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Progression of Cardiometabolic Risk Factors and Progression of Coronary Artery Calcification: Findings from the Multi-Ethnic Study of Atherosclerosis (MESA)

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PROGRESSION OF CARDIOMETABOLIC RISK FACTORS AND PROGRESSION OF CORONARY ARTERY CALCIFICATION: FINDINGS FROM THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS (MESA)

By

William Arguelles

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There are few published data describing the progression of cardiovascular disease (CVD) risk factors, the progression of coronary artery calcification (CAC; a measure of subclinical CVD), and how these processes relate to one another. Most previous studies have been limited by cross-sectional designs and small or restricted samples. The few prospective studies examining these relationships have used baseline CVD risk factor values to predict CAC change scores, and have yielded inconsistent findings. This study used latent growth modeling to examine how progression in specific cardiometabolic risk factors (CRFs; waist circumference, body mass index, systolic and diastolic blood pressure, high-density and low-density lipoprotein cholesterol, triglycerides, and glucose) relates to incidence and progression of CAC in a multi-ethnic cohort of 4,560 asymptomatic individuals, controlling for baseline risk factor and CAC values, age, race/ethnicity, smoking, family history of CVD, income, and time-varying use of antihypertensive, lipid-lowering, and glucose-lowering medications. All analyses were conducted separately on men (n = 2,132) and on women (n = 2,428). Consistent with an earlier study of this sample (Kronmal et al., 2007), several CRFs at baseline were associated with CAC incidence and progression. Some gender differences in these associations were further outlined. Among individuals that had undetectable CAC at

baseline, change over time in CRFs was not related to incidence of CAC in either men or women. Among women who had detectable CAC at baseline, regression (or less progression) in systolic ($B = -3.173$, $p < .05$) and diastolic blood pressure ($B = -8.558$, $p < .05$), as well as low-density lipoprotein cholesterol ($B = -2.485$, $p < .05$), was each univariately associated with greater CAC progression. These associations appeared to be influenced by medication use, such that women taking antihypertensive and lipid-lowering medications exhibited greater CAC progression despite showing average decreases in respective CRF levels over time. Furthermore, when change in blood pressure and change in low-density lipoprotein cholesterol level were both included as predictors of CAC progression, only change in low-density lipoprotein cholesterol level remained inversely associated with CAC progression. No significant associations between change in CRFs and CAC progression were observed in men who had detectable CAC at baseline. To our knowledge, this is the first study systematically reporting on how change in various CVD risk factors relates to progression of CAC. A brief discussion regarding these findings, as well as suggestions for future research, are provided.

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Chapter 1: Introduction

Cardiovascular Disease

Cardiovascular disease (CVD) is a general term for disorders affecting the heart and blood vessels, and encompasses conditions such as atherosclerosis, cerebrovascular disease, and hypertension (National Heart, Lung, and Blood Institute, 2009). Over recent years, death rates from CVD have declined in the US (National Center for Health Statistics, Centers for Disease Control and Prevention, 2009), likely attributable to advances in evidence-based medical therapies and modified risk factors in the population (Ford, Ajani, Croft, Critchley, Labarthe, et al., 2007). However, the burden of CVD in the US remains high.

Accounting for nearly 2,400 deaths each day, CVD continues to be the leading cause of mortality for both men and women in the US (National Center for Health Statistics, Centers for Disease Control and Prevention, 2009). It is estimated that 1 in 3 Americans have at least one type of CVD, and that the direct health expenditure plus lost productivity costs associated with CVD morbidity and mortality will surpass $475 billion in 2009 (Lloyd-Jones, Adams, Carnethon, De Simone, Ferguson, et al., 2009). As suggested by preliminary mortality data, over 34% of all deaths in the US in 2006 were attributable to CVD (Lloyd-Jones et al., 2009). The largest percentage of those deaths, 52%, was purportedly due to coronary heart disease (Lloyd-Jones et al., 2009)

Coronary Heart Disease and Atherosclerosis

Coronary heart disease (CHD) is a type of CVD resulting from the narrowing of the coronary arteries, which supply the heart muscle with the oxygenated blood it needs to function properly (National Heart, Lung, and Blood Institute, 2009). The underlying cause of CHD, as well as most other clinical CVD events, is atherosclerosis. Atherosclerosis is a systematic disease process characterized by the build-up of fatty deposits, inflammatory factors, platelets, calcium, and scar tissue within the inside lining of artery walls, forming a plaque which may harden and narrow arteries over time, consequently restricting blood flow to corresponding organs (Libby, 2003). The atherosclerotic process is gradual, and associated plaque is typically manifest decades before the onset of a clinical event or symptoms (Stary, 2001).

Recent advances in non-invasive imaging technologies have made it possible to detect and quantify atherosclerotic plaque burden at different stages and across various vascular beds, thus allowing for the identification of subclinical disease in asymptomatic individuals. Given that 50% of men and 64% of women who die suddenly of CHD experience no previous symptoms (Thom, Kannel, Silbershatz, & D'Agostino, 2001), the investigative and clinical utility of these techniques may hold great prognostic promise. One of the most widely used and studied of these modalities is high-speed cardiac computed tomography, which allows for the evaluation of the amount of calcium accumulated in the coronary arteries (O'Rourke, Brundage, Froelicher, Greenland, Grundy, et al., 2000).

Coronary Artery Calcification

The accumulation of calcium in the coronary arteries, termed coronary artery calcification (CAC), is an active process involving complex enzymatic and cellular pathways (e.g., inflammation, lipid accumulation, etc.) that are intimately associated with vascular injury and atherosclerosis (Alexopoulos & Raggi, 2009; Budoff, Achenbach, Blumenthal, Carr, Goldin, et al., 2006). CAC is absent in the walls of normal vessels, occurs almost exclusively in the presence of atherosclerosis (Wexler, Brundage, Crouse, Detrano, Fuster, et al., 1996), and occurs in proportion to the severity and extent of atherosclerosis (Rifkin, Parisi, & Folland, 1979). CAC appears in smaller amounts in early atherosclerotic lesions and in larger amounts in advanced lesions (Stary, 2001). It has also been strongly correlated with total coronary atherosclerotic disease burden as measured by histological specimens (Rumberger, Simons, Fitzpatrick, Sheedy, & Schwartz, 1995). As a result, CAC has become a widely employed measure of atherosclerosis. Using the common Agatston score quantification (Agatston, Janowitz, Hildner, Zusmer, Viamonte, et al., 1990), a CAC score > 0 suggests the presence of at least some atherosclerotic plaque and a score ≥ 100 suggests a clinically significant amount of plaque, with a score ≥ 400 warranting further diagnostic evaluation for CHD (Greenland, Bonow, Brundage, Budoff, Eisenberg, et al., 2007; Budoff, Achenbach, et al., 2006). While its role in plaque stability versus instability continues to be debated, the current consensus is that CAC can help identify high-risk individuals (Alexopoulos & Raggi, 2009).

Results of large prospective studies have consistently demonstrated a positive graded association between CAC score and incident CHD events (Arad, Goodman, Roth,

Newstein, & Guerci, 2005; LaMonte, FitzGerald, Church, Barlow, Radford, et al., 2005; Taylor, Bindeman, Feuerstein, Cao, Brazaitis, et al., 2005; Vliegenthart, Oudkerk, Hofman, Oei, van Dijck, et al., 2005). For example, controlling for standard CVD risk factors, the Multi-Ethnic Study of Atherosclerosis showed that compared to individuals with a CAC score of 0, those with a score between 1 and 100 were 4 times more likely to experience a CHD event, and those with a score > 100 were 7 to 10 times more likely to experience such events (Detrano, Guerci, Carr, Bild, Burke, et al., 2008). Similarly, a meta-analysis of 4 studies evaluating the prognostic value of CAC in asymptomatic individuals showed that compared to individuals with a CAC score of 0, those with a score of 1 to 100 and those with a score > 400 had a relative CHD-event risk ratio of 2.1 and as high as 10, respectively (Pletcher, Tice, Pignone, & Browner, 2004). CAC has also been related to CHD events as well as other measures of advanced CHD (i.e., obstructive angiographic disease and myocardial perfusion abnormalities) in symptomatic and type 2 diabetic samples (Anand, Lim, Hopkins, Corder, Shaw, et al., 2006; Knez, Becker, Leber, White, Becker, et al., 2004; Budoff, Diamond, Raggi, Arad, Guerci, et al., 2002; Haberl, Becker, Leber, Knez, Becker, et al., 2001). Additionally, absence of CAC has been highly associated with positive prognosis, even in symptomatic and high-risk individuals (Laudon, Vukov, Breen, Rumberger, Wollan, et al., 1999; Georgiou, Budoff, Kaufer, Kennedy, Lu, et al., 2001).

Data also suggests that the prevalence of CAC, paralleling that of CHD, increases with age, is higher in middle-aged men compared to middle-aged women, and is higher in whites compared to blacks, Hispanics, and Chinese (Detrano et al., 2008; Loria, Liu, Lewis, Hulley, Sidney, et al., 2007; Bild, Detrano, Peterson, Guerci, Liu, et al., 2005).

Additionally, CAC appears to predict CHD events similarly between genders (Vliegenthart et al., 2005; Raggi, Shaw, Berman, & Callister, 2004) and across different ethnic groups (Detrano et al., 2008). Furthermore, a number of studies have reported that CAC adds incremental value in predicting CHD events above and beyond traditional (e.g., age, sex, family history of CVD, smoking, obesity, hypertension, dyslipidemia, insulin resistance, etc.) and novel (e.g., CRP and other inflammatory markers, thrombotic factors, etc.) CVD risk factors (Elkeles, Godsland, Feher, Rubens, Roughton, et al., 2008; Arad et al., 2005; Taylor et al., 2005; Vliegenthart et al., 2005; Greenland, LaBree, Azen, Doherty, & Detrano, 2004). Moreover, a recently published study using MESA data showed that the introduction of CAC scores to standard risk prediction models led to significant improvements in identifying participants as either high or low risk based on incident CHD events (Polonsky, McClelland, Jorgensen, Bild, Burke, et al., 2010).

Thus, CAC appears to be a valid measure of subclinical CHD. In support, CAC has been commonly associated with other extensively used measures of atherosclerosis (i.e., carotid intima-media thickness; Manolio, Arnold, Post, Bertoni, Schreiner, et al., 2008) and has been shown to be a better predictor of incident CVD events, comparatively (Folsom, Kronmal, Detrano, O'Leary, Bild, et al., 2008). In fact, although not currently a standard of care practice, recent scientific statements from the American Heart Association and the American College of Cardiology acknowledge a benefit of CAC testing for individuals at intermediate CHD risk (Greenland et al., 2007; Budoff, Achenbach, et al., 2006).

Risk Factors for Coronary Artery Calcification

Given the extensive health and economic burdens associated with CVD, and in light of recent technological advances that allow for the detection of subclinical CVD (i.e., CAC), the investigation of factors that pose significant risk for subclinical CVD and its progression seem warranted. In fact, utilizing subclinical endpoints as opposed to the occurrence of overt clinical events offers important advantages including (1) providing a more accurate and quantifiable measure of CVD, thus precluding distortions in risk relations due to underdetection, misclassification, and biased ascertainment of clinical events, (2) providing the ability to characterize CVD before it has become clinically manifest and apparent to the individual, thus precluding biased prospective risk relations due to health behavior changes (i.e., lifestyle modifications and medication use) following clinical events, (3) providing a continuous versus dichotomous measure of disease, thus allowing for an increase in power to detect risk relations, and (4) allowing for the examination of risk factors associated with earlier stages of disease development and progression (Bild, Bluemke, Burke, Detrano, Diez-Roux, et al., 2002). Investigations of this sort could further our understanding of how risk factors influence CVD development and progression, and thus guide clinical decision-making as to which factors should be the focus of primary and secondary prevention strategies.

Accordingly, several studies examining risk factors associated with measures of atherosclerosis, such as CAC, have been recently published. However, most of these studies have been limited by issues such as small sample sizes, inclusion of restricted and non-representative samples (i.e., chronic kidney diseased, diabetic, and hypertensive patients; Caucasians; males), and cross-sectional designs. Moreover, while established

CVD risk factors have been commonly associated with CAC presence, extent, and progression across the majority of these studies in univariate analyses, inconsistent findings have emerged in cross-sectional, retrospective, and prospective studies regarding the independent effects of risk factors in multivariate analyses. Risk factors that have been independently associated with CAC prevalence and progression are described below.

Age. Age has been strongly and independently correlated with CAC in several cross-sectional studies. For example, in a study of 6,086 asymptomatic individuals, age was the strongest independent correlate of CAC prevalence in both men and women, and this association was nearly twice as high as any other traditional CVD risk factor besides gender (Allison & Wright, 2005). Age has also been independently associated with CAC in other samples of asymptomatic individuals (Arad, Newstein, Cadet, Roth, & Guerci, et al. 2001; Folsom, Evans, Carr, Stillman, & ARIC investigators, 2004), black and white women (Khurana, Rosenbaum, Howard, Adams-Campbell, Detrano, et al. 2003), Chinese individuals (Shisen, Leung, & Juergens, 2005), older adults aged 67 to 99 (Newman, Naydeck, Sutton-Tyrrell, Feldman, Edmundowicz, et al. 2001), patients with type 2 diabetes (Godsland, Elkeles, Feher, Nugara, Rubens, et al. 2006) and CHD patients (Mayer, Lieb, Radke, Gotz, Fischer, et al. 2007). Furthermore, CAC has been shown to increase dramatically after age 50 in men and after age 60 in women (Hoff, Chomka, Krainik, Daviglus, Rich, et al. 2001; Uretsky, Rifkin, Sharma, & Reddy, 1988).

However, findings from retrospective and prospective studies have been inconsistent. For example, age was not independently associated with CAC progression in samples of asymptomatic individuals (over a mean of 25 months; Yoon, Emerick, Hill,

Gjertson, & Goldin, 2002) and post-menopausal women (over a mean of 3.3 years; Hsia, Klouj, Prasad, Burt, Adams-Campbell, et al. 2004), but was associated with CAC progression in a larger sample of CHD patients independent of other established risk factors (over 4 years; Shemesh, Koren-Morag, Apter, Rozenman, Kirwan, et al. 2004). Thus, while CAC appears to increase as a function of age, there is mixed evidence suggesting that older age is associated with an increased rate of CAC progression.

Gender. Male gender has also been commonly associated with increased CAC prevalence in cross-sectional studies of asymptomatic individuals (Allison & Wright, 2005; Folsom et al., 2004; Arad et al., 2001), younger black and white adults aged 28 to 40 years (Bild, Folsom, Lowe, Sidney, Kiefe, et al. 2001), older adults aged 67 to 99 years (Newman et al. 2001), Chinese individuals (Shisen et al., 2005), individuals with a family history of hypercholesterolemia (Martinez, Miname, Bortolotto, Chacra, Rochitte, et al. 2008), and patients with type 2 diabetes (Godsland et al. 2006). Other studies have demonstrated that while a gender difference in prevalent CAC exists in non-diabetic individuals, this gender difference is lost in patients with type 1 diabetes after controlling for insulin resistance (Dabelea, Kinney, Snell-Bergeon, Hokanson, Eckel, et al. 2003; Colhoun, Rubens, Underwood, & Fuller, 2000). Given that atherosclerosis tends to develop an average of ten years later in women (Frink, 2009), gender differences in CAC prevalence may be more evident in middle-aged samples. By about ages 65 to 70, however, this gender difference dissipates and men and women exhibit similar prevalence of CAC (Janowitz, Agatston, Kaplan, & Viamonte, 1993). Gender has not been shown to independently relate to rate of CAC progression in any of the retrospective or prospective studies reviewed (e.g., Yoon et al., 2002).

Race/Ethnicity. Results from multi-ethnic cohort studies have generally demonstrated that whites have higher prevalence of CAC compared to other ethnic groups. For example, a study of 6,814 asymptomatic individuals showed that compared to whites, and controlling for other CVD risk factors, blacks, Hispanics, and Chinese had less presence and quantity of CAC (Bild et al., 2005). Similar findings of lower CAC prevalence in blacks and Hispanics compared to whites was found in another large study (Kawakubo, LaBree, Xiang, Doherty, Wong, et al., 2005). In a different study of 16,560 asymptomatic individuals, compared to whites and controlling for other risk factors, black men and Asian men and women again showed significantly lower prevalence of CAC, but black women showed significantly higher prevalence of CAC, and there was no difference in CAC prevalence between whites and Hispanics (Budoff, Nasir, Mao, Tseng, Chau, et al., 2006). Further, a study of 782 symptomatic individuals showed that prevalence of CAC was lower in blacks and Hispanics compared to whites, but not in Asians (Budoff, Yang, Shavelle, Lamonte, & Brundage, 2002), and other smaller studies have shown no independent race differences in CAC in young adults (Bild et al., 2001) or postmenopausal women (Khurana et al., 2003). Thus, in general, whites appear to have higher prevalence of CAC compared to blacks and other ethnic groups, but this relationship seems to be most pronounced in men and in the elderly (Orakzai, Orakzai, Nasir, Santos, Edmundowicz, et al., 2006; Newman, Naydeck, Whittle, Sutton-Tyrrell, Edmundowicz, et al., 2002).

White race has also been independently associated with CAC progression in at least 2 prospective studies. A study of 828 asymptomatic adults with CVD risk factors showed that compared to whites, both blacks and Hispanics showed less CAC

progression over 7 years independent of other risk factors, while Asians/Pacific Islanders did not (Kawakubo et al., 2005). White race was also independently associated with CAC progression over an average of 1.8 years in a small sample of renal transplant patients with no history of incident CVD (Schankel, Robinson, Bloom, Guerra, Rader, et al., 2007). Exploration of why such race differences in CAC progression have been observed across studies warrants further attention.

Family History of Cardiovascular Disease. Positive family history of CVD has also been independently associated with increased CAC prevalence in large asymptomatic samples (Nasir, Budoff, Wong, Scheuner, Herrington, et al., 2007; Taylor, Bindeman, Bhattarai, Feuerstein, & O'Malley, 2004; Arad et al., 2001), in individuals across different ethnic groups (Nasir et al. 2007), in individuals at both low and intermediate risk for CVD (Nasir et al. 2007), in type 2 diabetic patients (Wagenknecht, Bowden, Carr, Langefeld, Freedman, et al., 2001), and in patients with CHD (Mayer et al., 2007). Interestingly, one study showed that parental history of myocardial infarction was significantly predictive of CAC in whites but not blacks, while parental history of stroke was significantly predictive of CAC in blacks but not whites (Fornage, Lopez, Roseman, Siscovick, Wong, et al., 2004). Furthermore, positive family history of CVD was also found to be independently predictive of CAC progression over an average interval of 2.4 years in a large, asymptomatic, multiethnic sample of men and women (Kronmal, McClelland, Detrano, Shea, Lima, et al., 2007). These findings suggest that genetic factors may play a significant role in individual differences in CAC prevalence and progression.

Smoking. Smoking has also been found to be an independent predictor of CAC scores in asymptomatic samples of men and women (Folsom et al., 2004; Arad et al., 2001), as well as in older adults (Newman et al., 2001), but has been associated with relatively small odds ratios. In patient samples, however, the effect of smoking on CAC prevalence appears to be greater. For instance, smoking was independently associated with a 7.1-fold increase in CAC score in a large sample of type 2 diabetic patients (Cleary, Orchard, Genuth, Wong, Detrano, et al., 2006), and with a nearly 5-fold increase in prevalent CAC in a smaller sample of young type 1 diabetics aged 17 to 28 years (Starkman, Cable, Hala, Hecht, & Donnelly, 2003). Smoking was also shown to be independently associated with CAC progression over 4 years in a prospective study of 383 patients with clinically stable CHD (Shemesh et al., 2004).

Medication Use. Several observational studies have demonstrated that use of cholesterol-lowering medications, such as statins and calcium channel blockers, have been associated with lower rates of CAC progression in asymptomatic individuals (Achenbach & Daniel, 2004; Callister, Raggi, Cooil, Lippolis, Russo, et al., 1998) and diabetic patients (Anand, Lim, Darko, Bassett, Hopkins, et al. 2007). However, these findings have not been consistent, with at least two clinical trials showing no association between statin treatment and progression of CAC in asymptomatic adults (Arad, Spadaro, Roth, Newstein, & Guerci, 2005) and postmenopausal women (Raggi, Davidson, Callister, Welty, Bachmann, et al., 2005). In the former study, though, CAC progression was significantly reduced in participants that had baseline CAC scores > 400. Studies examining how pharmacological treatment of other CVD risk factors (e.g., hypertension and diabetes) relate to CAC progression are lacking and warrant further investigation.

Adiposity. Several measures of adiposity have been independently related to CAC in large cross-sectional studies of asymptomatic men and women. For example, one study demonstrated that men and women with a body mass index (BMI) in the fourth quartile of the study sample had a 101% and 68% increased risk of detectable CAC, respectively and independent of other risk factors, compared to those in the first quartile (Allison and Wright, 2004). In this study, visceral fat content (VFC) as measured by electron beam computed tomography (EBCT) was also independently associated with CAC presence, but only in men. However, no significant age-adjusted correlations between BMI, VFC, or total body fat percentage and CAC extent were observed. In a different large study of asymptomatic men and women, though, EBCT-measured intra-abdominal obesity was independently associated with extent of CAC (Arad et al., 2001). Additionally, BMI has been independently associated with CAC prevalence in asymptomatic young black and white individuals (Bild et al., 2001) and Chinese men (Hsu, Chang, Hwang, & Chou, 2007). Waist-to-hip ratio (WHR) has also been independently associated with present and elevated CAC scores in individuals with both type 1 (Cleary et al., 2006) and type 2 diabetes (Elkeles, Fehert, Flather, Godsland, Richmond, et al., 2004), with visceral adiposity, subcutaneous adiposity, and BMI also being independently associated with CAC extent in a different sample of type 2 diabetic patients (Conway, Miller, Costacou, Fried, Kelsey, et al., 2007). However, in a study of 410 asymptomatic persons aged 55 to 88 years, neither BMI, WHR, waist-girth, or EBCT-measured visceral or subcutaneous fat were related to CAC score in either sex (Kim, Bergstrom, Barrett-Connor, & Laughlin, 2008).

Measures of adiposity have also been independently associated with progression of CAC in prospective studies. For example, BMI at baseline was independently associated with CAC progression over an average of 2.4 years in a large multi-ethnic cohort of 5,756 asymptomatic men and women (Kronmal et al., 2007). A smaller study of asymptomatic individuals found that in addition to BMI, baseline measures of waist circumference and WHR were also associated with progression of CAC over an average interval of 8.9 years (Cassidy, Bielak, Zhou, Sheedy, Turner, et al., 2005). However, these associations were only present in individuals at low CHD risk based on the Framingham Risk Algorithm, were not statistically significant in those defined as high risk, and were largely attenuated after adjustment for fasting glucose levels. In a sample of type 2 diabetic patients, central adiposity was related to CAC progression over a mean interval of 4 years, independent of baseline CAC score (Elkeles, Godsland, Rubens, Feher, Nugara, et al., 2008). However, adjustments for other risk factors were not reported in this study. In a small sample of renal transplant patients, BMI was shown to be an independent predictor of annualized rate of CAC change (Schankel et al., 2007). Thus, while several studies have demonstrated adiposity to independently predict CAC presence and progression, inconsistent findings have emerged regarding the independent effects of different measures of adiposity, with other studies failing to show such independent associations.

Dyslipidemia. Various cross-sectional studies have demonstrated an independent association between low-density lipoprotein cholesterol (LDL-C) level and CAC. For example, LDL-C level, and not high-density lipoprotein cholesterol (HDL-C) or triglyceride (TG) levels, has been independently associated with CAC presence in studies

of young black and white adults (Bild et al., 2001), active-duty Army men and women (Taylor, Feuerstein, Wong, Barko, Brazaitis, et al., 2001), and asymptomatic men with elevated levels of systolic blood pressure (Musunuru, Nasir, Pandey, Campbell, Carvalho, et al., 2008). Additionally, LDL-C level was the only lipid measure independently associated with extent of CAC in a large asymptomatic sample of 1,160 men and women (Arad et al., 2001). In contrast, a larger study of 6,093 asymptomatic individuals not taking lipid-lowering medications found that HDL-C was predictive of CAC presence independent of LDL-C, and was 3-times more highly correlated with extent of CAC compared to LDL-C (Allison & Wright, 2004). However, other CVD risk factors were not controlled for in this study. In a smaller asymptomatic sample, total cholesterol was associated with an elevated CAC score independent of other CVD risk factors, while LDL-C and TG levels were not (Folsom et al., 2004). In a sample of older adults aged 67 to 99 years, TG level was independently associated with CAC scores in the highest quartile, while LDL-C, HDL-C, and total cholesterol were not (Newman et al., 2001). And in a large sample of type 1 diabetic patients, hypercholesterolemia, defined by LDL-C level ≥ 130 mg/dL or lipid-lowering medication use, was independently associated with a 2.8-fold increased CAC score (Cleary et al., 2006).

Mixed findings regarding independent effects of lipid measures have also emerged in prospective studies. In a sample of 761 asymptomatic individuals, higher levels of HDL-C were independently associated with less CAC progression, while no independent association between LDL-C or TG levels on CAC progression were observed (Wong, Kawakubo, LaBree, Azen, Xiang, et al., 2004). In contrast, HDL-C was not an independent predictor of CAC progression in a different study of 869

asymptomatic adults, in which a diagnosis of dyslipidemia (undefined by the authors) emerged as one of the strongest predictors of CAC progression over a mean of 2 years (Lee, Fortmann, Fair, Iribarren, Rubin, et al. 2009). Collectively, these studies suggest that various measures of the dyslipidemic process may exert important effects on the atherosclerotic process and should be further studied.

Blood Pressure. In a cross-sectional study of 1,620 Caucasian men aged 45 to 75 years, hypertension, defined as JNC stage 1 or 2 and/or hypertensive medication use, emerged as the overall strongest independent predictor of CAC score (Bauer, Mohlenkamp, Lehmann, Schmermund, Roggenbuck, et al., 2009). However, this study did not examine measures of blood pressure as continuous variables. In a different study of asymptomatic men and women not taking hypertensive medications, age-dependent effects of different blood pressure measures on CAC score were observed (Bielak, Turner, Franklin, Sheedy, & Peyser, 2004). While diastolic blood pressure (DBP) was the strongest positive predictor of CAC score in persons aged < 50 years, it was inversely associated with CAC in persons aged ≥ 50 years, with SBP emerging as an independent positive predictor of CAC in this group. In another study of asymptomatic men, elevated SBP levels showed the strongest independent association with CAC when in the presence of elevated LDL-C levels (Musunuru et al., 2008). Hypertension, defined by SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, was independently associated with CAC score in patients with type 1 diabetes (Cleary et al., 2006), while SBP was independently associated with CAC in both type 2 diabetic (Elkeles et al., 2004) and CHD patient samples (Mayer et al., 2007).

Retrospective and prospective studies have shown hypertension diagnosis to be independently associated with CAC progression in asymptomatic men and women (Lee et al. 2009; Yoon et al., 2002). In addition, increasing categories of SBP (Kramer, von Muhlen, Gross, Laughlin, & Barret-Connor, 2009), as well as DBP and pulse pressure (Lee et al., 2009), have also been independently associated with progression of CAC in older asymptomatic individuals. DBP was also independently associated with annualized rate of CAC change in a study of renal transplant patients (Schankel et al., 2007), while SBP was associated with CAC progression in a study of type 2 diabetics that controlled for baseline CAC but not for other risk factors (Elkeles et al., 2008). Again, these studies suggest that blood pressure may be an important risk factor for CAC development and progression.

Insulin Resistance. Measures of insulin resistance have also been independently associated with CAC, but again, inconsistently so across studies. For example, while one study of 860 asymptomatic individuals showed that insulin resistance, measured by the homeostatic model assessment (HOMA), was cross-sectionally associated with CAC score independent of other CVD risk factors, metabolic syndrome diagnosis, and C-reactive protein (Qasim, Mehta, Tadesse, Wolfe, Rhodes, et al., 2008), a different study of asymptomatic individuals showed that higher insulin resistance-related CAC prevalence rates were greatly attenuated when adjusted for other risk factors (Meigs, Larson, D'Agostino, Levy, Clouse, et al., 2002). An attenuated relationship between impaired fasting glucose level and CAC presence was also observed in another asymptomatic sample after controlling for other risk factors, although an independent association between impaired fasting glucose and CAC score persisted in women

(Moebus, Stang, Mohlenkamp, Dragano, Schmermund, et al., 2009). In yet a different study of 1,160 asymptomatic individuals, neither fasting glucose level, fasting insulin level, or HOMA were independently associated with CAC score (Arad et al., 2001). Examinations of CAC between individuals with and without diabetes have also demonstrated mixed results, with some studies showing diabetes to be independently associated with CAC presence (Wong, Sciammarella, Polk, Gallagher, Miranda-Peats, et al., 2003) and severity (Wolfe, Iqbal, Gefter, Mohler, Rader, et al., 2002), and others not (Folsom et al., 2004). In studies of type 1 diabetic patients, the association between diabetes and CAC seems to be more pronounced in females compared to males, and possibly attributable to differences in body fat distribution (Dabelea et al., 2003; Colhoun et al., 2000). CAC score was independently associated with duration of diabetes in a sample of type 2 diabetic patients (Godsland et al., 2006), and independently associated with HOMA in a sample of patients with chronic kidney disease (Kobayashi, Oka, Maesato, Ikee, Mano, et al., 2008). A study of 108 sudden cardiac death victims showed diabetes to be the sole independent correlate of CAC at time of autopsy, but this association was significant only in women (Burke, Taylor, Farb, Malcom, & Virmani, 2000).

In retrospective and prospective studies of asymptomatic individuals, diabetes has been shown to independently predict CAC progression (Lee et al., 2009; Yoon et al., 2002), with this association being stronger for blacks, intermediate for whites and Chinese, and weaker for Hispanics (Kronmal et al., 2007). Fasting insulin (Lee et al., 2009) and fasting glucose (Kramer et al., 2009) levels have also been independently associated with CAC progression. Furthermore, suboptimal glycemic control has been

independently associated with progression of CAC in both type 1 (Snell-Bergeon, Hokanson, Jensen, MacKenzie, Kinney, et al., 2003) and type 2 diabetic samples (Anand, Lim, Darko, et al., 2007). Duration of diabetes was also independently associated with CAC progression in the type 1 diabetic sample studied by Snell-Bergeon et al. Taken together, these studies suggest that insulin resistance appears to significantly impact CAC presence and progression in both asymptomatic and patient samples, but may have differential effects across gender and ethnicity which warrants further investigation.

Other Risk Factors. Other risk factors that have been independently associated with CAC in cross-sectional studies of asymptomatic individuals have included C-reactive protein (Wang, Larson, Levy, Benjamin, Kupka, et al., 2002) and other inflammatory markers (see Hamirani, Pandey, Rivera, Ndumele, Budoff, et al., 2008 for a review), fibrinogen (Bielak, Klee, Sheedy, Turner, Schwartz, et al., 2000), cortisol (Matthews, Schwartz, Cohen, & Seeman), leptin (Qasim et al., 2008), adiponectin (Steffes, Gross, Lee, Schreiner, & Jacobs, 2006), antioxidants (Tanaka, Fukui, Tomiyasu, Akabame, Nakano, et al., 2009), and sleep (Sorajja, Gami, Somers, Behrenbeck, Garcia-Touchard, et al., 2008). In addition, independent prospective associations with CAC progression have also been noted for fibrinogen (Green, Foiles, Chan, Schreiner, & Liu) and sleep (King, Knutson, Rathouz, Sidney, Liu, et al., 2008). However, these findings have been much more inconsistent and have not been replicated in the majority of studies examining these factors.

Baseline Coronary Artery Calcification. It should also be noted that CAC at baseline has been shown to be one of the strongest predictors of CAC progression in asymptomatic individuals (Yoon et al., 2002), postmenopausal women (Hsia et al., 2004),

type 2 diabetic patients (Elkeles et al., 2008), renal transplant patients (Schankel et al., 2007), and patient with clinically stable CHD (Shemesh et al., 2004), suggesting a positive feedback loop in which CAC might itself induce further CAC. Nevertheless, it has been contended that baseline CAC is not a confounder, but rather intricately involved in the CAC progression process, given that baseline CAC levels and subsequent progression are likely determined in large part by progression of CAC before baseline, which may be reasonably assumed to have been influenced by long-term risk factors (Kronmal et al., 2007).

Proposed Study

In summary, inconsistent findings have emerged across studies examining how individual CVD risk factors independently relate to CAC prevalence and progression. Previous studies have been predominantly cross-sectional in design and have typically included homogeneous ethnic (e.g., Caucasians) and/or patient (e.g., chronic kidney disease, diabetes, or hypertension) samples, limiting the generalizability of findings. The few prospective studies available have used baseline risk factor values in analyses, failing to account for the influence of their respective progressions on CAC. Published data are lacking on the progression of CAC and associated cardiometabolic risk factors (CRFs), as well as how these processes are related. To our knowledge, no study to date has examined how changes in CRFs predict change in CAC, particularly in a large multi-ethnic asymptomatic sample. Additionally, these associations have not been examined separately between men and women, for which observed differences in the predictive utility of various risk factors and risk algorithms (Gami, Witt, Howard, Erwin, Gami, et al., 2007; Michos, Nasir, Braunstein, Rumberger, Budoff, et al., 2006), as well as the

clinical development of symptomatic CHD (Lloyd-Jones et al., 2009), exist. Furthermore, no study to date has used latent variable growth curve modeling to characterize progression of CRFs, CAC, or their relationship.

The present study employed latent variable growth curve modeling to analyze how the progression of specific CRFs (waist circumference, body mass index, systolic and diastolic blood pressure, high-density and low-density lipoprotein cholesterol, triglycerides, and glucose)[1] relate to the progression of CAC in a large multi-ethnic asymptomatic cohort. All analyses were conducted separately for men and women in order to draw gender-specific conclusions. All analyses controlled for age, race/ethnicity, smoking, family history of CVD, socioeconomic status, and the time-varying use of antihypertensive, lipid-lowering, and glucose-lowering medications. The study had the following specific aims:

Specific Aim 1: To examine whether progression of CAC can be characterized over the study's mean 4.9-year time period using latent growth modeling in men and women with detectable CAC at baseline.[2]

Specific Aim 2: To examine whether progression of each CRF can be characterized over the study's mean 4.9-year time period using latent growth modeling.

Specific Aim 3: To examine how progression of each CRF relates to incidence and progression of CAC

[1] Insulin was not included in this study because it was collected only at baseline, and not at following examinations.

[2] Following the convention in the scientific literature, these growth estimates will be used as the outcome for those individuals with detectable CAC at baseline, while a dichotomous incident CAC outcome will be used for those individuals with undetectable CAC at baseline.

Chapter 2: Methods

Participants

Participants were those of the Multi-Ethnic Study of Atherosclerosis (MESA), a prospective epidemiological study initiated in July 2000 by the National Heart, Lung, and Blood Institute to investigate the prevalence, correlates, and progression of subclinical CVD in men and women of four racial/ethnic groups (Bild et al., 2002). Participants were recruited from 6 communities across the United States (Forsyth County, North Carolina; Northern Manhattan and the Bronx, New York; Baltimore and Baltimore County, Maryland; St. Paul, Minnesota; Chicago, Illinois; and Los Angeles County, California). At time of enrollment, participants had to be free of clinically apparent CVD, between 45 and 84 years of age, and identify as either white, black, Hispanic, or Chinese. An approximately equal number of men and women were recruited at each site according to prespecified age and race/ethnic proportions. Samples of participants recruited at each field center varied in size and ethnic composition. The final sample included 6,814 participants (47.2% men; 38.5% white, 27.8% black, 21.9% Hispanic, and 11.8% Chinese) with a mean age of 62.2 years (27% were 45 to 54 years of age, 28% were 55 to 64 years of age, 30% were 65-74 years of age, and 17% were 75 to 84 years of age).

Measures

Cardiometabolic Risk Factors. Height and weight were measured to the nearest 0.1 cm and 0.5 kg, respectively. Body mass index (BMI) was calculated as kg/m2. Waist circumference (WC) was measured at the umbilicus to the nearest 0.1 cm using a steel

measuring tape (standard 4 oz. tension). Resting blood pressure was measured 3 times in the right arm using an automated oscillometric method (Dinamap) and appropriate cuff sizes. Readings were taken after 5 minutes in the seated position. The second and third readings were averaged to obtain the systolic and diastolic blood pressure levels to be used in analyses.

Blood samples were collected via venipuncture and shipped at weekly intervals to a Central Laboratory (Collaborative Studies Clinical Laboratory at Fairview-University Medical Center, Minneapolis, MN) for assay. High-density lipoprotein (HDL) cholesterol was measured in EDTA plasma using the cholesterol oxidase cholesterol method (Roche Diagnostics) after precipitation of non-HDL-cholesterol with magnesium/dextran. Triglyceride level was measured in EDTA plasma using Triglyceride GB reagent (Roche Diagnostics, Indianapolis, IN 46250) on the Roche COBAS FARA centrifugal analyzer. This assay performs an automated glycerol bank by taking a spectrophotometric reading after endogenous glycerol has reacted and before lipase is added to release the glycerol from the triglyceride. Low-density lipoprotein (LDL) cholesterol was calculated in plasma specimens having a triglyceride value < 400 mg/dL using the formula proposed by Friedewald, Levy, and Fredrickson (1972). Serum glucose was measured by rate of reflectance spectrophotometry using thin film adaptation of the glucose oxidase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY 14650). Insulin was determined by a radioimmunoassay method using the Linco Human Insulin Specific RIA Kit (Linco Research, Inc., St. Charles, MO 63304). This assay utilizes ^{125}I-labeled Human Insulin and a Human Insulin antiserum to determine the level of insulin. The Central Laboratory had an operating control program in place to assess

and control within-run variability, accuracy, precision, and long-term drift for all blood measurements.

Coronary Artery Calcification. CAC was measured with an electron-beam computed tomography (EBCT) scanner (Imatron C-150, Imatron) at 3 study sites (Chicago, Los Angeles, and New York sites), and with a multidetector row helical computed tomography (MDCT) scanner (Lightspeed, General Electric or Siemens, Volume Zoom) at 3 study sites (Baltimore, North Carolina, and Minnesota sites). Each participant received two consecutive scans. These scans were performed over radiographic phantoms containing identical and known calcium concentrations, which were later used to calibrate the identification and quantification of CAC. Scans were read by a cardiologist at a centralized reading center (Harbor-UCLA Research and Education Institute). Scans were read blindly with respect to scan pairs and other participant data using a computer interactive scoring system similar to that previously described by Yaghoubi, Tang, Wang, Reed, Hsiai, et al. (1995). The amount of calcium present in each scan was quantified using the Agatston scoring method (Agatston et al., 1990), and scores from both scans for each participant were averaged. The presence of CAC was defined as an average Agatston score > 0, or an Agatston score > 0 on either scan. Interobserver (κ-statistic = 0.90) and intraobserver (κ-statistic = 0.93) agreement with regard to CAC presence was excellent, and the intraclass correlation coefficient for the Agatston score between readers was 0.99. A more detailed description of the methods used by MESA to acquire and interpret scans has been previously published (Carr, Nelson, Wong, Gray, Arad, et al., 2005). Raw Agatston scores were used to model CAC progression, as conventional log transformations are not appropriate for modeling growth over time.

Covariates. Standard questionnaires were used to collect information about demographic characteristics (age, gender, race/ethnicity), smoking, family history of CVD, socioeconomic status, and medication use. Age was used as a continuous variable. Race/ethnicity was represented by three dummy coded variables: Black, Hispanic, and Chinese, with White serving as the reference group. Smoking behavior at baseline was represented by 2 dummy coded variables: former smoking and current smoking, with never smoking serving as the reference group. Family history of CVD (history of myocardial infarction in either parents, siblings, or children) was represented as a dichotomous variable: positive or negative. Total gross family income was used as an indicator of socioeconomic status, with the following 13 categories: < $5,000; $5,000 to $7,999; $8,000 to $11,999; $12,000 to $15,999; $16,000 to $19,999; $20,000 to $24,999; $25,000 to $29,999; $30,000 to $34,999; $35,000 to $39,999; $40,000 to $49,999; $50,000 to $74,999; $75,000 to $99,999; and ≥ $100,000. Use of each medication class (antihypertensive, lipid-lowering, and glucose-lowering) was represented as a dichotomous variable (yes or no) at each exam time point.

Procedure

Sampling. The sampling frame and methods varied at each field center depending on site-specific recruitment plans and logistics. The emphasis of sampling was to obtain balanced recruitment across strata defined by gender, ethnicity, and age group rather than to represent the demographic distribution of the source communities. Selection from the sampling frames differed by site. Three field centers (Wake Forest, Columbia, and Northwestern) selected random samples, stratified by age and gender, from the sampling frames. The other three field centers (Minnesota, Johns Hopkins, and UCLA) used

sampling frames that did not contain demographic information and recruited samples along geographic boundaries (Minnesota and Johns Hopkins) or by random digit dialing of target areas (UCLA). Multiple eligible participants residing in the same household were allowed to participate in the study. A detailed description of the site-specific sampling procedures can be found in the MESA protocol available at www.mesa-nhlbi.org.

Recruitment. Specific recruitment procedures were developed for each field center according to the characteristics of its community, past experience, available resources, and site-specific logistics. Each site aimed to recruit 1,100 eligible participants, equally divided between men and women, from two or more of the following ethnic groups (in prespecified proportions): Caucasians, African Americans, Hispanics, and Chinese Americans. Overlapping ethnic groups were recruited across different field centers to minimize confounding of ethnicity by site. All sites that recruited Hispanics and/or Chinese Americans employed staff fluent in Spanish and/or Cantonese and Mandarin, respectively.

The purpose, rationale, and design of MESA were publicized to residents of target communities prior to, and concurrent with, recruitment. Targeted households or individuals were mailed letters and brochures, followed by personal contacts via telephone or in person. Phone calls were the primary method of recruitment at all field centers. Since multiple eligible persons in the same household could be recruited, the interviewer first enumerated all age-eligible persons in a household using a Household Enumeration Form. Name, gender, and relationship to the first respondent were obtained, followed by attempts to interview all age-eligible persons on one or multiple calls.

During the interview, a Screening Questionnaire was administered to further determine eligibility, as well as willingness to participate.

The progress of recruitment was monitored regularly to maintain balanced distributions across gender-, age-, and ethnic group-defined strata. During the last stages of enrollment, supplemental resources (i.e., lists of Medicare beneficiaries and referrals by participants) were used to meet recruitment goals for the elderly and minorities. A detailed description of the recruitment procedures employed at each field center can be found in the MESA protocol available at www.mesa-nhlbi.org.

Screening. Eligible participants were defined as persons (1) living within the specified geographic boundaries for each field center, (2) between the ages of 45 and 84 years, and (3) of Caucasian, African American, Hispanic, or Chinese American race/ethnicity.

Participants were considered ineligible if they had known clinical CVD at time of enrollment (given that the primary objective of the study is to investigate the determinants and natural history of subclinical CVD) and if they met any of the following exclusion criteria (mostly related to the long-term nature of the study or to incompatibility with certain study exam components): age younger than 45 or older than 84 years; physician-diagnosed heart attack; physician-diagnosed angina or taking nitroglycerin; physician-diagnosed stroke or transient ischemic attack; physician-diagnosed heart failure; current atrial fibrillation; having undergone procedures related to CVD (coronary artery bypass graft surgery, angioplasty, valve replacement, pacemaker or defibrillator implantation, any surgery on the heart or arteries); active treatment for cancer; pregnancy; any serious medical condition that would have prevented long-term

participation; weight > 300 pounds; cognitive inability as judged by the interviewer; living in a nursing home or on the waiting list for a nursing home; plans to leave the community within five years; language barrier (spoke language other than English, Spanish, Cantonese, or Mandarin); or chest computed tomography scan in the past year.

Eligibility or ineligibility status was determined from self-reported information, and no attempt was made to validate participant responses. Potential participants who responded "Don't know" to questions regarding medical conditions were not considered ineligible. At the end of screening, eligible and consenting persons were scheduled for assessments.

Assessments. Participants received 4 clinic and 3 CAC examinations between July 2000 and February 2008. The first clinic examination took place between July 2000 and August 2002, and included review of eligibility, signing of informed consent, collection of questionnaire information (demographic characteristics, medical history, medication use, etc.), phlebotomy, anthropometry, and measurement of blood pressure. Participants also received a CAC measurement around the time of their first clinic visit. Initial CAC measurements took place between July 2000 and December 2002.

The second examination took place between September 2002 and February 2004 (mean time between first and second examination was 1.6 years), and included repeats/updates of questionnaires and history information, phlebotomy, anthropometry, and measurement of blood pressure. At about this time, a randomly selected half of the cohort (n = 2,953) underwent a repeat CAC measurement (with a mean time of 1.6 years between first and second CAC measurement). These CAC measurements also took place between September 2002 and February 2004.

The third examination took place between March 2004 and September 2005 (mean time between first and third examination was 3.2 years), and again included repeats/updates of questionnaires and history information, phlebotomy, anthropometry, and measurement of blood pressure. At about this time, the other half of the cohort (n = 2,805) underwent a repeat CAC measurement (with a mean time of 3.2 years between first and second CAC measurement). These CAC measurements took place between March 2004 and October 2005.

The fourth examination took place between September 2005 and May 2007 (mean time between first and fourth examination was 4.8 years), and also included repeats/updates of questionnaires and history information, phlebotomy, anthropometry, and measurement of blood pressure. At about this time, one-fourth of the cohort (n = 1,406) underwent a second repeat CAC measurement (with a mean time of 4.9 years between first and second CAC measurement). These CAC measurements took place between October 2005 and February 2008.

Table 01 describes the number of participants who received each assessment pertinent to the proposed study at each of the 4 exam time-points, stratified by gender. Detailed information regarding all of the components administered at each of the four examinations can be found in the MESA protocol available at www.mesa-nhlbi.org.

Chapter 3: Data Analysis Plan

Preliminary Analyses

Data Screening

Univariate distributions for all observed measures were examined for normality. Additionally, the relative variances between variables were also assessed.

Missing Data

Missing data on CRFs and CAC over the study period were handled using the full information maximum likelihood (FIML) approach. FIML estimation uses all available data to estimate group parameters by obtaining a likelihood function for each participant based on the data that is present for that participant (Arbuckle, 1996). The likelihoods are then summed across participants. Thus, all participants with any available data relevant to a given parameter can contribute to that parameter's estimation. The use of FIML assumes that missing data are either missing completely at random (MCAR; missing data in a variable are unrelated to other observed variables and to the values of that variable itself) or missing at random (MAR; missing data in a variable are related to other observed variables available for analysis).

Participants with missing data on covariates – age, race/ethnicity, smoking, family history of CVD, income, and medication use – were excluded from analyses as missingness in these variables does not allow for their use as independent predictors in growth models. All variables of interest were compared between participants with and without missing data on control variables. In addition, to examine whether the retained

sample was representative of the overall sample, all growth and prediction models without covariates were compared between these two groups.

Primary Analyses

Latent Growth Modeling

Latent variable growth curve modeling (LGM) is a longitudinal analysis technique performed within the structural equation modeling (SEM) framework that allows for the examination of growth trajectories over time within and across individuals (Duncan, Duncan, Strycker, Li, & Alpert, 1999; Hancock & Lawrence, 2006). Specifically, trajectories of change over repeated measurements of a variable are computed for each individual, and for linear models, described in terms of initial level (or any other reference point desired) and change from (or to) those levels (Duncan et al., 1999). In addition to obtaining average trajectories, one can also quantify individual variation in those trajectories, representing an advantage over other traditional longitudinal techniques (i.e., repeated measures analysis of variance; Duncan et al., 1999). Moreover, LGM-derived change parameters can serve as both dependent and independent variables in models, allowing for the examination of both predictors and sequelae of change, as well as the examination of multiple parallel processes (Duncan et al., 1999). Other important advantages of LGM include (1) the ability to estimate parameters separate from measurement error, thus averting attenuation in parameter magnitudes due to measurement error, (2) the ability to maximize the use of all available data by using likelihood functions to incorporate missing observations and/or unequally spaced observations across individuals, and (3) the ability to incorporate time-varying covariates (Duncan et al., 1999; Llabre, Spitzer, Siegel, Saab, & Schneiderman, 2004).

These models are similar to mixed models, random regression, or multilevel models, and may be recognized by these labels in the medical literature.

In the proposed study, LGM was used to examine changes over time in CAC (see Step 1 below) as well as in each CRF (see Step 2 below). Specifically, a random effects approach was employed, in which time variables were used to reflect individually varying times of observations across repeated measurements. A linear model was specified to capture change because of the limited number of time points. The change parameters of interest were the baseline mean levels and variability across participants, and the mean slopes (the rates of change over repeated measurements) and variability across participants. The slope estimates were specified to describe rate of change per year. The proposed study examined how change in each CRF related to change in CAC in separate analyses. Men and women were assessed separately in order to draw gender-specific conclusions. All analyses were conducted using Mplus software (version 4.21; Muthén & Muthén, 1998-2007).

Step 1: Model and examine progression of CAC. LGM was used to examine linear change in CAC for participants with detectable CAC (CAC score > 0) at baseline (see Figure 1). This change was defined by an intercept (baseline CAC value) and slope (rate of change in CAC per year). The intercept and slope of CAC were represented as latent variables, and acted as the outcome in the proposed CAC prediction models for participants with detectable CAC at baseline. CAC values collected at each of the 3 exam time points were utilized to estimate the mean, variance, and covariance of these CAC growth estimates, accounting for individually-varying times between repeated observations across participants.

Following the conventional approach in the CAC literature, a dichotomous variable representing CAC incidence served as the outcome for participants with undetectable CAC (CAC ≤ 0) at baseline. For these participants, incident CAC was defined as having a detectable CAC score (CAC > 0) at either of the two following CAC examinations. SEM allows for the testing of dichotomous outcomes. In our analyses of CAC incidence, a restricted maximum likelihood estimation method was employed (Muthén & Muthén, 1998-2007).

Step 2: Model and examine progression of each CRF. LGM was used to examine linear change in each CRF (see Figure 2). This change was defined by an intercept (baseline CRF value) and slope (rate of change in CRF per year). The intercepts and slopes of each CRF were represented as latent variables, and acted as predictor variables in the proposed CAC prediction models. CRF values collected at each of the 4 exam time points were utilized to estimate the mean, variance, and covariance of each CRF's growth estimates, accounting for individually-varying times between repeated observations across participants.

Step 3: Examine how progression of each CRF relates to progression of CAC. For participants with detectable CAC at baseline, each CRF slope variable predicted the CAC slope variable, controlling for the baseline value (intercept variable) of that CRF (see Figure 3). Separate models were analyzed for each CRF. In each model, the direct effect (Path A) of the CRF slope variable on the CAC slope variable was evaluated for significance (p-value < .05). Each model also allowed for the examination of how the baseline value of each CRF related to (1) the baseline value of CAC (by evaluating Path B) and (2) the progression of CAC (by evaluating Path C).

For participants with undetectable CAC at baseline, each CRF slope variable predicted CAC incidence (represented as a dichotomous outcome), controlling for the baseline value (intercept variable) of that CRF (see Figure 4). Separate models were analyzed for each CRF. In each model, the direct effect (Path A) of the CRF slope variable on the CAC incidence outcome was evaluated for significance (p-value < .05). Each model also allowed for the examination of how the baseline value of each CRF related to incident CAC (by evaluating Path B).

Covariates. For participants with detectable CAC at baseline, each covariate at baseline independently predicted the CAC intercept and slope variables in a multivariate model (see Figure 5).[3] The direct effects of the covariates on the CAC intercept variable (Paths a-k) and CAC slope variable (Paths A-K) were evaluated for significance (p-value < .05).

For participants with undetectable CAC at baseline, each covariate at baseline independently predicted CAC incidence (represented as a dichotomous outcome) in a multivariate model (see Figure 6). These direct effects (Paths A-K) were evaluated for significance (p-value < .05).

Initially, all analyses of CRFs predicting progression of CAC were conducted without the inclusion of covariates in order to assess total effects. Further analyses then controlled for age, race/ethnicity, smoking, family history of CVD, and income by including the baseline values of these variables as simultaneous predictors of CAC progression, as well as controlling for the time-varying use of antihypertensive, lipid-lowering, and glucose-lowering medications by simultaneously regressing each of the 3

[3] Medication use was included as a time-varying covariate when analyzing all covariates. When analyzing baseline use of each medication type, uses of other medication types were also included as time-varying covariates.

time-specific observed CAC variables on medication use data at those corresponding times.[4] Finally, these analyses were examined when further controlling for baseline CAC level.

[4] Time-varying use of these medications can only be included in analyses of individuals with detectable CAC, in which CAC is being modeled using LGM. For individuals with undetectable CAC at baseline, use of these medications was controlled by including the baseline data on medication use as simultaneous predictors of incident CAC.

Chapter 4: Results

Preliminary Analyses

Data Screening and Transformations

A dichotomous incident CAC variable was created for use as the outcome in individuals with undetectable CAC at baseline, and was defined as having a detectable CAC score at any follow-up CAC examination (either each participant's second or, if received, third examination) following an undetectable CAC score at baseline.

Missing Data and Sample Description

2,254 (33.1%) participants were excluded due to missing data on covariates, leaving 4,560 participants for analysis. This sample was 46.8% male, 40.5% white, 25.7% black, 21.8% Hispanic, and 12.0% Chinese. The average age was 61.35 (SD = 9.963) at baseline. 20.7% had a gross family income below $20,000, 26.5% between $20,000 and $40,000, 28% between $40,000 and $75,000, and 24.8% greater than or equal to $75,000. Approximately 42.7% had a positive family history of CVD. About 51.1% of the sample had never smoked cigarettes, 36.8% were former smokers, and 12.1% were current smokers at baseline. At baseline, approximately 35.6% were taking antihypertensive medications, 16.8% were taking lipid-lowering medications, and 8.4% were taking glucose-lowering medications. The average WC was 97.98 cm (SD = 14.42) and the average BMI was 28.32 (SD = 5.41). The average systolic and diastolic blood pressures were 125.10 mg Hg (SD = 20.67) and 71.72 mg Hg (SD = 10.11), respectively. The average high-density and low-density lipoprotein cholesterol levels were 50.99

mg/dL (SD = 14.68) and 117.12 mg/dL (SD = 31.07), respectively. The average triglyceride level was 130.36 mg/dL (SD = 82.45) and the average glucose level was 95.91 mg/dL (SD = 27.44). Gender-stratified baseline demographic and risk factor information is presented in Table 02.

Participants who were excluded due to missing data on covariates were slightly older (mean age of 63.8 vs. 61.4 years), less affluent (mean income category of 7.8 vs. 8.8), more likely to be Black (31.9% vs. 25.7%) and less likely to be White (34.4% vs. 40.5%), more likely to be current smokers (15.1% vs. 12.1%), more likely to have detectable CAC (53.6% vs. 48.0%), had higher systolic (129.60 vs. 125.10 mm Hg) and diastolic (72.30 vs. 71.72 mm Hg) blood pressures, had higher glucose levels (100.35 vs. 95.91 mg/dL), and were more likely to be on antihypertensive (40.6% vs. 35.6%) and glucose-lowering (12.1% vs. 8.4%) medications.

To examine possible bias in the retained versus overall sample, all growth and prediction models without covariates were compared between these two groups. Growth parameters for all CRFs in those individuals that had undetectable CAC at baseline were similar between both groups, with the retained sample exhibiting slightly less regression (or more progression) in certain CRFs (SBP for both men and women; TG for women) compared to the total sample. In those individuals that had detectable CAC at baseline, growth parameters for most CRFs were also similar between both subsamples with the exception of SBP, with the retained sample exhibiting slightly lower baseline levels as well as less regression (or more progression) over time for both men and women compared to the entire sample. Regarding CAC for individuals that had detectable CAC at baseline, the retained sample had slightly lower baseline values but similar rates of

progression for both men and women compared to the entire sample. CRFs also appeared to be associated with CAC incidence and CAC progression similarly between the retained and entire samples for both men and women.

Primary Analyses

Results will first be presented for individuals that had undetectable CAC at baseline (stratified by gender), followed by results for individuals that had detectable CAC at baseline (stratified by gender). In each growth model, the residual variances of corresponding variables were assumed equal across all time points. In addition, the effects of medications on CAC, when included as time-varying covariates, were also assumed equal across all time points. These assumptions did not detract from model fit and resulted in more parsimonious models. An alpha value of 0.05 was used for all analyses.

Individuals with Undetectable Coronary Artery Calcification at Baseline

Incidence of CAC in participants with undetectable CAC at baseline. Table 03 and Table 04 present CAC incidence prevalence for men and women, respectively.

Men. All 2,132 men in our sample had CAC data at baseline and at a second examination. CAC data at a third examination were available for 462 (21.7%) of these men. At baseline, 872 (40.9%) men had undetectable CAC. Of those, 180 (20.6%) went on to develop CAC at their second examination, which was administered an average of 2.46 years (SD = 0.87) following their baseline examination. Of those that had undetectable CAC at baseline and available data at a third examination (n = 190; 78.2%

had missing data), 75 (39.5%) had developed CAC by the third examination, which was administered an average of 4.90 years (SD = 0.51) following their baseline examination.

Women. All 2,428 women in our sample had CAC data at baseline and at a second examination. CAC data at a third examination were available for 487 (20.1%) of these women. At baseline, 1,498 (61.7%) women had undetectable CAC. Of those, 208 (13.9%) went on to develop CAC at their second examination, which was administered an average of 2.46 years (SD = 0.85) following their baseline examination. Of those who had undetectable CAC at baseline and available data at a third examination (n = 303; 79.8% had missing data), 68 (22.4%) had developed CAC by the third examination, which was administered an average of 4.96 years (SD = 0.50) following their baseline examination.

Progression of CRFs for participants with undetectable CAC at baseline. Table 05 and Table 06 present the CRF intercept (average baseline level and variance across individuals) and slope (average rate of change per year and variance across individuals) estimates for men and women, respectively.

Men. On average, WC (0.222 cm per year), BMI (0.041 units per year), HDL-C (0.413 mg/dL per year), and glucose (1.038 mg/dL per year) increased over time, while DBP (-0.250 mm Hg per year) and LDL-C (-0.559 mg/dL per year) decreased over time. The average rate of change in SBP and TG was also negative, but not significantly different from zero. Significant variability in baseline levels was observed for all CRFs. With the exception of HDL-C, TG, and glucose, there was also significant variability in the rates of change of CRFs. Significant inverse correlations between baseline level and rate of change were observed for SBP (r = -0.231) and DBP (r = -0.205), indicating that

higher initial levels were associated with more regression (or less progression) over time in these CRFs. Non-significant inverse correlations between baseline level and rate of change were observed for WC, LDL-C, TG, and glucose, while non-significant positive correlations were observed for BMI and HDL-C.

Women. On average, WC (0.326 cm per year), BMI (0.039 units per year), HDL-C (0.133 mg/dL per year), and glucose (1.079 mg/dL per year) increased over time, while DBP (-0.300 mm Hg per year) decreased over time. The average rate of change in SBP, LD-C, and TG was also negative, but not significant. Significant variability in baseline levels and rate of change was observed for all CRFs, except for rate of change in TG. Significant inverse correlations between baseline level and rate of change were observed for SBP (r = -0.374), DBP (r = -0.389), and LDL-C (r = -0.351), indicating that higher initial levels were associated with more regression (or less progression) over time in these CRFs. Non-significant inverse correlations between baseline level and rate of change were observed for BMI, HDL-C, TG, and glucose, while a non-significant positive correlation was observed for WC.

Covariate and CAC Analyses in participants with undetectable CAC at baseline. Table 07 and Table 08 present the multivariate associations between covariates at baseline and incidence of CAC for men and women, respectively.

Men. Age was the only covariate independently and significantly associated with incident CAC (B = 0.05), indicating that older age is associated with greater incidence of CAC, independent of race/ethnicity, smoking, family history of CVD, income, and baseline antihypertensive, lipid-lowering, and glucose-lowering medication use. No significant independent association with CAC incidence was observed for race/ethnicity

(relative to whites), smoking (relative to never smoking), family history of CVD, income, or baseline antihypertensive, lipid-lowering, or glucose-lowering medication use.

Women. Age (B = 0.042), as well as baseline use of antihypertensive (B = 0.488) and glucose-lowering (B = 1.107) medications, was independently and significantly associated with incident CAC, indicating that older age and baseline use of these medications was associated with a greater incidence of CAC, independent of race/ethnicity, smoking, family history of CVD, income, and baseline use of lipid-lowering medications. No significant independent association with CAC incidence was observed for race/ethnicity (relative to Whites), smoking (relative to never smoking), family history of CVD, income, or baseline lipid-lowering medication use.

CRF and CAC Analyses in participants with undetectable CAC at baseline. Table 09 and Table 10 present the univariate associations between CRF growth estimates (baseline levels and rates of change) and incidence of CAC for men and women, respectively.

Men. Baseline values of WC (B = 0.044), BMI (B = 0.096), and SBP (B = 0.028) were significantly and positively associated with CAC incidence in univariate analyses, indicating that higher levels of these CRFs at baseline were associated with greater incidence of CAC. After controlling for covariates, these associations remained significant (WC B = 0.041, BMI B = 0.117, and SBP B = 0.023), and baseline DBP also became an independent and positive predictor of CAC incidence (B = 0.042). Baseline values of HDL-C, LDL-C, TG, and glucose were not significantly associated with CAC incidence in univariate analyses.

Rate of change in LDL-C was significantly and inversely associated with incident CAC (B = -0.195) in univariate analysis, but this relationship did not remain significant after controlling for covariates. No significant univariate association between rate of change in other CRFs and incident CAC was observed.

Women. Baseline values of WC (B = 0.003), BMI (B = 0.069), SBP (B = 0.024), HDL-C (B = -0.030), and glucose (B = 0.023) were all significantly and positively (HDL-C inversely) associated with CAC incidence in univariate analyses, indicating that higher levels of these CRFs (lower levels of HDL-C) at baseline were associated with greater incidence of CAC. These associations remained significant after controlling for covariates with the exceptions of SBP and glucose, which no longer remained significantly associated with CAC incidence (WC B = 0.029, BMI B = 0.072, and HDL-C B = -0.039). Baseline values of DBP, LDL-C, and TG were not significantly associated with incident CAC in univariate analyses.

No significant univariate associations between rate of change in CRFs and incident CAC were observed.

Individuals with Detectable Coronary Artery Calcification at Baseline

Progression of CAC in participants with detectable CAC at baseline. Table 11 and Table 12 present the CAC intercept (average baseline level and variance across individuals) and slope (average rate of change per year and variance across individuals) estimates for men and women, respectively.

Men. All 2,132 men in our sample had CAC data at baseline and at a second examination. CAC data at a third examination were available for 462 (21.7%) of these men. At baseline, 1,260 (59.1%) men had detectable CAC. Of those men, 988 (78.4%)

did not have data at a third examination. For men with detectable CAC at baseline, the average time between the baseline CAC examination and the second and third CAC examination was 2.37 years (SD = 0.85) and 4.90 years (SD = 0.57), respectively.

The average CAC score for these men at baseline was 324.774, and significant variability around this baseline score was observed (SD = 57.63). On average, CAC increased by 57.146 units per year, with significant variability observed in the rate of change in CAC (SD = 78.59). Baseline CAC level was significantly and positively correlated with CAC rate of change (r = 0.691), indicating that CAC progressed at a more rapid rate over time for men who initially had higher levels compared to those who had lower levels.

Women. All 2,428 women in our sample had CAC data at baseline and at a second examination. CAC data at a third examination were available for 487 (20.1%) of these women. At baseline, 930 (38.3%) women had detectable CAC. Of those women, 746 (80.2%) did not have data at a third examination. For women with detectable CAC at baseline, the average time between the baseline CAC examination and the second and third CAC examination at baseline was 2.44 years (SD = 0.86) and 4.97 years (SD = 0.57), respectively.

The average CAC score for these women at baseline was 180.454, and significant variability around this baseline score was observed (SD = 32.44). On average, CAC increased by 39.098 units per year, with significant variability observed in the rate of change in CAC across these women (SD = 63.88). Baseline CAC level was significantly and positively correlated with CAC rate of change (r = 0.809), indicating that CAC

progressed at a more rapid rate over time for women who initially had higher levels compared to those who had lower levels.

Progression of CRFs in participants with detectable CAC at baseline. Table 13 and Table 14 present the CRF intercept (average baseline level and variance across individuals) and slope (average rate of change per year and variance across individuals) estimates for men and women, respectively.

Men. On average, WC (0.076 cm per year), HDL-C (0.469 mg/dL per year), and glucose (0.661 mg/dL per year) increased over time, while SBP (-0.647 mm Hg per year), DBP (-0.709 mm Hg per year), LDL-C (-2.781 mm/dL per year), and TG (-2.611 mg/dL per year) decreased over time. The average rate of change in BMI was negative, but not significantly different from zero. Significant variability in baseline levels and rate of change was observed for all CRFs, except for rate of change in TG. Significant inverse correlations between baseline level and rate of change were observed for SBP (r = -0.296), DBP (r = -0.232), LDL-C (r = -0.281), and glucose (r = -0.476), suggesting that higher initial levels were associated with greater declines (or less progression) over time in these CRFs. For HDL-C, a significant and positive correlation between baseline level and rate of change was observed (r = 0.413), suggesting that higher initial levels were associated with greater progression (or less regression) over time. Non-significant inverse correlations between baseline levels and rates of change were observed for WC, BMI, and TG.

Women. On average, HDL-C (0.221 mg/dL per year) and glucose (0.905 mg/dL per year) increased over time, while BMI (-0.035 units per year), SBP (-0.487 mm Hg per year), DBP (-0.413 mm Hg per year), LDL-C (-1.895 mg/dL per year), and TG (-1.596

mg/dL per year) decreased over time. The average rate of change in WC was positive, but not significantly different from zero. Significant variability in baseline levels and rate of change was observed for all CRFs, except for rate of change in TG and glucose. Significant inverse correlations between baseline level and rate of change were observed for SBP (r = -0.340), DBP (r = -0.346), and LDL-C (r = -0.314), suggesting that higher initial levels were associated with more regression (or less progression) over time in these CRFs. Non-significant inverse correlations between baseline level and rate of change were observed for BMI, HDL-C, TG, and glucose. A non-significant positive correlation between baseline level and rate of change was observed for WC.

Covariate and CAC Analyses in participants with detectable CAC at baseline. Table 15 and Table 16 present the multivariate associations between covariates at baseline and CAC growth estimates (baseline levels and rates of change) for men and women, respectively.

Men. Age (B = 16.180), family history of CVD (B = 74.656), and baseline glucose-lowering (B = 149.772) medication use were all significantly and independently associated with baseline CAC level in a positive direction. In addition, former smokers had significantly and independently higher baseline CAC levels relative to individuals who never smoked (B = 67.217). No significant independent association with baseline CAC level was observed for race/ethnicity (relative to Whites), current smoking (relative to never smoking), income, or baseline antihypertensive or lipid-lowering medication use.

Age (B = 1.860) and family history of CVD (B = 11.203) were also significantly and independently associated with change in CAC in a positive direction, indicating that

increased age and a positive family history of CVD were both associated with greater progression in CAC. However, these relationships did not remain significant after further controlling for baseline CAC level. Baseline use of antihypertensive (B = 18.133) and glucose-lowering medications (B = 33.813) were also significantly and independently associated with increased CAC progression, even after controlling for baseline CAC level (B = 12.215 and 20.312, respectively). No significant independent association with CAC progression was observed for race/ethnicity (relative to Whites), smoking (relative to never smoking), income, or baseline use of lipid-lowering medications.

Women. Age (B = 8.870), baseline glucose-lowering medication use (B = 120.443), and current smoking (relative to never smoking; B = 75.402) were all significantly and independently associated with baseline CAC level in a positive direction. In addition, Hispanics had significantly and independently lower baseline CAC levels relative to Whites (B = -79.313). No significant independent association with baseline CAC level was observed for Blacks or Chinese (relative to Whites), former smokers (relative to never smokers), family history of CVD, income, or baseline use of antihypertensive or lipid-lowering medications.

Age was also significantly and independently associated with change in CAC in a positive direction (B = 1.193), indicating that increased age was associated with greater progression in CAC. However, this relationship did not remain significant once baseline CAC level was controlled for. Baseline use of glucose-lowering medications was also significantly and independently associated with change in CAC (B = 43.694), and this relationship remained significant even after further controlling for baseline CAC (B = 24.623). No significant independent association with CAC progression was observed for

race/ethnicity (relative to Whites), smoking (relative to never smoking), family history of CVD, income, or baseline use of antihypertensive or lipid-lowering medications.

CRF and CAC Analyses in participants with detectable CAC at baseline. Table 17 and Table 18 present the univariate associations between CRF growth estimates (baseline level and rate of change) and CAC growth estimates (baseline level and rate of change) for men and women, respectively.

Men. Baseline values of SBP (B = 4.382) were significantly and positively associated with baseline CAC levels in univariate analyses, while baseline values of DBP (B = -7.665) and LDL-C (B = -2.378) were significantly and inversely associated with baseline CAC levels. However, these relationships did not remain significant after controlling for covariates. Baseline levels of WC, BMI, HDL-C, TG, and glucose were not significantly associated with baseline levels of CAC in univariate analyses.

WC at baseline was significantly and positively associated with change in CAC (B = 0.407), but this relationship did not remain significant after controlling for covariates. After controlling for covariates and baseline CAC, baseline levels of SBP (B = 0.665), TG (B = 0.070), and glucose (B = 0.342) were significantly and positively associated with rate of change in CAC, indicating that higher initial levels of these factors were associated with greater progression in CAC independent of covariates and baseline CAC level. In addition, after controlling for covariates and baseline CAC, baseline levels of HDL-C (B = -0.651) and LDL-C (B = -0.250) were significantly and inversely associated with rate of change in CAC, indicating that higher levels of these factors were associated with less progression in CAC independent of covariates and baseline CAC

level. Baseline levels of BMI and DBP were not significantly associated with change in CAC in univariate analyses.

Rate of change in DBP (B = -8.508) and TG (B = -0.523) was significantly and inversely associated with CAC progression in univariate analyses, but these relationships did not remain significant after controlling for covariates. Rate of change in WC, BMI, SBP, HDL-C, LDL-C, and glucose were not significantly associated with change in CAC in univariate analyses.

Women. Baseline values of SBP (B = 02.36) were significantly and positively associated with baseline CAC levels in univariate analyses, while baseline values of LDL-C (B = -0.932) were significantly and inversely associated with baseline CAC levels. However, these relationships did not remain significant after controlling for covariates. After controlling for covariates, baseline values of BMI (B = 4.993) and glucose (B = 1.241) were significantly and positively associated with baseline CAC levels, and baseline values of HDL-C (B = -1.389) were significantly and inversely associated with baseline CAC levels. Baseline levels of WC, DBP, and TG were not significantly associated with baseline levels of CAC in univariate analyses.

Baseline level of SBP was significantly and positively associated with change in CAC in univariate analyses (B = 0.410), but this relationship did not remain significant after controlling for covariates. Baseline level of BMI was also significantly and positively associated with change in CAC in univariate analyses (B = 0.984), and this relationship remained significant after controlling for covariates (B = 1.374) but not after further controlling for baseline CAC level. After controlling for covariates and baseline CAC level, baseline levels of both WC (B = 0.248) and glucose (B = 0.366) remained

significantly and positively associated with CAC progression, indicating that higher initial levels of WC and glucose were associated with greater CAC progression independent of covariates and baseline CAC level. In addition, after controlling for covariates and baseline CAC level, baseline level of LDL-C was significantly and inversely associated with CAC progression (B = -0.157), indicating that higher initial levels of LDL-C were associated with less progression in CAC independent of covariates and baseline CAC level. Baseline levels of DBP, HDL-C, and TG were not significantly associated with change in CAC in univariate analyses.

Rate of change in SBP (B = -3.827), DBP (B = -9.882), and LDL-C (B = -2.890) were significantly and inversely associated with CAC progression in univariate analyses, and these relationships remained significant after controlling for covariates and baseline CAC level (SBP B = -3.173, DBP B = -8.558, and LDL-C B = -2.485). These results indicate that regression (or slower progression) in SBP, DBP, and LDL-C was associated with greater progression in CAC, independent of covariates as well as baseline CAC. Rate of change in WC, BMI, HDL-C, TG, and glucose was not significantly associated with change in CAC in univariate analyses.

The following table summarizes the results of how baseline CRFs and change in CRFs were associated with CAC incidence (controlling for covariates) and progression (controlling for covariates and baseline CAC), for individuals with undetectable and detectable CAC at baseline, respectively.

		Baseline CRF & CAC Incidence/Progression Associations								CRF Change & CAC Incidence/Progression Associations							
		WC	BMI	SBP	DBP	HDL	LDL	TG	GLC	WC	BMI	SBP	DBP	HDL	LDL	TG	GLC
Undetectable CAC at Baseline	Men	+	+	+	+												
	Women	+	+			-											
Detectable CAC at Baseline	Men			+		-	-	+	+								
	Women	+					-		+			-	-		-		

Post-hoc Analyses

Post-hoc analyses were conducted to 1) explore whether the observed significant associations between rate of change in SBP and DBP on CAC progression were independent of the observed significant association between rate of change in LDL-C and CAC progression, and 2) explore whether the observed significant inverse associations between rate of change in SBP, DBP, and LDL-C on CAC progression were influenced by medication treatment.

Results suggested that the observed univariate significant associations between rate of change in SBP and DBP on CAC progression were not independent of the association between rate of change in LDL-C on CAC progression in women with detectable CAC at baseline. When rate of change in LDL-C was included in the analyses examining the associations between rate of change in SBP and DBP on CAC progression, these associations did not remain significant. However, in these analyses, rate of change in LDL-C did remain significantly and inversely associated with CAC progression (B = -2.181 and -2.117, when controlling for SBP and DBP, respectively), suggesting that the significant associations observed for changes in SBP and DBP on CAC progression may have been confounded by the effects of change in LDL-C.

To explore whether the observed significant inverse associations between rate of change in certain CRFs (SBP, DBP, and LDL-C in women with detectable CAC at baseline) and change in CAC were influenced by medication treatment, post-hoc analyses separately examining individuals never receiving medications (corresponding to CRFs of interest) versus individuals always receiving such medications throughout the study period were conducted. Specifically, change in these CRFs, CAC, and their association were modeled separately between women on and off medications targeting the specific CRF of interest to further evaluate these relationships.

In terms of CAC modeling, results showed that individuals not receiving either antihypertensive or lipid-lowering medications had lower mean baseline CAC values compared to those receiving these medications (124.087 vs. 208.396 for women receiving antihypertensive medications; and 151.492 vs. 217.722 for women receiving lipid-lowering medications) as well as lower mean rates of CAC progression (22.587 vs. 47.356 for women receiving antihypertensive medications; and 30.029 vs. 48.215 for women receiving lipid-lowering medications). Additionally, the positive correlations between baseline CAC level and CAC progression were greater for women receiving these medications versus those not receiving these medications.

In terms of CRF modeling, results showed that individuals not receiving antihypertensive medications had lower mean baseline SBP (117.948 vs. 136.667 mm Hg) and DBP (65.705 vs. 69.143 mm Hg) levels, while individuals not receiving lipid-lowering medications had higher mean baseline LDL-C levels (117.565 vs. 101.019 mg/dL). For these three CRFs, the average annual rate of change was positive for individuals not receiving medication and negative for individuals receiving medication

(SBP: 0.666 mm Hg, $p < .05$ vs. -0.678 mm Hg, $p < .05$; DBP: 0.060 mm Hg, $p = 0.46$ vs. -0.489 mm Hg, $p < .05$; and LDL: 0.225 mg/dL, $p = 0.35$ vs. -1.256 mg/dL, $p < .05$), suggesting that individuals not receiving medications targeting these CRFs showed average increases in their levels over time whereas individuals receiving these medications showed average and significant decreases in their levels. Additionally, the inverse correlation between baseline level and rate of change in these CRFs was greater for individuals receiving medications versus those not receiving medications.

In terms of exploring associations between rate of change in CRFs and rate of change in CAC, results showed that for women receiving antihypertensive medications, change in SBP ($B = -4.039$) and change in DBP ($B = -12.051$) remained significantly and inversely associated with change in CAC. However, for women not receiving antihypertensive medications, a non-significant inverse association between change in SBP and change in CAC was observed ($B = -0.368$, $p = 0.84$), while a non-significant positive association between change in DBP and change in CAC was observed ($B = 0.748$, $p = 0.85$). The association between rate of change in LDL-C and rate of change in CAC remained negative but was non-significant for women both receiving ($B = -4.351$, $p = 0.23$) and not receiving ($B = -1.312$, $p = 0.48$) lipid-lowering medications. It should be noted that the consequent decreases in sample size for these post-hoc analyses that further stratified individuals might have resulted in a loss of power to detect significant associations.

Chapter 5: Discussion

Using data from MESA, initial levels and subsequent rates of change in both CRFs and CAC and their relationships, were modeled in men and women using LGM over an average 4.9-year time period. As previously reported on a subset of this sample (Kronmal et al., 2007), several CRFs at baseline were associated with CAC incidence and progression, with certain factors appearing to exhibit differential influences on these two endpoints. The current study further illustrated possible gender differences in these relationships, as well as presented novel findings on how changes over time in CRFs relate to both the incidence and progression of CAC.

Controlling for covariates, individual baseline predictors of CAC incidence among men who had undetectable CAC at baseline included greater levels of WC, BMI, SBP, and DBP. In women who had undetectable CAC at baseline, individual baseline predictors of CAC incidence also included higher levels of WC and BMI, as well as lower levels of HDL-C and baseline use of antihypertensive and glucose-lowering medications. There were no observed associations for either men or women between incidence of CAC and baseline levels of LDL-C, TG, or glucose.

Among both men and women who had detectable CAC at baseline, CAC increased over time by an average of 57.2 and 39.1 Agatston units per year, respectively. Consistent with prior studies (Yoon et al., 2002; Hsia et al., 2004; Elekeles et al., 2008; Schankel et al., 2007), a positive correlation between baseline CAC level and rate of CAC change was observed, indicating that higher initial levels of CAC were associated with greater progression over time. These findings are similar to those reported by

Kronmal et al. (2007), who observed average annual CAC increases of 54 and 36 Agatston units for men and women, respectively, using participants' first follow-up CT exam. Significant variability was observed among individuals in both baseline levels and rates of change in CAC.

Controlling for covariates, individual baseline predictors of CAC progression among men who had detectable CAC at baseline included higher levels of SBP, TG, and glucose, and lower levels of LDL-C. When further controlling for baseline CAC, these factors remained significantly associated with CAC progression, and lower levels of HDL-C emerged as a baseline predictor. In women who had detectable CAC at baseline, individual baseline predictors of CAC progression also included higher levels of glucose and lower levels of LDL-C, as well as higher levels of WC and BMI. With the exception BMI, these factors remained significantly associated with CAC progression when controlling for baseline CAC level. The inverse relationship between LDL-C and CAC progression observed in both men and women who had detectable CAC at baseline appeared to be influenced by use of lipid-lowering medications. Individuals not receiving these medications throughout the study period did not exhibit this significant inverse relationship, whereas those receiving these medications throughout the study period did (data not shown). This suggests that for individuals receiving lipid-lowering medications, having a lower level of LDL-C is associated with greater progression in CAC.

Among both men and women who had undetectable CAC at baseline, average increases over time were observed for WC, BMI, HDL-C, and glucose, while an average decrease over time was observed for DBP. In these men, there was also an average decrease in LDL-C levels over time. These average decreases in DBP and LDL-C (in

men) appeared to be the result of medication use, with individuals taking medications throughout the study period that targeted these CRFs showing average decreases in their levels over time, whereas those not taking these medications showed average increases or no significant change in their levels over time (data not shown). There was also an inverse correlation between baseline level and rate of change for SBP and DBP in both men and women, and LDL-C in women, indicating that individuals with higher baseline levels of these CRFs (and thus more likely to be prescribed medication to treat these) tended to exhibit greater decline (or less progression) in levels over time. No significant average change over time was observed for SBP or TG in either men or women who had undetectable CAC at baseline. Significant variability across individuals in the rates of change of all CRFs was observed with exception of TG in both men and women, and HDL-C and glucose in men.

No significant associations were observed between rate of change in any CRF and incidence of CAC in either men or women who had undetectable CAC at baseline. Rate of change in LDL-C was inversely associated with CAC incidence in men, but this relationship did not remain significant when adjusting for covariates.

Among both men and women who had detectable CAC at baseline, HDL-C and glucose increased over time on average, while SBP, DBP, LDL-C, and TG decreased over time on average. An average increase over time in WC was also observed in these men, while an average decrease over time in BMI was observed in these women. As discussed above, the average decrease over time observed in SBP, DBP, LDL-C, and TG appeared to be the result of medication use, although men not taking medications targeting DBP and LDL-C continued to exhibit average decreases in these CRFs over

time (data not shown). Similar to individuals who had undetectable CAC at baseline, there was an inverse correlation between baseline level and rate of change for SBP, DBP, and LDL-C in both men and women, indicating that individuals with higher baseline levels of these CRFs tended to exhibit greater decline (or less progression) in those levels over time, likely due to treatment. An inverse correlation between baseline level and rate of change in glucose was also observed in men, as well as a positive correlation for HDL-C. There was significant variability across these individuals in the rates of change of all CRFs with the exception of TG in both men and women, and glucose in women.

No significant associations were observed between rate of change in any CRF and progression of CAC in men that had detectable CAC at baseline when controlling for covariates. Rates of change in DBP and TG were inversely associated with CAC progression in these men, but these relationships did not remain significant when adjusting for covariates. In women that had detectable CAC at baseline, no significant associations were observed between rates of change in WC, BMI, HDL-C, TG, or glucose on CAC progression. However, regression (or less progression) in SBP, DBP, and LDL-C were each individually associated with greater progression of CAC controlling for covariates in these women. These relationships remained significant after further adjusting for baseline CAC level, suggesting that existing calcification level did not influence these associations.

Results of post hoc analyses suggested that these inverse associations observed in women that had detectable CAC at baseline might be influenced by the use of antihypertensive and lipid-lowering medications aimed to treat these factors. Women that received these medications throughout the study period showed significant average

decreases in SBP, DBP, and LDL-C, with the greatest decreases being observed for those women that had the highest initial levels (correlation not significant for LDL-C). On the other hand, women not receiving these medications throughout the study period showed either average increases or no significant change over time in these factors. Additionally, individuals on these medications had higher average baseline CAC levels as well as showed greater average progression of CAC compared to individuals not receiving these medications. Furthermore, when examining women receiving and not receiving these medications separately, the observed inverse relationships between rates of change in SBP, DBP, and LDL-C on CAC progression became more evident and remained significant (LDL-C not significant) in those receiving respective medications, but not in those not receiving these medications. Additional post hoc analyses showed that the inverse associations between rates of change in SBP and DBP on CAC progression were not independent of rate of change in LDL-C, with rate of change in LDL-C remaining inversely associated with CAC progression independent of rates of change in SBP and DBP.

This may suggest that individuals receiving medications, and thus likely to have a higher level and longer history of underlying pathology, may continue to exhibit increased CAC progression despite showing regression (or less progression) in their CRF levels. For instance, these individuals may continue to express greater underlying pathology not detected in serial measures of CRFs due to treatment, which may continue to impact the calcification process (Kronmal et al., 2007). These findings are in line with one recently published study showing that longitudinal cholesterol changes over a median of 5.9 years were not related to CAC progression in individuals receiving and not

receiving statin and/or fibrate treatment (Tenenbaum, Shemesh, Koren-Morag, Fisman, Adler, et al., 2010), as well as at least two clinical trials reporting no effects of statin treatment on CAC progression amidst regression and/or stabilization of cholesterol levels (Arad et al., 2005; Raggi et al., 2005). It should be noted that these analyses only examined women who had received or not received these medications continuously throughout the study period, and thus excluded individuals that may have been prescribed or taken off these medications during this time.

Additionally, baseline levels of CRFs were controlled in models examining change associations. It is possible that including baseline CRF levels may have also controlled previous changes in CRFs, which would have already manifested themselves in that baseline level. Post-hoc analyses on a select number of variables were conducted to examine this. Results of these analyses suggested that removing the influence of baseline CRF levels on CAC outcomes did not greatly influence estimates of change associations.

In this study, separate analyses were conducted to examine associations between each CRF and CAC, and therefore associations independent of other CRFs were not assessed, with the exception of post hoc analyses described above. Caution should be taken when comparing these results to previous findings, given the various differences in analytic approaches, operationalizations of CAC progression (i.e., change scores, percent change from baseline, log-transformations, etc.), as well as scanning methodologies employed across past studies, all of which may influence parameter estimates (Kronmal et al., 2007). Additionally, previous studies have generally analyzed both men and women simultaneously.

Some aspects of these findings (baseline CRF and CAC incidence/progression associations) are consistent with a previous report (Kronmal et al, 2007). However, several differences between that study and the present study should be noted, most prominently that 1) the present study modeled CAC progression using LGM whereas Kronmal et al. (2007) used an absolute difference score between participants' first follow-up and baseline CT exams, 2) the present study used data collected at two follow-up CT exams whereas Kronmal et al. (2007) used data from only an initial follow-up CT exam, 3) the present study used FIML to account for missing data on CRFs and CAC measures, thus using all available data, whereas Kronmal et al. (2007) excluded individuals that had missing data on their initial follow-up CT exam, 4) we controlled covariates when examining individual CRF relationships (age, race/ethnicity, smoking, family history of CVD, income, and medication use) whereas the study by Kronmal et al. (2007) controlled for age, gender, and length of follow-up in initial univariate analyses, and then examined multivariate models using a backward selection approach in which all variables were included, some of which were not included in the present study (i.e., fribrinogen, CRP, and creatinine), 5) in CAC progression analyses, the present study controlled for medication use as a time-varying covariate whereas Kronmal et al. (2007) examined medication use at baseline, 6) the study by Kronmal et al. (2007) adjusted for scanner type and scanner pair changes whereas the present study did not (Kronmal et al. (2007) reported scanner type was not related to progression in their analyses, however they did report that scanner pair changes may have influenced CAC progression estimates), 7) the present study used SEM to analyze CRF and CAC associations whereas Kronmal et al. (2007) used relative risk and robust regression analyses, and 8) the present

study analyzed men and women separately, whereas Kronmal et al. (2007) tested for gender interactions in their analyses (no significant gender interactions in how CRFs related to CAC progression were reported).

Although we did not directly test for between-gender differences, our findings suggest that there may be some gender differences in how CRFs relate to CAC incidence and progression. For instance, among individuals that had undetectable CAC at baseline, baseline levels of SBP and DBP were associated with CAC incidence in men and not women, whereas baseline levels of HDL-C were associated with CAC incidence in women but not men. Additionally, among individuals that had detectable CAC at baseline, baseline levels of SBP, HDL-C, and TG were associated with CAC progression in men and not women, whereas baseline levels WC as well as rates of change in SBP, DBP, and LDL-C were associated with CAC progression in women but not men. This is interesting and warrants further investigation, but may indicate that analyzing men and women simultaneously could mask effects. Previous research has demonstrated that compared to men and before the age of about 70, the development of CAC in women generally lags behind by about 10 years (Frink, 2009; Janowitz et al., 1993).). This trend was observed in our sample in terms of incident CAC (i.e., compare Table 03 and Table 04). Whether the observed differences in how CRFs relate to CAC between genders is a function of this lag in CAC development (suggesting that some CRFs may be more strongly associated with earlier stages of CAC whereas others may be more influential at later stages), or actual biological differences between them in how CRFs influence the calcification process, warrants further investigation.

To our knowledge, no previous study has systematically reported on rates of change in CRFs, CAC, and how they are related to one another, and thus our results lack comparison and merit replication. Contrary to what was hypothesized, regression (or less progression) – and not progression – in certain CRFs were related to greater progression of CAC in women. However, this appeared to be influenced by the use of medications, and thus future studies are needed to systematically investigate these relationships in the context of medication use. Controlling for medication use by including the variable as a covariate may not be adequate as such an analysis assumes no interaction between the covariate and other predictors in the model. Our post hoc analyses revealed that medication use interacted with change in specific CRF's to differentially predict change in CAC. Nonetheless, our findings are somewhat consistent with recently published studies of different samples showing that decreases in cholesterol levels are not paralleled by decreases in CAC progression (Arad et al., 2005; Raggi et al., 2005; Tenenbaum, Shemesh, Koren-Morag, Fisman, Adler, et al., 2010). Studies longitudinally examining how pharmacological treatment of CRFs other than cholesterol influence rates of CRF and CAC change are lacking.

Several other factors could be postulated that account for the null and inverse associations observed between changes in CRFs and CAC incidence and progression in our sample. For instance, it may be reasonable to assume that changes in CRFs influence CAC in a time-lagged, as opposed to directly parallel, fashion, and that the MESA study period averaging 4.9 years may not be conducive to assessing these effects (in fact, average rates of change in CRFs during the study period were quite small). For example, if we assume that a particular CRF level for an individual increased dramatically prior to

the study period, but then stabilized or even regressed during that period due to a possible physiological ceiling effect or intervention, and that the prior increase in that CRF led to an increased rate of CAC progression within the study period, then that effect may have gone undetected or may have even been observed as an inverse association. If these, and/or other possible scenarios may have influenced our results given the large MESA sample remains unknown. A longer study period, ideally across individuals' lifespan or beginning at an earlier age, may be needed to accurately assess how changes in CRFs influence the development and progression of CAC, which can begin to manifest itself as early as the second decade of life (Alexopoulos & Raggi, 2009). Previous studies suggest that associations between measures of CAC and actual events are not apparent within short time period (e.g., 3 years follow-up), but emerge after a longer passage of time (e.g., 6 years follow-up) (Detrano, Wong, Doherty, Shavelle, Tang, et al., 1999; Park, Detrano, Xiang, Ibrahim, LaBree, et al., 2002), and it could be that the effects of CRFs on CAC mirror observation.

Also, it is premature to assume that changes in different CRFs influence CAC in the same temporal fashion, given that these variables may exert their effects on the calcification process through diverse mechanisms. It is also possible that CRFs progress and/or regress differently across different stages of their pathology, and that this may obscure their actual effects on CAC when simultaneously examining heterogeneous samples of individuals in terms of gender, age, risk profiles, medication use, etc. Future research may consider examining these relationships within different subgroups of individuals, for instance, further stratifying by age and/or risk categories. It could be that changes in CRFs are positively associated with CAC progression in younger and/or

lower-risk individuals, and that these associations change as individuals become older and/or transition into higher-risk categories, when various lifestyle and pharmacological interventions are likely to be introduced.

The measurement of CAC may pose an additional concern when analyzing our results, as well as those of previous studies. It has been noted that technical factors related to computed tomography procedures can influence variability in CAC measurement that is not physiological in nature, and it is unknown whether such "noise" is a random process or possibly related to existing calcification level (Kronmal et al., 2007). There is also little research addressing the precision and reliability of different scanning methods to detect CAC, specifically across various levels of subclinical disease. For example, measurement of CAC may be more precisely and reliably quantified at low to moderate levels of disease, but may be less sensitive to detecting change in the presence of initially large volume of disease. If this is the case, unit differences across different stages of disease may not be comparable, which has important implications for the modeling of CAC progression. Furthermore, research has not yet detailed the trajectory of CAC progression over the lifespan, yet currently employed methods of modeling CAC progression assume a linear functional form. If CAC indeed follows some form of nonlinear trajectory, then the interpretations of these and previous findings warrant considerable caution, as any absolute or percent change in CAC at different stages of subclinical disease may not be equivalent in terms of the risk information it conveys (i.e., a smaller, but possibly riskier increase in CAC at an initially high level may be more important to predict to than a larger change in CAC at a much lower level). Moreover, the functional form of CAC progression may be different across individuals

receiving medications or other interventions, and thus grouping such individuals together in analyses may be not be appropriate.

There is also debate regarding whether the calcification process is purely maladaptive, reparative or stabilizing, or some combination of the two (i.e., certain types of plaque may be advantageous while others may not; Alexopoulos & Raggi, 2009). If this is the case, indiscriminate quantification of whole plaque presence may not accurately distinguish between individuals as greater risk of events, and could bias results. Taking this possibility into consideration, an alternative postulation regarding the observed inverse relationships between regression (or less progression) in CRFs and progression of CAC is that improving CRF levels may be associated with the development of stabilizing or protective plaque.

Additionally, the possibility of sample bias in our study should be considered. Firstly, persons with clinical CVD were excluded from MESA, and thus these results do not generalize to such individuals. Secondly, among all individuals participating in MESA, those included in our analyses were slightly older, less affluent, more likely to be Black and less likely to be White, as well as slightly unhealthier in terms of smoking, blood pressure, glucose levels, and use of antihypertensive and glucose-lowering medications, which may have led to weakened risk factor associations. Thirdly, attrition rates were higher for individuals not receiving medications, and it is unknown whether such individuals included healthier persons or unhealthier samples of individuals facing obstacles to receiving treatment (i.e., low income, lack of medical insurance, etc.). Lastly, the older individuals participating in MESA may inherently represent a biased healthier sample in that they were alive and able to participate, and thus changes over time in their

CRFs and CAC, as well their relationships, may underestimate what would be expected in the general population of individuals their age.

Finally, the supposition that changes in risk factors over time does not greatly influence CAC progression should not be discounted. While it has been demonstrated that increased levels of certain risk factors at baseline are associated with increased progression of CAC, multivariate models including many factors have only been able to explain very little of the variability in such progression (i.e., Kronmal et al., 2007). It may be that risk factors exhibit a greater influence on the initiation of plaque development as opposed to its progression. The fact that CAC has been shown to add incremental value in predicting CVD events above and beyond these CRFs suggest that these processes are somewhat independent and could possibly proceed differently over time for some individuals. This does not imply that increases in various CRFs over time are unrelated to worse cardiovascular prognoses and outcomes independent of their effects on CAC, possibly acting on other mechanisms. An interesting extension to the present study might be to evaluate how changes in CRFs relate to clinical outcomes.

While many limitations to the interpretation of the present study's findings have been outlined, and other hypotheses are likely to emerge, there are also many strengths in terms of the MESA study and our methodology that deserve recognition. In addition to having a large sample size, a community-based as opposed to referral-based recruitment approach, and a longitudinal design incorporating standardized data collection procedures, the MESA study also had representation of both genders as well as different racial/ethnic groups. Although racial/ethnic groups were not examined separately in our study, race/ethnicity was included as a covariate in our models. Adjusting for covariates,

we found no race/ethnic differences (relative to Whites) in rates of CAC incidence or progression, which is consistent with previous findings suggesting that CAC has similar predictive value in terms of events across racial/ethnic groups (Detrano et al., 2008). However, these findings cannot address whether different racial/ethnic groups exhibit differential associations between changes in CRFs and CAC progression. Of note, Kronmal et al. (2007) noted racial/ethnic differences in the predictive power of baseline diabetes on CAC progression. The employment of LGM in the present study also allowed for use of all collected data as well as the modeling of progression in these variables devoid of measurement error, while also allowing for the control of varied medication use across all exam time points. LGM also allowed for the examination of how baseline levels of our variables related to their rate of change over time. It should be noted that many statistical analyses were conducted in this study, and thus some of the observed significant associations may represent Type 1 error.

To our knowledge, this is the first study systematically reporting on how rates of change in various CVD risk factors relate to the incidence and progression of CAC. These findings, as well as results of how baseline characteristics/risk factor levels are associated with CAC incidence and progression, were further presented for men and women separately. To date, little is known regarding the pathogenesis of CAC or the factors involved in its progression. Given the significant and continued burden posed by atherosclerotic disease in our society despite major advances in prevention and treatment over recent years, research aimed at further elucidating these mechanisms seems warranted. The development of improved prediction models that can account for the complexity of risk factor trajectories and interactions, along with a better understanding

of CAC pathophysiology and its relationship to atherosclerosis and CVD events, could help curb this burden. Research aimed at continuing to elucidate how changes in risk factors over time relate to the progression of subclinical disease, before the occurrence of an irreversible event, may have important implications for the identification of effective targeted therapies that can improve CVD outcomes. We believe our findings may serve as an informative reference point for such future studies directed at further clarifying these inherently complex and multifaceted associations, with the hope of furthering our understanding of heart disease risk, development, progression, and ultimately, prevention

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Appendix: Tables

Table 01

Number of Participants with Available Data on Variables of Interest at Each Exam Time Point, Stratified by Gender

	Men				Women			
Variable	Exam 1	Exam 2	Exam 3	Exam 4	Exam 1	Exam 2	Exam 3	Exam 4
Gender, Age, Race/Ethnicity	3,213	------	------	------	3,601	------	------	------
Income	3,088	------	------	------	3,453	------	------	------
Family History of CVD	2,995	------	------	------	3,400	------	------	------
Smoking	3,203	------	------	------	3,589	------	------	------
Medication Use	3,213	2,844	2,775	2,647	3,598	3,128	3,070	2,984
Waist Circumference	3,212	2,969	2,810	2,692	3,601	3,262	3,126	3,008
Body Mass Index	3,213	2,969	2,810	2,693	3,601	3,262	3,129	3,009
Systolic/Diastolic Blood Pressure	3,211	2,969	2,809	2,691	3,600	3,261	3,127	3,007
HDL Cholesterol	3,204	2,951	2,796	2,666	3,584	3,232	3,095	2,967
LDL Cholesterol	3,156	2,904	2,743	2,635	3,545	3,210	3,067	2,942
Triglycerides	3,204	2,952	2,796	2,666	3,587	3,233	3,096	2,968
Glucose	3,203	2,952	2,798	2,665	3,586	3,232	3,089	2,969
CAC	3,213	1,397	1,343	677	3,601	1,556	1,462	729

Table 02

Gender-Stratified Demographic and Risk Factor Information for the Entire and Retained Samples

	Entire Sample (N = 6,814)				Retained Sample (N = 4,560)			
	Men (n = 3,213)		Women (n = 3,601)		Men (n = 2,132)		Women (n = 2,428)	
Variable	*M* or *%*	(*SD*)	*M* or *%*	(*SD*)	*M* or *%*	(*SD*)	*M* or *%*	(*SD*)
Age	62.18	(10.21)	62.13	(10.26)	61.38	(9.93)	61.31	(10.00)
Race/Ethnicity								
White	39.2%		37.9%		41%		40%	
Black	26.2%		29.2%		24.4%		26.9%	
Hispanic	22.4%		21.5%		22.1%		21.6%	
Chinese	12.1%		11.5%		12.5%		11.5%	
Family History of Heart Attack	39.2%		45.9%		39.4%		45.6%	
Income								
< $20K	19%		28.3%		16.1%		24.7%	
$20K to < $40K	23.7%		29.4%		23%		29.5%	
$40K to < $75K	29.2%		24.7%		30.2%		26%	
≥ $75K	28.1%		17.7%		30.6%		19.7%	
Smoking								
Never	40.5%		59.1%		41.6%		59.4%	
Former	44.9%		29.2%		45.1%		29.6%	
Current	14.6%		11.7%		13.3%		11%	
Antihypertensive Medications	35.8%		38.5%		34.4%		36.6%	
Lipid-lowering Medications	16.2%		16.1%		17.2%		16.4%	
Glucose-lowering Medications	10.3%		9%		9.1%		7.7%	
Body Mass Index	27.86	(4.45)	28.76	(6.22)	27.90	(4.38)	28.69	(6.15)
Waist Circumference (cm)	99.30	(12.24)	97.14	(16.03)	99.31	(12.16)	96.81	(16.06)
Systolic Blood Pressure (mm Hg)	126.03	(19.33)	127.10	(23.22)	124.83	(18.68)	125.35	(22.27)
Diastolic Blood Pressure (mm Hg)	75.05	(9.41)	69.12	(10.17)	75.05	(9.09)	68.80	(10.07)
HDL Cholesterol (mg/dL)	45.04	(11.78)	56.25	(15.27)	44.83	(11.34)	56.41	(15.13)
LDL Cholesterol (mg/dL)	116.66	(31.01)	117.69	(31.86)	117.13	(30.63)	117.12	(31.45)
Triglycerides (mg/dL)	135.38	(95.40)	128.21	(82.33)	134.93	(93.51)	126.34	(71.10)
Glucose (mg/dL)	100.22	(32.91)	94.84	(27.47)	98.60	(28.94)	93.54	(25.82)
Detectable CAC	61.1%		39.8%		59.1%		38.3%	
CAC score	223.63	(540.65)	76.87	(241.78)	194.09	(474.53)	69.85	(222.21)

Table 03

CAC Incidence Prevalence for Men with Undetectable CAC at Baseline

	Using Second CAC Exam Data; M = 2.46 years, SD = 0.865 from baseline		Using Third CAC Exam Data; M = 4.90 years, SD = 0.514 from baseline	
Age Range	Rate	(n)	Rate	(n)
All	20.6%	(872)	39.5%	(190)
45-54	13.7%	(422)	32.3%	(93)
55-64	23.2%	(254)	32.7%	(49)
65-74	32.3%	(155)	62.5%	(40)
75-84	31.7%	(41)	50%	(8)

Table 04

CAC Incidence Prevalence for Women with Undetectable CAC at Baseline

	Using Second CAC Exam Data; M = 2.46 years, SD = 0.848 from baseline		Using Third CAC Exam Data; M = 4.96 years, SD = 0.498 from baseline	
Age Range	Rate	(n)	Rate	(n)
All	13.9%	(1,498)	22.4%	(303)
45-54	9.2%	(629)	14.5%	(138)
55-64	15.5%	(477)	24.4%	(90)
65-74	19%	(327)	34.4%	(61)
75-84	21.5%	(65)	35.7%	(14)

Table 05

CRF Growth Model Estimates for Men with Undetectable CAC at Baseline

CRF	Baseline *M*	(*SD*)	Change *M*	(*SD*)	Standardized Baseline and Change Correlation
WC (cm)	97.238*	(11.14*)	0.222*	(0.71*)	-0.047
BMI	27.530*	(4.06*)	0.041*	(0.26*)	0.089
SBP (mm Hg)	120.435*	(14.84*)	-0.098	(1.68*)	-0.231*
DBP (mm Hg)	74.610*	(7.37*)	-0.250*	(0.92*)	-0.205*
HDL (mg/dL)	44.814*	(9.88*)	0.413*	(0.65)	0.258
LDL (mg/dL)	116.041*	(25.16*)	-0.559*	(2.86*)	-0.124
TG (mg/dL)	133.586*	(66.01*)	-0.665	(3.87)	-0.151
Glucose (mg/dL)	95.842*	(20.98*)	1.038*	(2.00)	-0.368

* $p < .05$

Table 06

CRF Growth Model Estimates for Women with Undetectable CAC at Baseline

CRF	Baseline *M*	(*SD*)	Change *M*	(*SD*)	Standardized Baseline and Change Correlation
WC (cm)	95.533*	(15.53*)	0.326*	(0.82*)	0.018
BMI	28.690*	(6.24*)	0.039*	(0.34*)	-0.054
SBP (mm Hg)	121.199*	(18.28*)	-0.184	(1.86*)	-0.374*
DBP (mm Hg)	68.463*	(8.74*)	-0.300*	(0.87*)	-0.389*
HDL (mg/dL)	57.146*	(14.09*)	0.133*	(1.10*)	-0.012
LDL (mg/dL)	116.246*	(26.17*)	-0.315	(3.88*)	-0.351*
TG (mg/dL)	121.533*	(56.71*)	-0.435	(2.06)	-0.027
Glucose (mg/dL)	92.418*	(22.33*)	1.079*	(3.12*)	-0.354

* $p < .05$

Table 07

Multivariate Path Estimates (and Odds Ratios) of Covariates Predicting Incident CAC for Men with Undetectable CAC at Baseline

Covariate	Unstandardized Beta	(Odds Ratio)
Age	**0.050***	**(1.052*)**
Race/Ethnicity (Relative to Whites)		
Blacks	-0.416	(0.659)
Hispanics	-0.260	(0.771)
Chinese	-0.903	(0.405)
Smoking (Relative to Never Smokers)		
Former Smokers	0.463	(1.588)
Current Smokers	0.293	(1.341)
Family History of CVD	0.311	(1.365)
Income (categories)	0.023	(1.024)
Antihypertensive Med Use	0.159	(1.172)
Lipid-Lowering Med Use	0.308	(1.361)
Glucose-Lowering Med Use	0.713	(2.039)

* $p < .05$

Table 08

Multivariate Path Estimates (and Odds Ratios) of Covariates Predicting Incident CAC for Women with Undetectable CAC at Baseline

Covariate	Unstandardized Beta	(Odds Ratio)
Age	**0.042***	**(1.043*)**
Race/Ethnicity (Relative to Whites)		
Blacks	-0.128	(0.880)
Hispanics	0.178	(1.195)
Chinese	-0.212	(0.809)
Smoking (Relative to Never Smokers)		
Former Smokers	0.270	(1.310)
Current Smokers	-0.038	(0.963)
Family History of CVD	0.234	(1.263)
Income (categories)	-0.032	(0.969)
Antihypertensive Med Use	**0.488***	**(1.629*)**
Lipid-Lowering Med Use	0.209	(1.233)
Glucose-Lowering Med Use	**1.107***	**(3.024*)**

* $p < .05$

Table 09

Univariate Path Estimates (and Odds Ratios) of CRF Baseline and Change Values Predicting Incident CAC for Men with Undetectable CAC at Baseline

	Univariate Path Estimate		Univariate Path Estimate Controlling for Covariates	
CRF	Unstandardized Beta	(Odds Ratio)	Unstandardized Beta	(Odds Ratio)
WC (cm)				
Baseline	**0.044***	**(1.045*)**	**0.041***	**(1.042*)**
Change	-0.123	(0.884)	0.018	(1.019)
BMI				
Baseline	**0.096***	**(1.100*)**	**0.117***	**(1.124*)**
Change	-0.801	(0.449)	-0.543	(0.586)
SBP (mm Hg)				
Baseline	**0.028***	**(1.028*)**	**0.023***	**(1.024*)**
Change	0.051	(1.052)	0.056	(1.057)
DBP (mm Hg)				
Baseline	0.023	(1.024)	**0.042***	**(1.043*)**
Change	-0.209	(0.811)	0.028	(1.029)
HDL (mg/dL)				
Baseline	-0.011	(0.989)	-0.009	(0.991)
Change	0.296	(1.344)	0.054	(1.056)
LDL (mg/dL)				
Baseline	0.004	(1.004)	0.009	(1.009)
Change	**-0.195***	**(0.823*)**	-0.118	(0.889)
TG (mg/dL)				
Baseline	0.001	(1.001)	0.002	(1.002)
Change	-0.184	(0.832)	-0.150	(0.861)
Glucose (mg/dL)				
Baseline	0.010	(1.010)	0.009	(1.009)
Change	0.058	(1.060)	0.090	(1.094)

* $p < .05$

Table 10

Univariate Path Estimates (and Odds Ratios) of CRF Baseline and Change Values Predicting Incident CAC for Women with Undetectable CAC at Baseline

	Univariate Path Estimate		Univariate Path Estimate Controlling for Covariates	
CRF	Unstandardized Beta	(Odds Ratio)	Unstandardized Beta	(Odds Ratio)
WC (cm)				
Baseline	**0.003***	**(1.033*)**	**0.029***	**(1.029*)**
Change	-0.075	(0.928)	-0.007	(0.993)
BMI				
Baseline	**0.069***	**(1.071*)**	**0.072***	**(1.075*)**
Change	-0.454	(0.635)	-0.337	(0.714)
SBP (mm Hg)				
Baseline	**0.024***	**(1.024*)**	0.011	(1.011)
Change	0.037	(1.037)	0.052	(1.054)
DBP (mm Hg)				
Baseline	0.006	(1.006)	0.009	(1.009)
Change	-0.308	(0.735)	-0.148	(0.863)
HDL (mg/dL)				
Baseline	**-0.030***	**(0.971*)**	**-0.039***	**(0.962*)**
Change	0.069	(1.071)	0.178	(1.194)
LDL (mg/dL)				
Baseline	0.002	(1.002)	0.006	(1.006)
Change	-0.066	(0.936)	-0.046	(0.955)
TG (mg/dL)				
Baseline	0.008	(1.008)	0.009	(1.009)
Change	-0.209	(0.812)	-0.233	(0.792)
Glucose (mg/dL)				
Baseline	**0.023***	**(1.023*)**	0.015	(1.015)
Change	0.012	(1.012)	0.030	(1.031)

* $p < .05$

Table 11

CAC Growth Model Estimates for Men with Detectable CAC at Baseline (Agatston Units)

n	Baseline *M* (*SD*)	Change *M* (*SD*)	Standardized Baseline and Change Correlation
1,260	324.774* (57.63*)	57.146* (78.59*)	0.691*

* $p < .05$

Table 12

CAC Growth Model Estimates for Women with Detectable CAC at Baseline (Agatston Units)

n	Baseline *M* (*SD*)	Change *M* (*SD*)	Standardized Baseline and Change Correlation
930	180.454* (32.44*)	39.098* (63.88*)	0.809*

* $p < .05$

Table 13

CRF Growth Model Estimates for Men with Detectable CAC at Baseline

CRF	Baseline *M* (*SD*)	Change *M* (*SD*)	Standardized Baseline and Change Correlation
WC (cm)	100.364* (11.93*)	0.076* (0.79*)	-0.104
BMI	28.168* (4.43*)	-0.004 (0.26*)	-0.003
SBP (mm Hg)	126.945* (15.06*)	-0.647* (2.07*)	-0.296*
DBP (mm Hg)	74.650* (7.53*)	-0.709* (1.04*)	-0.232*
HDL (mg/dL)	45.080* (10.63*)	0.469* (0.76*)	0.413*
LDL (mg/dL)	115.860* (25.85*)	-2.781* (4.22*)	-0.281*
TG (mg/dL)	138.449* (77.21*)	-2.611* (12.99)	-0.345
Glucose (mg/dL)	100.672* (25.68*)	0.661* (3.98*)	-0.476*

* $p < .05$

Table 14

CRF Growth Model Estimates for Women with Detectable CAC at Baseline

CRF	Baseline *M*	(*SD*)	Change *M*	(*SD*)	Standardized Baseline and Change Correlation
WC (cm)	98.274*	(15.09*)	0.085	(0.89*)	0.004
BMI	28.710*	(5.85*)	-0.035*	(0.37*)	-0.067
SBP (mm Hg)	130.665*	(18.56*)	-0.487*	(2.58*)	-0.340*
DBP (mm Hg)	68.514*	(8.29*)	-0.413*	(1.10*)	-0.346*
HDL (mg/dL)	55.244*	(13.69*)	0.221*	(1.07*)	-0.073
LDL (mg/dL)	117.836*	(25.80*)	-1.895*	(4.58*)	-0.314*
TG (mg/dL)	136.761*	(62.18*)	-1.596*	(6.58)	-0.282
Glucose (mg/dL)	97.017*	(24.13*)	0.905*	(2.65)	-0.186

* $p < .05$

Table 15

Multivariate Path Estimates of Covariates Predicting CAC Baseline and Change for Men with Detectable CAC at Baseline

	Multivariate Path Estimates		Multivariate Path Estimates Controlling for Baseline CAC	
Covariate	Baseline	Change	Baseline	Change
Age	**16.180***	**1.860***	**16.180***	0.401
Race/Ethnicity (Relative to Whites)				
Blacks	-79.357	-4.443	-79.358	2.713
Hispanics	-9.734	-10.712	-9.733	-9.835
Chinese	-80.063	-12.644	-80.066	-5.422
Smoking (Relative to Never Smokers)				
Former Smokers	**67.217***	4.164	**67.221***	-1.902
Current Smokers	63.714	9.714	63.713	3.972
Family History of CVD	**74.656***	**11.203***	**74.657***	4.289
Income (categories)	4.407	0.352	4.406	-0.045
Baseline Antihypertensive Med Use	65.650	**18.133***	65.648	**12.215***
Baseline Lipid-Lowering Med Use	42.031	6.389	42.035	2.595
Baseline Glucose-Lowering Med Use	**149.772***	**33.813***	**149.765***	**20.312***

* $p < .05$

Table 16

Multivariate Path Estimates of Covariates Predicting CAC Baseline and Change for Women with Detectable CAC at Baseline

	Multivariate Path Estimates		Multivariate Path Estimates Controlling for Baseline CAC	
Covariate	Baseline	Change	Baseline	Change
Age	**8.870***	**1.193***	**8.871***	-0.211
Race/Ethnicity (Relative to Whites)				
Blacks	-25.995	2.225	-26.007	6.350
Hispanics	**-79.313***	-9.171	**-79.321***	3.383
Chinese	-9.961	-4.845	-9.962	-3.278
Smoking (Relative to Never Smokers)				
Former Smokers	37.415	10.748	37.409	4.832
Current Smokers	**75.402***	11.283	**75.404***	-0.650
Family History of CVD	20.337	5.611	20.347	2.380
Income (categories)	-2.413	-0.848	-2.411	-0.467
Baseline Antihypertensive Med Use	14.597	5.181	14.603	2.863
Baseline Lipid-Lowering Med Use	13.312	0.321	13.321	-1.800
Baseline Glucose-Lowering Med Use	**120.443***	**43.694***	**120.458***	**24.623***

* $p < .05$

Table 17

Univariate Path Estimates of CRF Baseline and Change Values Predicting CAC Baseline and Change for Men with Detectable CAC at Baseline

	Univariate Path Estimate		Univariate Path Estimate Controlling for Covariates		Univariate Path Estimate Controlling for Covariates and Baseline CAC	
CRF	Baseline	Change	Baseline	Change	Baseline	Change
WC (cm)						
Baseline	1.517	**0.407***	0.347	0.301	0.375	0.269
Change		-0.550		0.390		0.396
BMI						
Baseline	-1.631	0.605	-0.107	0.889	-0.077	0.898
Change		0.434		4.930		4.935
SBP (mm Hg)						
Baseline	**4.382***	**1.118***	1.479	**0.789***	1.479	**0.655***
Change		-1.185		-0.940		-0.940
DBP (mm Hg)						
Baseline	**-7.665***	-0.332	-1.063	0.366	-1.063	0.463
Change		**-8.508***		-6.722		-6.722
HDL (mg/dL)						
Baseline	3.441	-0.290	1.724	-0.493	1.719	**-0.651***
Change		-2.011		-4.587		-4.613
LDL (mg/dL)						
Baseline	**-2.378***	**-0.480***	-1.132	**-0.352***	-1.132	**-0.250***
Change		-1.809		-1.083		-1.083
TG (mg/dL)						
Baseline	-0.369	0.009	0.072	**0.076***	0.072	**0.070***
Change		**-0.523***		-0.395		-0.395
Glucose (mg/dL)						
Baseline	0.612	**0.363***	0.442	**0.382***	0.442	**0.342***
Change		-0.020		0.338		0.338

* $p < .05$

Table 18

Univariate Path Estimates of CRF Baseline and Change Values Predicting CAC Baseline and Change for Women with Detectable CAC at Baseline

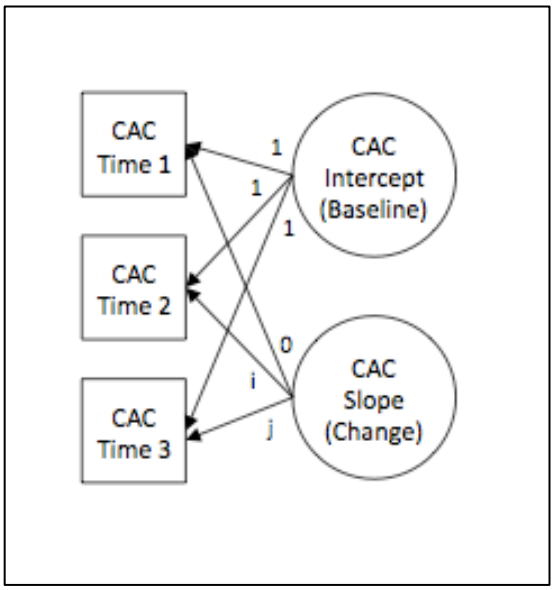
	Univariate Path Estimate		Univariate Path Estimate Controlling for Covariates		Univariate Path Estimate Controlling for Covariates and Baseline CAC	
CRF	Baseline	Change	Baseline	Change	Baseline	Change
WC (cm)						
Baseline	0.960	**0.437***	1.318	**0.456***	1.317	**0.248***
Change		2.474		2.290		2.290
BMI						
Baseline	1.557	**0.984***	**4.993***	**1.374***	**4.979***	0.587
Change		6.795		7.976		7.946
SBP (mm Hg)						
Baseline	**2.367***	**0.410***	0.986	0.183	0.985	0.028
Change		**-3.827***		**-3.167***		**-3.173***
DBP (mm Hg)						
Baseline	-1.268	-0.215	0.914	0.023	0.918	-0.121
Change		**-9.882***		**-8.570***		**-8.558***
HDL (mg/dL)						
Baseline	-0.463	-0.116	**-1.389***	-0.250	**-1.388***	-0.030
Change		0.797		0.762		0.757
LDL (mg/dL)						
Baseline	**-0.932***	**-0.253***	-0.288	**-0.202***	-0.287	**-0.157***
Change		**-2.890***		**-2.487***		**-2.485***
TG (mg/dL)						
Baseline	-0.006	-0.012	0.094	0.029	0.096	0.013
Change		-0.451		-0.315		-0.321
Glucose (mg/dL)						
Baseline	1.013	**0.516***	**1.241***	**0.561***	**1.246***	**0.366***
Change		-1.510		-1.094		-1.119

* $p < .05$

Appendix: Figures

Figure 1

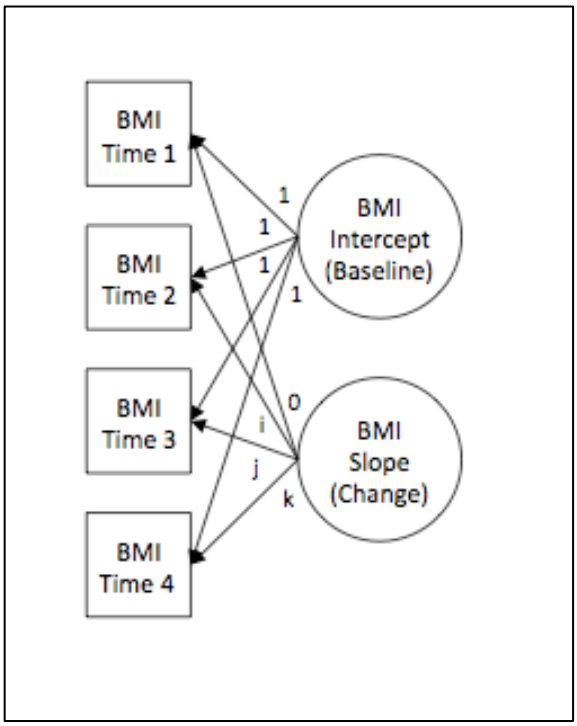
Model of CAC Progression



The loadings *i* and *j* reflected the time structure of the data.

Figure 2

Model of CRF Progression

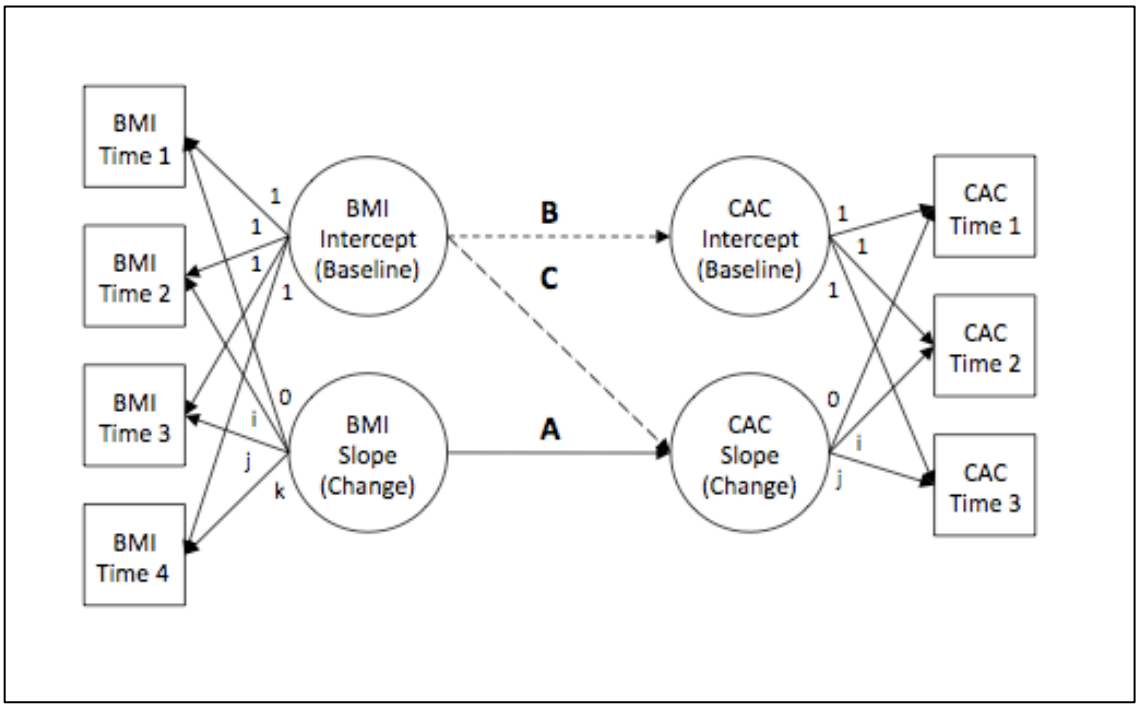


The loadings *i*, *j*, and *k* reflected the time structure of the data.

This latent growth model was also conducted on the other CRFs of interest (waist circumference, systolic blood pressure, diastolic blood pressure, HDL cholesterol, LDL cholesterol, triglycerides, and glucose).

Figure 3

Univariate Model of CRF Progression Predicting CAC Progression (Path A)

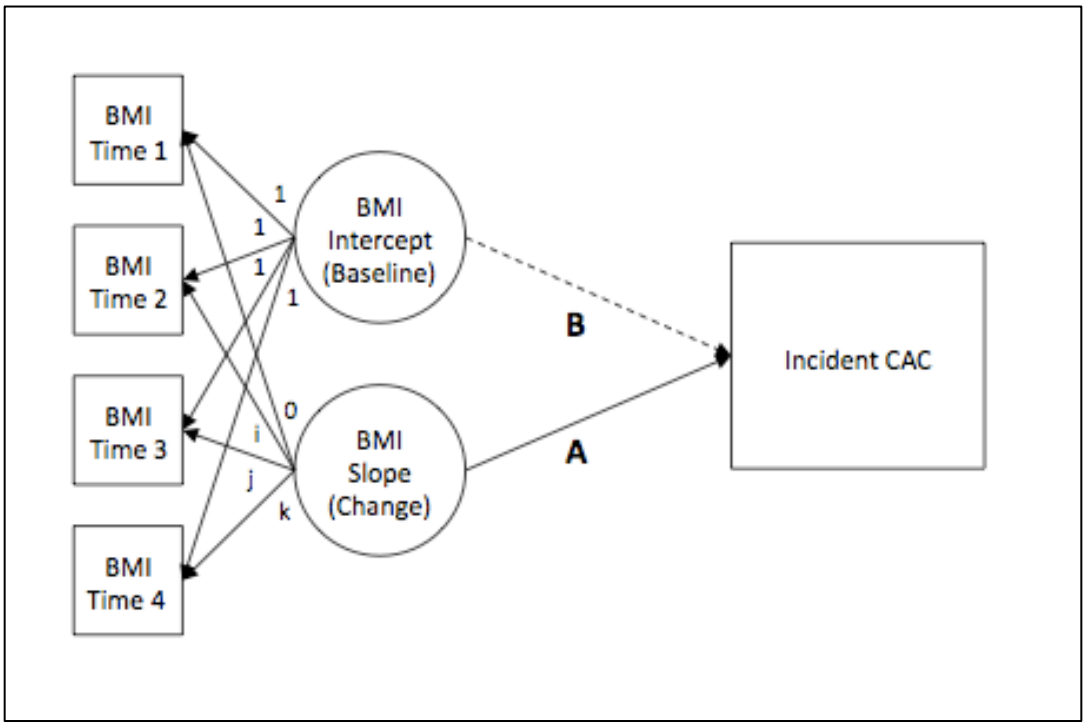


This structural equation model was also conducted using the other CRFs of interest (waist circumference, systolic blood pressure, diastolic blood pressure, HDL cholesterol, LDL cholesterol, triglycerides, and glucose) as predictors of CAC progression.

This model also allowed for the examination of how the baseline value of each CRF univariately related to (1) the baseline value of CAC (Path B) and (2) the progression of CAC (Path C).

Figure 4

Univariate Model of CRF Progression Predicting CAC Incidence (Path A)

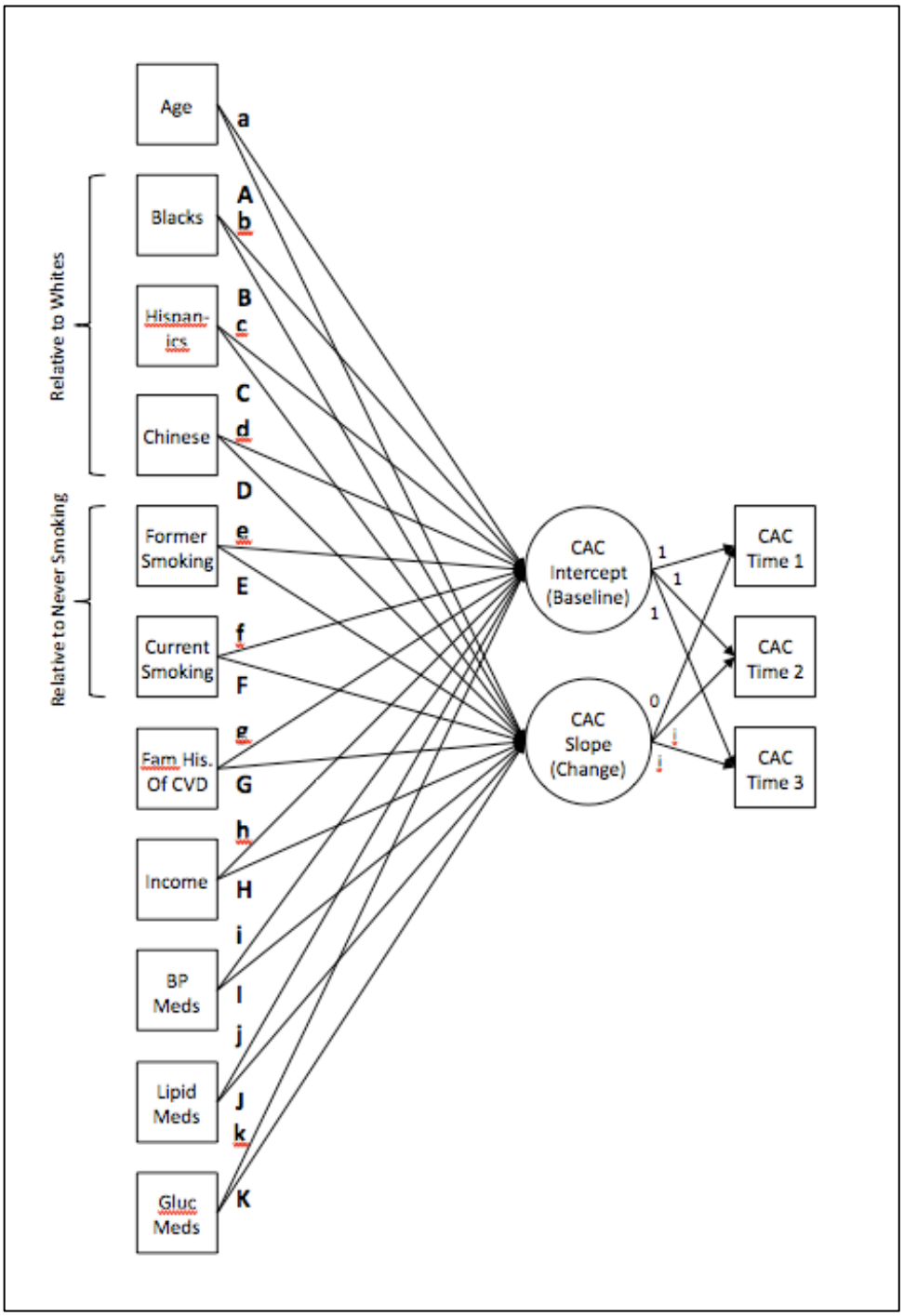


This structural equation model was also conducted using the other CRFs of interest (waist circumference, systolic blood pressure, diastolic blood pressure, HDL cholesterol, LDL cholesterol, triglycerides, and glucose) as predictors of CAC incidence.

This model also allowed for the examination of how the baseline value of each CRF univariately related to CAC incidence (Path B).

Figure 5

Multivariate Model of Covariates Predicting CAC Progression (Paths A-K)



This model also allowed for the examination of how covariates independently related to the baseline values of CAC (Paths a-k).

Figure 6

Multivariate Model of Covariates Predicting CAC Incidence (Paths A-K)