher SBP, glucose levels, and waist circumferences. HDL-C, DBP, LDL-C, age, triglycerides,

educational status, pulse rate, or smoking status did not differ significantly between those women who returned for follow-up and those who did not. Additional participants were excluded from analysis for the following reasons: implausible or unreadable PWV scans at baseline or follow-up (n=7), missing all plasma measurements (n=1), began usage of anti-hypertensive medications between the screening and baseline exams (n=5). The final sample of 303 women with two PWV scans included 204 Caucasians and 99 African Americans.

3.3.2 Measurement of Aortic Pulse Wave Velocity

Arterial stiffness was assessed by the gold standard, carotid-femoral PWV. In brief, arterial flow waves were simultaneously and non-invasively recorded at the carotid and femoral arteries of supine participants, using unidirectional transcutaneous Doppler flow probes (model 810-a, 10 MHz, Parks Medical Electronics, Aloha, OR). Aortic PWV is calculated as distance/transit time (cm/seconds). The transit time of the pulse wave was calculated as the delay between the averaged carotid and femoral waveforms. The distance traveled by the pulse waveform was estimated by measurement over the participant's torso. The distance from the carotid to aortic site was subtracted from the sum of the aortic to umbilicus and umbilicus to femoral site to adjust for the opposite direction of the blood flow in that arterial branch. A higher PWV indicates a stiffer vessel. This measure has been demonstrated to have good reproducibility, with an overall laboratory intraclass correlation of 0.77. [69] PWV values at follow-up were normally distributed.

The following plasma, physical, and covariate measurements were taken at the SWAN visit coincident with or closest in time to each participant's baseline SWAN Heart visit (SWAN years 4-7).

3.3.3 Plasma Measures

Blood was drawn once, usually during days 2 to 5 of the follicular phase of the menstrual cycle and after a 12 hour fast. Plasma samples were maintained at 4°C until separated, and then were frozen at –80°C and shipped on dry ice to the Medical Research Laboratories (Lexington, KY) which is certified by the National Heart Lung and Blood Institute, Centers for Disease Control Part III program. Low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were analyzed on EDTA-treated plasma. HDL-C was isolated using heparin-2M Mn(II)Cl. Triglycerides were analyzed by enzymatic methods via a Hitachi 747 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN, USA). Glucose was quantified via a hexokinase-coupled reaction (Boehringer Mannheim Diagnostics).

3.3.4 Physical Measures

Resting blood pressure was measured three times after each participant had been seated for five minutes, and the average of the final two readings was recorded via a standard mercury sphygmomanometer. Participants wore light, loose-fitting clothing for body size assessments. Height and weight were used to calculate BMI (kg/m^2). Waist circumference was measured at the natural waist, which is the narrowest aspect of the torso as seen from the anterior aspect. If the natural waist was difficult to detect, waist circumference was measured at the smallest horizontal circumference between the lowest ribs and the iliac crest.

3.3.5 Covariate Measures

Following a 5-minute rest, pulse rate (beats per minute) was calculated by multiplying each participant's pulse at 30 seconds by a factor of two.

Ethnicity, age, hypertensive medication usage (yes/no), educational attainment, smoking status, menopausal status, and study site (Chicago or Pittsburgh) were assessed via self-administered or interview-administered questionnaires. Education was originally coded as one of five options, but was collapsed to the following three categories due to low frequencies: high school education or less, some college (including associate's degree and college degree), or postgraduate education. Current smoking status (yes/no/unknown) was defined as intake of at least one cigarette per day between the previous SWAN visit and the SWAN Heart baseline year. Women with missing smoking data (n=26) were assigned as unknown smoking status.

Menopause status was determined via self-reported menstrual patterns. Pre-menopause was defined as menstrual bleeding within the prior 3 months without changes in regularity, early peri-menopause was defined as menstrual bleeding within the prior 3 months with change in regularity, late peri-menopause was defined as no menstrual bleeding within the prior 3 months but bleeding within the prior 12 months, and natural post-menopause was defined as no menstrual bleeding within the prior 12 months or longer. Hysterectomy was defined as removal of the uterus and/or double oophorectomy. Women who did not report menstrual bleeding patterns or who reported using exogenous estrogen within the past year were designated as unknown menopausal status. Due to small counts, menopausal status was categorized as follows: premenopause or early peri-menopause (n=175), late peri- or postmenopause (n=103), and hysterectomy/unknown/hormone use (n=25).

3.3.6 Data Analysis

T-tests and Chi-Square tests were used to assess ethnic differences in CVD risk factors and covariates. PWV progression was analyzed as follow-up PWV values adjusted simultaneously for both the continuous baseline PWV values and the time between SWAN Heart visits. To these minimally-adjusted models, baseline levels of LDL-C, HDL-C, glucose, SBP, DBP, waist circumference, and triglycerides were added either separately or in combination to investigate the relationships of CVD risk factors with PWV progression. Fully-adjusted models

predicting follow-up PWV included the following covariates: baseline PWV measurements, time between SWAN Hear visits, participant age, menopausal status, education, smoking status, and pulse rate. BMI and waist circumference were highly correlated in this sample ($r=0.90$, $p<0.0001$). To assess the effects of body size on arterial stiffness but to avoid collinearity, only waist circumference was included in the regression models. Waist circumference explained more of the variance in PWV than did BMI, and overall was a strong predictor of PWV at follow-up in minimally- and fully-adjusted models.

To formally test whether the effects of CVD risk factors on PWV progression were affected by ethnicity, interaction terms between ethnicity and each CVD risk factor were included in each minimally-adjusted linear regression models. All models were two-tailed with alpha=0.05. SAS version 9.1 software (SAS Institute, Cary, NC) was used for this analysis.

3.4 RESULTS

Participants were on average fifty years old, the majority had at least some college education and most were pre-or early peri-menopausal. Participants had somewhat elevated BMI, LDL-C, SBP and waist circumferences. Mean pulse rate, DBP, HDL-C, fasting glucose, and triglyceride levels were within normal ranges. African American women had significantly higher SBP, DBP, BMI, and waist circumferences than did Caucasian women; Caucasian women had higher triglyceride and marginally higher HDL-C levels than did African American women. Baseline PWV did not significantly vary by ethnicity, although the mean baseline value among African Americans was 35.5 cm/s higher than among Caucasians. Follow-up PWV was significantly higher among African American women (Table 1).

Standardized regression coefficients of follow-up PWV on each CVD risk factor or ethnicity are presented in Table 2. African American ethnicity, SBP, DBP, waist circumference were each positively associated with follow-up PWV in minimally-and fully-adjusted models. HDL-C was negatively and significantly related to higher follow-up PWV in minimally-adjusted models, but this association was not significant in the fully-adjusted models. LDL-C was marginally associated with higher follow-up PWV both in minimally- and fully-adjusted models. Triglyceride and glucose levels appeared to be unrelated to follow-up PWV.

CVD risk factors and ethnicity were entered simultaneously into a fully-adjusted model predicting follow-up PWV (Table 3). SBP and waist circumference remained significantly associated with greater PWV progression. African American ethnicity was not independently related to higher PWV after adjustment for SBP (African American ethnicity β(S.E.)= 35.4 (22.9), p=0.12). LDL-C, DBP, HDL-C, triglycerides, glucose, and the covariates were not related to follow-up PWV in this model.

To determine whether associations between each CVD risk factor and PWV progression varied by ethnicity, interaction terms between ethnicity and individual CVD risk factors were examined in minimally-adjusted models. No interactions were observed between ethnicity and waist circumference, HDL-C, or triglycerides. However, significant interaction terms were observed between ethnicity and the following covariates: SBP ($p=0.03$), DBP ($p=0.0001$), and LDL-C ($p=0.01$). A marginally significant interaction term was observed between ethnicity and glucose ($p=0.06$). LDL-C, SBP, DBP, and glucose were separately entered into minimally- and fully-adjusted models that were stratified by ethnicity. Because waist circumference was highly related to PWV progression in earlier analyses, it was added as a covariate in the fully-adjusted models. Table 4 presents the results of these analyses and the model variance in follow-up PWV explained by each CVD risk factor.

SBP was associated with higher follow-up PWV among Caucasians and African Americans, although the relationship between SBP and PWV was stronger among African Americans than among Caucasians (Fig. 1). SBP also explained more of the model variance in follow-up PWV among African Americans than among Caucasians (Table 4). Among African-Americans but not Caucasians, DBP and LDL-C were each associated with higher follow-up PWV values (Fig.'s 2, 3). DBP and LDL-C also explained more of the model variance in follow-up PWV among African Americans in both the minimally- and fully-adjusted models (Table 4). Glucose levels were associated with higher follow-up PWV only among African Americans, which was largely accounted for by waist circumference (β (S.E.) for glucose= 35.4 (22.9), $p=0.12$ after adjustment for waist circumference) (Fig. 3, Table 4).

3.5 DISCUSSION

In the current study of middle-aged women, baseline SBP and waist circumference measures were most strongly associated with higher two-year progression of aortic PWV after adjustments for age, cardiovascular, biological, and psychosocial risk factors. Associations between CVD risk factors and PWV progression varied by ethnicity. DBP and LDL-C levels were associated with greater PWV progression only among African American women. To a lesser extent, glucose levels were associated with higher PWV progression among African Americans, but this difference was explained by waist circumference. SBP was related to PWV progression among Caucasians, but this association was weaker than that observed among African Americans. These relationships were not attributed to menopausal status, educational attainment, pulse rate, waist circumference, or smoking status. To our knowledge, our findings are novel in a population of healthy women.

A healthy artery must be sufficiently compliant, durable, and stable to withstand a range of hemodynamic forces. Reduction of elasticity in the aorta normally occurs with age, and is accompanied by increases in collagen content and hypertrophy of vascular smooth muscle cells.[91] Abnormally accelerated arterial stiffening may also occur in response to certain stimuli, including higher BMI, hypertension, type 2 diabetes mellitus, and the metabolic syndrome. [70, 75, 92, 93] A stiffer artery is more susceptible to endothelial injury.[13] Infiltration of lipids through the damaged endothelium may lead to atherosclerotic plaque formation in the vascular wall and culminate in clinical outcomes. Arterial stiffening also results in increased blood pressure, which in turn leads to additional arterial damage and stiffening; this reinforcing feedback cycle is linked to clinical outcomes such as stroke and cerebrovascular disease.[21]

An earlier study of adult males by Ferreira and colleagues observed that Afro-Brazilians presented with a greater SBP-dependent increase in cross-sectional PWV measurements than did

Caucasians, resulting in substantially higher PWV among Afro-Brazilians with hypertension as compared to Caucasians with hypertension.[97] Our research supports this finding, and indicates that blood pressure measures are also strongly related to higher PWV among African American women. Hyperlipidemia and hyperglycemia also appear to play important roles in the pathogenesis of arterial stiffening and ultimately, in clinical outcomes among African American women.

Because higher PWV is associated with greater risk of clinical cardiovascular disease events,[1, 77-80] part of the excess burden of clinical disease among African American women may be attributed to accelerated arterial stiffening in this group. Results from the current study suggest that even African American women without hypertension, hyperlipidemia, and/or hyperglycemia may have higher risk of arterial stiffening-- and ultimately, adverse clinical outcomes—than do Caucasians with similar risk factors; excess systolic blood pressure among African Americans appears to be the cause of this association. Therefore, additional exposure to CVD risk factors may be particularly detrimental to the vasculature of African American women. Given the disproportionate prevalence of obesity, hypertension, and type 2 diabetes mellitus among African American women, this area of research has considerable clinical implications. Our findings underscore the importance of aggressive and early clinical management of these risk factors in order to prevent clinical outcomes in this group.

Few studies have examined structural or mechanical differences of the central arteries by ethnicity, and it remains unclear why the vasculature of African Americans may be more susceptible to adverse remodeling upon exposure to specific CVD risk factors. Several related pathways have been proposed. First, African Americans have been observed to experience excess dermatologic collagenization, or keloid synthesis, as an aberrant response to injury. Investigators have hypothesized that a similar process may occur in the vasculature in response to hypertension-related injuries or damage from cytokines related to atherosclerosis.[135] Increased intravascular collagen content could contribute to greater central arterial stiffness among African Americans. Alternatively, recent work by the Bogalusa Study indicated that luminal enlargement associated with atherosclerosis was more strongly related to mean arterial pressures and vascular wall thickness among young African American adults than among

Caucasians. This finding suggests that in a milieu of atherosclerotic or pressure-related risk factors, the vasculature of African Americans is more inclined to undergo compensatory remodeling.[98] This mechanism may initially preserve perfusion, but the reserve capacity of the vessels is limited. If exhausted, adverse responses to risk factors may contribute to increased arterial collagenization and stiffening. Lastly, endothelial injury may enhance PWV progression by limiting the endogenous nitric oxide supply needed for normal vasodilation. African Americans generally have less of a vasodilatory response to nitric oxide than do Caucasians, [99] and damage to the endothelium from hypertension or through early plaque formation may disproportionately lead to accelerated PWV progression in this group.

Further research is needed to clarify the mechanisms by which SBP, waist circumference, hyperlipidemia, and hyperglycemia contribute to accelerated arterial stiffness among all women. Hyperglycemia may stimulate aberrant protein cross-linking and increased collagen deposition in the vascular wall.[18] Atherosclerosis, initiated by lipid infiltration into the vascular wall, may contribute to localized arterial stiffening.[25] Diabetes mellitus, excess adiposity, and hypertension are also independently associated with an increased inflammatory milieu. In one proposed pathway, inflammatory molecules may promote leukocyte infiltration into the arterial wall, leading to vascular smooth muscle cell infiltration, overproduction of dysfunctional collagen, disordered endothelial cells, broken elastin molecules, and a thicker arterial wall.[15, 16] Endothelial dysfunction may be a secondary effect of hypertension or inflammation, and result in reduced synthesis and/or release of nitric oxide.[16, 17] Examining whether these pathways differ across various ethnic groups may help to further explain the differences in vascular remodeling observed in the current study.

Low HDL-C and high triglyceride levels are considered important risk factors for clinical cardiovascular events, but were not associated with PWV progression in our analyses. In this sample, mean HDL-C and triglyceride levels fell within normal ranges, and therefore may not have been as strongly associated with accelerated arterial stiffening as other CVD risk factors. Similarly, Caucasian women had marginally lower PWV progression than did African American women, and the extent of progression may have been insufficient to detect associations with CVD risk factors. Future research is needed to identify CVD risk factors that contribute to PWV

progression among Caucasian women, particularly since clinical disease is also the leading cause of mortality in this group.

Our study has several limitations. Baseline levels of certain CVD risk factors appeared to exert measurable effects on arterial stiffness during a 2-year follow-up period. However, it is possible that CVD risk factors measured at baseline changed during the follow-up period for some women. Wildman and colleagues examined associations of body size measures at baseline and over two years with respect to PWV progression. Generally, baseline measures were most strongly associated with PWV progression, although some measures of body size changes were associated with PWV progression.[93] Similarly, changes in CVD risk factors over time should also be assessed in future studies. This may provide additional insight regarding how changes in CVD risk factors may exert either positive or negative effects on the progression of arterial stiffness.

In conclusion, in this sample of healthy, middle-aged African American and Caucasian women, we found that SBP and waist circumference were associated with accelerated PWV progression. SBP, DBP, LDL-C, and glucose levels were particularly robust predictors of PWV progression among African American women, and SBP was also associated with greater PWV progression among Caucasian women. Early and aggressive management of these CVD risk factors may reduce the risk of adverse vascular stiffening and prevent clinical sequelae. Future studies should consider whether the current clinical recommendations for acceptable risk factor levels—particularly with regard to LDL-C, glucose, SBP and DBP-- are adequate to prevent adverse clinical outcomes among African American women.[137]

Table 3-1 Characteristics of the Total Sample and by Ethnicity

	Total (n=303)	**Caucasian** (n=204)	**African American** (n=99)	*P* value (Ethnicity)
Age, years	50.1 (2.6)	50.3 (2.7)	49.7 (2.5)	0.068
BMI, kg/m^2	28.6 (6.3)	27.8 (5.7)	30.4 (7.0)	0.002
SBP, mm Hg	117.5 (15.1)	114.0 (14.0)	124.8 (14.9)	<0.0001
DBP, mm Hg	74.8 (9.7)	72.6 (9.0)	79.2 (9.6)	<0.0001
Waist Circumference, cm	87.6 (13.7)	86.2 (13.3)	90.5 (14.1)	0.012
LDL-C, mg/dL	119.6 (34.7)	119.3 (34.3)	120.3 (35.6)	0.82
HDL-C, mg/dL	57.7 (14.1)	58.7 (14.3)	55.6 (13.4)	0.075
Triglycerides, mg/dL	117.4 (88.4)	124.7 (100.0)	102.2 (55.8)	0.013
Glucose mg/dL	90.8 (15.3)	90.3 (16.8)	91.8 (11.5)	0.35
Baseline PWV, cm/s	800.1 (193.9)	788.6 (190.0)	824.1 (200.6)	0.14
Follow-up PWV, cm/s	868.5 (195.5)	839.5 (179.1)	928.4 (214.5)	0.0005
Pulse rate, beats/minute	70.8 (9.3)	70.4 (8.7)	71.7 (10.4)	0.31
Menopausal Status % (N)				
Late Peri/Post-menopause	34.2 (104)	34.1 (70)	34.3 (34)	0.28
Pre-/Early Peri-menopause	57.6 (175)	55.6 (114)	61.6 (61)	
Other or missing	8.2 (25)	10.2 (21)	4.0 (4)	
Educational Level % (N)				
High School or less	17.8 (52)	17.6 (35)	18.1 (17)	0.99
Any College	51.5 (151)	51.2 (102)	52.1 (49)	
Post-Graduate Education	30.7 (90)	31.2 (62)	29.8 (28)	

Mean (S.D.) unless indicated

Missings: DBP (n=5), Waist Circumference (n=9), LDL-C (n=1), Educational Level (n=11)

Table 3-2 Individual Regression Coefficients of Follow-up PWV Scores on Each CVD Risk Factor or Ethnicity

	Model 1 Adjustments				Model 2 Adjustments		
	β (S.E.)	*P* value	Change in Model R^2		β (S.E.)	*P* value	Change in Model R^2
Ethnicity African American Caucasian	79.9 (22.7) Referent	0.0005	0.038		86.8 (24.2) Referent	0.0004	0.004
SBP	4.56 (0.68)	<0.0001	0.12		5.00 (0.76)	<0.0001	0.12
DBP	5.84 (1.08)	<0.0001	0.088		6.42 (1.20)	<0.0001	0.08
Waist Circumference	4.58 (0.79)	<0.0001	0.098		4.52 (0.83)	<0.0001	0.08
LDL-C	0.61 (0.32)	0.053	0.012		0.55 (0.33)	0.097	0.01
HDL-C	-1.70 (0.76)	0.027	0.018		-1.37 (0.81)	0.09	0.01
Triglycerides	0.08 (0.12)	0.51	0.002		0.06 (0.13)	0.66	0
Glucose	0.84 (0.72)	0.24	0.005		0.64 (0.76)	0.39	0

β=Beta-coefficient, S.E.=Standard Error; Model 1 Adjustments: Baseline PWV and time between scans, **Model R^2 = 0.082**; Model 2 Adjustments: Model 1 adjustments, age, pulse rate, study site, menopausal status, educational level, smoking status, **Model R^2= 0.11;** Each risk factor or ethnicity was assessed individually with either Model 1 or Model 2 adjustments.

Table 3-3 Associations of CVD Risk Factors and Ethnicity on Follow-Up PWV Scores: Multivariable Linear Regression Models

	β (S.E.)	*P* value
Ethnicity		
African American	34.6 (24.9)	0.17
Caucasian	Referent	
SBP	3.46 (1.25)	0.006
DBP	0.34 (1.87)	0.86
Waist Circumference	2.92 (0.95)	0.0023
LDL-C	0.32 (0.32)	0.32
HDL-C	-0.29 (0.88)	0.74
Triglycerides	-0.15 (0.20)	0.47
Glucose	-0.18 (0.76)	0.81
Age	6.63 (4.57)	0.15
Pulse Rate	1.63 (1.18)	0.17
Study Site		
Pittsburgh	-35.3 (24.8)	0.16
Chicago	Referent	
Menopausal Status		
Late	-14.6 (26.3)	0.58
Missing	3.48 (42.0)	0.93
Early	Referent	
Educational Level		
High School or Less	16.7 (32.5)	0.61
Any College	10.0 (24.4)	0.68
Post-graduate	Referent	
Smoking Status		
Smoker	20.2 (32.4)	0.53
Missing	-19.2 (55.7)	0.73
Non-Smoker	Referent	

Model also adjusted for baseline PWV and time between scans; Model R^2= 0.27

Table 3-4 Associations of Baseline LDL-C, SBP, DBP, or Glucose with Follow-Up PWV Scores Differ by Ethnicity

		Caucasian				African American		
Model No.	**Covariates**	β (S.E.)	*P* value	Model R^2		β (S.E.)	*P* value	Model R^2
Model 1	SBP	3.01 (0.86)	0.0005	0.14		6.37 (1.31)	<0.0001	0.24
Model 2	SBP	2.66 (1.07)	0.014	0.22		6.10 (1.48)	<0.0001	0.36
Model 1	DBP	2.35 (1.36)	0.086	0.11		10.0 (1.98)	<0.0001	0.26
Model 2	DBP	1.58 (1.57)	0.32	0.20		9.21 (2.27)	0.0001	0.35
Model 1	LDL-C	0.020 (0.36)	0.95	0.09		1.74 (0.58)	0.0035	0.14
Model 2	LDL-C	-0.27 (0.37)	0.47	0.20		1.44 (0.62)	0.024	0.27
Model 1	Glucose	0.080 (0.73)	0.91	0.09		3.51 (1.86)	0.062	0.09
Model 2	Glucose	-1.22 (0.78)	0.12	0.20		3.00 (2.29)	0.19	0.23

Model 1 Adjustments: Baseline PWV and time between scans, **Model R^2 = 0.082**; Model 2 Adjustments: Model 1 adjustments, age, pulse rate, study site, menopausal status, educational level, smoking status, **Model R^2= 0.11;** Each risk factor was assessed individually with either Model 1 or Model 2 adjustments.

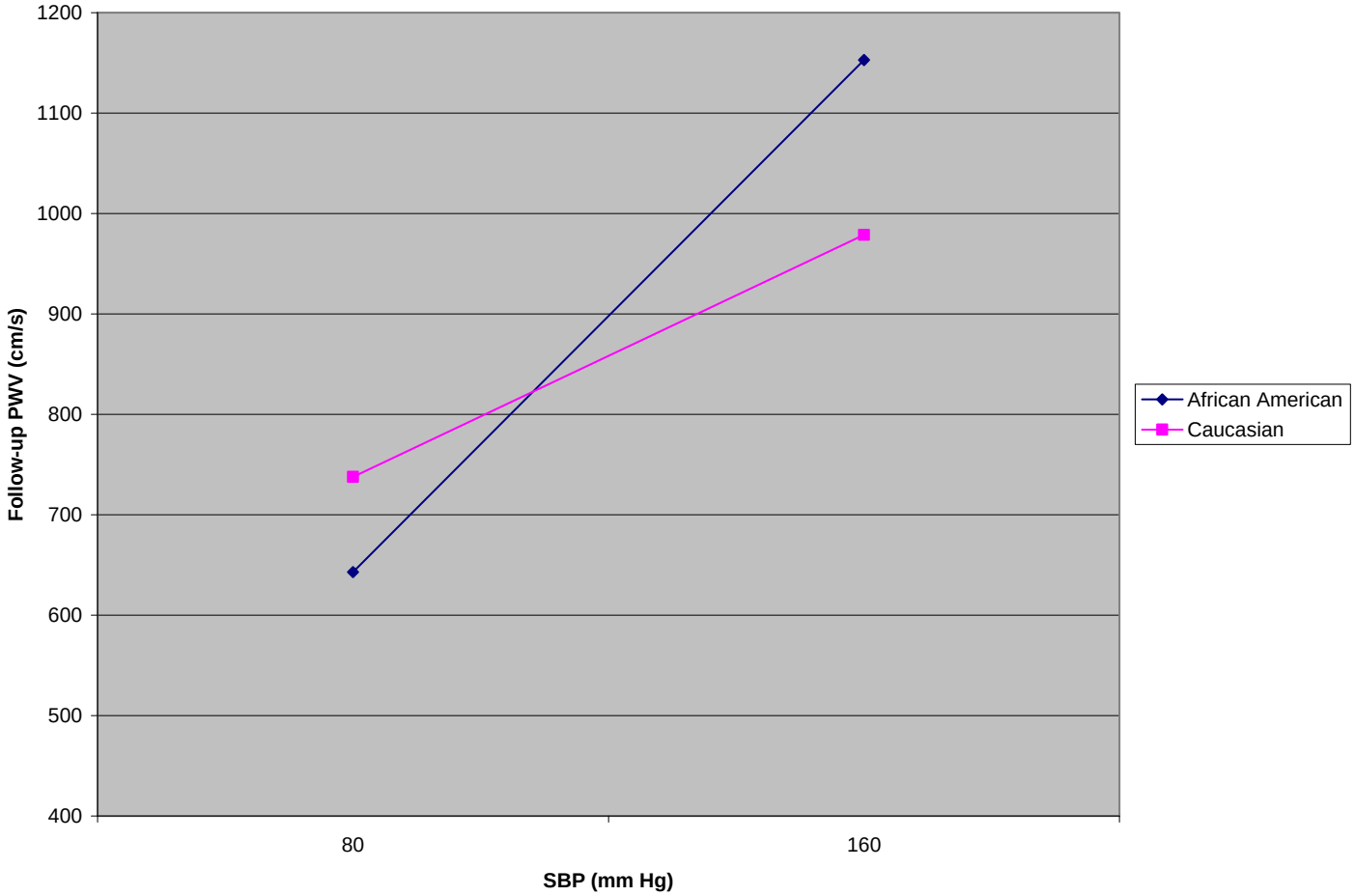

Figure 3-1 Relationship of SBP and PWV Progression by Ethnicity

Model adjusted for baseline PWV and time between scans; *p* for interaction = 0.03

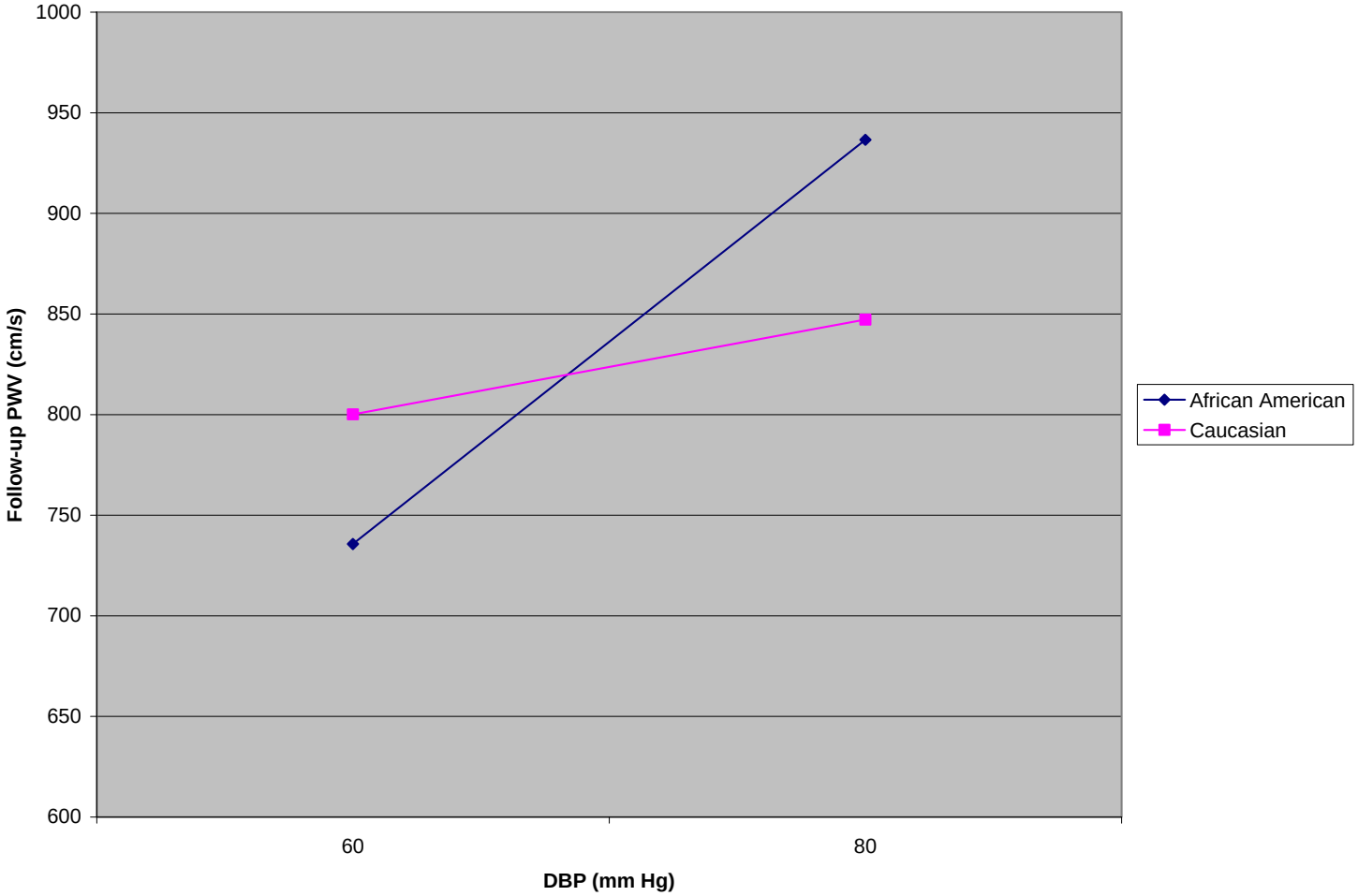

Figure 3-2 Relationship of DBP and PWV Progression by Ethnicity

Model adjusted for baseline PWV and time between scans; *p* for interaction = 0.001

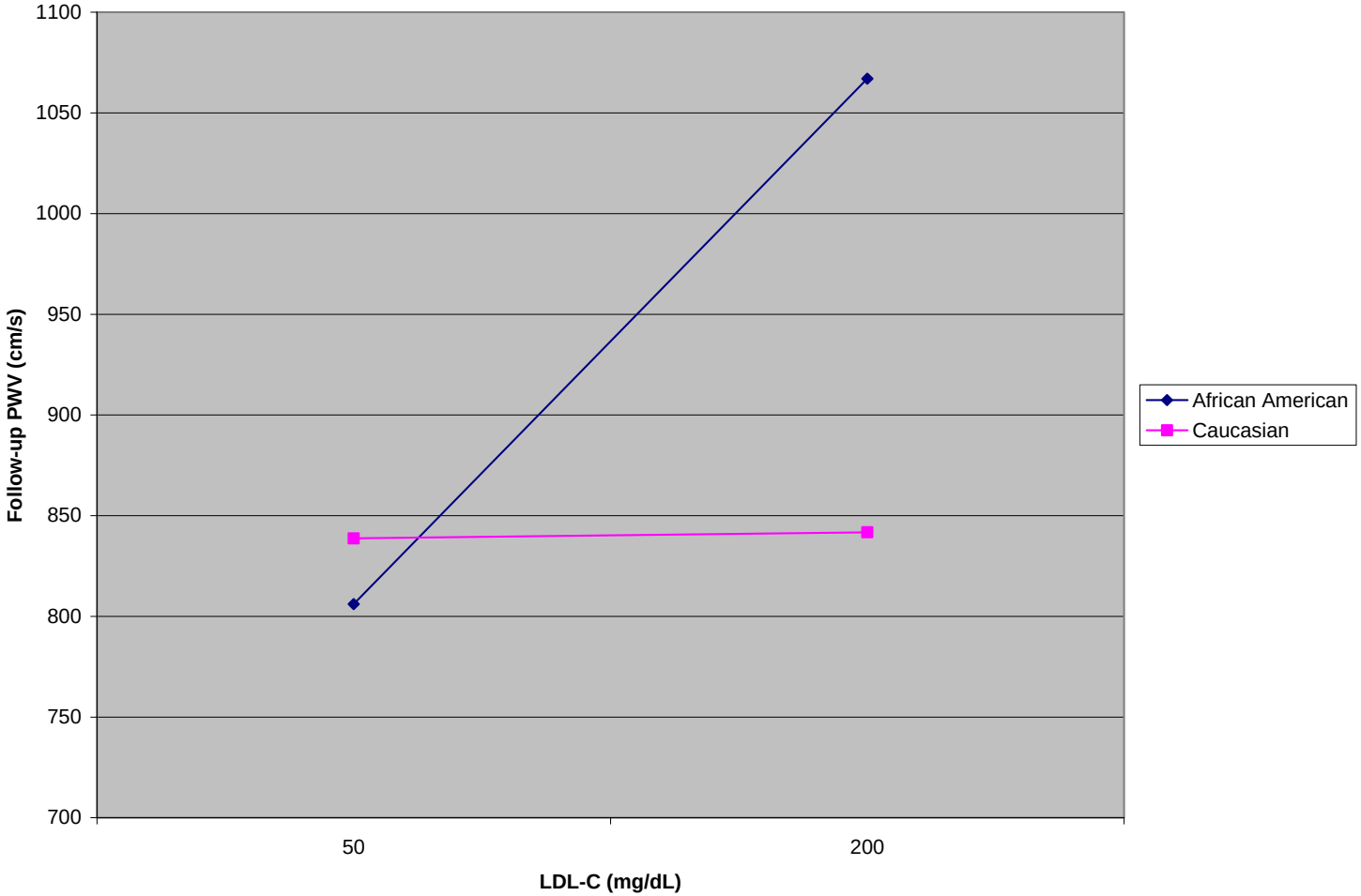

Figure 3-3 Relationship of LDL-C and PWV Progression by Ethnicity

Model adjusted for baseline PWV and time between scans; *p* for interaction = 0.01

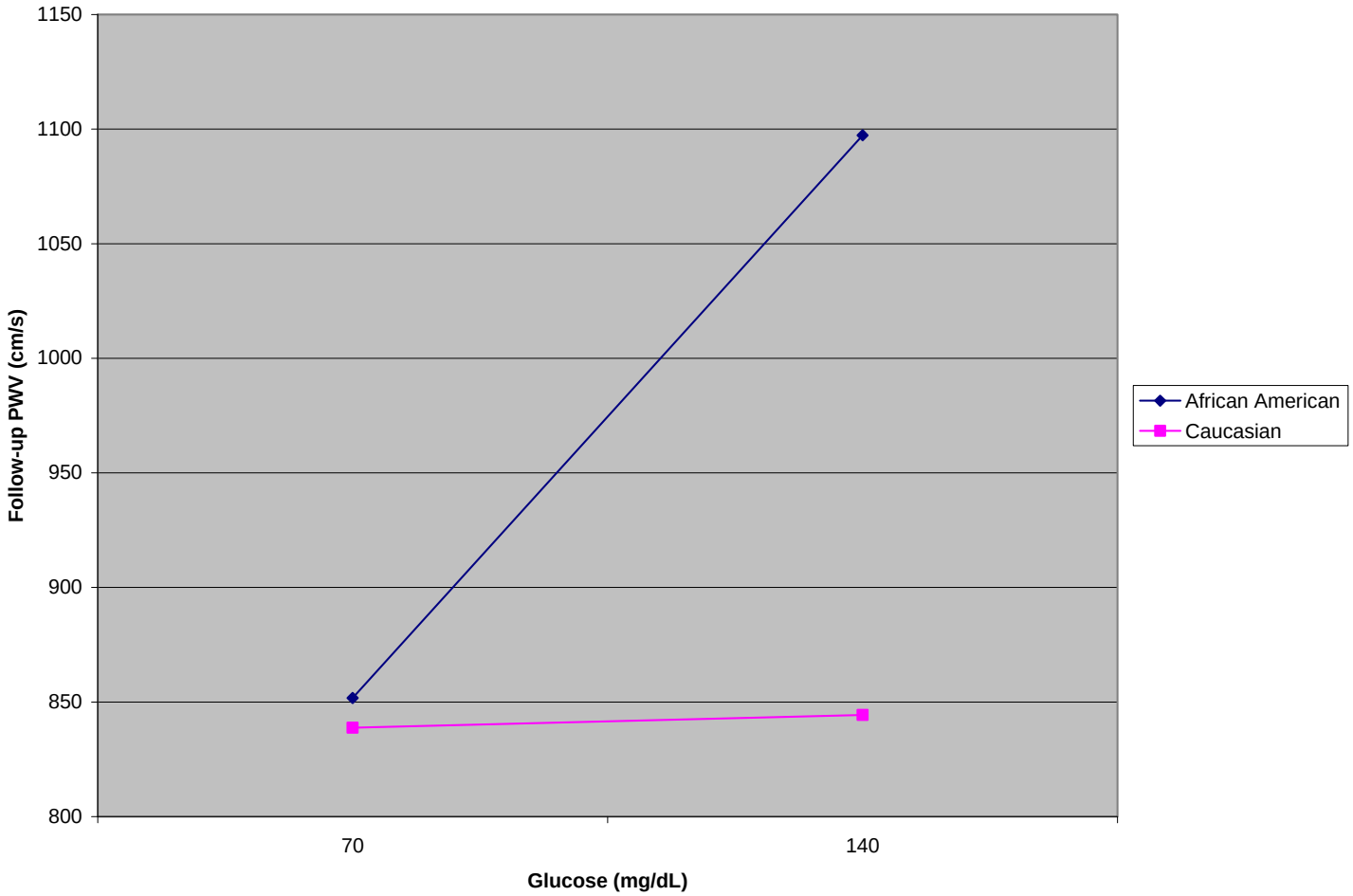

Figure 3-4 Relationship of Glucose and PWV Progression by Ethnicity

Model adjusted for baseline PWV and time between scans; *p* for interaction = 0.06

4.0 THE RELATIONSHIPS OF ETHNICITY AND SOCIOECONOMIC STATUS WITH SUBCLINICAL CARDIOVASCULAR DISEASE

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4.1 ABSTRACT

The independent and combined effects of ethnicity and socioeconomic status (SES) on subclinical cardiovascular disease (CVD) are poorly understood. Coronary artery (CAC) and aortic (AC) calcification, carotid artery intima-media thickness (IMT), and aortic pulse wave velocity (PWV) were measured in 536 middle-aged women (206 African American and 330 Caucasian) participating in the Study of Women's Health Across the Nation (SWAN) Heart cohort.

Compared to Caucasian women, African American women had higher IMT and PWV, but similar CAC and AC scores. After adjustment for educational attainment or income, African American women had higher IMT and PWV, although further adjustments for systolic blood pressure (SBP) and anti-hypertensive medication usage reduced the association with PWV to non-significance. After adjustment for ethnicity, low educational attainment and income were respectively associated with higher AC and PWV. Lower income was associated with higher PWV among African American women only. Both African American ethnicity and SES were related to indicators of subclinical CVD, although with variation across different SES and subclinical CVD measures.

Future research should examine whether the relationships between ethnicity, SES, and subclinical CVD change or remain static during the life course.

4.2 INTRODUCTION

The independent associations of African American ethnicity and low socioeconomic status (SES) with clinical cardiovascular disease (CVD) events in women are well-documented and striking. Among African American women, mortality rates from coronary heart disease (CHD) are approximately 40% higher than among Caucasian women; clinical disease also presents at younger ages and with greater severity among African Americans. [1] Similarly, low SES, a broad-spectrum measure of material resources and social prestige, is associated with higher incidence of clinical cardiovascular events among women. [4, 103, 138, 139]

Although African American women carry a disproportionate burden of clinical disease, a surprising observation is that this group does not consistently show higher levels of subclinical CVD. In a number of studies, African American women present with a lower prevalence [44, 45, 47, 140] or similar prevalence or extent [49, 141] of coronary artery calcification (CAC) as compared to Caucasians. Conversely, African American women present with greater mean or common carotid artery intima-media thickness (IMT) than Caucasians in several studies. [64, 66, 67] Early evidence suggests that African American women have greater arterial stiffness than do age-matched Caucasians, although statistical controls for hypertension and other clinical characteristics reduce this difference. [142]

Some inconsistencies in the associations of African American ethnicity and subclinical CVD may result from variations in sample size and cardiovascular risk factor distributions across studies. African American women are also more likely to be poorer, less-educated, and more disenfranchised from the health care system than are Caucasians. [90] Thus, some SES effects may actually be misclassified in extant literature as ethnic effects, and vice versa. [143] Low SES does appear to be independently associated with higher levels of subclinical CVD; for example, low educational attainment and income were related to greater prevalence and extent of CAC and aortic calcification (AC) in a study of middle-aged and older Caucasian women.[114]

Only four studies to our knowledge have examined the combined associations of African American or Caucasian ethnicity and SES in analyses of subclinical disease. The ARIC study

observed that higher income was associated with lower IMT progression in Caucasians, but higher IMT progression in African Americans; [68] a recent study of adolescents reported that low income was associated with higher PWV among African Americans but not among Caucasians, and that low neighborhood SES was related to higher IMT only among African Americans.[133] The CARDIA study reported that low educational attainment and Caucasian ethnicity were both associated with higher CAC,[115] and MESA observed that low educational attainment was related to higher carotid plaque and IMT among Caucasians only.[124] Cumulatively, these findings suggest that the role of SES may vary in the development of subclinical CVD among different ethnic groups.

To the extent that differences exist between African American or Caucasian ethnicities and/or SES indicators with regard to subclinical CVD, it is also important to understand the pathways that account for these associations. Population-based studies indicate that hypertension presents earlier and more severely among African Americans as compared to Caucasians, [1, 134] which may partly explain why levels of some subclinical CVD measures are higher in this group.

This paper investigates the independent and combined associations of African American and Caucasian ethnicities with education and income, in relation to subclinical CVD in a single cohort of healthy, middle-aged women. Examining ethnic differences across multiple subclinical disease measures within a single cohort could help to clarify the correlations between these measures. In addition, considering both the independent and combined relationships between SES and ethnicity may enhance our understanding of why the burden of subclinical CVD differs between some groups.

4.3 METHODS

4.3.1 Study Population

SWAN is a multi-site longitudinal study designed to examine the biological and psychological changes of women during the menopause transition. Between 1996 and 1997, participants (n=3302) received baseline clinical examinations through seven designated research centers: Detroit, MI; Boston, MA; Chicago, IL; Oakland, CA; Los Angeles, CA; Newark, NJ; and Pittsburgh, PA. The SWAN protocol was approved by the institutional review board at each site, and all participants provided written informed consent. Eligibility criteria for SWAN were as follows: age 42-52 at time of enrollment, intact uterus and at least one ovary, menstrual bleeding within the prior three months, no usage of reproductive hormones within the prior three months, and no pregnancy or breast-feeding. To enroll, women also had to identify themselves as one of five racial/ethnic groups depending on site: non-Hispanic Caucasian (all sites), African American (Boston, Chicago, Detroit, Pittsburgh), Chinese/Chinese-American (Oakland), Hispanic (Newark), or Japanese/Japanese-American (Los Angeles). Other recruitment details and enrollment procedures have previously been described. [136]

A sub-cohort of women (n=608) from the Chicago and Pittsburgh SWAN sites participated in the SWAN Heart Study, an ancillary study designed to assess subclinical CVD. Enrollment took place between 2001 and 2003, which was coincident with the 4th-7th annual SWAN visits for participants. SWAN participants were eligible to join SWAN Heart if they had consented to a baseline subclinical atherosclerosis scan in conjunction with an earlier SWAN visit and did not have a history of coronary heart disease, hysterectomy or bilateral oophorectomy, and did not use diabetes medication or hormone therapy. Participants were excluded from all analyses for the following reasons: between consent and the current subclinical CVD measurements, 32 participants began hormone therapy, 16 underwent hysterectomy/bilateral oophorectomy, 3 developed clinical CVD or diabetes, 3 did not answer any questions about hormone therapy or surgical menopause status, 15 did not keep their

appointment for subclinical CVD measurements, and 3 did not respond to questions about income or education.

Additional participants were excluded from select analyses. 122 women were missing at least one subclinical CVD measure, and were excluded from models that used that measure as a dependent variable. The 19 women who were missing educational attainment data did not vary from the rest of the sample by ethnicity, anti-hypertensive medication usage, age, BMI, or SBP. The 73 women who were missing income data were disproportionately African American ($p=0.01$) and had higher SBP ($p=0.002$). The final sample of 536 women was comprised of 62% Caucasians (n=330) and 38% African Americans (n=206).

4.3.2 Procedures

Upon initial enrollment into SWAN and at each annual visit, participants answered self- and interviewer-administered questionnaires, and received laboratory, clinical, and anthropometric assessments. Information on medical history, medication usage, educational attainment, and income were collected via questionnaires. Ethnicity was self-reported at the baseline parent SWAN visit, and used in this assessment. Information collected as part of the annual SWAN visit and coincident with or close in time to the SWAN Heart visit was also used in this analysis.

4.3.3 Socioeconomic Status Measures

Participants were asked at their baseline SWAN visit to indicate their annual total family income from 8 categories. These were combined into three categories in this analysis due to small cell counts (<$50,000, $50,000-74,999, ≥ $75,000). Participants were also asked at baseline to report years of completed education, which were categorized into high school or less, associate's degree or some college without degree attainment, college degree, and post-graduate

education. The Spearman correlation for income categories and educational attainment was 0.35 ($p < 0.0001$) for African Americans and 0.31 ($p < 0.0001$) for Caucasians.

4.3.4 Subclinical Disease Measures

Coronary Artery and Aortic Calcification CAC and AC were assessed using an Imatron C-150 electron-beam computed tomography (EBT) scanner.[144] Briefly, 30 to 40 contiguous, 3-mm thick transverse images were obtained from the level of the aortic root to the apex of the heart. Calcium scores, calculated by the Agatston method, [145] had high reproducibility, with an intraclass correlation of 0.98 for AC scores and 0.99 for CAC scores. [146]

Carotid Artery Intima-Media Thickness B-mode ultrasound was used to assess the thickness of the intima and media layers of the carotid arteries. The available duplex scanners for the Chicago and Pittsburgh sites were comparable in image quality. B-mode images were obtained from 8 locations: 4 locations each from the left and right carotid arteries. Images were taken from the near and far walls of the distal common carotid artery (1-cm proximal to the carotid bulb), and the far walls of the carotid bulb (the point where the near and far walls of the common carotid are no longer parallel, extending to the flow divider) and the internal carotid artery (from the flow divider to 1-cm distal to this point). IMT measures were performed by electronically tracing the lumen-intima interface and the media-adventitia interface across a 1-cm segment. The mean of all average readings across the 8 locations comprises the average IMT. The mean of the maximum reading from each segment was calculated. All readings were conducted at the University of Pittsburgh Ultrasound Research Laboratory. An intraclass correlation of 0.98 was yielded upon replicate readings of 20 IMT scans.

Aortic Pulse Wave Velocity Arterial stiffness was assessed by the gold standard, carotid-to-femoral PWV. In brief, arterial flow waves were simultaneously and non-invasively recorded at the carotid and femoral arteries of supine participants, using unidirectional transcutaneous Doppler flow probes (model 810-a, 10 MHz, Parks Medical Electronics, Aloha, OR). Aortic

PWV is calculated as distance/transit time (cm/seconds). The transit time of the pulse wave was calculated as the foot-to-foot delay between the averaged carotid and femoral waveforms. The distance traveled by the pulse waveform was estimated by measurement over the participant's torso. The distance from the carotid to aortic site was subtracted from the sum of the aortic to umbilicus and umbilicus to femoral site to adjust for the opposite direction of the blood flow in that arterial branch. A higher PWV indicates a stiffer vessel. This measure has been demonstrated to have good reproducibility, with an overall laboratory intraclass correlation of 0.77 [69].

4.3.5 Covariate Measures

Covariate measures were taken at the SWAN visit coincident with or closest in time to each participant's SWAN Heart visit. Body mass index (BMI) (kg/m^2) was measured via weight and height calculations obtained at the annual SWAN visit (to the nearest 0.01 kg and nearest 0.01 cm). Age was self-reported via questionnaire. Blood pressure was measured by trained personnel after the participant was seated for five minutes, and was averaged across two readings.

4.3.6 Data Analysis

Descriptive statistics for the study sample were determined by chi-square tests for categorical variables, and t-tests for continuous variables. IMT and PWV measures were normally distributed across the sample. Many women had no observed CAC or AC (50% and 29% of sample, respectively); to normalize these distributions, we added a constant to CAC and AC scores and log-transformed the sum scores.

Spearman partial correlations were used to assess associations between continuous subclinical measures in the total sample and by ethnicity, with adjustments for age, BMI, and site

of data collection. Linear regression was used to analyze the associations of SES and/or ethnicity measures with the continuous IMT, PWV, CAC and AC measures. All regression models included age, BMI, and site of data collection. Systolic blood pressure (SBP) and anti-hypertensive medication usage were added to specific models to assess the role of blood pressure in subclinical disease. To assess interactions between ethnicity and SES, linear regression models were created with each subclinical CVD measure as the outcome, and as predictors: 1) ethnicity and education or income, 2) the cross-product of ethnicity and education or income. Our sample provided 85% power to detect an interaction. All models were two-tailed with alpha=0.05. SAS 9.1 (Cary, NC) was used for all statistical analyses.

4.4 RESULTS

Table 1 presents characteristics of the sample by ethnicity. On average, study participants were 50 years old, overweight, and well-educated. Compared to Caucasian women, African Americans had lower household incomes and educational degrees; African American women also had higher BMI, SBP, and reported greater usage of anti-hypertensive medications. Women did not differ in unadjusted mean CAC or AC levels by ethnicity. African American women had significantly higher IMT and PWV levels than did Caucasian women.

Correlations among subclinical CVD measures were assessed separately among African American and Caucasian women (Table 2), revealing a modest but positive association between CAC and AC measures among women of both ethnic groups. No other correlations between subclinical CVD measures were observed.

Table 3 presents linear regression analyses that modeled ethnicity, income, or education onto each of the four subclinical CVD outcomes, with adjustment for age, BMI, and study site. African American ethnicity was associated with higher IMT and PWV. High school or less and some college education were associated with higher AC, and the high school education or less category was marginally associated with IMT. Low income was associated with higher IMT and PWV, and marginally associated with AC; middle-income was also marginally associated with PWV. To summarize briefly, African American ethnicity was associated with higher levels of IMT and PWV, and low SES was inversely associated with AC, IMT, and PWV. No associations were observed between ethnicity, SES and CAC.

Table 4 presents linear regression analyses that included both ethnicity and educational attainment as main effects. In these models, African American ethnicity was associated with higher IMT and PWV (Table 4; model 1). After further adjustment for SBP and hypertension medications, African American ethnicity remained associated with IMT, but the relationship

between African American ethnicity and PWV was reduced (p=0.053). Women with a high school education or some college had higher AC scores than women with post-graduate education (Table 4; model 1). This relationship remained significant after additional adjustments for blood pressure variables (Table 4; model 2). No significant interactions between ethnicity and education were observed for any of the subclinical CVD outcomes.

African American women had marginally higher IMT (p=0.07) and PWV (p=0.08), when income was included in lieu of education in linear regression models (Table 5; model 1). With ethnicity in the models, the lowest income level was significantly associated with higher IMT and PWV, and marginally associated with AC. Associations between African American ethnicity and both IMT and PWV were reduced to non-significance after adjustment for blood pressure variables. The relationship between low income and PWV remained significant, and low income and AC remained marginally significant after adjustment for blood pressure variables (Table 5, model 2).

Unadjusted mean PWV values indicated that low and middle-income African Americans had higher PWV than did Caucasians; this trend was reversed for higher-income African Americans, who had slightly lower PWV values than did Caucasians (Fig.1). In linear regression models, a significant interaction term between ethnicity and low income for PWV was also observed (p=0.01). When stratified by ethnicity and relative to high income women, low- and middle-income women had higher PWV among African Americans only [β (S.E.) for low income: 175.13 (43.5), p<0.0001; β (S.E.) for middle income: 150.94 (48.9), p=0.0024]. The variance in PWV explained by income was 11% among African Americans as compared to only 0.7% for Caucasians. After adjustments for age, BMI, study site, and blood pressure variables, the associations between PWV, and low and middle income as compared to high income remained significant for African Americans [β (S.E.) for low income: 149.2 (43.6), p=0.0008; β (S.E.) for middle income: 136.8 (47.6), p=0.005].

4.5 DISCUSSION

In a cohort of CHD-free, middle-aged women, African American women had similar levels of CAC and AC, and higher levels of IMT and PWV, as compared to Caucasians. As compared to women with higher SES, women with low educational attainment had higher AC and marginally higher IMT levels, and women with low incomes had higher IMT, PWV, and marginally higher AC levels. These results were generally consistent with prior analyses of the independent associations of African American and Caucasian ethnicity or SES with subclinical CVD. [44, 45, 47, 49, 66, 67, 140, 142]

Our analysis of the combined associations of ethnicity and SES across four different subclinical CVD measures is novel, and reveals that African American ethnicity and low SES are not interchangeable in their associations across multiple subclinical CVD measures. Compared to Caucasian women, African American women had higher IMT and PWV after adjustments for education, although ethnic differences in blood pressure partly explained associations for PWV. Low educational attainment was associated with AC before and after adjustments for blood pressure variables. When income was used in lieu of education in the analyses, associations between lower incomes and higher IMT and PWV were observed; the relations between African American ethnicity and IMT or PWV were reduced. Additional adjustments for blood pressure variables appeared to explain the relationship between low income and higher IMT. Our findings suggest that lower incomes but not lower educational attainment may partly explain the associations between African American ethnicity and PWV. The pathway by which low income and PWV are related was not explained by age, BMI, SBP, study site, or anti-hypertensive medication usage in our analyses; it is also unclear why low income and not low educational attainment is associated with higher PWV in this sample.

Analysis of the interactions between ethnicity and SES further revealed that low- and middle-income African Americans had higher PWV than did high-income African Americans; these results were not observed among Caucasians. Similar findings have been reported in the literature: Thurston and Matthews observed that among adolescents, low and medium-level household incomes were associated with higher PWV among African Americans, but not among

Caucasians.[82] At higher income levels, ethnicity may become a less salient characteristic with respect to vascular functioning. However, the synchronous impact of lower income with African American ethnicity may result in a "double jeopardy effect," culminating in higher risk for arterial stiffness—and ultimately clinical outcomes-- beginning in early life and extending through middle age. Further investigation of the interactions between African American ethnicity and SES with respect to PWV is needed to identify specific physiologic and psychosocial mediators that explain these associations.

We observed little overlap in the subclinical CVD outcomes predicted by income and education. Correlations between income and education were significant, but moderate in magnitude. Formal education typically is completed in early adulthood and thereafter remains stable; income may change dramatically during an individual's lifetime. Therefore, studies that use only one measure of SES to examine relationships with subclinical CVD may be incomplete in their scope.

To our knowledge, this is the first study that has examined the correlations between four subclinical CVD measures by ethnicity. Significant correlations between CAC and IMT, [22] and CAC and PWV [24] have been previously assessed. It was surprising, then, that only CAC and AC were significantly correlated. Low overall levels of subclinical CVD in this study may have influenced this observation, and these results should be replicated in populations with greater extent of subclinical CVD.

To the extent that ethnicity and SES differences exist in subclinical CVD, it is also important to identify pathways that account for these associations. Among individuals over 50 years old, SBP is a more important predictor of cardiovascular outcomes than is diastolic blood pressure or other blood pressure indicators.[147] SBP has also been shown to strongly and positively influence arterial stiffness, [20, 70, 142] IMT, [148, 149] and calcification. [26, 150] In this sample, SBP levels and anti-hypertensive medication usage were higher among African American women than among Caucasian women. The addition of SBP and anti-hypertensive medication usage to age, BMI and site-adjusted multivariable models attenuated some associations between African American ethnicity, SES and subclinical CVD. This suggests that

higher SBP is a mediator in the sclerotic and atheromatous processes that contribute to subclinical CVD. Aggressive clinical management of hypertension among African American and low-SES women may help to lower subclinical CVD in these populations-- particularly with regard to IMT and PWV—and may ultimately reduce clinical outcomes in these groups.

Our study has several limitations. In the interests of maximizing our statistical power and minimizing bias, we included women who had at least one recorded subclinical CVD measure. However, some participants did not receive all four measures, and some measures—namely PWV—were missing more values than others. Therefore, the women in each subclinical CVD group assessed by this study are not identical. Subgroup analysis showed that compared to the full sample, women missing any subclinical disease data did not significantly differ by age, BMI, or ethnicity.

Another limitation of this study is its cross-sectional analytic design. Whereas ethnicity is constant from birth, and educational attainment is fairly constant over adulthood, income is more dynamic. A longitudinal study would be particularly informative in assessing the cumulative impact of income on subclinical CVD over the lifecourse. This analysis represents an initial step in understanding the complex relationships between SES, ethnicity, and subclinical disease.

In conclusion, our findings suggest that middle-aged African American and low SES women are at greater overall risk for subclinical CVD than are Caucasian or higher SES women. Unexpectedly, subclinical CVD measures were poorly correlated, and income and education showed little overlap in the prediction of subclinical CVD. Important future directions should include a longitudinal assessment of atherosclerosis in this cohort to assess whether ethnicity and SES retain their predictive value. Also important will be a thorough examination of psychosocial, environmental, and physiological factors that may mediate these associations. Identification of such factors provides a valuable opportunity to inform clinical decisions in the subclinical phase of disease, and to impair progression towards adverse clinical cardiovascular events.

Table 4-1 Characteristics of the Total Study Population and by Ethnicity

	Mean (SD) or % (No.)			
	Total (n=536)	**Caucasian** (n= 330)	**African American** (n= 206)	*P* value (Ethnicity)
Age, years	50.2 (2.9)	50.1 (2.9)	50.4 (2.9)	0.25
BMI, kg/m^2	29.4 (6.4)	28.3 (5.9)	32.0 (6.8)	<0.001
Annual household income				
<$50K	30 (141)	23 (68)	43 (73)	<0.0001
$50K- <$75K	25 (118)	23 (69)	29 (49)	
≥$75K	44 (207)	54 (159)	28 (48)	
Educational Degrees				
High School	15 (78)	14 (44)	17 (34)	0.019
Incomplete College	30 (157)	26 (85)	37 (72)	
College	22 (115)	24 (76)	20 (39)	
Post-graduate	33 (170)	36 (118)	26 (52)	
SBP, mm Hg	120.0 (16.4)	115.9 (14.4)	126.3 (17.3)	<0.0001
BP Medications	4 (22)	3 (9)	6 (13)	0.042
CAC units	12.8 (43.7)	12.8 (40.8)	12.7 (48.0)	0.97
AC units	122 (342)	118 (324)	129 (370)	0.74
IMT (mm)	0.67 (0.1)	0.66 (0.1)	0.69 (0.1)	0.0004
PWV (cm/s)	796 (203)	774 (191)	835 (218)	0.002

BMI= Body Mass Index, SBP=Systolic Blood Pressure, BP=Blood Pressure.

Table 4-2 Spearman Correlations Between Subclinical CVD Measures, By Ethnicity

	CAC	AC	IMT	PWV
CAC	-	0.29*	0.073	0.15
AC	0.25*	-	0.067	0.086
IMT	0.026	0.084	-	-0.021
PWV	0.064	0.12	0.064	-

*p<0.05

Correlation coefficients above diagonal (shaded) are for African Americans, below diagonal are for Caucasians
Partial correlation coefficients were adjusted for age, BMI, and data collection site

Table 4-3 Minimally-Adjusted Associations Between Main Effects and Subclinical CVD Measures

	β (S.E.)			
Measure	**CAC** (n=514)	**AC** (n=512)	**IMT** (n=525)	**PWV** (n=458)
Ethnicity				
African American	-0.020 (0.11)	-0.078 (0.18)	0.025 (0.008)*	49.1 (19.2)*
Caucasian	Referent	Referent	Referent	Referent
Educational Attainment				
High School	0.28 (0.17)	0.81 (0.27)*	0.024 (0.012) †	-8.82 (29.0)
Incomplete College	-0.013 (0.14)	0.44 (0.22)*	0.013 (0.010)	18.8 (23.7)
College	-0.013 (0.15)	0.36 (0.24)	0.006 (0.011)	-4.77 (26.0)
Postgraduate	Referent	Referent	Referent	Referent
Income				
Low	0.06 (0.14)	0.42 (0.23) †	0.026 (0.001)*	78.4 (23.0)*
Middle	0.20 (0.14)	0.26 (0.24)	0.0036 (0.01)	45.9 (24.4)†
High	Referent	Referent	Referent	Referent

* $p<0.05$; † $0.05<p<0.10$
β=Beta-coefficient, S.E.=Standard Error
All models adjusted for age, BMI, and data collection site

Table 4-4 Linear Regression Analysis Examining Education, Ethnicity and Subclinical CVD

	Model 1†				Model 2‡			
	β (S.E.)§				β (S.E.)			
	CAC	**AC**	**IMT**	**PWV**	**CAC**	**AC**	**IMT**	**PWV**
African-American‖	-0.018 (0.12)	-0.19 (0.18)	0.024* (0.008)	52.2* (19.8)	-0.09 (0.12)	-0.22 (0.19)	0.018* (0.008)	39.0† (20.1)
Education ¶								
High School	0.28 (0.17)	0.83* (0.27)	0.020 (0.01)	-16.7 (29.0)	0.23 (0.17)	0.81* (0.27)	0.016 (0.012)	-28.2 (29.0)
Incomplete College	-0.010 (0.14)	0.47* (0.22)	0.0093 (0.01)	13.1 (23.7)	-0.062 (0.14)	0.44* (0.22)	0.0045 (0.01)	1.50 (23.9)
College	-0.012 (0.15)	0.37 (0.24)	0.0045 (0.01)	-6.48 (25.8)	-0.066 (0.15)	0.35 (0.24)	0.00021 (0.01)	-16.5 (25.8)

* $p<.05$; † $0.05<p<0.10$
† Model 1 adjusted for age, BMI, and data collection site
‡ Model 2 adjusted for Model 1 adjustments, SBP, and anti-hypertensive medication usage
§ Parameter estimates with corresponding standard errors are listed in table
‖ Caucasian ethnicity was referent for African-American ethnicity
¶ Post-graduate education was referent for education variables
Note: Each subclinical disease measure considered in separate model

Table 4-5 Linear Regression Analysis Examining Income, Ethnicity and Subclinical CVD

	Model 1†					Model 2‡			
	β (S.E.)§					β (S.E.)			
	CAC	**AC**	**IMT**	**PWV**		**CAC**	**AC**	**IMT**	**PWV**
African-American‖	-0.058 (0.13)	-0.14 (0.21)	0.016† (0.009)	37.1† (21.4)		-0.13 (0.13)	-0.19 (0.22)	0.011 (0.009)	27.1 (21.6)
Income¶									
<$50K	0.076 (0.14)	0.46† (0.24)	0.021* (0.01)	68.7* (24.4)		-0.0013 (0.14)	0.40† (0.24)	0.016 (0.01)	60.0* (23.9)
$50- <$75K	0.20 (0.15)	0.28 (0.24)	0.001 (0.01)	42.2† (24.4)		0.20 (0.14)	0.28 (0.24)	0.0008 (0.01)	44.7† (24.4)

* $p<.05$; † $0.05<p<0.10$
† Model 1 adjusted for age, BMI, and data collection site
‡ Model 2 adjusted for Model 1 adjustments, SBP, and anti-hypertensive medication usage
§ Parameter estimates with corresponding standard errors are listed in table
‖ Caucasian ethnicity was referent for African American ethnicity
¶ Annual income ≥ $75,000 was referent for the income variables
Note: Each subclinical disease measure considered in a separate model

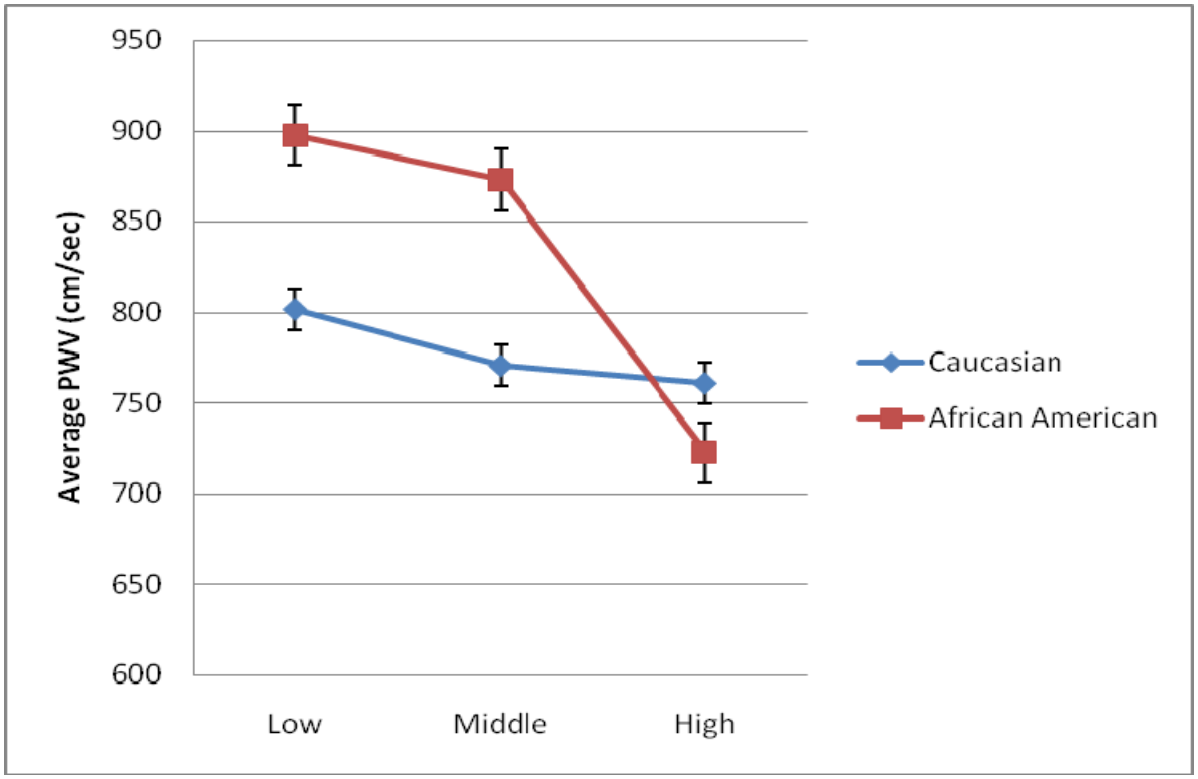

Figure 4-1 Average Pulse Wave Velocity and Income Gradients by Ethnicity.

Mean PWV score ± SE presented.

5.0 LOW EDUCATIONAL ATTAINMENT IS ASSOCIATED WITH CORONARY ARTERY CALCIFICATION PROGRESSION IN THE SWAN HEART STUDY

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5.1 ABSTRACT

While Caucasian ethnicity and low socioeconomic status (SES) are independently associated with higher cross-sectional measures of coronary artery calcification (CAC), little is known about the interrelationships of ethnicity, SES, and CAC progression in women. Fewer studies have examined psychosocial mediators that may explain these relationships.

A subgroup of 339 African American and Caucasian participants in the Study of Women's Health Across the Nation (SWAN) Heart Study underwent electron-beam computed tomography scans to assess for the presence and extent of CAC. Scans were conducted at SWAN Heart baseline and at a follow-up examination an average of 2.3 years later. Data were also collected regarding ethnicity, education, income, candidate psychosocial mediators (anxiety, hostility and financial strain), and coronary heart disease (CHD) risk factors. 20% of the sample (n=68) progressed at least 10 CAC units over the follow-up period. Women with high school or less education as compared to postgraduate education were 5.0 times more likely to have CAC progression of at least 10 units [95% CI: 1.75-14.3, p=0.003]. When stratified by ethnicity, low education was more strongly associated with higher CAC progression among Caucasians [OR=7.75, 95% CI: 1.97-30.4, p=0.003]. This observation was independent of anxiety, hostility, financial strain, baseline CAC scores, or CHD risk factors.

Low educational attainment appears to have a striking and deleterious association with coronary atherosclerosis progression in middle-aged women, especially among Caucasians. Future studies should attempt to identify risk factors that explain this observation. Additional research is also needed to identify risk factors that explain CAC progression among African American women.

5.2 INTRODUCTION

Coronary artery calcification (CAC) is a measure of calcified atherosclerotic plaque in the coronary vessels. Knowledge of the risk factors that contribute to CAC progression may clarify how early atherosclerotic disease develops into clinically-significant lesions. Existing literature indicates that Caucasian ethnicity[44, 45, 47, 49, 50, 140] and low socioeconomic status (SES)—assessed primarily by income or education[114, 125, 151]—are associated with higher CAC burden at a single timepoint. No studies to our knowledge have examined the relationships of these risk factors with CAC progression. Additionally, most cross-sectional studies examine the independent associations of ethnicity or SES with CAC, but do not examine their joint associations. Some reported associations between low SES and CAC may be explained by African American ethnicity--or vice versa—as African Americans are more likely to be in lower socioeconomic positions than are Caucasians across multiple indicators of SES. [89]

The present study investigates the combined associations of ethnicity with education, and ethnicity with income, in relation to CAC progression among healthy, middle-aged African American and Caucasian women. We also examine the roles of hostile attitudes, difficulty paying for basics (financial strain), and anxiety as mediators of the relationships between ethnicity, SES, and CAC progression. Associations between hostility and certain measures of atherosclerosis have been identified in prior studies,[65, 152] and hostility has also been associated with indicators of low SES.[153] While financial strain is related to income, it has been prospectively linked to recurrent coronary events among women independent of income, and may better reflect real-time adequacy of resources.[154] Several studies have hypothesized that anxiety reduces effective coping to adversity, which may be particularly detrimental to health outcomes among anxious, low-SES adults. [155, 156] Thus far, results have been inconclusive and no studies have assessed this hypothesis in early atherosclerotic disease or in atherosclerotic progression.

Based on findings from the cross-sectional CAC literature, we hypothesized that Caucasian ethnicity and low income or educational attainment would be associated with greater CAC progression over a two-year period. We also hypothesized that the burdens of financial hardship, hostility or anxiety would partly explain any observed relationships.

5.3 METHODS

5.3.1 Study Population

The SWAN study was designed to examine physiologic and psychological changes of women over the menopause transition. Descriptions of the study design and methods have been reported elsewhere. [136] Briefly, 3302 pre-menopausal or peri-menopausal women were recruited between 1996 and 1997 to one of seven research centers: Detroit, MI; Boston, MA; Chicago, IL; Oakland, CA; Los Angeles, CA; Newark, NJ; and Pittsburgh, PA. Eligibility criteria for the SWAN were as follows: aged 42-52 at enrollment, intact uterus and at least one ovary, menstrual bleeding within the prior three months, no current pregnancy or breast-feeding, no usage of reproductive hormones within the prior three months, and self-identification as a member of 1 of 5 ethnic groups depending on the research site: Caucasian (all sites), African American (Boston, Chicago, Detroit, Pittsburgh), Chinese/Chinese American (Oakland), Hispanic (Newark) or Japanese/Japanese American (Los Angeles).

SWAN Heart is an ancillary study designed to assess subclinical cardiovascular disease (CVD) in mid-life African American and Caucasian women. SWAN participants from the Chicago and Pittsburgh sites (n=608) were recruited to the SWAN Heart cohort between 2001 and 2003 if they met the following criteria: no history of coronary heart disease, stroke, hysterectomy, or postmenopausal status, and no usage of diabetes medications or hormone therapy.

SWAN Heart CAC measurements were assessed among 561 women at a baseline examination. Of these participants, 401 returned for a follow-up examination an average of 2.3 years later. Participants who met SWAN Heart eligibility criteria at the time of the scans and had readable CAC scans at both SWAN Heart baseline and at follow-up were eligible for

inclusion in this analysis. Baseline scans were missing for 27 women, who were excluded from further analysis. Participants were also excluded if they, between initial SWAN Heart screening and baseline measurements, received hysterectomies (n=7), transitioned into menopause (n=19), had missing data on menopausal status (n=3), or had strokes (n=1). Lastly, participants with unreadable EBCT scans at either baseline or at follow-up were excluded (n=5). Women who were excluded from our analysis had higher SBP and were six months older than women who were not excluded (p's <0.05), but did not vary by BMI, ethnicity, study site, annual total household income, or educational attainment. The final sample consisted of 339 participants; 64.6% of the sample consisted of Caucasian women (n=219), and the remaining 35.4% consisted of African American women (n=120).

5.3.2 Measurement of CAC

CAC was measured at both study sites via an Imatron C-150 electron-beam computed tomography (EBCT) scanner. We imaged at least 30 contiguous scan slices with 3-mm thickness from the level of the aortic root to the apex of the heart. Images were taken during holds in respiration, so that each 100 millisecond exposure was obtained during the same phase of the cardiac cycle (80% of the ECG RR interval). During a second pass, 6-mm contiguous images of the aorta were obtained from the aortic arch to the iliac bifurcation using a 300 millisecond exposure time. The Agatston method was used to calculate calcium scores, via a densitometric program available on the scanner. Inter-observer agreement was high (r=0.98 for AC scores, r=0.99 for CAC scores).[146]

5.3.3 Socioeconomic Status Measures

Participants reported at their baseline SWAN visit their educational degree attainment. Education was combined into the following categories: high school/G.E.D. or less, associate's degree or any college (with or without degree attainment), and post-graduate degree. At their

baseline SWAN Heart visit, participants were asked to indicate their annual total household incomes from 8 categories. Based on the sample distributions, we combined these into three categories (≤$50,000, $50,000-$75,000, ≥$75,000). Participants who chose not to indicate completed degree level (n=11) or income (n=35) were excluded from analyses involving education or income, respectively. Women with missing income information were more likely to be from Chicago, report African American ethnicity, and have higher SBP (p's<0.05). They did not differ from the remaining sample by age, BMI, smoking status or educational attainment. Women with missing educational information were more likely to be from Chicago (p<0.05), but did not vary from the remaining sample by ethnicity, age, BMI, SBP, smoking status, or income.

5.3.4 Covariate Measures

Covariate measures were taken at the SWAN visit coincident with or closest in time to each participant's SWAN Heart visit. Age and medication usage were assessed via questionnaire. Height and weight, measured at the annual SWAN visit, were used to calculate BMI (kg/m^2). Resting blood pressure was measured three times after each participant had been seated for five minutes, and the average of the final two readings was recorded. Current smoking status (yes/no/unknown) was defined as intake of at least one cigarette per day between the previous SWAN visit and the SWAN Heart baseline year. Women with missing smoking data (n=26) were designated to the unknown smoking status category.

5.3.5 Psychosocial Measurements for Mediational Analysis

Measures of psychosocial traits thought to be associated with risk for CVD were selected for this analysis. Cynical hostility was assessed using 13 items derived from the Cook-Medley Hostility scale, which evaluates cynical or hostile attitudes and behaviors. Higher scores are indicative of greater hostility. Cynical hostility was assessed only at the baseline SWAN visit (in 1996-1997) because this personality characteristic is stable across middle and later ages.[157, 158]

Women were asked during SWAN visits coincident with SWAN Heart follow-up years, "How hard is it to pay for basics?" Participants selected one of three options: Very hard, Somewhat hard, or Not at all hard; these data were later collapsed into two categories (Very hard or Somewhat hard versus Not at all hard) due to small cell sizes. Trait anxiety was assessed via the Spielberger State-Trait Anxiety Inventory.[159] Sum scores ranged from 10 to 40, and higher scores represented greater anxiety levels. Complete anxiety scores were imputed from SWAN visits coincident with or close to the corresponding SWAN Heart visit. Participants missing information on cynical hostility (n=10), difficulty paying for basics (n=28), or trait anxiety (n=8) were excluded from analyses involving that particular variable.

5.3.6 Data Analysis

We assessed CAC progression in two ways. First, the arithmetic difference between baseline and follow-up CAC readings was calculated for each participant. 20% of the sample had CAC change scores ≥10 units; the rest of the sample had less or no detectable progression. This cutoff has been used previously to assess significant CAC progression in a sample of older women.[68] Binomial logistic regression models were used to predict CAC progression outcomes of ≥10 units as compared to progression of <10 units. Ethnicity and income, or ethnicity and education variables were added to each model with postgraduate education or high income as the referents, respectively. Baseline CAC was assessed as a covariate in some models to assess the role of baseline CAC levels in the progression of CAC. Ethnicity, income, education, study site, and smoking status were considered as categorical variables; age, SBP, BMI, and baseline CAC were assessed continuously. Sensitivity analyses indicated that using an alternate cut point for CAC progression (≥ 5 versus < 5 units) did not alter the pattern of relationships between the main predictor variables, covariates and the outcome CAC measurements. We choose to report the primary findings from the ≥10 cutoff because it is more clinically meaningful and has been linked to cardiovascular outcomes.[36]

The raw change in calcium was also evaluated as a continuous variable. To normalize the distribution, we added a constant to each follow-up and baseline score, and took the natural log of each sum score. Linear regression models were used to assess the relationships between the covariates and CAC scores at follow-up. Ethnicity and income, or ethnicity and education variables were added to each model. Regression models were simultaneously adjusted for continuous baseline CAC scores, study site, age, BMI, SBP and smoking status.

To formally test whether the effects of ethnicity were altered by SES, interaction terms were created between ethnicity and education variables, and education and income variables, in separate models. The interaction effect was tested in linear and logistic regression models. To evaluate the role of hostility, anxiety and financial strain in observed relations between ethnicity, SES, and CAC progression, we assessed: 1) relations between SES or ethnicity and anxiety, hostility or financial strain, and 2) relations between anxiety, hostility or financial strain and CAC progression. We next examined relations between ethnicity, SES and CAC progression after addition of anxiety, hostility or financial strain to the models.

All logistic and linear regression models adjusted for time between CAC scans. Descriptive statistics for the sample were determined by chi-square tests for categorical variables, and t-tests for continuous variables. Spearman correlations were used to assess relationships between categorical variables. All models were two-tailed with $\alpha=0.05$. Analyses were performed using SAS v. 9.1 (Cary, NC).

5.4 RESULTS

5.4.1 Sample Description

In this sample, women were 50 years of age on average, and African American women as compared to Caucasian women had higher BMI, SBP, lower household incomes, higher cynical hostility scores, and greater difficulty paying for basics (Table 1).

The mean CAC score and standard deviation assessed at baseline was 10.4 ± 34.8 and at follow-up was 18.2 ± 50.7. CAC levels at baseline, follow-up, or change between baseline and follow-up did not vary by ethnicity. Forty-one percent of the sample (n=139) did not have detectable CAC at baseline or at follow-up. Twenty-percent of the sample (n=68) progressed at least 10 CAC units during the follow-up period. Women in this higher progression group were older by an average of 8 months, and had higher BMI and SBP at baseline than did women with CAC progression less than 10 units. The higher progression group also had greater difficulty paying for basics. These women did not differ from the rest of the sample by ethnicity, hostility level, trait anxiety score, baseline smoking status, educational attainment or income.

Table 2 lists Spearman correlations between the SES measures, anxiety, and financial strain, stratified by ethnicity. Among both African American and Caucasian women, income was correlated with educational categories, and financial strain and anxiety were marginally correlated. Among African Americans, educational categories were negatively correlated with hostility, and marginally but negatively correlated with anxiety. Hostility was negatively correlated with income for Caucasians.

5.4.2 Associations with CAC Progression as a Categorical Variable

Table 3 displays results from binomial logistic regression models that assess ethnicity, educational attainment, and traditional CVD risk factors as predictors of higher versus lower

CAC progression levels. Caucasians and women with high school education or less were more likely to exhibit CAC progression levels ≥ 10 units after adjustment for age, BMI, SBP, smoking status and study site (Table 3, Model 1). After an additional adjustment for baseline CAC level, low educational attainment remained significantly associated with the higher CAC progression level (Table 3, Model 2). Because baseline CAC was a strong, positive predictor of higher CAC change, it was retained as a covariate in all remaining multivariable models.

The interaction term between ethnicity and high school education or less only approached conventional levels of significance (p=0.10). However, we decided to stratify our analysis by ethnicity because this interaction term was significant using a lower cutoff of ≥5 units of CAC progression (p=0.02), which had a larger number of women in its high progression group (n=92). The results were consistent using either cutoff.

Our findings indicate that high school education or less as compared to post-graduate education is strongly associated with ≥10 units of CAC progression only among Caucasian women, after adjustment for all physiologic covariates and baseline CAC scores (Table 4). Low educational attainment was not associated with greater CAC progression among African American women [High school or less: OR= 2.53, 95% CI=0.41-15.8; Any College: OR=1.70, 95% CI=0.45-6.2].

5.4.3 Mediational Analysis with CAC Progression as a Categorical Variable

We next tested the hypotheses that anxiety, difficulty paying for basics, or hostility explained the relationships between low education and higher CAC progression among Caucasian women. Difficulty paying for basics was added to Table 4 covariates in a separate model. Although it was marginally associated with CAC progression among Caucasian women, it did not explain the associations between low education and higher CAC progression [OR= 3.07, 95% CI: 0.92-10.3, p=0.068]. Hostility and anxiety were not associated with greater CAC progression among Caucasian women (not shown).

While we did not observe a significant relationship between low education and CAC progression among African American women, for consistency, we tested whether anxiety, financial strain or hostility were related to higher CAC progression (not shown). When added to Table 4 covariates, difficulty paying for basics [OR=3.44, 95% CI: 0.90-13.2, p=0.071] was marginally associated with greater CAC progression among African American women. Similar to Caucasian women, hostility and anxiety were not related to greater CAC progression among African American women (not shown).

5.4.4 Associations with Continuous CAC Progression Scores in the Full Sample

Linear regression models that assessed change in calcium followed similar trends as the logistic regression models, although the interaction term between ethnicity and high school education or less was not significant (p=0.33). Low education was significantly associated and Caucasian ethnicity was marginally associated with higher levels of follow-up CAC after adjusting for baseline CAC, age, BMI, SBP, smoking status, and study site (Table 5, Model 1). Difficulty paying for basics was associated with higher follow-up CAC when added to Model 1 covariates, and appeared to partly explain the association between high school education and higher CAC (Table 5, Model 2). Anxiety was marginally associated with higher follow-up CAC when added separately to Model 1 covariates (not shown, p=0.098). Hostility was not associated with follow-up CAC (not shown). In all models, baseline CAC was strongly and positively associated with higher follow-up CAC.

When entered into logistic or linear regression models, income was not a significant predictor of CAC progression either independently or including the covariates used in the education analyses (not shown).

5.5 DISCUSSION

In a cohort of middle-aged women initially free of stroke and CHD, women with high school degrees or less were more likely than those with postgraduate degrees to have higher CAC progression. The inverse association between education and CAC progression appeared to be most pronounced among Caucasian women. Age, BMI, SBP, smoking status, baseline CAC, anxiety, or hostility, did not account for the associations between low educational attainment and higher CAC progression.

This investigation is the first to report an inverse relationship between education and CAC progression. Previous work has been limited to cross-sectional associations between SES and CAC. [114, 125, 151] Cross-sectional studies of CAC reveal how lifetime exposure to risk factors contributes to atherosclerosis, but studies of progression may identify factors that accelerate short-term atherosclerotic changes. Our findings indicate that low educational attainment is associated with adverse atherosclerotic progression over a two-year period.

There was some suggestion that associations between educational attainment and CAC progression were more pronounced among Caucasian women. These differences between African Americans and Caucasians should be interpreted with caution due to the marginal interaction between education and ethnicity, and the low frequency of African American women with low educational attainment in the sample. To better explain the interaction between Caucasian ethnicity and SES towards coronary atherosclerosis, a critical next research step will involve the identification of such risk factors in a larger, multiethnic cohort.

However, it is important to note that these findings do follow previously-reported trends. Education was inversely associated with cross-sectional measures of CAC in one study of middle-aged, predominately Caucasian women.[114] Moreover, MESA noted that low education was associated with higher CAC among Caucasians, but not among African Americans.[125] Stronger educational gradients in risk factors such as BMI tend to be observed among Caucasian as compared to African American women, which may help to explain these differences.[160] The

present findings underscore the importance of future work that examines ethnic differences with respect to SES and CAC progression.

Education and income were highly correlated in this sample, but income was not associated with CAC progression in any models. Annual household income reflects access to healthy lifestyles, material resources, and may contribute to perceptions of control and autonomy.[102] Questions relating to financial strain may yield different information about an individual's economic well-being as compared to objective reports of income. Many middle-aged women experience abrupt changes in economic conditions (e.g., retirement, care of elderly parents). Financial strain is a subjective and dynamic measure, and may better reflect how changing finances and associated stresses contribute to greater atherosclerotic burden progression. Our study found that difficulty paying for basics was not correlated with income among African Americans or Caucasian women; in this population, low income is not a proxy term for financial strain.

The relationships between education, financial strain and higher CAC progression varied across the analyses. In linear regression models that adjusted for education, financial strain appeared to explain the relationship between low educational attainment and high CAC at follow-up. However, while financial strain was associated with higher CAC progression in logistic regression models, it did not explain the inverse association between education and CAC progression. If CAC is indeed associated with financial strain, our sample may not have had enough economic hardship to consistently capture this relationship: at baseline, nearly 70% reported a household income over $50,000 and only 22% noted any difficulty paying for basics. This analysis should be replicated in a sample with a greater range of SES.

Anxiety is associated with higher incidence of CHD in some studies.[155, 161] The few studies that have examined relationships between anxiety and CAC are limited to cross-sectional analyses, and have found no associations between anxiety and CAC.[162, 163] Anxiety did not account for the association between education and higher CAC progression in our analyses, but was marginally associated with higher CAC progression in linear regression models. These results indicate that the role of anxiety in CAC progression may warrant further investigation.

Conversely, hostility was not associated with CAC progression in any models, and did not explain associations between education and CAC progression in the full sample or by ethnicity.

CAC scores in our sample were comparable to those observed in other studies of CAC progression among women.[146, 164] Consistent with extant literature, traditional CHD risk factors—namely age, smoking status, and SBP—were not reliably associated with higher CAC progression in this study. Kronmal *et al.* reported that the predictive value of diabetes mellitus towards CAC progression was highest among African Americans, but was less related to progression among Hispanics, Caucasians and Asians.[33] Several studies have observed that age, hypertension, and LDL cholesterol do not predict CAC progression. [164, 165] Cassidy *et al*. reported that higher BMI was associated with CAC progression, but only among adults at low CHD risk, similar to the findings observed here.[166] Other physiologic and psychosocial risk factors may better explain why CAC progresses over time, and exploring candidate risk factors should be a goal of future research studies.

Prior studies have found variation in the predictive value of baseline CAC towards CAC progression, while other studies caution that inclusion of baseline CAC in regression analyses may yield biased estimates. Therefore, we elected to model our findings with and without adjustments for baseline CAC. Our results were consistent across all analyses. Moreover, CAC progression was considered as both a categorical and continuous variable, with results generally consistent across models.

Our analysis has several limitations. First, our sample was well-educated, and our low education categories were relatively small. This limited our statistical power to assess differences in this group, particularly when we stratified our analyses by ethnicity. Second, over forty percent of our sample did not present with any CAC at either baseline or follow-up examinations. A longer period between examinations may have enabled more women to develop detectable CAC, which would have increased our statistical power to detect differences in CAC progression across SES categories.

In conclusion, we found that one in five CHD-and stroke-free, middle-aged women showed at least 10 units of CAC progression over a two-year period. Lower educational attainment was predictive of higher CAC progression after adjustment for financial strain, hostility, anxiety, and a number of traditional CVD risk factors. Caucasian women with low educational attainment appeared to have greater CAC progression than did African Americans with similar education. However, this finding must be confirmed in a study with a larger cohort of African Americans with low educational attainment. Additional research should examine specific factors that may play a role in the association between low educational attainment and higher atherosclerotic progression.

Table 5-1 Clinical characteristics of the study population at baseline by ethnicity

	Mean (SD) or % (No.)			
	Total Sample (n=339)	**Caucasian** (n=219)	**African American** (n=120)	*P* value (for ethnicity)
Age, years	50.1 (2.67)	50.2 (2.42)	50.0 (2.40)	0.48
BMI, kg/m^2	29.3 (6.46)	28.3 (5.43)	31.4 (6.13)	<0.0001
SBP, mm Hg	117.4 (15.2)	114.4 (13.5)	123.6 (16.7)	<0.0001
Annual household income				
<$50K	31.9 (97)	25.4 (52)	45.4 (45)	0.0003
$50K-<$75K	23.0 (70)	23.9 (49)	21.2 (21)	
≥$75K	45.1 (137)	50.7 (104)	33.3 (33)	
Educational Degree				
≤High School	15.8 (52)	15.5 (33)	16.5 (19)	0.44
Any College	52.7 (173)	50.7 (108)	56.5 (65)	
Post-graduate	31.4 (103)	33.8 (72)	27.0 (31)	
Cynical Hostility	3.61 (2.90)	3.00 (2.52)	4.83 (3.18)	<0.0001
Difficulty Paying for Basics	22.4 (68)	18.0 (37)	31.3 (31)	0.012
Trait Anxiety	16.0 (4.6)	15.9 (4.2)	16.0 (5.0)	0.85

N=Frequency, M=Mean, SD=Standard Deviation

Table 5-2 Spearman Correlations Between Measures of SES and Potential Mediators

	Educational Attainment	Income	Difficulty Paying for Basics	Cynical Hostility	Trait Anxiety
Educational Attainment	-	0.46 p<0.0001	-0.11 p=0.28	-0.26 p=0.006	-0.17 p=0.064
Income	0.24 p=0.0005	-	-0.034 p=0.75	0.0097 p=0.92	-0.11 p=0.26
Difficulty Paying for Basics	-0.032 p=0.65	-0.091 p=0.20	-	0.14 p=0.16	0.19 p=0.057
Cynical Hostility	-0.093 p=0.18	-0.15 p=0.028	0.061 p=0.38	-	0.090 p=0.35
Trait Anxiety	0.10 p=0.16	-0.054 p=0.44	0.14 p=0.050	0.081 p=0.24	-

* Shaded region indicates correlation coefficients for African Americans; unshaded region indicates correlation coefficients for Caucasians.

Table 5-3 Logistic Regression for Predictors of Coronary Artery Calcification Progression in Total Sample

	Model 1			**Model 2**	
	Odds Ratio (95% CI)*	*P* value		Odds Ratio (95% CI)*	*P* value
Ethnicity					
Caucasian	2.29 (1.12-4.65)	0.023		2.06 (0.96-4.41)	0.063
African American	1.00 (Referent)			1.00 (Referent)	
Education					
High school or less	3.42 (1.33-8.80)	0.011		5.00 (1.75-14.3)	0.0027
Any college	1.48 (0.69-3.2)	0.31		1.72 (0.73-4.07)	0.22
Post graduate	1.00 (Referent)			1.00 (Referent)	
Age	1.09 (0.97-1.22)	0.14		1.07 (0.94-1.22)	0.28
BMI	1.10 (1.04-1.16)	0.0004		1.06 (1.002-1.12)	0.04
SBP	1.03 (1.003-1.05)	0.028		1.02 (0.99-1.05)	0.10
Baseline CAC	-	-		1.05 (1.02-1.07)	<0.0001

*=95% Confidence Interval; Covariates in models include time between scans, smoking status and study site

Table 5-4 Logistic Regression for Predictors of Coronary Artery Calcification Progression among Caucasian Women

	Odds Ratio (95% CI)*	***P* value**
Education		
High school or less	7.75 (1.97-30.4)	0.003
Any college	1.53 (0.48-4.88)	0.47
Post graduate	1.00 (Referent)	
Age	1.10 (0.92-1.31)	0.29
BMI	1.12 (1.02-1.22)	0.013
SBP	1.05 (1.005-1.09)	0.027
Baseline CAC	1.05 (1.02-1.08)	0.0009

*=95% Confidence Interval; Covariates in model also include time between scans, smoking status and study site

Table 5-5 Linear Regression for Predictors of Coronary Artery Calcification Progression in Total Sample

	CAC Progression*				
	Model 1			**Model 2**	
	β (S.E.) †	*P* value		β (S.E.) †	*P* value
Ethnicity					
Caucasian	0.21 (0.12)	0.083		0.30 (0.13)	0.017
African American	Referent			Referent	
Education					
High school or less	0.35 (0.17)	0.040		0.28 (0.17)	0.10
Any college	0.15 (0.12)	0.22		0.11 (0.13)	0.41
Post graduate	Referent			Referent	
Age	0.008 (0.020)	0.71		0.004 (0.021)	0.84
BMI	0.013 (0.011)	0.24		0.014 (0.011)	0.23
SBP	0.005 (0.004)	0.23		0.006 (0.004)	0.15
Baseline CAC	0.86 (0.05)	<0.0001		0.84 (0.05)	<0.0001
Difficulty Paying for Basics	-	-		0.34 (0.13)	0.012

*Log-transformed CAC scores; †= β=Beta-coefficient, S.E.=Standard Error; Covariates in model include time between scans, smoking status, and study site

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7.0 GENERAL DISCUSSION

7.1 SUMMARY OF FINDINGS

This dissertation project investigated the independent and combined associations of cardiovascular risk factors, socioeconomic status (SES), and psychosocial factors with subclinical CVD in middle-aged women. Our sample included CHD- and stroke-free African American and Caucasian participants from the Study of Women's Health Across the Nation (SWAN) Heart Study. Coronary artery calcification (CAC), aortic calcification (AC), carotid artery intima-media thickness (IMT), and aortic pulse wave velocity (PWV) were measured among participants at a baseline examination and at a follow-up examination an average of 2.3 years later.

Overall, our analyses suggest that African American women are at greater risk of developing subclinical disease measures related to arteriosclerosis. We observed that IMT and PWV were higher among African American women than among Caucasian women. The excess of CVD risk factors among African American women may have increased the risk for developing measures of arteriosclerosis; consistent with the general population, [95] African American women in our study had higher BMI, waist circumference, SBP and DBP levels than did Caucasian women. In addition, SBP, DBP, LDL-C, and glucose appeared to have a stronger impact on PWV progression among African American women than among Caucasian women, which may have contributed to the accelerated arteriosclerosis observed in this group.

Conversely, our results indicated that CAC progression was higher in a low-SES subgroup of Caucasian women. This finding is consistent with earlier angiography and autopsy studies, which have reported a greater extent of coronary vessel disease among Caucasian

women as compared to African American women.[86] Caucasian women—particularly those with low educational attainment-- may be more prone to developing calcified atherosclerotic plaques in their coronary arteries.

Blood pressure variables explained several of the relationships between African American ethnicity, low income, and cross-sectional subclinical measures that were observed in Research Articles 2 and 3; this emphasizes the role of blood pressure in subclinical CVD development. Blood pressure also related to PWV progression in this sample, particularly among African American participants. Collectively, these findings underscore the importance of early blood pressure management in order to prevent the development of subclinical CVD among middle-aged women.

Our findings in Research Articles 2 and 3 indicated that low SES is independently and robustly associated with certain subclinical CVD measures. These associations were not completely explained by ethnicity or by modifiable risk factors, such as BMI. The specific mechanisms by which low SES exerts detrimental effects on the vasculature of this group of women remain unclear. However, our findings are consistent with other research studies of subclinical and clinical CVD, and confirm that low SES is an important predictor of subclinical CVD.[68, 82, 114-119, 151, 167]

With regard to SES, it is important to note that our analyses included an understudied population in the subclinical CVD literature—African American women with relatively high SES. Several large community-based studies of subclinical CVD report a wider range of SES in their samples than did SWAN Heart, but African Americans in their studies also tend to report substantially lower indicators of SES than observed in our study. In the ARIC study, only 17.6% of African American women had annual household incomes greater than $35,000 as compared to 51.2% of Caucasian women.[168] Similarly, 30.0% of African Americans in the MESA study had high school degrees or less as compared to 21.3% of Caucasians, and 11.0% of African Americans had annual household incomes less than $12,000 as compared to 4.0% of Caucasians.[169] The well-educated sample of African American women in the SWAN Heart Study is fairly unique as compared to other large, multi-ethnic studies of subclinical CVD.

Indeed, women recruited to the SWAN Heart Study generally reported relatively high indicators of SES; more than half of the sample in any one of our analyses had college educations or higher. While this may have limited our ability to detect the relationships between subclinical CVD and severe economic deprivation or hardship, our results likely indicate how variations in social status affect subclinical CVD. We did observe gradations in the extent of subclinical CVD between relatively low SES and higher SES participants. For example, even our "low income" group- which, in this sample, consisted of some women who had an annual household income close to $50,000 per year—had higher IMT and PWV levels.

Recruitment into the SWAN Heart Study was community-based, and involved the Chicago and Pittsburgh member study sites involved in the parent SWAN study. Community-based studies may limit selection biases observed in physician referral studies for the evaluation of subclinical CVD. In addition, both of the SWAN Heart sites recruited Caucasian and African American women; the Chicago site enrolled women from two different facilities in order to increase representation of African Americans. This recruitment strategy enabled us to enroll enough African American women to assess certain ethnic differences in subclinical CVD measures.

The SWAN Heart Study recruited healthy women who were CHD-free at the onset of the study. For this reason, the overall extent of subclinical CVD in this population was fairly low. It will be important to revisit the analyses of this dissertation project as the participants continue to age. The associations between ethnicity, SES, cardiovascular risk factors, and subclinical CVD progression that were observed in our analyses may remain robust or may become attenuated with time. Other risk factors may become increasingly important in predicting the course of subclinical CVD progression as these women transition through the menopause and into older age.

Examining our hypotheses early in the cardiovascular disease process and prior to clinical events is important. First, learning what factors contribute to subclinical CVD may help to identify targets early in the course of cardiovascular disease that ultimately can prevent clinical

outcomes. Furthermore, recall bias may be a factor in studies that require patients with clinical CVD to remember what their CVD risk factor levels were prior to their clinical event. Additionally, individuals who undergo clinical treatment for symptomatic CVD may have artificially-reduced risk factor levels that confound the relationships between risk factors and clinical disease.

Our general analytic strategy across the three research articles had several limitations. Only two ethnic groups were recruited to the SWAN Heart Study, and we recommend that our analyses be applied to cohorts that include women of other ethnicities. Indeed, subclinical CVD among Hispanic American and Asian American women is relatively understudied, although cardiovascular outcomes are major causes of mortality among women in these groups. In addition, not every woman in our study sample participated in each of the different subclinical CVD scans or received scans at both baseline and follow-up. In order to maximize statistical power, we retained those women who had at least one subclinical CVD measurement in the cross-sectional analysis, and those women with a baseline and a follow-up PWV or CAC measurement for the progression analyses. For this reason, the samples differ slightly between the three analyses. Lastly, we attempted to match cardiovascular and psychosocial risk factors assessed at annual SWAN visits to each participant's corresponding SWAN Heart baseline or follow-up year. However, because some women missed at least one SWAN visit, we had to impute covariate data from the closest SWAN year to our analyses. This was a consideration for a minority of women, but should still be noted as a limitation as their risk factors may have changed in the intervening time between their SWAN and SWAN Heart visits.

7.2 PUBLIC HEALTH SIGNIFICANCE

Clinical CVD is the leading cause of mortality among American women. The direct and indirect costs of CVD in the U.S. are estimated to be $475.3 billion dollars in 2009 alone.[170] Early risk factor management and preventive care could profoundly impact the overall health of the public, reduce the economic burden of CVD, and curtail morbidity and mortality from cardiovascular causes.

Investigating the interrelationships between risk factors that contribute to higher subclinical CVD may help to identify targets that prevent progression into clinical outcomes. In our analyses, we observed that blood pressure variables were important risk factors for the development of subclinical CVD—particularly for IMT and PWV. A recent meta-analysis suggests that usage of anti-hypertensive medications, including angiotensin-converting enzyme inhibitors and β-blockers, reduces IMT progression in populations with diabetes or CHD.[100] Treatment of pre-hypertension and hypertension in otherwise healthy women may also help to prevent the early cardiovascular changes that culminate in clinical outcomes.

Our findings indicated that the effects of SBP, DBP, and LDL-C may be stronger among African Americans than among Caucasians in relation to PWV progression, a measure of arteriosclerosis that is related to adverse clinical outcomes. Waist circumference and glucose also were related to PWV progression among the African American women in our sample. Differences in the magnitude of the effects of CVD risk factors on PWV progression in addition to an excess of CVD risk factors may contribute to the disproportionately high prevalence of adverse clinical outcomes among African American women. Even in our generally healthy, relatively high-SES sample of African American women, participants had marginally high SBP and lipid levels, and did not report that they were receiving treatment for these conditions at study baseline. Clinicians may need to manage these risk factors earlier and more aggressively in order to prevent clinical outcomes in this group. As reported by the International Society on

Hypertension in Blacks, "Undiagnosed, untreated, and inadequately treated hypertension results in an enormous burden of disease for African Americans… a key obstacle is the failure of medical providers to treat high blood pressure early and to continue treating it persistently to reach and maintain an appropriate target blood pressure."[171] This statement may also be valid for the treatment of hyperlipidemia, diabetes mellitus or pre-diabetes, and other conditions related to cardiovascular risk. Currently, treatment recommendations do not vary by ethnicity. However, our data suggest that even borderline levels of risk factors are associated with arterial stiffening over a two-year period. It is possible that clinicians are not treating these risk factors sufficiently or early enough in the pathogenesis of CVD to prevent clinical events. It is also possible that current clinical thresholds for CVD risk factors are insufficient to prevent clinical disease among African Americans. Suggested future work includes a reassessment of current clinical guidelines for healthy SBP, DBP and LDL-C targets among African Americans, in order to establish adequate levels for successfully managing hypertension and hyperlipidemia in this population.

It is more challenging to modify and "treat" socioeconomic status. Our findings indicate that lower SES is associated with certain measures of subclinical CVD, which may in part be explained by excess cardiovascular risk factors in this group. Although we did not examine this question directly, low-SES individuals are more likely to engage in "cigarette smoking, physical inactivity, poor diet, and substance abuse" than are high-SES individuals.[104] Certainly, these lifestyle factors are important targets for reducing subclinical CVD in this group. In addition, public policy efforts that facilitate upward mobility, improve the quality of education for all children, and encourage successful college degree completion among low-SES adolescents may diminish the psychological and health-related burdens associated with poverty in the United States.

We observed that psychosocial factors such as anxiety and financial strain were weakly but consistently related to greater CAC progression among Caucasian women with low educational attainment. Modifying certain psychosocial factors among low-SES women may lead to the prevention of cardiovascular outcomes. Improving the accessibility of services that assist individuals and families with low SES and enhance overall health would be one strategy; efforts could include providing credits for healthy foods or for activities that promote physical

health, or could include reducing costs and availability of medical and dental care in low-income neighborhoods. Another strategy is to improve the availability of mental health services to women of low SES. If women utilize effective coping strategies that ameliorate feelings of anxiety and strain, some prevention of clinical outcomes may ultimately be achieved. Encouraging accredited medical schools to teach better interviewing skills to students could be an additional approach. Special emphases could include improving cultural competency and eliciting information about the lifestyle concerns, needs, and coping strategies of low-SES patients. Asking these questions may reveal patients who may benefit from mental health services or psychotropic medications. While these types of questions should be considered standard for any patient-provider interview, they may be particularly important for identifying vulnerable low-SES women, and ultimately, improving cardiovascular outcomes in this group. It is important to note that the costs to the public for improved mental health services may ultimately be less than the costs for treating eventual clinical cardiovascular diseases and stroke.

7.3 FUTURE RESEARCH

In this dissertation project, we observed that blood pressure, and to a lesser extent, financial strain, were important mediators of the associations between ethnicity, low SES and subclinical CVD change. Additional research is needed to clarify the relationships between ethnicity, SES, and cross-sectional and longitudinal measures of subclinical CVD progression. Special attention to the CVD and psychosocial risk factors that may explain these associations may generate new or improved targets for clinical management. There is still much to learn about why certain women develop clinical outcomes. If we are better able to understand how and why the vasculature changes prior to these clinical outcomes, better interventions may be developed for preventing clinical disease.

Certainly, atherosclerosis and arteriosclerosis are cumulative, progressive diseases with extensive latent phases. To better characterize the roles of biological and psychosocial risk factors on the natural history of these diseases, it is important to examine them throughout the lifecourse. Our analyses investigated the associations of subclinical CVD with current or recent cardiovascular risk factors and SES indicators. However, we recommend future work to examine how changes in risk factors over time affect the progression of subclinical CVD. For example, studies that examine the effects of cumulative lifetime SES on subclinical CVD outcomes may be more informative for understanding how, why, and when SES begins to affect vascular health and functioning. Some of this work has been assessed in studies such as CARDIA, which has been pioneering in its longitudinal investigation of subclinical CVD beginning in young adulthood. A limitation of these studies is under-enrollment of diverse ethnic groups. CVD is a leading cause of mortality among Asian and Hispanic Americans as well. We also recommend that longitudinal assessments of atherosclerosis and arteriosclerosis in these populations should be examined in future work.

Future research should focus on the prevention of subclinical CVD progression. A meta-analysis by Wang and colleagues concluded that antihypertensive medication usage prevents progression of IMT among individuals with diabetes or symptomatic coronary heart disease.[172] However, no study has yet examined whether anti-hypertensive medications can be used to prevent subclinical CVD progression in relatively healthy populations with borderline or clinical hypertension. While SBP and DBP were observed to be some of the most potent risk factors for PWV progression in our CHD-free sample, the average SBP of our participants was only in the pre-hypertensive range, and DBP was in the normal range. We recommend that future clinical trials examine whether the following interventions are effective in reducing subclinical CVD progression in healthy populations with borderline hypertension: 1) lifestyle and behavioral interventions that reduce dietary sodium intake and tobacco usage, and increase physical activity, 2) pharmacologic treatment of marginally elevated blood pressure. Improved blood pressure control in the earliest stages of hypertension may be important in preventing adverse vascular remodeling over time.

As noted earlier, the effects of blood pressure on PWV progression were particularly robust among African American women. According to the JNC 7 on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, the current recommendation for blood pressure targets is 130/80 or less for individuals with non-diabetic renal disease or type 2 diabetes;[147] however, the optimal blood pressure target for preventing end-organ damage is now considered less than 120/80.[171] Thus far, no research studies have established whether these targets are adequate for preventing clinical outcomes among African American women.[147] Clinical trials are needed to examine which blood pressure targets—130/80, 120/80, or even lower—are most effective for preventing clinical outcomes among African Americans.

Our work suggests that even African American women with borderline hypertension may be at risk for accelerated arterial stiffening. A preventive strategy that should be examined in future research studies would include beginning African-American women on anti-hypertensive medication regiments if they are either pre-hypertensive or normotensive and have at least one additional cardiovascular risk factor (*e.g.*, obesity or a family history of CHD). Currently, there are no differences in clinical guidelines across different ethnic groups for treating hypertension

or pre-hypertension.[147] However, given the strong associations between blood pressure and subclinical disease and clinical cardiovascular outcomes among African Americans, this approach should be considered. It is important to note that certain pharmacologic treatments have well-characterized side effects, or are considered to be less effective for controlling blood pressure in African Americans (*e.g.,* ACE inhibitors);[171] therefore, analysis of the risks and benefits of starting early and aggressive blood pressure treatment in this population would be most safely considered in the setting of clinical trials.

It remains unclear why blood pressure, hyperlipidemia, and hyperglycemia rendered African American women in our study more vulnerable to PWV progression. It does appear that this susceptibility to adverse cardiovascular profiles begins early in life. The Pathobiologic Determinants of Atherosclerosis in Youth autopsy study observed that young African Americans had more extensive fatty streaks on autopsy in their coronary arteries and aortas than did young Caucasians.[173] Earlier findings also indicate that young African Americans have greater sodium sensitivity than do young Caucasians,[174] which may contribute to excessive salt and water retention, and ultimately, higher blood pressures beginning in childhood. Genetic studies may be important in elucidating what particular factors contribute to hypertension and hyperlipidemia among African Americans, and we encourage future research in this area.

Anxiety and psychological risk factors are associated with higher levels of subclinical CVD. In our study, high baseline anxiety levels were marginally related to higher CAC progression. Some researchers speculate that stress elicits an adrenergic response that cumulatively may contribute to hyperglycemia, hypercortisolemia, and autonomic dysregulation; this eventually may lead to clinical events.[175] Understanding the relationships between emotional and cognitive stimuli, biological and physiologic responses, and CVD is important. Future studies could investigate the efficacy of various mental health interventions in reducing negative affect and emotions, and examine whether these interventions are effective in reducing progression of subclinical CVD measures. Mental health interventions may be an efficacious component of preventive care.

7.4 CONCLUSION

Cardiovascular disease is a major cause of morbidity and mortality among American women, and particularly among African American women. In these analyses, we studied the associations of early subclinical cardiovascular changes with ethnicity, SES, and cardiovascular disease risk factors in a biracial sample of CHD-free, middle-aged women. We found cross-sectional and longitudinal associations between ethnicity and subclinical CVD measures. We observed that SBP, DBP, LDL-C, and glucose were stronger predictors of PWV progression among African American women than among Caucasian women. Generally, African American ethnicity was more strongly associated with higher levels of measures that relate to arteriosclerosis, including IMT and PWV; SBP appeared to partly explain higher PWV among African Americans. Women of low SES and Caucasian ethnicity also appeared to have greater progression of atherosclerotic coronary plaque. In addition, we observed that low SES was predictive of higher levels of AC, IMT, and PWV, independent of ethnicity. We also evaluated the associations of SES and progression of CAC, and found that Caucasian women with low educational attainment were more likely to develop higher CAC progression over the follow-up period. This association was partly explained by financial strain, and anxiety appeared to play a role in CAC progression in this group. In sum, our findings provide evidence for independent and combined associations between ethnicity, SES, and subclinical CVD. Our findings also suggest that psychosocial factors such as financial strain may mediate some of these relationships. We recommend that future work should examine the progression of subclinical CVD in this group of women, and attempt to identify other psychosocial and biological variables that explain these associations.

APPENDIX: SUMMARY OF EPIDEMIOLOGIC STUDIES ON SUBCLINICAL CVD MEASURES AND CVD OUTCOMES, AND ETHNIC DIFFERENCES IN SUBCLINICAL CVD MEASURES

Table A-1. Coronary Artery Calcification and Cardiovascular Events

Authors	Design	Study	Sample	Results	Conclusion/Comments
Budoff MJ, Shaw, LJ, et al., 2007. J Am Coll Cardiol.	Prospective, average 6.8-year follow-up. All-cause mortality endpoint.	Multi-site, UCLA investigators.	n=25,253 physician-referred, consecutive asymptomatic adults. Mean age 56 yrs, 50% male	1. 510 deaths. CAC predicted mortality. 2. Presence of CAC was associated with 2.2 increased risk, after adjustment for CVD risk factors.	1. The greater the amount of CAC, the greater the risk of death 2. Did not consistently adjust for other CVD risk factors, likely an overestimation of risk.
Church TS, Levine, BD, et al., 2007. Atherosclerosis.	Prospective, average follow-up of 3.5 years.	Physician- or self-referred population.	n=10,746 men and women.	1. 81 CHD death or non-fatal MI. 2. Low event rate for people with no CAC; CAC ≥100 associated with increased CHD risk (RR: 6.4-8.4) as compared to <100 units CAC (RR: 0.4-2.4), depending on number of CHC risk factors.	1. Physician-referred population. 2. EBCT method was slightly different, used Agatston method but different CT slice thickness than standard method.
Detrano R, Guerci AD, et al., 2008. NEJM.	Prospective, average follow-up of 3.8 years.	Multi-Ethnic Study of Atherosclerosis (MESA) cohort.	n=6722 African American, Chinese, Hispanic, Caucasians, aged 45-84 at baseline	1. 162 coronary events. 2. Compared to 0 CAC, CAC 1-300 (HR: 7.73, p<0.001), CAC>300 (HR: 9.67, p<0.001) associated with any coronary event	1. No differences in predictive value of CAC by ethnicity.
Detrano R, Wong ND, et al., 1999. Circulation.	Prospective, average f0ollow-up of 41 months.	South Bay Heart Watch.	n=1196 asymptomatic, high CHD-risk adults. Mean age 66.	1. 68% had CAC>0. 17 coronary deaths, 29 nonfatal MIs. 2. CAC did not change ROC area significantly when added to Framingham risk model variables.	1. CAC may not add incremental value to CHD risk assessment in high-risk groups 2. Very few CVD events, may have limited ability to see associations.

Table A-1 (Continued)

Folsom AR, Kronmal RA, et al., 2008. Arch Intern Med.	Prospective, average 5.3 years of follow-up.	MESA cohort. Comparison of predictive value of CAC and IMT towards CVD.	n=6698 African American, Chinese, Hispanic, Caucasians, aged 45-84 at baseline	1. 222 CVD events. 2. Each 1-SD increase in CAC associated with 2.1x increased risk of CVD. Adjustment for CVD risk factors (RFs). 3. For each 1-SD increase in IMT, 1.3x increased risk of CVD.	1. CAC was more related than IMT with risk of CVD. 2. Ethnicity-adjusted. No data present risks by ethnic group.
Lakoski SG, Greenland P, et al., 2007. Arch Intern Med.	Prospective, average follow-up of 3.75 years.	MESA cohort. Women-only. CAC scores and risk for cardiovascular events in women classified as "low risk" based on Framingham Risk Scores.	n=3601 women aged 45-84 at baseline. 90% of these women were classified as low risk based on FRS.	1. 58 CVD events. Prevalence of CAC was 32% (n=870, CAC>0) 2. Low-risk women with CAC were at significantly increased risk for CHD (HR: 6.5) and CVD events (HR: 5.2). The HRs remained significant and similar after exclusions of statin users and anti-hypertensive med users. 3. Advanced CAC (CAC score ≥ 300) was highly predictive of future CHD and CVD events over a 3.75-yr f/u period. Women who had CAC scores ≥ 300 were older, had higher LDL levels, and higher SBPs. 4. No ethnicity x CAC interaction in prediction of CHD/CVD events.	1. 95% of US women younger than 70 YO are judged to be at low risk for CHD based on FRS standards (NHANES III), so the FRS alone is not a good predictor for future CHD/CVD in women. This may enhance the importance of subclinical measures in this subgroup.

Table A-1 (Continued)

LaMonte MJ, Fitzgerald SJ, et al., 2005. Am Journal of Epidemiology.	Prospective, average follow-up of 3.5 yrs.	CAC score and CHD events in asymptomatic men and women. EBCT used.	3619 participants. Ages 22-96 YO. 20% were 40 YO. Mean age = 53.8 +/- 9.9 yrs. 64% men, >97% White. Participants received scanning as part of a preventative health exam or physician/self-referral. Aerobics Center Longitudinal Study.	1. Primary endpoint = CHD events (nonfatal MI or death from cardiac causes). Secondary endpoint = all CHD events (hard events + PTCA and CABG). 2. 287 CHD events in time pd (19 deaths, 62 nonfatal MIs, 206 revascularizations). 3. Zero CAC was seen among 20.4% of women with these events and 71.7% of women without these events	1. Questionnaire asked about CVD risk factors before CHD event; recall bias from questionnaire is likely. 2. More women than men had CHD deaths or nonfatal MIs 3. No CHD events were seen in younger group, but there were some young people with CAC. Authors suggest these types of people may benefit from EBCT screening.

Table A-2 Aortic Calcification and Cardiovascular Events

Authors	Design	Study	Measurements	Results	Conclusion/Comments
Walsch CR, Cupples LA, et al., 2002. Am Heart Journal.	Prospective, 22-year follow-up.	Framingham Study, n=2467 total, 1437 females. Free of CHD at study onset Participants received AAC measurements at year 10 (1966-1970)	Abdominal AC (AAC), lateral lumbar radiograph.	1. 141 cases of CHD among men, 169 among women. AAC was categorized into tertiles. 2. Among women, CHF risk was increased for the second (HR 1.8, 95% CI 1.1-2.9) and third (HR 3.2, 95% CI 2.0-5.1) tertiles compared with the lowest tertile of AAC.	1. Authors adjusted for existing CHD, because of the relationship between CHD and CHF. 2. Differences in prognostic value of AAC by ethnicity were not reported.
Wilson PWF, Kauppila LI, et al., 2001. Circulation.	Prospective. 28-year follow-up.	Framingham Heart Study, 1049 men and 1466 women, mean age 61 years.	AAC on lateral lumbar radiograph. Adjustment for a number of risk factors.	1. 454 CHD cases, 709 CVD cases, 365 CVD deaths. 2. 2 highest tertiles of AC were significantly associated with greater CHD and CVD mortality among women (RR: 1.25, 95% CI: 0.95-1.65), (RR: 1.78, 95% CI: 1.33-2.38), respectively.	1. Differences in prognostic value of AAC by ethnicity were not reported. 2. It is unclear whether calcification in thoracic wall and abdomen are interchangeable.
Witteman JC, Kannel WB, et al., 1990. Am J Cardiol.	Prospective, 12-year follow-up.	Framingham Study, n=5209.	Thoracic AC, chest X-ray	1. Extent of AC approximately doubled in each decade of life 2. Presence of AC was associated with doubled CVD risk over follow-up 3. Presence of AC was associated with doubled risk of CHD and claudication among women, less so among men	1. The prognostic value of AC was decreased with increasing age 2. Framingham Heart Study is not ethnically-diverse, unclear what associations are for Blacks

Table A-3 Carotid Artery Intima-Media Thickness and Cardiovascular Events

Authors	Design	Study	Measurements	Results	Conclusion/Comments
Bots ML, Hoes AW, et al., 1999. J Int Med.	Prospective, 10-12 year follow-up.	Rotterdam, Netherlands. 1683 men and women, mean age 70.	Common-carotid artery IMT (CCA-IMT). Stroke, CHD, and death were endpoints. CCA-IMT divided into quintiles. Low versus high CCA-IMT values were reported. Fairly high CCA-IMT levels among women in sample (0.79±0.16 mm)	1. 10-year risk of stroke: 4.8% (95% CI: 3.8-5.8) for lowest quintile of CCA-IMT versus 16.1% (12.3-21.9) for subjects in highest quintile. 2. 10-year risk of CHD: 13.1% (95% CI: 12.0-14.2) to 23.4% (95% CI: 21.4-25.4) 3. Risk of death in 11.5 yrs: 15.0% (95% CI: 12.8-17.4) versus 46.0% (42.8-49.3%)	1. Sample is not ethnically-diverse and is elderly. 2. Risk of death was very high in this sample, much moreso than other studies 3. No adjustments of RFs for CVD risk factors—a limitation for interpretation 4. Average SBP values were marginally hypertensive for women
Chambless LE, Folsom AR et al., 2003. Journal of Clinical Epidemiology	Prospective, median 10.2 year follow-up.	Atherosclerosis Risk in Communities Study (ARIC). Coronary heart disease risk prediction in ARIC. Used nontraditional (non-Framingham; total cholesterol, HDL, current smoking, diabetes, BP) risk factors to explore individual risk of incident CHD.	15972 men and women in 4 US communities. Assessed BMI, WHR, sport activity index, FEV, plasma fibrinogen, Factor 8, VWF, LP, pack years, IMT. Longitudinal (baseline visit: 1987-1989, subsequent f/u exams in 1990-2, 1993-5, 1996-8). Blacks and Whites.	1. Black women had higher incident CHD rates than White women ($p<.05$) and Black men had lower rates than White men ($p<.05$). 2. For ARIC Black women, hazard rate ratios (HRR) were higher for hypertension and current smoking than Framingham women. For ARIC white women, HRRs were higher for diabetes and current smoking. 3. IMT did not bring a significant increase in the CHD prediction model when added to covariates, although it did add to the area under the ROC curve of at least 0.005 for women of each ethnicity.	1. IMT does not independently predict CHD incident events but does add to individual risk (probability that a person who had an incident event within the 10-yr time pd had a higher risk score than a person who did not have an event by that time).

Table A-3 (Continued)

Lorenz MW, Markus HS, et al., 2007. Circulation.	Meta-analysis.	Examined 8 relevant studies, including ARIC, Rotterdam, CHS, and CAPS.	Pooled age- and sex-adjusted ORs over the studies.	1. Per 1-SD CCA-IMT difference, relative risk of MI was 1.26 (95% CI: 1.21-1.30) 2. Per 1-SD CCA-IMT difference, relative risk of stroke was 1.32 (95% CI: 1.27-1.38) 3. Per 0.10-mm increase in CCA-IMT, relative risk of MI was 1.15 (95% CI: 1.12-1.17) 4. Per 0.10-mm increase in CCA-IMT, relative risk of stroke was 1.18 (95% CI: 1.16-1.21)	1. Important meta-analysis 2. Data not reported by gender or ethnicity 3. Graded increase in cardiovascular risk for each category increase in IMT
O'Leary DH, Polak JF, et al., 1999. NEJM	Carotid IMT thickness as a risk factor for new-onset MI and stroke in older adults.	N=5858, subjects ≥ 65 YO. Mean age= 72.5. Black and White men and women with no prior history of CVD. Examined prospectively for median 6-7 yrs. Cardiovascular Health Study.	Incidence of CVD events correlated with IMT. Relative risk of MI or stroke increased with IMT.	1. RR of MI/stroke (adjustment for age and sex) for highest thickness quintile as compared to lowest quintile was 3.87. 2. After adjustment for traditional risk factors, association between CV events and IMT was significant. RFs: age, sex, DBP, SBP, pack years of smoking, LDL/HDL, diabetes, atrial fibrillation.	1. Common carotid IMT and combined IMT were better predictors of stroke than internal carotid IMT; combined was overall better for predicting events. 2. IMT is a strong predictor of new CVD events. 3. An increase of 1 SD in combined IMT thickness was associated with a RR of 1.36 for combined end point of MI or stroke after adjustment for age, sex, and other risk factors

Table A-3 (Continued)

Rosvall M, Janzon L, et al., 2005. Atherosclerosis.	Prospective, 7-year follow-up.	Malmo Study, Sweden. 5163 men and women. Mean age= 57.5 yrs.	Common carotid IMT. 22.6% current smokers, 25.1% had low activity, normal waist circumferences.	1. 86 incident cases of stroke (41 for men, 45 for women). 2. Age- and gender-adjusted carotid IMT were related to future stroke ($p<0.05$). Graded increase between IMT and stroke risk.	1. Population of Europeans, not ethnically-diverse 2. Highest categories of IMT were most strongly and significantly related to stroke. HRRs in these groups ranged from 3.20-2.84. 3. CVD endpoints were not gender-stratified, and CVD risk factors and IMT levels were not reported by gender.

Table A-4 Aortic (Carotid-Femoral) Pulse Wave Velocity and Cardiovascular Events

Authors	Design	Study	Measurements	Results	Comments/Conclusions
Meaume A, Benetos A, et al., 2001. Arterioscler. Thromb. Vasc. Biol.	Prospective, mean follow-up 30 months.	182 consecutive patients into 3 Paris hospitals. 141 consented and had readable scans. Mean age 87.1 years.	Complior device was used for aortic PWV measurements.	1. 56 patients died, 27 from CV events. Age (p=0.005) and loss of autonomy (p=0.01) were best predictors of mortality. 2. Aortic PWV was major risk predictor (OR: 1.19, 95% CI: 1.03-1.37; p=0.016) 3. Mean blood pressure, SBP, prior history of CV were associated with higher CV mortality.	1. Antihypertensive drug treatment and blood pressure had no additive role on CV risk, but this could be partly due to age of the patients and comorbidities 2. Plasma glucose, age, plasma albumin, and CRP were not related to CV events. 3. French sample of men and women, sex-adjusted ORs
Boutouyrie P, Tropeano AI, et al., 2002. Hypertension.	Prospective, mean follow-up 5.7 yrs.	1045 hypertensives. Mean age 51 YO, n=674 men, n=371 women. Asymptomatic for CV. France.	Carotid-femoral PWV, Framingham risk score.	1. 53 coronary events, 97 CV events. 2. RR for CHD events: 1.42 per 3.5 m/s PWV (p<0.01). For all CVD events, RR: 1.41 (p<0.001). 3. Framingham risk score (FRS) predicted CHD and CVD in population (p<0.001 and p<0.0001, respectively). 4. After adjustment for FRS, PWV was still associated with coronary events (RR: 1.34, p=0.039).	1. This is one of the first studies to show an association between aortic stiffness and CHD and CVD 2. French sample of men and women, sex-adjusted RRs 3. Participants had already been treated for hypertension; while mean SBP was high (150 mm Hg), treatment might confound results

Table A-4 (Continued)

Sutton-Tyrrell K, Najjar SS, et al., 2005. Circulation.	Prospective, mean follow-up 4.6 years	2488 participants in Health, Aging, Body Composition (ABC) Study. Ages: 70-79, 40% Black, 48% male.	Carotid-femoral PWV.	1. 265 deaths. 111 were from CVD. 341 CHD, 94 strokes, 181 CHF events. 2. Average PWV: 810 cm/s (641-1052) 3. Higher PWV associated with higher total mortality (p=0.019 between lowest and highest PWV quartiles), CV mortality (p=0.004 between lowest and highest PWV quartiles) after adjustments for age, gender, race, SBP, known CV disease. 4. High PWV quartiles associated with CHD (p=0.007) and stroke (p=0.001)	1. Older sample, relatively well-functioning, PWV values are low for this age. 2. PWV was not associated with CHF
Mattace-Raso F, van der Cammem T, et al., 2006. Circulation.	Prospective, mean follow-up for stroke (3.2 yrs), mean follow-up for CHD (4.1 yrs)	2835 subjects in Rotterdam study. Mean age: 71.7 yrs, 39.2% men.	Carotid-femoral PWV.	1. 101 subjects developed CHD, 63 developed stroke, 352 subjects died. 2. Average IMT: 0.86±0.14 mm. Average PWV: 1330±290 m/s. 3. HR for CHD in the 2nd and 3rd tertiles of PWV: 1.72 (0.91-3.24), 2.45 (1.29-4.66), after adjustment for age, gender, MAP, and HR. 4. HR for stroke in the 2nd and 3rd tertiles of PWV: 1.22 (0.55-2.70) and 2.28 (1.05-4.96).	1. PWV was adjusted for IMT in some models, which did not explain the association between PWV and CV events 2. Aortic PWV had additive predictive value above traditional CVD risk factors and IMT 3. Low numbers of stroke could have reduced the ORs for these associations

Table A-5. Ethnic Differences in Coronary Artery and Aortic Calcification

Authors	Study	Sample	Measurements	Results	Comments/Conclusions
Bild DE, Detrano R, et al. 2005. Vascular Medicine.	Cross-sectional	MESA study. 6814 White, Black, Hispanic, Chinese men and women ages 45-84 YO. Mean age = 62-63 among all age groups.	Blacks had highest SBP and DBP, lowest total cholesterol and triglyceride levels, highest rate of current smoking (18%), and high levels of diabetes (21%).	1. After adjustments for CV risk factors, relative risks for coronary CAC were 0.78 in Blacks, 0.85 in Hispanics, 0.92 in Chinese. 2. Amount of CAC was greatest among Whites, followed by Chinese (77% that of Whites), Hispanics (74% that of Whites), and Blacks (69% that of Whites). 3. White men had the highest prevalence of CAC of all groups (70.4%); of women, Whites had the highest prevalence (44.6%).	1. Increased BMD associated with lower vascular CAC. 2. Blacks have lowest RR of CAC and lowest prevalence of CAC. 3. CAC may not be a good prognostic index for Blacks/Hispanics, or a lower limit should be considered. 4. BMI associated with CAC in Whites only
Bild DE, Folsom AR, et al. Arterioscler Thromb Vasc Biol. 2001.	Cross-sectional	Coronary Artery Risk Development in Young Adults (CARDIA). 443 men and women, ages 28-40. Volunteers from the larger CARDIA sample. EBCT scans for this study were done at year 10. Mean age-35 YO across groups.	No participants had a history of CVD. Presence of CAC was positively associated with age, male sex, BMI, weight, SBP, and total + LDL cholesterol at baseline and year 10.	1. Presence of CAC was seen in 16.1% of Black men, 11.8% of Black women, 17.1% of White men, and 4.6% of White women (p=0.04).	1. White men had the most CAC, White women had the least CAC. 2. A longitudinal analysis of CAC progression over the 10-year period would have been interesting for assessing long-term effects of CV risk factors on CAC progression

Table A-5 (Continued)

Budoff MJ, Yang TP, et al., 2002. Coronary Artery Disease.	Cross-sectional	782 patients undergoing coronary angiography due to evidence of CVD (angina most common). White (mean age= 58 YO, 75% men), Blacks (55 YO, 53% men), Hispanics (55 YO, 64% men), Asians (58 YO, 73% men). EBCT. UCLA medical center.	Asians and Blacks had highest hypertension levels (65 and 66% respectively) compared to Whites and Hispanics (44% and 66%). Statistical controls for age, gender, and risk factors (hypertension, tobacco, diabetes, age, gender, family history, hypercholesteremia, statin usage).	1. In Whites, 84% prevalence of CAC and significant obstruction on angiogram was 71%. 2. Blacks had a lower prevalence of CAC (62%, p<.001) and angiographic disease (49%, p<.01). 3. Hispanics had a lower prevalence of CAC (p<.001) and angiographic obstruction (p<.01). 4. Asians were not significantly different to Whites with regard to CAC or angiographic stenosis.	1. Blacks and Hispanics have less CAC and obstructive coronary disease. 2. Whites and Asians have comparable levels of CAC and obstructive coronary disease
Budoff MJ, Nasir K, et al., 2006. Atherosclerosis.	Cross-sectional	UCLA physician-referred population. 16560 asymptomatic patients with high CHD-risk. 70% males, average age 52. Whites, Blacks, Asians, Hispanics.	Whites had more dyslipidemia, but Blacks and Hispanics had more hypertension, smoking, and diabetes.	Relative risks for men having CAC compared to Caucasians were 0.64 for Blacks, 0.88 for Hispanics, 0.66 for Asians. For women, compared to Caucasians, risks were 1.58 for Blacks, 0.84 for Hispanics, 0.71 for Asians.	1. Black women had more CAC than did any other ethnic group, but also had more RFs. 2. Physician-referred population. 3. Presents data by gender.

Table A-5 (Continued)

Diez Roux AV, Detrano R, et al., Circulation. 2005.	Cross-sectional	MESA. 6814 White, Black, Hispanic, Chinese men and women ages 45-84 YO (median ages across ethnic/gender groups: 61.3-62.4)	Median sex distributions and ages were similar (~61-62) across ethnic groups. Prevalence of calcification was higher in white non-Hispanics. CAC differences were controlled in analyses by smoking, BMI, LDL, HDL, hypertension, and diabetes.	1. Prevalence of CAC highest among Whites 2. Low education associated higher prevalence of CAC among Whites (RP: < high school vs. college, 1.17; 95% CI: 1.05 to 1.32) but with lower prevalence of calcification in Hispanics (RP: 0.91; 95% CI, 0.77 to 1.09) (*p* for interaction=0.02)→ Hispanic paradox	1. Not being born in the US was associated with a lower prevalence of CAC in Blacks and Hispanics after adjustment for age, sex, income, and education. 2. Years in US were positively associated with prevalence of CAC in non-US born Chinese and non-US born Blacks. 3. Income was inversely associated with CAC (Blacks in lowest income categories had 12% higher probability of calcification than those in highest category).
Doherty TM, Tang W, et al., 1999. J Am Coll Cardiol.	Cross-sectional	South Heart Bay Watch. 1375 high-risk but asymptomatic adults (n=93 Blacks, 1282 Whites).	Similar Framingham risk scores.	1. Prevalent CAC in 59.9% of Whites, 35.5% of Blacks (p=0.0001). 2. After 70 months of follow-up, 23.7% of Blacks vs. 14.8% of Whites (p=0.04) had either CHD death, MI, angina, or revascularization. 3. Blacks were 2.16 times more likely to have at least one event than were Whites, after adjustment for age, gender, and risk factors.	1. Small number of Blacks, not enough to stratify results by gender 2. Despite lower prevalence of CAC, Blacks had more CHD events than did Whites 3. High-risk population. Only one measure of subclinical CVD was assessed. 4. Authors suggest that differences in Ca2+ metabolism, differing importance of risk factors, and greater left ventricle mass among Blacks may explain ethnic differences in CVD outcomes.

Table A-5 (Continued)

Jain T, Peshock R, et al., 2004. J Am Coll Cardiol.	Cross-sectional	Dallas Heart Study 528 Whites (242 women, 286 men) and 761 Blacks (380 women, 381 men). Women were apprx. 54 YO (+/- 5 yrs), men were apprx. 51 yrs old.	Assessed clinical characteristics of black and white participants by gender. Threshold status for CAC was≥10 vs. < 10 units. ORs to assess differences. .	1. No sig. differences were found in the prevalence of CAC between the two ethnic groups. 2. For Black and White men, prevalence of CAC: 37% v 41% (p=0.35), for Black and White women, prevalence of CAC: 29% v. 23% (p=0.21)	1. No SES adjustments 2. Sig. predictors of CAC were smoking, SBP, DBP, BMI, and plasma cholesterol, HDL, triglycerides, and glucose. 3. No difference in CAC ORs between blacks and whites were seen after adjusting for age and gender
Khurana C, Rosenbaum CG, et al., 2003. Am Heart Journal.	Cross-sectional	Women's Health Initiative-Observation Study (WHI-OS) 128 Black women, 733 White women. Postmenopausal, CAD-free. CAC in black and white women.	Framingham algorithm used to assess 10-year risk of CVD.	1. Black women had higher dietary fat consumption, higher BMI, and greater prevalence of hypertension, diabetes, and smoking than did White women. 2. DM and not exercising 3x per week were independently associated with higher CAC in Whites only. 3. Educational level, BMI, dietary fat consumption, family history of premature CAD, hypertension, and smoking were not associated with CAC in Blacks, Whites, or the combined cohort. 4. Black and White women had similar CAC scores despite higher RFs among Blacks.	1. Consistent with SWAN Heart in that educational level is not associated with CAC in Blacks and Whites 2. Inconsistent in that educational level, BMI, and hypertension are not associated with CAC in Blacks and Whites 3. Black and White women were both well-educated in this sample

Table A-5 (Continued)

Lee TC, O'Malley PG, et al., 2003. J Am Coll Cardiol.	Cross-sectional	1000 adults, asymptomatic, active-duty personnel. Prospective Army Coronary Calcium (PACC) Project. Mean age 42.	EBCT, plasma and biologic, physiologic measurements.	1. Blacks had more RFs, 3x the hypertension, LDL-C, inflammation, but had less waist circumference. After adjustments for RFs, 2. CAC was prevalent among 19.2% of Whites and 10.3% of Blacks (p=0.004). 3. After adjustment for CVD risk factors and SES, Blacks were 39% as likely to have any CAC present (p=0.007).	1. Blacks had less CAC than did Whites, but low SES and high CVD risk explain some CAC in Blacks 2. Regardless of excess CVD risk factors among Blacks, Whites had more prevalent CAC 3. Data were not presented by gender.
Lewis TT, Everson-Rose SA, et al., 2009. Psychosomatic Medicine.	Cross-sectional	SWAN Heart Study. 508 African American and Caucasian women, 38% African American.	EBCT, CES-D depression scale. CAC and AC	1. CAC was present among 76.8% of Black women and 64.0% of White women (p=0.002). 2. 23.7% and 21.3% of Black and White women, respectively, had AC above 100 units. 3. 58.8% of Blacks and 41.4% of Whites had CAC (p=0.0001).	1. Blacks had higher CAC and AC prevalence than did Caucasian women 2. No ethnic differences in the women who had high levels of AC 3. Black women with depressive symptoms had higher AC, but there was no association between depression and AC among Whites.

Table A-5 (Continued)

Newman A, Naydeck BL et al., 2002. Arterioscler. Thromb. Vasc. Biol.	Cross-sectional	614 elderly adults. Cardiovascular Health Study study, Pittsburgh site. 59% women, 23% Black. Ages 67-99.	EBCT	1. Median CAC scores. 2. For Black v. White women, 134 units versus 233 units of CAC, respectively (p=0.02). 3. After adjustment for age, CVD, and CVD risk factors (although association was significant after adjustment only for men). 4. Hypertension was related to higher CAC among White men only. Diabetes was not related to CAC score. Significant ethnicity x gender interaction was observed: CAC association was stronger for White men. 5. Blacks had lower odds of having a CAC score after adjustment for age and clinical CVD.	1. Blacks showed less CAC than Whites, even after control for CVD risk factors and CVD. More pronounced among men. 2. Older Blacks may exist with CAC for longer than Whites (survival effect). 3. Should examine the associations between CAC and risk factors within each ethnic group and within each gender/ethnicity designation.

Table A-6. Ethnic Differences in Carotid Artery IMT

Authors	Design	Study	Measurements	Results	Comments/Conclusions
D'Agostino RB, Burke G, et al., 1996 Stroke.	Cross-sectional	Insulin Resistance Atherosclerosis Study (IRAS). Blacks (n=281), Whites (n=329), Hispanics (n=410). Ages 40-69 YO. Non-diabetics.	CCA-IMT and internal carotid artery (ICA) IMT Unadjusted CCA means: Blacks : 855.3 (SE=13.1) μm Hispanics: 736.9 (8.7) μm Whites: 814.5(12.7) μm at one study site, 785.0 (14.5) μm at second site Unadjusted ICA means: Blacks: 909.7 (22.6) μm Hispanics: 736.9 (8.7) μm Whites: 887.3 (27.8) at one study site, 798.8 (25.9) μm at second site	1. 4 adjustments: 1) demographics (age, sex, center), 2) demographics + HDL, LDL, smoking status and hypertension, 3) model 2 + insulin sensitivity 4) model 3 + fasting glucose 2. Blacks had higher CCA-IMT than Whites after all 4 adjustments 3. Hispanics had less CCA-IMT than Whites after all 4 adjustments 4. No sig. differences in ICA-IMT between ethnic groups	1. Ethnic differences seen in CCA but not in ICA. 2. Men and women were pooled together (women = 50% of study)—possible limitation 3. Blacks and Hispanics not directly compared
Everson-Rose SA, Lewis TT, et al., 2006. Am Heart J	Cross-sectional	SWAN Heart study, women-only Blacks (n=213), Whites (n=376). Avg. age=50.3.	Mean and max IMT Unadjusted Mean IMT: Blacks: 0.689 (0.10) Whites: 0.656 (0.09) Unadjusted Max IMT: Blacks: 0.896 (0.13) Whites: 0.854 (0.12) Blacks had higher mean and max IMT than Ws (p's<.0001)	1. Black ethnicity entered into models with Whites as referent group. 2. Controlling for cynical hostility, age, ethnicity, and education, ethnicity was sig. predictor of mean and max IMT (p's<0.01) 3. Additional controls for BMI, SBP, and smoking make ethnicity NS	1. Women only 2. Association with increased IMT among Blacks disappears with adjustments for CVD risk factors

Table A-6 (Continued)

Howard G, Sharrett R, et al., 1993. Stroke.	Cross-sectional	ARIC. Black Females (n=2219), Black Males (n=1391), White Females (n=5377), White Males (n=4837). Ages: 45-64 YO	CCA, BIF (Bifurcation IMT), ICA IMT Incomplete data for all carotid segments. CCA had highest number of complete data points, ICA had lowest Unadjusted estimates of mean wall thickness over 3 age categories (45-54, 55-64, 65+): Black Females: 0.58-0.75 White Females F: 0.55-0.73 Black Males: 0.64-0.86 White Males: 0.62-0.80	1. 1-year, age-related progression rates were estimated: 2. BIF: 0.015 mm/y in women, 0.018 mm/y in men 3. ICA: 0.010 mm/y for women, 0.014 for men 4. CCA: 0.010 mm/y in both sexes	1. BIF-IMT>CCA-IMT, ICA more variable 2. Black females and White males had a flattening of higher percentiles at left BIF: cannot be explained by the cross-sectional design
Kalra L, Rambaran C, et al., 2005. Arterioscler Thromb Vasc Biol.	Cross-sectional	n=78 Afro-Caribbeans and n=82 age-and-sex-matched Whites Ages: 35-75 YO	Carotid IMT (CIMT) = mean of differences between blood/intima borderline and media/adventitia borderline Mean CIMT of Blacks greater than Whites: 0.81 mm v. 0.75 mm (p=0.02)	1. Black ethnicity sig. associated with CIMT (p=0.04) after adjustments for age (per 5-yr category), Waist-Hip-Ratio (WHR), SBP (per 5mmHg increase), current smoker, White ethnicity	1. Blacks had higher BMI and DBP but comparable abdominal girth, SBP, Glucose, HDL, and triglycerides 2. Blacks had higher TNF-α, IL-6, and fasting insulin.

Table A-6 (Continued)

Kieltyka L, Urbina EM, et al., 2003. Atherosclerosis.	Cross-sectional	Bogalusa Heart Study Black Females (n=87), White Females (n=226), Black Males (n=63), White Males (n=141) Ages: 20-37 YO	CCA-IMT, Bulb-IMT, ICA-IMT Unadjusted CCA-IMT: Black Females: 0.69±0.09 White Females: 0.65±0.08 ethnicity p=0.001 Unadjusted Bulb-IMT: Black Females: 0.89±0.16 White Females:0.65±0.08 Black Males: 0.89±0.18 White Males: 0.89±0.17 ethnicity (BF/WF) p=0.001 sex (WM/WF) p=0.001 Unadjusted ICA-IMT: Black Females: 0.69±0.11 White Females: 0.66±0.14 ethnicity p=ns	1. Black ethnicity sig. associated with CCA-IMT after adjustments for FRS, log triglycerides, log BMI. 2. Black ethnicity sig. associated with Bulb-IMT after adjustments for FRS. 3. ICA-IMT not associated with ethnicity	1. FRS was not sig. different by ethnicity 2. FRS explained more of the variance of Bulb-IMT (9%) than the CCA (5%) or ICA (3%)
Manolio TA, Burke GL, et al., 1994. J Clin Epidemiol.	Cross-sectional	Cardiovascular Health Study (CHS), aged ≥65 YO n=4926 Whites, n=244 Blacks Mean ages: 72.3-73.3 YO across ethnic and gender groups (NS)	Blacks had generally higher CVD risk factors than Whites except for hyperlipidemia Unadjusted CCA-IMT Black Females: 1.03 mm White Females: 0.97 mm Black Males: 1.12 mm White males 1.05 mm Unadjusted ICA-IMT Black Females: 1.36 mm White Females: 1.40 mm Black Males: 1.56 mm White males 1.67 mm	1. Regression results adjusted for age, SES, risk factors, and prevalent CHD: For women: Max IMT: 0.04 (95%CI: 0.01-0.08) ICA-IMT: -0.12 (-0.24-0.01)	1. High IMT levels in sample 2. Black women had approximately 0.05 mm-thicker IMT than White women, which remained unchanged across analyses ($p<0.001$) 3. Black women had slightly lower ICA-IMT than did White women

Table A-6 (Continued)

Ranjit N, Diez-Roux AV, et al., 2006. Arterioscler Thromb Vasc Biol	Cross-sectional and prospective	ARIC, 12085 adults, CHD-free. Mean age: approximately 53, 2-3 observations 5-9 years	Mean CCA baseline (μm) (adjusted for age/site): White Males: 641.1 (2.17) Black Males: 690.0 (7.0) White Women: 582.0 (1.57) Black Women: 640.2 (5.04) 5-yr change (μm): White Men: 45.8 (1.77) Black Men: 35.8 (3.44) White Women: 46.8 (1.35) Black Women: 37.3 (2.37) SES at Baseline: Highest v. lowest income: Whites: -6.3 (3.7) μm (p=0.05); Blacks: -19.6 (7.7) μm (p=0.009) Highest v. Lowest Education: Whites: -27.2 (4.4) μm (p<0.0001); Blacks: -26.7 (6.9) μm (p=0.0001) *p's are for trend SES and Progression: Highest v. lowest income: Whites: 11.5 (3.0) μm (p<0.005); Blacks: -11.1 (5.7) (p=0.039); Low v. high education NS Mean IMT diff. per unit decrease in combined SES score: Whites: -0.9 (NS) Blacks: 2.1 (0.8) (p=0.007)	1. Study examined SES and ethnicity interactions with respect to cross-sectional/longitudinal IMT 2. SES was inversely associated with cross-sectional IMT among both Blacks and Whites 3. Low SES was associated with higher IMT progression among Whites, but high SES was associated with higher IMT progression among Blacks	1. Unclear why high-SES Blacks had higher IMT progression than did low-SES Blacks 2. Authors refute a "ceiling effect" in IMT among Blacks 3. Authors are not able to explain this observation, and it remains robust after adjustments for multiple CV risk factors 4. Suggests that high-SES Blacks have a greater risk of arteriosclerotic/atherosclerotic progression with time, but the risk factor mediating that observation is not known 5. Authors did not examine candidate psychological mediators in this population

Table A-6 (Continued)

Sutton-Tyrrell K, Zeigler-Johnson C, et al., 1998. CVD Prevention.	Cross-sectional	3 female cohorts (HOPE, WHLP, HWS) were pooled; all in Pittsburgh n=382 premenopausal (n=90 Blacks; n=292 Whites), n=253 postmenopausal (n=53 Blacks, n=200 Whites) Carotid plaque, median IMT, max IMT	Median IMT of whole group: 0.71 mm (range: 0.51-1.51) Higher IMT among postmenopausal women than premenopausal: 0.75 vs. 0.70 mm Unadjusted median IMT levels were higher among B than W: 0.79 mm vs. 0.70 mm. Significant Spearman correlations with IMT: older age, higher IMT, SBP, LDL, cholesterol, and glucose. Premenopausal women: ethnicity was not associated with CCA-IMT (p=0.992) but was associated with ICA-IMT (p<0.001). Association disappeared with adjustment for hysterectomy. Postmenopausal women: ethnicity was associated with CCA-IMT (p=0.004) but not ICA (p=0.162).	After adjustments for smoking, age, BMI, SBP, DBP, PP, cholesterol, LDL, and triglycerides: ethnicity was not associated with focal plaque. Independent associations with IMT: Black ethnicity, older age, smoking and higher LDL, SBP, and BMI	1. Women only 2. Black ethnicity was associated with IMT in pre- and post-menopausal women. 3. Different RF distribution: premenopausal Black women had higher BMI and BP, postmenopausal Black women were younger, had higher BMI, lipid and glucose levels. Fewer Black women took HRT than Whites.

Table A-7. Ethnic Differences in Aortic Pulse Wave Velocity

Authors	Design	Study	Measurements	Results	Comments/Conclusions
Chaturvedi N, Bulpitt CJ, et al., 2004. J of Hypertension.	Cross-sectional	103 Europeans, 99 Afro-Caribbeans, ages 40-65, England. Sample was recruited from a family medicine registry in London, and individuals were invited to participate	Carotid-femoral, carotid-radial, femoral -dorsalis PWV, interventricular septal thickness (IVST)	1. PWV was higher among Blacks than Whites (12.7 vs. 11.2 m/s, $p<0.0001$). 2. Afro-Caribbeans had higher IVST than did Whites (9.6 vs. 9.1 mm, $p=0.0005$) 3. No ethnicity x IVST differences, no ethnicity x SBP differences with regard to PWV 4. No carotid-radial differences between Blacks and Whites 5. Femoral-dorsalis pedis PWV was higher among Blacks, and entirely explained by higher blood pressures	1. Blacks had higher cf-PWV (central aortic stiffness) than did Whites 2. Blood pressure measures or waist-hip-ratio did not explain association between Black ethnicity and cf-PWV 3. Blood pressure fully explained femoral-dorsalis PWV difference between Blacks and Whites 4. Extent of clinical disease in population was unclear 5. Selection bias may be a limitation of this study
Ferreira AV, Viana MC, et al., 1999. J of Hypertension.	Cross-sectional	82 White (49 untreated hypertensive and 33 normotensive) and 38 Black (24 normotensive and 14 untreated hypertensive) male volunteers. Mean ages: 23-29 across ethnic and hypertensive categories. Brazil.	PWV via Complior	1. PWV was correlated with age, weight, BMI, SBP, and DBP, not glycemia, cholesterol, height, or heart rate. 2. In the normotensive group, Whites had higher PWV than did Blacks. In the hypertensive group, Blacks had higher PWV than did Whites. 3. Among hypertensives, Whites had lower PWV than did Blacks 4. Interaction between race and blood pressure status determining PWV ($p<0.001$).	1. Important article: the magnitude of the effect of elevated blood pressure may confer greater arterial stiffness among Blacks than among Whites 2. The small frequencies in this study may limit the ability to detect some differences 3. The sample consisted of Black and White police soldiers who were of similar socioeconomic status (SES) 4. Age, then SBP, were the strongest predictors of PWV in the sample

Table A-7 (Continued)

Strain WD, Chaturvedi N, et al., 2006. Am J Hypertens.	Cross-sectional	Europeans (49 with diabetes, 100 without) and Afro-Caribbeans (66 with diabetes, 88 without) Sample was recruited from a family medicine registry in London, and individuals were invited to participate.	Carotid-femoral, carotid-radial, femoral - dorsalis PWV, interventricular septal thickness (IVST)	1. Cf-PWV was highest among diabetics and among Blacks 2. Blacks with diabetes had significantly higher cf-PWV than those who did not; no similar association between whites (interaction between diabetes and ethnicity) 3. Blacks with diabetes had higher femoral-dorsalis PWV than did Whites with diabetes (p=0.008); no ethnic differences in femoral-dorsalis pedis among non-diabetics	1. Diabetes has a disproportionate impact on cf-PWV among Blacks as compared to Whites 2. Black ethnicity seems most strongly related to higher cf-PWV segment, not related to carotid-radial
Thurston RC, Matthews, KA 2009. Social Sci and Med.	Cross-sectional	214 Black (n=81) and Caucasian adolescents (n=78), ages 12-14	PWV, IMT, and socioeconomic status measures	1. Blacks had significantly higher PWV (571.4 vs. 525.3 cm/s, p=0.01) and similar IMT levels (0.54 vs. 0.53, p=0.05) compared to Whites, after controlling for age, gender, BMI, and SBP 2. Low or medium family income and lower neighborhood SES were also associated with higher PWV, after controls for age, gender, BMI, and SBP; low family assets were associated with higher IMT after same adjustments 3. Lower neighborhood SES was associated with higher IMT among Blacks only, low and medium family incomes were associated with higher PWV among Blacks only	1. No White ethnicity x SES interactions were observed for PWV or IMT, but low counts in the low SES categories could have explained that 2. Even in adolescence, Blacks have higher PWV and marginally higher IMT 3. SBP and DBP were in normal ranges, but both Black and White adolescents were slightly overweight on average; no significant difference in BMI across ethnic groups

Table A-7 (Continued)

Wildman RP, Farhat GN, et al., 2005. Hypertension.	Prospective, 2 years (1.3-3.7)	152 Whites and Blacks Aged 20-40 (mean=30.4) 45% male, 44% Black	Carotid-femoral PWV, waist girth, body weight, BMI, annual weight gain	1. Range in PWV change: -141.1 cm/s-194.2 cm/s 2. Blacks had higher PWV increases than Whites, even after adjustments for baseline PWV (Beta co-efficient: 21.8, $p<0.0001$) 3. After adjustments for weight and weight change, Blacks had 15 cm/s larger annual increase in PWV than Whites ($p=0.024$) 4. Waist girth, body weight, and BMI were all related to PWV progression 5. 4.5 kg- weight loss or more was associated with PWV change of -29.9 cm/s, and 18.2 cm/s gain for those with 4.5-kg weight gain	1. Weight change was related with decreased PWV 2. No significant ethnicity x weight interactions with regard to PWV progression, although it appeared that for a 5-lb weight gain, the effect on PWV progression was greater for Blacks than for Whites (6.1 cm/s per year vs. 3.7 cm/s/per year, respectively) 3. Effect of weight change on the vasculature may be stronger among Blacks than among Whites, but the sample is likely too small to assess significant differences

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