Association of air pollution with longitudinal changes in arterial stiffness and correlates of longitudinal change in arterial stiffness in the Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

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Background: Many studies have shown associations between particulate matter with diameter of less than 2.5 micrometers in aerodynamic diameter ($PM_{2.5}$), also called fine particulate air matter, and cardiovascular disease (CVD) events. Improved understanding of the biological mechanisms linking air pollution to cardiovascular health effects is crucial to giving further support and justification for limiting air pollution. Arterial function measures, which measure arterial elasticity and stiffness, may be part of mechanisms linking air pollution and CVD events. Limited research has been done to examine how predictive a wide range of arterial stiffness measures is of CVD events in a single cohort. Few studies have examined determinants of longitudinal change in arterial stiffness.

Objectives: The overall objective of this dissertation is to examine whether long-term air pollutant exposures impact cross-sectional measurements of arterial function measures and longitudinal change in arterial function measures. We also investigated how short-term air pollutant exposures affect cross-sectional measurements of arterial function measures. We

looked at how these arterial stiffness measures predict subsequent cardiovascular disease (CVD) events. In addition, the correlates of longitudinal change in arterial stiffness measures were also examined in order to better understand how these measures may be on the biological pathway connecting traditional cardiovascular risk factors and CVD events.

Methods: First, we compared the predictive value of five measures of arterial function, both arterial stiffness and arterial elasticity, assessed at Exam 1 of the Multi-Ethnic Study of Atherosclerosis (MESA study) (2000-2002) on the time to occurrence of the first coronary heart disease event (CHD) in the MESA study using Cox proportional hazards regression. To assess the ability of each arterial function measure to improve discrimination of events, we used receiver-operating characteristic curves and areas under the receiver-operating characteristic curves (AUC). The arterial function measures we used for this analysis included C1 and C2, which are measures of arterial elasticity obtained via radial tonometry, aortic distensibility (AD), which is a measure of arterial elasticity obtained via aortic MRI, and carotid distensibility (CD) and Young's modulus (YM) at the carotid artery, which are measures of arterial elasticity and arterial stiffness obtained via carotid ultrasound. Next, we investigated the association between traditional cardiovascular risk factors and longitudinal change in four arterial functional measures between Exam 1 (2000-2002) and Exam 5 (2010-2012) of the MESA study utilizing linear mixed models with a fixed slope and random intercepts. As sensitivity analyses, we also examined these relationships using simple linear regression models. Finally, we utilized linear mixed models to examine the association between long-term air pollution and cross-sectional measurements of arterial function measures, long-term air pollution and longitudinal change in arterial function measurements, and short-term pollution and cross-sectional measurements in

arterial function measurements. The Multi-Ethnic Study of Atherosclerosis Air study (MESA Air) estimated the outdoor ambient individual concentrations of fine particulate matter ($PM_{2.5}$) and oxides of nitrogen (NOx) based on spatiotemporal air pollution exposure models. These models incorporated a wide range of geographic covariates and data from cohort-specific air pollution models. For short-term air pollution analyses, we utilized city-wide daily average fine particulate matter ($PM_{2.5}$) from Air Quality System (AQS) monitors. The arterial function measures used to investigate the relationship of traditional cardiovascular risk factors with arterial function measures and the relationship between air pollution exposure with arterial function measures included Pressure Time Constant 1 (PTC1) and Pressure Time Constant 2 (PTC2), which are measures of arterial elasticity obtained via radial tonometry, and distensibility coefficient (DC) and Young's Elastic modulus (YEM) at the carotid artery, which are measures of arterial elasticity and arterial stiffness obtained via carotid ultrasound. PTC1 and PTC2, as well as DC and YEM, are calculated using slightly different formulas than C1 and C2, as well as CD and YM, respectively.

Results: In our analysis of the predictive value of arterial function measured at baseline of the MESA study, we found that the hazard ratio of CHD event per standard-deviation higher value of arterial function was 0.97 (95% Confidence Interval (CI): 0.86, 1.10) for C1, 0.73 (95% CI: 0.63, 0.86) for C2, 0.98 (95% CI: 0.86, 1.11) for carotid distensibility, 0.99 (95% CI: 0.90, 1.09) for Young's modulus, and 0.90 (95% CI: 0.74, 1.10) for aortic distensibility. C2 provided additional discrimination for the prediction of CHD (area under the curve= 0.736 vs. 0.743, p=0.04). Arterial stiffness increased in all measures as anticipated over time, though different risk factors were associated with changes in specific arterial function measures: Being of male

gender was associated with larger declines for PTC2. Higher heart rate was associated with smaller declines in PTC1. Higher BMI at baseline was associated with smaller declines in DC. Having diabetes at baseline was associated with larger increases in YEM. Increased age at baseline was associated with smaller declines in PTC1, PTC2, DC (deceleration of stiffening), but larger increases in YEM (acceleration of stiffening) over follow-up. In addition, increased systolic arterial pressure (SBP) were associated with smaller declines in PTC1, PTC2. However, higher mean arterial pressure (MAP) was associated with larger increases in YEM (acceleration of stiffening). We found that a one interquartile (IQR) increase in annual average exposure to NOx during year 2000 (IQR= 44.5 ppb) was associated with a 0.220 $(seconds*10)^{-1}$ decrease in PTC1 (95% confidence interval (CI): -0.437 to -0.003) measured at Exams 1 and 5 (less arterial elasticity). We also found associations between increased short-term air pollution exposure with smaller cross-sectional measurements of arterial elasticity (less elasticity) and larger cross-sectional measurements of arterial stiffness (more stiffness). There were no statistically significant associations between long-term pollutant exposures and the rate of change in any of the arterial function measures.

Conclusions: Our findings provide additional data on the relationships between CVD risk factors, arterial functional measurements and CVD events. Of the five arterial function measures at baseline that we analyzed, only C2 showed an association with subsequent CHD events. Lower C2 at baseline (less elasticity) was associated with higher risk of future CHD events over follow-up. We observed different directions of the association of age with longitudinal change in arterial stiffness and between blood pressure measures with longitudinal change in arterial stiffness. We observed that higher mean arterial pressure and having increased age at baseline

were associated with larger increases in YEM over follow-up. However, we saw higher systolic blood pressure was associated with smaller declines in PTC1 and PTC2. Also, increased age at baseline was associated with smaller declines in PTC1, PTC2, and DC. Higher long-term traffic-related air pollution was associated with less arterial elasticity, when assessed by cross-sectional measurements of PTC1 at Exams 1 and 5. Higher short-term fine particulate air matter exposure was associated with reduced arterial elasticity and increased arterial stiffness, as assessed by PTC2, DC, and YEM. However, these findings do not support that long-term air pollution is associated with rate of change in arterial function measures. Additional studies of the short-term effects of air pollution and arterial function measures may help us better understand the biological mechanisms by which air pollution is related to cardiovascular disease events.

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飲水思源

Jam^{2} seoi^{2} si^{1} jyun^{4} (Cantonese) Yǐn shuǐ sī yuan (Mandarin)

"When you drink water, remember the source." -Chinese proverb

My grandparents, Jing Wong and Yue Sum, Kenneth and King Fong Lee, Caroline and Jack have inspired me with their hard work, sacrifice, perseverance and hope. Their struggles for racial, economic, and social justice in the past feel relevant to me today. My parents, Alden and Desiree, my uncle Timothy, my sister and brother-in-law, Jacqueline and James, my brother, Kenneth, my friends, Kirsty, Sachi, Kalina, Tiffany, Shari, Mary, Amanda and Mike, Nok and Mike, Adel, Sun, Jia and Bin, Meng and Junting, and Kristin have blessed me with their love, encouragement, and care of small children. I especially thank my aunt Tanya, who has made great personal sacrifice to help me complete my degree. My husband, Phayong, has been close to my heart and offered continual support and humor along the way. His commitment to train the next generation of health care workers in rural Thailand encourages me as well. Improving public health and expanding education go hand in hand.

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DEDICATION

This dissertation is dedicated to my children, Sirada, Lucas, and Noah. You all have taught me to savor moments of fun, silliness, and beauty!

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Chapter 1. Introduction

1.1 Global perspective on connection between air pollution and cardiovascular disease

From a global perspective, air pollution is a significant contributor to death and loss of healthy years of life. The Global Burden of Disease study estimated that ambient particulate matter air pollution contributed about 4.2 million deaths and ambient ozone pollution contributed about 300,000 deaths worldwide in 2015.(Forouzanfar et al. 2016) There has been a 7.8% increase in deaths attributed to ambient particulate air pollution and a 22.7% increase in deaths attributed to ambient ozone pollution from 2005 to 2015, according to this same study. Furthermore, cardiovascular disease is the leading cause of death in the world. It accounts for more than 17.3 million deaths per year in 2013, which represents 31% of all global deaths. In the United States, coronary heart disease accounts for 1 in 7 deaths, which is 360,000 deaths in a year.(Benjamin et al. 2017)

Air pollution is also a unique risk factor for cardiovascular disease because it may affect cardiovascular health on both acute and long-term time scales. In hours to days after exposure, inhalation of particulate air pollution has been documented as a trigger for cardiovascular events.(Tofler and Muller 2006) In addition, there has been a wealth of evidence showing that long-term exposure to air pollution is associated with clinical CVD events.(R D Brook et al. 2010) For example, the Harvard Six Cities study and the American Cancer Society study were two early cohort studies that found that mean city-wide pollutant concentrations were associated increased clinical CVD events, even after controlling for individual cardiovascular risk factors.(Dockery et al. 1993; Pope et al. 1995) Additional studies have also shown that exposure

to air pollution is associated with subclinical measures of CVD such as increased diastolic blood pressure (Urch et al. 2005), increased carotid intima-media thickness (CIMT) (Künzli et al. 2005), dysregulation of vascular tone and impaired endogenous fibrinolysis (Mills et al. 2005), and increased left ventricular mass index.(VanHee et al. 2009) More recent studies have also shown evidence that higher exposure to air pollution is associated accelerated progression of carotid intima-media thickness (CIMT) in specific subgroups of participants from several different randomized trials (Künzli et al. 2010) and accelerated rates of coronary artery calcification (CAC) in a multi-ethnic population of older adults.(Kaufman et al. 2016)

Some may argue that other factors such as an unhealthy diet and lack of regular exercise contribute most of the risk of clinical cardiovascular disease events. However, polluted air is a risk factor that individuals have little choice about whether or not they are exposed. People must breathe the air of the environment that they live and work in. So even a small, added risk among the entire population has a potentially large public health impact (Brook R et al. Circulation 2010). Furthermore, since the passage of the original Clean Air Act of 1970 in the United States, exposure to major air pollutants such as particulate matter, ozone, carbon monoxide, nitrogen dioxide, and sulfur dioxide, has declined on a national level.(Samet 2011) Subsequent analysis of the Clean Air Act regulations by the EPA found that the benefits of regulation greatly exceeded the costs, having an immensely positive public health impact.(U.S. Environmental Protection Agency 2011) Better understanding of the biological mechanisms that link air pollution to cardiovascular health effects is important to give further support and justification for regulations limiting air pollution. Greater knowledge of the biological mechanisms of air pollution's effects

on the cardiovascular system can also help us better protect vulnerable subpopulations and construct effective air pollution regulations.(Campen, Lund, and Rosenfeld 2012)

1.2 Biological effects of particulate matter air pollution on cardiovascular system

Air pollution may be composed of many different components. Particulate matter air pollution is a complex heterogeneous mixture of both solid particles and liquid particles which are suspended in the air. $PM_{2.5}$, which refers to particulate matter that is less than 2.5 micrometers (μm) in diameter, is about the size of an average bacterium and can penetrate small airways and alveoli. Because of concerns that $PM_{2.5}$ may be more harmful to the body because of its small size, recent regulatory efforts and health studies have focused on this categorization of particulate matter.

There is evidence for three different general biological mechanisms for the impact of particulate matter on the cardiovascular system. First, lung-based cells can release of pro-inflammatory mediators such as cytokines and molecules that interact with the vascular cells such as endothelin or histamine. This may lead to systemic oxidative stress and inflammation. Studies have shown that short-term exposure to ambient particulate matter is associated to higher levels of proinflammatory biomarkers such as C-reactive protein (CRP) and fibrinogen. (Pope 3rd et al. 2004; Rueckerl et al. 2006) Secondly, interactions between particles and lung receptors or nerves may cause disturbances in the systemic autonomic nervous system balance. Researchers have found increased heart rate (Pope 3rd, Dockery, et al. 1999; Peters et al. 1999) and decreased heart rate variability (Liao et al. 1999; Pope 3rd, Verrier, et al. 1999) associated with particulate

matter. Thirdly, particulate matter or particle components such as organic compounds or metals may actually enter into systemic circulation.

1.3 Arterial function measures as a subclinical measure of cardiovascular disease

Arterial function measures are useful subclinical measures of cardiovascular disease. Arterial functional measures help us better understand and quantify the extent of arteriosclerosis in an individual. Arteriosclerosis is a diffuse, ubiquitous process that leads to stiffening and lengthening of the aorta and proximal arteries.(Izzo and Shykoff 2001) Arteriosclerosis tends to occur with aging. The adventitia and media of the arterial wall uniformly thicken due to increases in the volume of the cells in the extracellular matrix and vascular smooth muscle cells. There is also increased deposition of collagen, fragmentation and loss of elastin, and increased amounts of calcium in the medial layer of the arterial wall.(McEniery, Wilkinson, and Avolio 2007)

Increased arterial stiffness affects the cardiovascular system in several different ways. In previous studies, increased arterial stiffness has been associated with stroke (Yang et al. 2012), congestive heart failure (Arnold et al. 1991), and decline in renal function.(Carmen A Peralta et al. 2012)

First, increased arterial stiffness results in decreased cushioning in the arteries. Using the example of the aorta, a young, elastic aorta tends to retain a fraction of the cardiac stroke volume

in proximal arteries during systole.(Izzo and Shykoff 2001) Remaining stroke volume delivered from peripheral arteries during diastole has a relatively smooth profile and the resulting pulse pressure is narrow. However, an older, more rigid aorta has less elasticity, which causes the full stroke volume to be delivered to the resistance arterioles during systole.(Izzo and Shykoff 2001) As a result, there is increased systolic blood pressure and decreased diastolic blood pressure, and thus increased pulse pressure. There is minimal, reduced flow from the peripheral arteries during diastole. This leads to increased systolic blood pressure, decreased blood pressure, and increased pulse pressure. Decreased diastolic blood pressure results in reduction of aortic pressure during diastole. This can lead to decreased coronary perfusion pressure and myocardial ischemia.(Michael F O'Rourke 2008) Increased pulse pressure can also lead to more turbulent blood flow and disturbances to the vessel walls. This can also cause a variety of cardiovascular disease events.

Secondly, increased arterial stiffness also causes incident and reflected pulse waves to travel with greater speed. As a result, the aortic pressure and pressure to the left ventricle increases during systole.(Adji, Rourke, and Namasivayam 2011) This process causes increased load to the left ventricle, and left ventricle hypertrophy, which is the increase in size of the cells in the left ventricle. As a result, the left ventricle must work harder, causing the chamber to grow thicker, lose elasticity, and stiffen. This prevents the chamber from filling properly and leads to increased pressure in the heart. The enlarged heart muscle tissue compresses its own blood vessels and restricts its own blood supply.(Mayo Foundation for Medical Education and Research (MFMER) 2015) This left ventricle dysfunction can cause an unfavorable oxygen supply and demand ratio.

Ultimately, the overworked muscle weakens and does not pump as well. Eventually, this can lead to congestive heart failure.

Third, increased arterial stiffness also affects microvascular flow, affecting the flow to highly perfused vascular beds like those in the brain or kidney.(Adji, Rourke, and Namasivayam 2011) Flow to the highly perfused vascular beds tend to be highly pulsatile, meaning there are large periodic variations in the blood flow with cardiac contractions. When the microvasculature is young and elastic, the arteries are able to absorb most of the pulsatility. However, in microvasculature that is older and stiff, there is a loss in ability to cushion pulsatility of blood flow. This can predispose a person to rupture of arterial walls, micro-hemorrhages, thrombotic obstruction of tiny arteries, and microinfarcts, which is dead tissue due to lack of blood supply.(Michael F O'Rourke and Safar 2005) These processes increase risk of stroke.

1.4 Past studies on association between arterial function and clinical CVD events

This study will also help address the question of which arterial stiffness measures are most strongly associated with CVD events, and thus are most useful to study with respect to air pollution. Previous studies have shown association between arterial stiffness (or elasticity) measures and CV events. Aortic pulse wave velocity (PWV) was highly correlated with actual cardiovascular disease outcomes independent of traditional risk factors in multiple studies.(Sutton-Tyrrell et al. 2005; Hansen et al. 2006b; Meaume et al. 2001; Tomoki Shokawa et al. 2005) A meta-analysis of 17 longitudinal studies that followed a total of 15,877 patients for a mean of 7.7 years found that an increase in aortic PWV by 1 standard deviation (SD) was associated with the pooled relative risk (RR) in total CV events of 1.47 (95% CI: 1.31,

1.64).(Charalambos Vlachopoulos, Aznaouridis, and Stefanadis 2010) Within the MESA cohort, small artery elasticity (SAE) , but not large artery elasticity (LAE) has been associated with CVD events beyond traditional risk factors.(D A Duprez et al. 2011) This analysis will examine an expanded group of arterial stiffness measures and will take advantage of a longer period of follow-up. This analysis enables the comparison of five different arterial stiffness measures in a single, multi-ethnic cohort with physician-adjudicated CVD events with extended follow-up.

1.5 Modeling arterial function with arterial stiffness and arterial elasticity measures

The mechanical behavior of arteries is complex and difficult to model mathematically. The structure of the arterial wall is divided into three concentric layers or regions, including the tunicas intima, media, and adventitia.(Nichols, O'Rourke, and Vlachopoulos 2011a) The tunica intima contains the vascular endothelium and a thin layer of elastin and collagen fibers. The intima has important load-bearing capacity. The tunica media is a major part of the arterial wall and a key determinant the arterial wall's mechanical properties. It contains elastin, smooth muscle, and collagen that are interlocked together. When studied, these heterogeneous histological components have appeared to act as a homogenous material in a mechanical sense.

Arteries have anisotropy, meaning that stiffness measured in one axis is different than stiffness measured on another axis. To model the behavior of the arterial wall, Holzapfel and Ogden visualized stress and stretch acting three-dimensionally upon three concentric layers in a circular cylindrical tube.(Gerhard A Holzapfel and Ogden 2010) This model was based on experimental studies regarding the mechanical behavior of different layers of the arterial wall that were performed on human aortas that had no or minimal signs of atherosclerosis upon

autopsy.(Gerhard A. Holzapfel et al. 2007) Holzapfel and Ogden also designed a mathematical model in which bending and stretching occur in both circumferential and axial directions on each layer of the wall.(G. A. Holzapfel and Ogden 2010)

Different sections of the arterial tree also differ in their collagen, elastin, and smooth muscle content.(Nichols, O'Rourke, and Vlachopoulos 2011a) Collagen is a much stiffer material than elastin. The elastic modulus of collagen ($1000*10^6$ dyne/cm^2), which is a measure of a material's stiffness, is much higher than that of elastin ($3*10^6$ dyne/cm^2). In the proximal aorta, closer to the heart and considered a central artery, elastin is the dominant component. However, in the distal abdominal aorta, which is considered a peripheral artery, collagen is the dominant component. Thus as the distance from the heart increases, the arteries become stiffer and elastic modulus of the arteries increase. Generally, central elastic arteries are more elastic and deliver more buffering capacity than more peripheral, muscular arteries.(Stephane Laurent et al. 2006)

Studies also suggest that vascular remodeling is different in elastic versus muscular arteries.(Ernesto L. Schiffrin 2012) The larger, elastic arteries have shown outward hypertrophic remodeling and increased stiffness with aging.(M. E. Safar, Girerd, and Laurent 1996; M. E. Safar, Levy, and Struijker-Boudier 2003; Mitchell et al. 2003) Hypertrophic remodeling means that cross-sectional area of the intima media increases and the ratio of the media to lumen cross-sectional area increases. In contrast, smaller, more muscular arteries have shown two types of remodeling: inward eutrophic or inward hypertrophic remodeling.(Heagerty et al. 1993; E. L. Schiffrin, Deng, and Larochelle 1993; Mulvany et al. 1996; Ernesto L. Schiffrin 2004) With

eutrophic remodeling, the media to lumen cross-sectional area increases, but the intima media cross-sectional area remains the same.

In light of these differences, it makes sense that studies suggest that there are differences in age-related changes in different arterial functional measures. For example, aortic pulse wave velocity, which is a measure of arterial stiffness of the aorta, tends to increase more dramatically after age 50. (A Redheuil et al. 2010; McEniery et al. 2005) Yet, augmentation index, which is an indirect measure of arterial stiffness that show the effects of reflected waves, tends to show its largest increases before age 50.(McEniery et al. 2005) In addition, brachial PWV, which is a measure of the arterial stiffness of the brachial artery, tends to increase linearly with age.(McEniery et al. 2005) It is hypothesized that brachial PWV may behave uniquely because there is a higher proportion of smooth muscle in this part of the arterial system than in the aorta.(McEniery et al. 2005) Another factor is that arterial remodeling may differ between different areas of the arterial system.

To describe the mechanical behavior of arteries and the stiffness of arteries, various models have been developed. Correspondingly, various indices of arterial stiffness have been proposed. Each of these indices has different strengths and weaknesses. Each of these indices seeks to describe a different set of functions and characteristics of arteries. None of these terms alone fully describes the elasticity of the arteries.(Izzo and Shykoff 2001) Different indices of arterial stiffness to have different units because they are measured using different methodologies and aim to different capture different properties.

We will discuss three popular methods of measuring arterial stiffness non-invasively including: 1) pulse wave velocity, 2) assessing diastolic pressure waveforms, and 3) use of medical imaging to obtain geometrical measurements of the arteries. For the latter two methods, we included descriptions of arterial function measures that were analyzed in this dissertation. Table 1.1 shows a list of the arterial function measures from the Multi-Ethnic Study of Atherosclerosis that were available only at Exam 1 and the arterial function measures that were available at Exam 1 and Exam 5. Four of these measures, C1 (also called large artery elasticity, LAE) and C2 (also called small artery elasticity, SAE), Pressure Time Constant 1 (PTC1) and Pressure Time Constant 2 (PTC2) were obtained via radial tonometry. Carotid ultrasound images were used to assess the elasticity of the carotid artery and the stiffness of the carotid artery material. Two different methods were used to calculate carotid distensibility (CD) and distensibility coefficient at the carotid artery (DC). In addition, two different methods were used to calculate Young's modulus (YM) at the carotid artery and Young's elastic modulus (YEM) at the carotid artery. The methods and formulas used to calculate these measured are described in detail in the next sections.

1.6 Pulse wave velocity

Pulse wave velocity is based on the "propagative model" in which the arterial tree is thought of as a viscoelastic tube. The pulse wave moves in a forward pressure wave along the tube and through numerous branch points. There is a higher level of resistance at the end of the tube. As a result, wave reflections occur and retrograde waves are produced at the periphery arteries. This model also assumes that the pulse wave velocity has a finite value.(Stephane Laurent et al. 2006)

Pulse wave velocity, the measure of arterial stiffness for this model, gives the speed at which the pulse wave travels. As the arterial stiffness increases, the forward pressure wave moves faster and the pulse wave velocity is increased. Pulse wave velocity is considered to be a regional measure of stiffness because it reflects the part of the arterial system where successive waveforms are measured. Pulse wave velocity is calculated by measuring the surface distance between two waveform recording sites, and then dividing by the time delay between the feet of the two waveforms. The units for this measure are in length divided by time (ie. meters/second).

There has been extensive literature showing a positive association between the pulse wave velocity and CV events. In a meta-analysis of 17 longitudinal studies that followed a total of 15,877 patients for a mean of 7.7 years, Vlachopoulous and colleagues found that an increase in aortic PWV by 1 SD was associated with the pooled RR in total CV events of 1.47 (95% CI: 1.31, 1.64).(C Vlachopoulos, Aznaouridis, and Stefanadis 2010) This provides evidence that suggests that pulse wave velocity is a good measure of arterial stiffness.

We will not be using pulse wave velocity measures in these analyses because they were not available in the MESA study at the time these analyses were conducted. However, this measure warrants explanation because carotid-femoral PWV, which is measured along the aortic and aorto-illiac pathway is considered the gold-standard of arterial stiffness measures.(Stephane Laurent et al. 2006)

1.7 Arterial function measures via radial tonometry

The arterial function measures that were obtained via radial tonometry were calculated using formulas based on the Windkessel model. In the Windkessel model, the arterial system is compared to a fire house system. In this system, the heart pumps blood from the proximal elastic arteries, which are represented by the air-filled dome or Windkessel, through the conduit arteries, which are represented by the hose, to the non-elastic peripheral arteries, which are represented by the nozzle.(M. O'Rourke 2006)

Applanation tonometry was used to acquire peripheral artery waveforms. The arterial pressure waveform was measured at the radial artery. Then the waveform was calibrated to brachial blood pressure.

1.7.1 Calculation of C1 (also called large artery elasticity, LAE) and C2 (also called small artery elasticity, SAE) from diastolic pulse contour analysis for MESA Exam 1 data

Values for C1 and C2 from exam 1 were generated using proprietary software developed by Hypertension Diagnostics, Inc., the manufacturer of the device collecting radial tonometry data at Exam 1. C1 and C2 were calculated by taking the product of estimated systemic vascular resistance (SVR) and a function of modified third-order Windkessel model parameters estimated from a calibrated subset of "diastolic pulse contours". The model consisted of an exponential term and exponentially dampened cosine term:

$$P(t) = a_1 \exp(-a_2 t) + a_3 \exp(-a_4 t) \cos(a_5 t + a_6)$$

Where P(t) is the radial pressure at time t since the "start of diastole", "exp" represents the exponential function, $a_1, \ldots, a_6$ are parameters to be estimated and "cos" represents the cosine function.

C1 and C2 are then calculated as:

$$C1*SVR = 2a_4[(a_2+a_4)^2 + a_5^2]/[a_2(2a_4+a2)(a_4^2+a_5^2)]$$

$$C2*SVR = 1/(2a_4 + a_2).$$

1.7.2 Calculation of PTC1 and PTC2 from pulse wave analysis for MESA Exam 1 and 5 data

MESA investigators used three steps to estimate these novel indices of the radial pressure waveform:

First, they segmented each participant's 30-second set of raw waveform data into segmented waveforms corresponding to each cardiac cycle or beat by finding the steep rises to maximum pressures about every 1 second. A complete waveform for a specific beat was defined by two adjacent starts of steep rise. They considered complete beat-specific waveforms with lengths between 0.5 and 2 seconds to be acceptable for further processing, thus excluding incomplete beat-specific waveforms that were unusually long (greater than 2 seconds) or short (less than 0.5 seconds).

Second, the analysis used standard nonlinear regression methods (Bates and Watts 1988) to fit models to the pressure decay of each beat-specific waveform. The models started from the time of maximum pressure and continued until the end of the beat-specific waveform. A modified

third-order Windkessel model was used to describe the arterial system and the corresponding radial artery pulse wave form. Thus, the model consisted of an intercept, exponential term, and exponentially dampened cosine term:

$$P(t) = a_o + a_1 \exp(-a_2 t) + a_3 \exp(-a_4 t) \cos(a_5 t + a_6)$$

Where P(t) is the radial pressure at time t since the maximum pressure, "exp" represents the exponential function, $a_0, \ldots, a_6$ are parameters to be estimated and "cos" represents the cosine function. For model identifiability, the investigators forced to a_5 to be positive via reparameterization (Bates and Watts, 1988) and a_6 to be in $[0, \pi]$.

This model was used to obtain Pressure Time Constant 1 (PTC1), whose formula is shown below, and Pressure Time Constant 2 (PTC2), which was defined as 1/(twice the decay rate parameter of the dampened cosine plus exponential rate parameter).

PTC1 $\equiv 2a_4[(a_2 + a_4)^2 + a_5^2]/[a_2(2a_4 + a_2)(a_4^2 + a_5^2)]$

PTC2 $\equiv (2a_4 + a_2)^{-1}$

Third, the investigators calculated the weighted average of the beat-specific parameter estimates to create one estimate of each index from each participant's set of 30-second raw waveform data. The weights were proportional to the inverse of the approximate variance of the beat-specific estimates; ie. estimates with larger variance were given less weight. Thus, the weighted mean of all PTC1 and PTC2 values for 1 set in exam 1 were calculated for each participant. The weighted means of all PTC and PTC2 values for 2-3 sets in exam 5 were calculated to produce PTC1 and

PTC2 values for exam 5. Weighted means were used instead of simple means because they are less sensitive to outliers.

1.8 Arterial function measures via carotid ultrasound

1.8.1 Calculation of carotid distensibility (CD) and Young's modulus (YM) at carotid artery at Exam 1

At Exam 1, carotid distensibility (CD) was calculated by the relative change in the cross-sectional area of the carotid artery by the pulse pressure at the brachial artery. Because relatively small changes in arterial diameter are expected, a first-order approximation of the change in area is used. The formula for carotid distensibility (CD) was: $CD = (2* \Delta D)/(D_S * \Delta P)$. ΔD is the change in carotid artery diameter between systole and diastole. D_S is the carotid diameter at peak systole. ΔP is the pulse pressure at the brachial artery.(Gamble, Zorn, Sanders, MacMahon, et al. 1994) The units for CD were $mmHg^{-1}$.

At Exam 1, Young's modulus (YM) was calculated by dividing Peterson's elastic modulus by the wall thickness of the aorta. Peterson's elastic modulus was calculated as pulse pressure divided by relative change in diameter of the carotid artery between systole and diastole. The formula for Young's modulus (YM) was: $YM= (D*\Delta P)/(\Delta D*H)$. ΔP is pulse pressure. D is average carotid diameter. ΔD is change in aortic diameter between systole and diastole. H is wall thickness of the carotid artery based on IMT.(Gamble, Zorn, Sanders, and Al 1994) The units for YM were mmHg/mm.

1.8.2 Distensibility coefficient (DC) and Young's elastic modulus (YEM) at the carotid artery at Exams 1 and 5

At Exams 1 and 5, DC was calculated as the relative change in lumen area divided by the change in pressure between the systole and diastole.

Thus, the formula for DC was: $DC = (D_s^2-D_d^2)/(D_d * \Delta P)$. D_s is the internal carotid artery diameter at peak systole. D_d is the internal carotid diameter at the end-diastole. ΔP is the pulse pressure at the brachial artery. The units for DC were $(mmHg*1000)^{-1}$.

For Exams 1 and 5, YEM was calculated as circumferential stress divided by circumferential strain. During systole, the heart pumps blood out into the arteries. While during diastole, blood returns from the arterial system back to the heart. Pulse pressure, which is the difference between systolic and diastolic blood pressure, measures the force felt in the arteries as blood is delivered. Pulse pressure causes both lengthening of the artery and circumferential tension in the artery wall.

Generally, stress is the force applied over a cross-sectional area when a body undergoes loading and deformation. In our case, circumferential stress is the tension applied to the cross-sectional area of the blood artery wall, which is represented by the wall thickness of the carotid artery. For the artery, tension is pulse pressure multiplied by internal radius, which is the diameter of the carotid artery at end-diastole. Thus, circumferential stress is the pulse pressure measured at the

brachial artery multiplied by the diameter of the carotid artery at end-diastole divided by the wall thickness of the carotid artery.

Circumferential Stress

$$= \frac{Tension\ applied\ to\ cross-sectional\ area\ of\ carotid\ artery\ wall}{Wall\ thickness\ of\ carotid\ artery} =$$

$$= \frac{Pulse\ pressure * Diameter\ of\ carotid\ artery\ at\ end-diastole}{Wall\ thickness\ of\ carotid\ artery} = \frac{\Delta P * D_d}{h}$$

Generally, strain is the fractional change in length of a body that occurs along the direction of the force applied to the body. In our context, the force of the blood flow causes the cross section of the artery to widen. This results in a change in the diameter of the artery. Thus, circumferential strain is the change in diameter of the carotid artery between systole and diastole divided by the diameter of the carotid artery at end-diastole.

Circumferential strain

$$= \frac{Change\ in\ diameter\ of\ carotid\ artery}{Diameter\ of\ carotid\ artery\ at\ end-diastole} = \frac{\Delta D}{D_d}$$

Thus, the formula for YEM was:

$$\text{YEM} = \frac{stress}{strain} = \frac{\frac{\Delta P * D_d}{h}}{\frac{\Delta D}{D_d}} = \frac{\frac{D_d}{h}}{\frac{\Delta D}{D_d * \Delta P}} = \frac{\frac{D_d}{h}}{DC}$$

YEM= $(D_d/h)/(DC)$. D_d is the internal carotid diameter at the end-diastole. H is wall thickness of the carotid artery during end-diastole (external carotid artery diameter minus internal carotid artery diameter). The units for YEM were mmHg.

Note: DC, distensibility coefficient at the carotid artery, calculated for the YEM formula is:

$$DC = \frac{\Delta D}{D_d * \Delta P}$$

The numerator for the formula for DC found in the YEM formula is slightly different from that of the previous formula for DC described earlier in this section. In the formula for DC in the YEM formula, the numerator was the difference between diameter at systole and diameter at diastole. In the previous formula for DC described earlier in this section, the numerator was the difference between the squared diameter at systole and the squared diameter at diastole.

1.8.3 Comparing two methods for calculating carotid distensibility and Young's elastic modulus

One key difference is that for the methodology used for longitudinal data collected at Exams 1 and 5, DC and YEM utilize diameter at the carotid artery at the end-diastole as the reference diameter. However, for the methodology used for data collected only at Exam 1, CD uses the diameter at peak systole and YM uses the average diameter between systole and diastole as the "reference diameter." Thus, "reference diameter" for CD and YM measured only at Exam 1, which was the carotid artery diameter at peak systole, was larger than "reference diameter" for DC and YEM measured in longitudinal data for Exams 1 and 5, which was the carotid artery diameter at end-diastole. Absolute values of CD were smaller than DC. Absolute values for YM were be larger than YEM.

A more subtle difference is that DC uses the exact formula for change in cross-sectional area of the carotid artery (D_s^2-D_d^2). However, CD uses a 1st order approximation for change in cross-sectional area of the carotid artery: $dA = (1/4)*2\pi D*\Delta D$.

Another difference is we calculated YEM using the elastic modulus formula of circumferential stress divided by circumferential strain. Thus, YEM has units of pressure (mmHg). In contrast, YM is calculated using the pressure-strain modulus (Peterson's modulus), which is the inverse of CD and dividing it by the arterial wall thickness. YM describes arterial stiffness per length of wall thickness. Thus, YM has units of pressure divided by length (mmHg/mm).

1.9 Past studies on connection between cardiovascular risk factors and change in arterial function measures over time

Previous studies have also found associations between various cardiovascular risk factors and CVD events. The Framingham Heart Study showed that smoking, unhealthy diet, physical inactivity, obesity, elevated blood cholesterol, elevated blood pressure, and diabetes are strong risk factors for CVD.(Mendis 2010) If a CVD risk factor was strongly associated with longitudinal change in an arterial stiffness measure, this could suggest that the arterial stiffness measure may be part of a pathway linking the CV risk factor and CVD events. Past investigation has demonstrated there are differences in cross-sectional arterial stiffness (or elasticity) for various groups defined by traditional cardiovascular risk factors such as gender, race/ethnicity, age, hypertension, and HDL levels.(D A Duprez et al. 2009; Valappil et al. 2008; Ashkan Aa Malayeri et al. 2008; A Redheuil et al. 2010) Yet, there have been relatively few studies investigating the effects of cardiovascular risk factors on longitudinal change in arterial stiffness compared to the number of cross-sectional studies. Each of these different arterial function

measures in our study may reflect different aspects of the arterial elasticity and stiffness. Thus, we hypothesize that they may integrate the effects of different cardiovascular risk factors on the arterial system function. Therefore, we looked closely at the association between cardiovascular risk factors, and our outcome of interest, longitudinal change in arterial stiffness.

Several studies have investigated the association between metabolic syndrome (MetS), with longitudinal change in stiffness. An individual is considered to have MetS when they have three or more metabolic risk factors such as abdominal obesity, impaired glucose tolerance, elevated triglyceride levels, low HDL cholesterol, and elevated blood pressure.(American Heart Association 2016) MetS has been associated with increased risk of cardiovascular disease.(Mottillo et al. 2010) One 6-year study of young Finnish participants found that having persistent MetS compared to those that recovered from MetS was associated with greater increases in common carotid distensibility.(Koskinen et al. 2010) Another study found that subjects with MetS had a higher brachial-ankle PWV (baPWV) after 3 years of follow-up compared to those without MetS.(Li et al. 2011a) Increases in waist circumference and increases in blood pressure have been associated with increases in YM (Ferreira et al. 2012) and decreases in CD.(Koskinen et al. 2012) In a study of participants with impaired glucose tolerance, increases in blood pressure were associated with decreased CD.(van Dijk et al. 2000a) Increased insulin levels have also been associated with decreases in CD (Koskinen et al. 2012) and having increased baPWV group.(Li et al. 2011a) Several previous studies were of relatively short follow-up time.(Li et al. 2011a; Koskinen et al. 2012) In addition, some of the past study populations were mostly ethnically homogenous (Koskinen et al. 2010; Li et al. 2011a; Koskinen et al. 2012) or young.(Koskinen et al. 2010; Koskinen et al. 2012) Therefore, this proposed

analysis will help provide important new data needed on correlates of longitudinal change in arterial stiffness in a large, ethnically diverse, older study population.

1.10 Hypotheses on how arterial function may mediate connection between air pollution and risk of CVD events

In this analysis, we are particularly interested in how arterial function, specifically as measures of arterial elasticity and arterial stiffness fit into two of the aforementioned general pathways: 1) systemic oxidative stress and inflammation, and 2) autonomic nervous system imbalance may lead to changes in arterial function.

Previous literature suggests that acute exposure to ambient particulate matter may affect trigger systemic inflammation and oxidative stress, down-regulation of nitric oxide synthase, release of endothelins.(Bouthillier et al. 1998; Glantz 2002) Acute exposure to ambient particulate matter may also initiate changes in the autonomic nervous system such as heart rate variability.(Gold et al. 2000) Systemic inflammation and oxidative stress, as well as imbalance in the autonomic nervous system can both result in endothelial dysfunction, vasoconstriction, ventricular remodeling, and increased blood pressure.(Robert D. Brook et al. 2002; Sørensen et al. 2003; Ying et al. 2009) Endothelial dysfunction may result in the infiltration of cells and the adhesion of cells to the intimal surface of the artery, leading to reduced flow in the arteries.(Ross 1993; Gibbons and Dzau 1994; Gimbrone 1995) These functional and structural changes in small arteries could alter reflected waves and increase vascular resistance.(Daniel A Duprez and Cohn 2006) Thus, increase in stiffness in small arteries may be an early manifestation of damage to arteries due to hypertension.(C A Peralta et al. 2009) Adverse ventricular remodeling and increased arterial stiffness may result in elevated pulse pressure, which is the difference between

systolic and diastolic blood pressure.(M. E. Safar, Levy, and Struijker-Boudier 2003; Gosse et al. 2010) The connections between increased stiffness in the small arteries and increased pulse pressure with occurrence of CVD events have been described earlier in this chapter.

1.11 Previous studies on air pollution and arterial stiffness

The proposed analysis will also provide additional data on the relationship between long-term exposure to $PM_{2.5}$ and NO_X with arterial stiffness using an improved air pollution exposure model compared to previous studies. There has been mixed evidence that long-term air pollution is associated with arterial stiffness. Closer distance of residence to major roadway, a proxy for traffic-related air pollution, was associated with increased carotid arterial stiffness in children.(Iannuzzi et al. 2010) Long-term NO_2 exposure, a proxy for traffic-related air pollution, and long-term SO_2 exposure, another gaseous pollutant, was associated with increased aortic pulse wave velocity and increased augmentation index, which signify increased arterial stiffness, in healthy young adults.(Lenters et al. 2010) However, this same study did not find positive associations between long-term $PM_{2.5}$ and these measures. Another study with the MESA cohort also found no significant association between estimated long-term 20-year exposure to $PM_{2.5}$ with C_1 (LAE), C_2 (SAE), or Young's modulus measured at the carotid artery.(Marie S. O'Neill et al. 2011) This same study also found that observed and imputed PM_{10}, as well as imputed $PM_{2.5}$, were not associated with Young's Modulus at the carotid artery, C_1 (LAE), or C_2 (SAE) after covariate adjustment. These previous studies do not show an association between air pollution and various arterial stiffness measures in the MESA study. However, the analysis in this dissertation takes advantage of an improved air pollution exposure model.

1.12 Multi-Ethnic Study of Atherosclerosis (MESA)

The Multi-Ethnic Study of Atherosclerosis (MESA) is an ongoing longitudinal study of subclinical atherosclerosis which is funded by the National Heart Lung and Blood Institute.(Bild et al. 2002) At baseline, 6,814 men and women between the ages of 44 to 84 were recruited. Participants did not have clinical cardiovascular disease at enrollment and were recruited from six field centers: Baltimore City and Baltimore County, MD (Johns Hopkins University); Chicago, IL (Northwestern University); Forsyth County (Winston-Salem), NC (Wake Forest University); Los Angeles County (Alhambra), CA (UCLA); New York, NY (Columbia University); St. Paul, MN (University of Minnesota). The initial Exam 1 was completed from 2000 to 2002. The ethnic distribution of the cohort at the initial exam was 38.5% white, non-Hispanic, 27.8% African-American, 21.9% Hispanic, and 11.8% Chinese. Exam 5 was completed from 2010 to 2012.

All cardiovascular outcomes included in the study were obtained through medical record abstraction by trained personnel and adjudicated by the clinicians who are part of the MESA data review committee.

Information on cardiovascular risk factors was collected as part of the MESA study. During the recruitment, participants reported their age, race/ethnicity (Caucasian, African-American, Hispanic, Chinese-American), and sex. At baseline, demographic information was verified and height and weight were measured with participants wearing light clothing and no shoes. Body mass index was calculated as weight (kg) divided by height squared (m^2). Resting seated systolic and diastolic blood pressure was measured three times using a Dinamap model Pro 100

automated oscillometric sphygmomanometer (Critikon, Tampa, Florida), with the average of the last 2 measurements used. Heart rate (beats per minute) was monitored and recorded at the time of the MRI exam. A central laboratory (University of Vermont, Burlington, Vermont) measured levels of total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, plasma glucose, and high-sensitivity C-reactive protein (hsCRP). Smoking status (never smoked, ever smoked, current smoker), use of blood pressure medication, body mass index (BMI), use of cholesterol lowering medication were assessed using standardized questionnaires and examining medication containers. Diabetes was defined as having a fasting plasma glucose greater or equal to 126 mg/dL (7.0 mmol/l) or receiving treatment for diabetes, which is consistent with the 2003 American Diabetes Association fasting criteria algorithm.(Saul Genuth et al. 2003)

1.13 MESA Air Study

MESA Air is an ancillary study that was specifically designed to examine the association between individual-level estimates of long-term air pollution with the progression of subclinical measures of atherosclerosis and incidence of cardiovascular disease events.(Kaufman et al. 2012) Examples of the subclinical measures included coronary artery calcification (CAC), carotid intima-medial wall thickness (CIMT), and arterial function measures, such as arterial elasticity and arterial thickness. MESA Air invested significant resources to develop a state-of-the-art air pollution exposure assessments of $PM_{2.5}$, which is particulate matter less than 2.5 micrometers in diameter, oxides of nitrogen (such as nitrogen dioxide), and black carbon. The MESA Air study started in 2004.

A majority of participants in MESA Air were recruited from the parent MESA study when participants came into the clinical study center to complete Exam 3 or Exam 4. Other participants were recruited from another ancillary study, MESA Family, which was designed to investigate the genetic aspects of subclinical CVD in African-American and Hispanic-American participants. Additional MESA Air participants were also recruited in a community-based manner. Neighborhoods within communities were selected by census tract to match ethnicity and community-based status with the local MESA cohort to avoid confounding. Though the cohort is community based, the sampling was done to obtain balanced recruitment across strata defined by ethnicity, age group, socio-economic status, and distance from roadway. Emphasis was not on representing the demographic distribution of the source communities.

More subjects were also recruited by MESA Air to increase exposure heterogeneity. About 300 new participants were recruited from two geographic areas in the Los Angeles basin near the UCLA Field Center (Santa Monica/Coastal LA County and Rubidoux/Riverside County) and one area in New York City region near the Columbia Field Center (Rockland County). Informed consent was obtained from all participants prior to each of the exams that they participated in.

In order to develop air pollution exposure estimates, an additional questionnaire by MESA Air collected information on home geographic characteristics, local pollution sources, building characteristics, ventilation characteristics, indoor combustion sources, and time-location patterns. MESA Air also collected 7,420 2-week air samples in 6 MESA cities and 3 additional areas of new recruitment between July 2005 and July 2009.

These samples were analyzed for $PM_{2.5}$, light-absorbing carbon, NO_X, NO, O_3, SO_2, and trace elements. MESA Air also utilized Air Quality System (AQS) monitoring data, geographic data such as roadway density and land use, and dispersion model outputs in exposure models to identify seasonal and shorter term time trends, to capture key sources of spatial variability, and to account for underlying spatial and spatio-temporal correlation.

1.14 Organization of chapters

This dissertation explored the association between air pollution and arterial function measures, in the form of arterial stiffness and arterial elasticity measures, in the Multi-Ethnic Study of Atherosclerosis (MESA). Arterial stiffness is a subclinical measure that itself has been associated with clinical cardiovascular disease events. The overall objective of this dissertation was to examine whether air pollutant exposures impact longitudinal change in arterial stiffness as evaluated by a set of functional physiological measurements, and how these measures predict subsequent cardiovascular disease (CVD) events.

In Chapter 2, we compared the predictive value of five measures of arterial function assessed in Exam 1 of the MESA study (2000-2002) on the time to occurrence of first coronary heart disease event and first congestive heart failure event in the MESA cohort, adjusting for traditional cardiovascular risk factors.

In Chapter 3, we examined the association between traditional cardiovascular disease risk factors and longitudinal change in arterial function measures between Exam 1 (2000-2002) and Exam 5 (2010-2012) of the MESA study.

In Chapter 4, we examined the association between long-term exposure and short-term exposure to air pollutants and longitudinal change in arterial function measures. We evaluated the association between long-term air pollution exposure assessed during the year 2000 with cross-sectional measurements of arterial function at Exams 1 and 5. We characterized the association between long-term air pollution exposure, estimated between Exams 1 and 5 with longitudinal change in arterial function measures between Exams 1 and 5. We also examined the association between short-term air pollution exposure and cross-sectional measurements of arterial function at Exams 1 and 5.

In Chapter 5, we summarized the findings in this dissertation and made recommendations about future research regarding air pollution and arterial function measures.

A diagram of how the analyses from these different chapters fit together is shown in Figure 1.1.

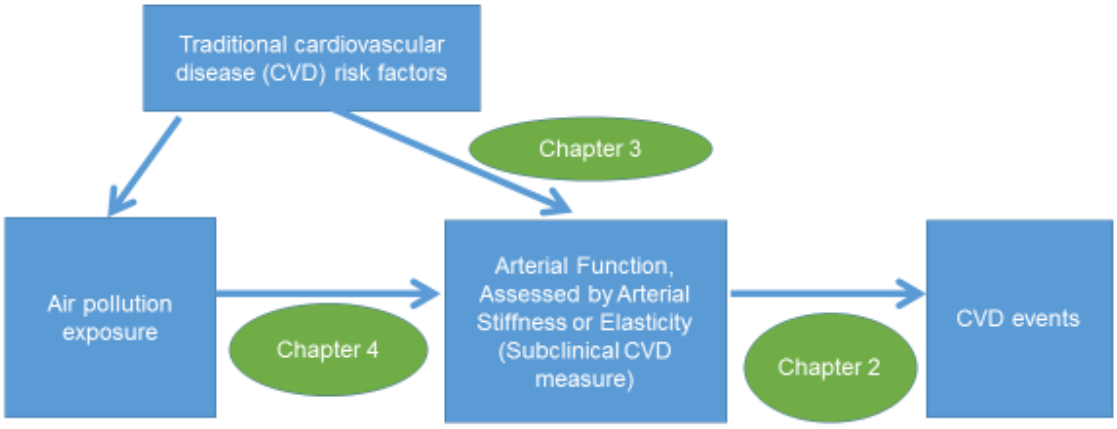

Figure 1.1 Framework for analyses

Table 1.1 Measures of arterial function from Multi-Ethnic Study of Atherosclerosis

Exam	Radial tonometry	Aortic Magnetic Resonance Imaging (MRI)	Carotid ultrasound
Exam 1	• C1 (Large artery elasticity) • C2 (Small artery elasticity)	Aortic Distensibility (AD)	• Carotid Distensibilty (CD) • Young's Modulus (CD)
Exam 1 and 5	Different radial tonometry device used and different formulas used: • Pressure Time Constant 1 (PTC1) • Pressure Time Constant 2 (PTC2)	Not available at time of analysis	Ultrasounds re-read and different formulas used: • Distensibility Coefficient (DC) at carotid artery • Young's Elastic Modulus (YEM)

Chapter 2. Comparing Arterial Function Parameters in Prediction of Coronary Heart Disease Events: The Multi-Ethnic Study of Atherosclerosis (MESA)

2.1 Abstract

Arterial dysfunction has been linked to decline in cardiac function and increased risk of cardiovascular disease events. We calculated the predictive value of arterial function measured at baseline (2000-2002) in the Multi-Ethnic Study of Atherosclerosis (MESA) participants on time to first coronary heart disease (CHD) event (median follow up= 10.2 years). Measures included C1 and C2 derived from diastolic pulse contour analysis from the radial artery blood pressure waveform obtained by tonometry (n=6,336), carotid distensibility and Young's modulus at the carotid artery derived from carotid artery ultrasonography (n=6,531 and 6,528), and aortic distensibility from cardiac magnetic resonance imaging (n=3,677). After adjustment, the hazard ratio of CHD event per standard-deviation higher value of arterial function was 0.97 (95% Confidence Interval (CI): 0.86, 1.10) for C1, 0.73 (95% CI: 0.63, 0.86) for C2, 0.98 (95% CI: 0.86, 1.11) for carotid distensibility, 0.99 (95% CI: 0.90, 1.09) for Young's modulus, and 0.90 (95% CI: 0.74, 1.10) for aortic distensibility. The area under the curve for the most fully adjusted model plus each measure was examined. C2 provided additional discrimination for the prediction of CHD (area under the curve= 0.736 vs. 0.743, p=0.04). Lower C2 was associated with higher risk of future CHD events. This chapter is largely based on an article that was co-authored with MESA collaborators and published in a peer-reviewed journal (Hom et al. 2016).

2.2 Introduction

An increase in arterial stiffness, or a decrease in elasticity, has been described in the process of vascular aging. Various methods have been developed to estimate increases in arterial stiffness or decreases in arterial elasticity in order to detect early changes in arterial function beyond arterial blood pressure. In this paper, arterial elasticity and stiffness measures will be referred to as "arterial function measures." These techniques have been implemented to identify vascular disease at early stages before the occurrence of cardiovascular disease (CVD) events. Thus, arterial function measures may identify people that are likely to progress to clinical events, beyond what can be estimated using only traditional cardiovascular risk factors.(Cohn and Duprez 2008) We hypothesized that a functional derivative from the arterial blood pressure waveform would be more predictive of future coronary events than measures derived from cardiac-cycle dependent changes in cross-sectional area. We examined the predictive value of the following measures of arterial function: 1) derivatives of the arterial blood pressure waveform: C1 and C2, and 2) derivatives of cross-sectional analysis of arteries: aortic distensibility (AD), carotid artery distensibility (CD), Young's elastic modulus at the carotid artery (YM) This study investigated which of these arterial function measures are most strongly associated with coronary heart disease (CHD) events and if these predict CHD events beyond traditional CVD risk factors.

2.3 Methods

2.3.1 Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is an ongoing longitudinal study funded by the National Heart Lung and Blood Institute.(Bild et al. 2002) The full MESA cohort contains 6,814 men and women between the ages of 45 to 84 years at baseline. Participants did not have clinical CVD at enrollment and were recruited from six field centers in the United States. The

initial baseline examination (Exam 1) was completed from July 2000 to August 2002. This study was approved by the Institutional Review Boards of all MESA study sites and all participants gave their informed consent.

2.3.2 **Data collection and definitions of baseline cardiovascular risk factors**

Age, race/ethnicity (Caucasian, African-American, Hispanic, Chinese-American), sex, and smoking status were obtained by self-report. Body mass index was calculated as weight (kg) divided by height squared (m^2). Resting seated systolic and diastolic blood pressure were measured three times using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida), with the average of the last 2 measurements used. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive medication. Heart rate (beats per minute) was measured from the study baseline 12-lead electrocardiogram (ECG). Use of blood pressure medication and use of cholesterol lowering medication were assessed using standardized questionnaires and by examining medication containers.

A central laboratory (University of Vermont, Burlington) measured concentrations of total cholesterol, high density lipoprotein cholesterol, triglycerides, plasma glucose, and high-sensitivity C-reactive protein obtained after 12-hour fast. Diabetes was defined as having fasting plasma glucose greater or equal to 126 mg/dL (7.0 mmol/L) or a history of receiving medical treatment for diabetes.

2.3.3 **Parameters derived from diastolic pulse contour analysis (C1 and C2)**

During the baseline examination, C1 and C2 were calculated from the diastolic pulse contour derived from the radial artery blood pressure waveform obtained by applanation tonometry using HDI/PulseWave CR-2000 (Hypertension Diagnostics, Inc., Eagan, Minnesota). Details on these measurements in MESA have been previously published.(D A Duprez et al. 2011) C1 and C2 are each the product of estimated systemic vascular resistance (SVR) and a function of modified third-order Windkessel model parameters estimated from the pulse wave form. SVR is estimated from participant characteristics including age, mean arterial blood pressure, heart rate, height, and weight. C2 multiplied by SVR (C2*SVR) and C1 multiplied by SVR (C1*SVR) are each a function of the pulse waveform only.

A previous study among 131 MESA participants found that correlations between two measurements performed on the same day by the same technician was 0.74 for C1, 0.84 for C2, 0.58 for C1*SVR, and 0.74 for C2*SVR.(Brumback et al. 2010)

2.3.4 **Aortic distensibility (AD)**

Aortic distensibility was measured by using 1.5-T whole-body MRI systems: Signa CV/i or Signa LX (GE Medical Systems, Waukesha, Wisconsin). Descriptions of AD measurement in MESA has been previously published.(Cheung et al. 2007; Stacey et al. 2010) Aortic distensibility was calculated by dividing the relative change in the cross-sectional area of the ascending aorta between systole and diastole, by the pulse pressure at the brachial artery.(M F O'Rourke et al. 2002; A A Malayeri et al. 2008a) Blood pressure was measured immediately before and after MRI aortic measurements while the patient was in the supine position on the

MRI scanner gantry. The average systolic and diastolic values were used to calculate pulse pressure.

Aortic distensibility obtained by MRI in 20 healthy volunteers aged 20 to 70 years old in a non-MESA study showed coefficient of variation for intra-observer and inter-observer variability of 1% and 2%, respectively, indicating high reproducibility.(Nelson et al. 2009)

2.3.5 **Carotid distensibility (CD) and Young's elastic modulus (YM)**

Carotid distensibility (CD) and Young's elastic modulus (YM) were measured using B-mode ultrasound at the distal right common carotid artery with a Logiq 700 machine (General Electric Medical Systems, Milwaukee, WI). This method has been described previously.(Blaha et al. 2009) Carotid distensibility was calculated by the relative change in the cross-sectional area of the carotid artery by the pulse pressure at the brachial artery. The brachial blood pressure measurement was made on the right arm using the automated upper arm sphygmomanometer (Dinamap Pro 100; Critikon, Inc., Tampa, FL) once at the time of the carotid artery ultrasound. Young's modulus was calculated by dividing Peterson's elastic modulus by the wall thickness of the aorta. Peterson's elastic modulus was calculated as pulse pressure divided by relative change in diameter of the carotid artery between systole and diastole.

In a study of 211 MESA participants, intraobserver class correlation for CD was 0.71 and for YM was 0.69. Among 10 interobserver correlations of MESA participants, the interobserver class correlation coefficients were 0.85 and 0.84 for CD and YM, respectively. These results indicate good agreement within and between observers for CD and YM.(Blaha et al. 2009)

Additional information on the acquisition and calculation of arterial function measures are in the Appendix section of this chapter (Page 64).

2.3.6 **Follow-up**

The MESA study recorded new symptomatic and adjudicated CVD events for the follow-up period from July 2000 until December 2011. For CHD events, the median follow-up time was 10.2 years (Standard Deviation (SD) = 2.6 years, Interquartile Range = 9.6-10.7 years). All CVD outcomes included in the study have been obtained through medical record abstraction by trained personnel and adjudicated by the clinicians who are part of the MESA data review committee. Adjudication procedures in MESA have been previously published and can be found in the MESA Protocol at www.mesa-nhlbi.org.

The main outcome of interest, CHD events, included myocardial infarction, resuscitated cardiac arrest, definite angina, probable angina (if followed by revascularization), and CHD death. All CVD events and congestive heart failure (CHF) events were examined as secondary outcomes. All CVD events included all outcomes in CHD events plus stroke, CHD death, other atherosclerotic death, and other CVD death. CHF included probable and definite CHF. More detail on the classification of events can be found in the MESA Events Manual of Operation at www.mesa-nhlbi.org.

2.3.7 **Statistical analysis**

Cox proportional hazards regression was used to examine the associations between CHD and each measure of arterial function: C2, C2*SVR, C1, C1*SVR, AD, CD, and YM. The hazard ratio per one standard deviation higher value in arterial function measure was calculated. The standard deviations for the different measures are shown in Table 2.1. The time scale of this analysis was the number of years from the participant's Exam 1 radial tonometry exam (for C2, C2*SVR, C1, C1*SVR), Exam 1 aortic MRI exam (for AD), or Exam 1 carotid ultrasound exam (for CD, YM) until occurrence of first CHD event.

The hazard ratio comparing the first, second, and third quartiles of C2, C1, CD, and AD to the fourth quartile of these measures (most elastic) and the hazard ratio comparing the second, third, and fourth quartiles of YM with the first quartile of these measures (most elastic) were calculated to assess if observed trends in the relationship were consistent with the linearity assumption of the model with the corresponding continuous predictor variable.

The minimal model adjusted for demographics and anthropometrics including age, sex, race/ethnicity, clinical center site, and height. Height was included in minimal adjustment as a measure of frame size related generally to arterial bore. The proportional hazards assumption was satisfied for all covariates in the minimal model. After examination of the proportional hazards assumption, the most fully adjusted model was stratified to allow for different baseline hazards by diabetes status and adjusted for all the covariates listed in the minimal model plus other traditional CVD risk factors including mean arterial pressure, use of blood pressure medication, body mass index, smoking, total cholesterol, high density lipoprotein, cholesterol,

triglycerides, use of cholesterol lowering medication, high-sensitivity C-reactive protein. For C2 and C1 only, the most fully adjusted model included heart rate as a covariate. Heart rate is a potential confounder for models containing C2 and C1 because heart rate is a component of the C2 and C1 formula and is associated with increased cardiovascular morbidity.(Finkelstein and Cohn 1992; Perret-Guillaume, Joly, and Benetos 2009) Mean arterial pressure was examined as a potential modifier of the association between arterial function and CHD event by observing whether the two-sided P-value of the interaction term, containing mean arterial pressure multiplied by the arterial function measure, was less than 0.05.

To assess the ability of each arterial stiffness measure to discriminate between participants who do and do not have events, receiver-operating characteristic curves and areas under the receiver-operating characteristic curves (AUC) were used. We obtained the predicted risks of CHD from the minimal and most fully adjusted models with and without the arterial function measures. Then we treated CHD as uncensored and binary to estimate and test differences in AUCs from models with and without each arterial function measure. Differences in AUCs from models with and without each arterial function measure were compared using an algorithm suggested by DeLong and colleagues and implemented using the *roccomp* command in Stata (Stata Corporation, College Station, Texas).(DeLong, DeLong, and Clarke-Pearson 1988) We also calculated Harrell's *c*-statistic for censored data.(Harrell, Lee, and Mark 1996)

The same analysis steps were used for the secondary outcomes, all CVD events and CHF. The most fully adjusted model for all CVD events was stratified by using separate baseline hazards

for race/ethnicity groups and diabetes. The most fully adjusted model for CHF was stratified by using separate baseline hazards for tertiles of total cholesterol. All analyses were performed using Stata version 11.2.

2.4 Results

2.4.1 Study cohort

Participants in the MESA study chose whether to participate in the radial tonometry, cardiac magnetic resonance imaging, and carotid artery ultrasonography procedures used to obtain the arterial function measures. Thus, three overlapping subgroups of the MESA study were examined in this analysis and their characteristics are shown in Table 2.1. The groups that underwent carotid ultrasound (n=6,531) and radial tonometry (n=6,336) were very similar in terms of total participants and descriptive statistics of covariates. A much smaller group (n=3,677) underwent aortic MRI compared to the other procedures. Compared to the other two groups, the group that had aortic MRI had a slightly higher proportion of white participants, slightly lower proportion taking medications for hypertension, slightly lower proportion having diabetes, slightly lower mean age, and slightly lower mean triglyceride concentration. Due to one or more missing variables, 1.75% of participants with C2 and C1 measured, 1.39% with AD measured and 1.33% with YM measured were excluded from the analyses.

Each subgroup had different numbers of CHD events: 417 for those with C1 and C2 measured, 220 for those with AD measured, 435 for those that had CD and YM measured. The number of all CVD and CHF events for the three subgroups are listed in Table 2.3.

2.4.2 Association between arterial function measures and incident CHD, all CVD, CHF events

In the minimal model, with adjustment for demographics and anthropometrics only, higher values of C2, C2*SVR, and C1 were associated with lower predicted risk of CHD (Table 2.2). After adjustment for demographics, anthropometrics, and traditional CVD risk factors in the most fully adjusted model, only increased values of C2 and C2*SVR, showed protective associations with CHD events of statistical significance ($p<0.05$). The hazard ratio (HR) of CHD event per standard-deviation higher value of arterial function measure was 0.73 (95% CI: 0.63, 0.86) for C2 and 0.78 (95% CI: 0.69, 0.91) for C2*SVR.

After adjustment for demographics, anthropometrics, and traditional CVD risk factors, the hazard ratio of all CVD events per standard-deviation of higher arterial function measure was 0.75 (95% CI: 0.66, 0.86) for C2 (Table 2.4). After adjustment for demographics, anthropometrics, and traditional CVD risk factors, the hazard ratio of CHF per standard-deviation of higher arterial function measure was 0.70 (95% CI: 0.56, 0.88) for C2 and 0.77 (95% CI: 0.62, 0.94) for C1 (Table 2.5).

Analysis of CHD, all CVD, and CHF events over quartiles of the arterial function measures did not suggest departure from linearity (Table 2.6, Table 2.7,Table 2.8).

Mean arterial pressure was not found to be a consistent modifier for the association between any of the arterial function measures with CHD, all CVD, or CHF events in the most fully adjusted

model. Mean arterial pressure was only found to be a modifier for the association between C1*SVR and CHD. (Data not shown)

2.4.3 Change in discrimination for CHD events with addition of arterial function measures

The results based on AUCs for uncensored outcomes and *c*-statistics for censored data were identical up to the hundredths decimal place. Only the AUCs assuming uncensored outcomes were reported.

For CHD events, the difference between the AUC with C2 and the AUC with covariates only was statistically significant for both the minimal model (difference=0.013, p=0.01, Figure 2.1) and most fully adjusted model (difference=0.007, p=0.04, Figure 2.2). Similar results were shown for C2*SVR. For CHD events, a statistically significant difference was not detected between the AUC with arterial function measure and AUC with covariates only from minimal or fully adjusted models with each of the other arterial function measures (Table 2.9).

We calculated 0-<6%, >=6-20%, and >20% risk of CHD events for 10-year follow up time using a model with only established cardiovascular risk factors, and with the new model, which added C2 to previous risk factors (Appendix section of this chapter, Page 67; Table 2.10). There was a small increase in the percentage of non-cases that were classified into the lowest risk category and small increase in the percentage of cases that were classified into the highest risk category.

For all CVD events, the difference between AUC with C2 and AUC with covariates only was statistically significant for the most fully adjusted model (difference=0.006, p=0.015) (Appendix section of this chapter, Page 69).

For CHF events, the difference between AUC with arterial function measure added and AUC with covariates only was not statistically significant for any of the arterial function measures for the most fully adjusted model (Appendix section of this chapter, Page 70).

2.4.4 Sensitivity analysis

Fewer MESA participants had AD (by cardiac MRI) compared to C1 and C2 (by radial tonometry) or CD and YM (by carotid ultrasound). As a result, there is a wider confidence interval around the hazard ratio with AD compared to the other four arterial function measures. As a sensitivity analysis, the analysis was repeated in a subgroup of 3,297 MESA participants that had all five measures. Similar results for the relationship between C2, AD, CD, and YM each with CHD were found in this subgroup as the original analysis (Table 2.11). The hazard ratio of CHD per one standard deviation higher value of C2 was 0.79 (95% CI: 0.63, 0.98) with the subgroup of 3,297 participants compared to 0.73 (95% CI: 0.63, 0.86) with all 6,336 participants, after adjustment for demographics, anthropometrics, and traditional CVD risk factors. The difference in AUC in the fully adjusted model with C2 and without C2 was 0.003 (p=0.533) with the subgroup compared to 0.007 (p=0.04) with all participants (Table 2.12).

2.5 Discussion

In this large, multi-center, multi-ethnic cohort free of overt CVD at baseline, we assessed the predictive capability of five measures of arterial function and found that C2, an arterial function measure derived from the blood pressure waveform, was more strongly associated with CHD than C1, another arterial function measure derived from the blood pressure waveform, and other elasticity measures derived from cross-sectional measures of the artery (AD, CD, YM). Only C2 predicted risk of CHD events during follow-up after adjusting for demographics, anthropometrics, and other cardiovascular disease risk factors. We also observed a small, statistically significant increase in the discrimination as measured by *c*-statistic of the risk prediction of CHD with the addition of C2. The other measures (C1, AD, CD, YM) did not increase discrimination of the model for CHD risk prediction.

Our analysis suggests that—of the measures evaluated—C2, designed to estimate the global arterial function of the more distal part of the arterial circulation, is the most useful in the prediction of CHD. C2 was also an important independent predictor of additional outcomes found in "all CVD events" including stroke, other atherosclerotic death, and other CVD death and of CHF. C2 has previously been called distal compliance, oscillatory compliance, and small artery elasticity. Duprez and colleagues have suggested that C2 represents different activities that occur to produce oscillations during the diastole when the left ventricle is filling with blood.(D A Duprez et al. 2011)

C1 provides useful information in prediction of CHD events that is largely attenuated when adjusting for other known CVD risk factors. C1 is designed to estimate the global arterial

function of more proximal part of the arterial circulation. C1 has previously been called proximal compliance, capacitive compliance, and large artery elasticity. C1 was an independent predictor of CHF in this analysis. Our finding suggests that C1 may reflect the development of CHF. It is consistent with the theory that increased stiffness of the large arteries increases left ventricular load, eventually leading to left ventricular dysfunction and finally congestive heart failure.(Gosse et al. 1999; Roman and Devereux 2006)

Our results suggest that arterial function measures aimed to capture the elastic properties at a local arterial site such as AD, CD, and YM may have little predictive value for CHD. AD and CD are designed to quantify the elastic properties of the ascending aorta and carotid artery, respectively. YM was designed to capture the elastic properties of the arterial wall material itself at the carotid artery. However, Redheuil and colleagues found that AD was predictive of hard CVD events among MESA participants with low to intermediate risk of CVD based on the Framingham risk category.(Alban Redheuil et al. 2014) "Hard CVD events" included myocardial infarction, resuscitated cardiac arrest, stroke and stroke death, and CHD death.

Some of our results were similar to those of previous epidemiological studies, which studied the arterial function in different study cohorts. The Rotterdam study (n=2,835) also showed a lack of independent association between CD and CHD.(F. U. Mattace-Raso et al. 2006) The Hoorn study (n=579) reported an association (not robust to adjustment for CV risk factors) between decreased CD and CVD events larger than we observed (22% increase in CV event per 1 standard deviation decrease in CD; 95% CI: -5%, 56%).(van Sloten et al. 2014) Hoorn

investigators reported that increased Young's modulus at the carotid artery was associated with increased risk of CV events.(van Sloten et al. 2014) The outcomes assessed are not completely comparable, since "CV events" in the Hoorn study included cerebrovascular disease and heart failure, while our "CHD events" outcome did not. The Hoorn study participants included nearly twice the proportion of diabetics as MESA. It is possible that the predictive value of an arterial function measure is dependent on the risk factor profile of the group being studied, so studies which demonstrate associations can be difficult to generalize to broader populations.(Henry et al. 2003)

Our study had some limitations. Blood pressure was assessed in the brachial artery in the calculation of AD, CD and YM. This is the typical approach in observational studies, since direct measurement of aortic and carotid artery pressures, though ideal, requires invasive procedures. It has been observed that the brachial measurement can result in differential misclassification of carotid distensibility among subjects that develop CVD events compared to those that did not develop CVD events, leaving open the possibility that there is bias in these findings.(F. U. Mattace-Raso et al. 2006)

The assessment of multiple arterial function measures raises concern regarding detecting falsely positive findings due to multiple comparisons. Since our goal was to examine the relationship between arterial function and CHD events using different measures, we did not use a statistical correction for multiple comparisons. Each measure represents distinct and different aspects of the arterial system's functional behavior.

Because of the small number of participants that were reclassified into the correct category for both cases and non-cases, our observations may not support use of C2 or the other measures in a clinical setting to predict cardiovascular disease outcomes.

A strength of this study is that it features a large, multi-ethnic, community-based population. Another strength of this study is that it is one of the few studies that have looked at the association between multiple, different arterial stiffness measures and CHD events in the same population free of overt CVD at baseline.

Only C2 was predictive of subsequent coronary heart disease events after adjusting for demographics, anthropometrics, and other traditional CVD risk factors. C1, aortic distensibility, carotid distensibility, and Young's modulus at the carotid artery were not predictive of subsequent CHD events after full covariate adjustment. There appears to be slight improvement in the risk prediction model for coronary heart disease events with the addition of C2, but not for other arterial function measures.

2.6 Appendix

2.6.1 Additional information about C1 and C2

Systemic vascular resistance (SVR) is estimated as mean arterial blood pressure divided by cardiac output. Cardiac output is estimated from ejection time observed in the pulse waveform, heart rate, age, height, and weight (Finkelstein and Cohn 1992).

A solid-state pressure transducer array (tonometer) was placed over the radial artery of the dominant arm to record the pulse contour. A 30-second analog tracing of the radial waveform, constituting continuous pressure changes during diastole, was digitized at 200 samples per second. There was an accompanying automated, oscillatory blood pressure measurement at the brachial artery of the contralateral arm. Radial tonometry data was read and interpreted by MESA investigators at the University of Minnesota and the University of Washington. The units for C2 is mL/mmHg *100, and the units for C1 is mL/mmHg *10.

2.6.2 Additional information about Aortic Distensibility (AD)

Gradient-echo phase-contrast cine MRI with electrocardiographic gating was performed to evaluate the distensibility of the aorta. Measurements of the aortic wall were made using the Magnetic Resonance Analysis Software System (MASS) vessel wall, version 5.1 (MEDIS Medical Imaging Systems, Leiden, The Netherlands).To determine aortic distensibility, the minimum and maximum cross-sectional areas of the ascending aorta were measured with software FLOW (MEDIS Medical Imaging Systems) using an automated contour technique that has been previously utilized (A A Malayeri et al. 2008b). Aortic MRIs were read and interpreted by MESA investigators at Johns Hopkins University. There was a single MRI reader who was blinded to all variables of the study subjects except their identification numbers.

The formula for aortic distensibility is AD= [(maximum area of the ascending aorta– minimum area of the ascending aorta)] / [PP x (minimum area of the ascending aorta)*1000]. Pulse pressure (PP) was the difference between systolic and diastolic blood pressure measurements at the brachial artery. The units of AD were $mmHg^{-1}*10^{-3}$.

2.6.3 Additional information about Carotid Distensibility (CD) and Young's Modulus (YM) at the Carotid Artery

In order to capture images of the carotid artery, the ultrasound technician placed the transducer on the participant's neck, approximately 1 cm below the carotid bulb (Riley et al. 1992). Images were taken for 30 seconds. Blood pressure measurements were made by upper arm automated sphygmomanometer (brachial artery) before and after the ultrasound image acquisition. The digitized carotid arterial diameter data from the ultrasound were then read to obtain the average diastolic and systolic diameters from as many as ten cardiac cycles. These images were read repeatedly by different readers to estimate variability. The wall thickness measurements were calculated from the B-mode images, representing the combined thickness of the intima, media, and adventitia (Gamble, Zorn, Sanders, MacMahon, et al. 1994). Ultrasound images were read and interpreted by MESA investigators at Tufts Medical Center that were blinded to all subject clinical information.

The formula for CD was: $CD = (2* \Delta D)/(D_S * \Delta P)$. ΔD is the change in carotid artery diameter between systole and diastole. D_S is the carotid diameter at systole. ΔP is the pulse pressure at the brachial artery (Gamble, Zorn, Sanders, MacMahon, et al. 1994). The units for CD were $mmHg^{-1}$.

The formula for YM was: $YM= (D*\Delta P)/(\Delta D*H)$. ΔP is pulse pressure. D is average carotid diameter. ΔD is change in aortic diameter between systole and diastole. H is wall thickness of the carotid artery based on IMT (Gamble, Zorn, Sanders, MacMahon, et al. 1994). The units for YM were mmHg/mm.

2.6.4 Clinical Relevancy of C2

To address clinical relevancy, we calculated 0-<6%, >=6-20%, and >20% risk of CHD events for 10-year follow up time using the old model, which only included established cardiovascular risk factors, and with the new model, which included established cardiovascular risk factors plus C2 (Table 2.13).

Table 2.13 shows that for those that did not experience an event, there was a larger percentage of participants that were classified into the lowest risk category. The percentage of those categorized into the lowest risk category was 62.92% with the addition of C2 versus 62.13% without C2. This corresponded to 46 participants who ended up being non-cases being reclassified into the lowest risk category. For those that did experience an event, there was a larger percentage of participants that were classified into the highest risk category. The percentage of those categorized into the highest risk category was 12.59% with the addition of C2 versus 12.35% without C2. This corresponded to 1 participant who ended up being a case being reclassified into the highest risk category. Because of the small number of participants that were reclassified into the correct category for both cases and non-cases, we would not recommend use of C2 in a clinical setting.

Another important point is that with the addition of C2, there were more participants that would be classified out of the intermediate category and into either the lowest or highest risk category. For non-events, the percentage of those categorized into the intermediate category with C2 added to the model was 33.13% versus 34.66% without C2, corresponding to 89 participants. For

events, the percentage of those categorized into the intermediate category with C2 added to the model was 59.81% versus 60.29% without C2, corresponding to 2 participants. This is helpful to clinicians because it is easier to decide whether or not to recommend treatment or preventative therapy for someone in a low or high risk category, rather than for someone in the intermediate category.

2.6.5 Association between arterial function measures and incident all CVD events

In the minimal model, with adjustment for demographics and anthropometrics only, higher values for C2, C2*SVR, C1, C1*SVR, AD, and CD were associated with lower predicted risk of all CVD events (Table 2.4). After full adjustment for demographics, anthropometrics, and traditional CVD risk factors, only higher values of C2 and C2*SVR were associated with lower risk of all CVD events of statistical significance (P-value for arterial function measure term in Cox regression model was less than 0.05). The hazard ratio (HR) of all CVD events per standard-deviation higher value of arterial function measure was 0.75 (95% CI: 0.66, 0.86) for C2 and 0.81 (95% CI: 0.72, 0.90) for C2*SVR. (Table 2.4).

2.6.6 Association between arterial function measures and incident CHF events

In the minimal model, with adjustment for demographics and anthropometrics only, higher values of C2, C2*SVR, C1, C1*SVR, and CD were associated with lower predicted risk of CHF events. (Table 2.5). After full adjustment for demographics, anthropometrics, and traditional CVD risk factors, only higher values of C2, C2*SVR, C1 and C1*SVR were associated with lower risk of CHF events of statistical significance ($p<0.05$). The hazard ratio (HR) of CHF

event per standard-deviation higher value of arterial function measure was 0.70 (95% CI: 0.56, 0.88) for C2 and 0.77 (95% CI: 0.62, 0.94) for C1 (Table 2.5).

2.6.7 Association between arterial function measures and CHD, all CVD, and CHF events by quartile

In the most fully adjusted model, the point estimates for the hazard ratios comparing other quartiles of arterial function measures to most elastic quartile were graded in magnitude for: C2*SVR and C1 for CHD events (Table 2.6); C2 and C1*SVR for all CVD events (Table 2.7); C2, C1, and CD for CHF events (Table 2.8).

2.6.8 Change in discrimination for all CVD events with addition of arterial function measures

For all CVD, the difference between AUC from the minimal model with C2 and the AUC from the minimal model with covariates only was statistically significant (difference=0.014, p=0.001). For all CVD events, the difference between the AUC from the fully adjusted model with C2 and the AUC from the fully adjusted model without C2 was also statistically significant (difference=0.006, p=0.015). Similar results were shown for C2*SVR. For all CVD events, a statistically significant difference was not detected between the AUC from minimal or fully adjusted models with each of the other arterial function measures (Data available on request).

2.6.9 Change in discrimination for CHF events with addition of arterial function measures

For CHF events, the difference between AUC from the minimal model with covariates only and the AUC from the minimal model with arterial function measures added (C2 and C1, separately) were statistically significant for C2 and C1 (difference=0.012, 0.015; p=0.010, 0.007, respectively). However, for CHF events, the difference between the AUC from the fully adjusted model with covariates only and the AUC from the fully adjusted model with arterial function measures added (C2 and C1, separately) were not statistically significant (difference=0.006, 0.002; p=0.089, 0.684, respectively). For CHF events, a statistically significant difference was not detected between the AUC from minimal or fully adjusted models with each of the other arterial function measures (Data available on request).

Table 2.1 Descriptive Statistics by Arterial Functional Measure Group for Multi-Ethnic Study of Atherosclerosis (MESA) Participants at Baseline Exam, United States, 2000-2002.

Characteristic	C2 [a] (n=6,336)			Aortic Distensibility (AD) (n=3,677)			Carotid Distensibility[b] (CD) (n=6,531)		
	N	%	Mean (SD)	N	%	Mean (SD)	N	%	Mean (SD)
Site									
Forsyth County, NC	1050	16.57		623	16.94		1051	16.09	
New York, NY	1024	16.16		738	20.07		1061	16.25	
Baltimore, MD	867	13.68		762	20.72		994	15.22	
St.Paul, MN	1000	15.78		332	9.03		1031	15.79	
Chicago, IL	1111	17.53		735	19.99		1111	17.01	
Los Angeles, CA	1284	20.27		487	13.24		1283	19.64	
Race/Ethnicity									
White	2412	38.07		1575	42.83		2517	38.54	
Chinese	769	12.14		399	10.85		783	11.99	
Black	1723	27.19		1075	29.24		1779	27.24	
Hispanic	1432	22.60		628	17.08		1452	22.23	
Cigarette smoking[c]									
Never	3215	50.85		1877	51.24		3287	50.48	
Former	2297	36.33		1303	35.57		2379	36.53	
Current	810	12.81		483	13.19		846	12.99	

Use of hypertension medication[c]	2348	37.08		1286	35.00		2410	36.92	
Use of any lipid lowering medication[c]	1007	15.90		562	15.30		1047	16.04	
Diabetes mellitus[c,d]	802	12.70		374	10.20		816	12.53	
Age (years)			62.02 (10.23)			60.55 (9.97)			62.18 (10.24)
Weight (lbs.)			173.40 (38.13)			171.17 (35.79)			172.88 (37.79)
Height (cm)			166.42 (10.03)			166.90 (9.86)			166.35 (10.03)
Heart Rate (beats/min.)			63.09 (9.62)			62.96 (9.47)			63.09 (9.63)
Systolic blood pressure (mmHg)			126.46 (21.33)			124.81 (21.11)			126.55 (21.50)
Diastolic blood pressure (mmHg)			72.00 (10.25)			71.96 (10.32)			71.94 (10.26)
Total cholesterol (mg/dL)			194.15 (35.66)			194.05 (34.62)			194.08 (35.77)
High density lipoprotein cholesterol (mg/dL)			50.83 (14.69)			51.88 (15.21)			50.91 (14.75)
Triglycerides (mg/dL)			131.91 (87.03)			126.95 (83.29)			131.56 (87.67)

C-reactive protein (mg/L)			3.71 (5.77)			3.64 (5.81)			3.74 (5.89)
C2 (mL/mmHg*100)			4.5(2.8)						
C2*SVR (seconds*10)			0.5 (0.3)						
C1 (mL/mmHg*10)			13.3(5.6)						
C1*SVR (seconds)			1.6(0.6)						
AD (mmHg-1 * 10^-3)						1.9 (1.3)			
CD (mmHg-1)									2.50*10^-3 (1.10*10^-3)
YM (mmHg/mm)									1300.5 (645.8)

Abbreviations: SD=Standard Deviation, AD=Aortic Distensibility, CD=Carotid Distensibility, YM=Young's modulus at carotid artery

[a] Population that had C1 (Mean=13.3 mL/mmHg*10, SD=5.6) measured (N=6,336) is the same as population that had C2 measured

[b] Population of participants that had Young's Modulus (YM) (Mean=1300.5 mmHg/mm, SD=645.8) measured (N=6,528) is almost identical to population that had CD measured (N=6,531)

[c] There were participants with missing data for this variable such that the subgroups do not sum the totals for the groups which had C2 measured, AD measured, and CD measured. Refer to Web Table 11 for number of participants with missing data for different variables.

[d] Diabetes was defined as having fasting plasma glucose greater or equal to 126 mg/dL (7.0 mmol/L) or a history of receiving medical treatment for diabetes.

Table 2.2 Hazard Ratio for Coronary Heart Disease (CHD) Events by Standard Deviation of Arterial Function Measure for Multi-Ethnic Study of Atherosclerosis (MESA) Participants, United States, 2000-2011.

	Hazard Ratio per Standard Deviation of Measure		
	Estimate	95% CI	Two-sided P-value [c]
C2			
Minimally adjusted model [a] (n=6,308)	0.69	0.60, 0.80	<0.001
Fully adjusted model [b] (n=6,205)	0.73	0.63, 0.86	<0.001
C2*SVR			
Minimally adjusted model (n=6,308)	0.73	0.64, 0.83	<0.001
Fully adjusted model (n=6,241)	0.78	0.69, 0.91	<0.001
C1			
Minimally adjusted model (n=6,308)	0.87	0.77, 0.98	0.026
Fully adjusted model (n=6,205)	0.97	0.86, 1.10	0.638
C1*SVR			
Minimally adjusted model (n=6,308)	0.93	0.84,1.04	0.196
Fully adjusted model (n=6,205)	0.99	0.89,1.10	0.844
Aortic Distensibility (AD)			
Minimally adjusted model (n=3,660)	0.81	0.66,1.01	0.064
Fully adjusted model (n=3,612)	0.90	0.74,1.10	0.315
Carotid Distensibility (CD)			
Minimally adjusted model (n=6,500)	0.89	0.79,1.01	0.074

Fully adjusted model (n=6,421)	0.98	0.86,1.11	0.700
Young's modulus at carotid artery (YM)			
Minimally adjusted model (n=6,497)	1.03	0.94,1.12	0.585
Fully adjusted model (n=6,418)	0.99	0.90,1.09	0.809

Abbreviations: CI, confidence interval

[a] Minimally adjusted model: age, gender, clinical center site, and height, race/ethnicity

[b] Fully adjusted model: Minimally adjusted model covariates + heart rate (beats/minute) (C2, C1 only), mean arterial pressure (mmHg), use of blood pressure medication, weight, smoking (never smoked, ever smoked, current smoker), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, use of cholesterol lowering medication, high-sensitivity C-reactive protein; stratified by diabetes

[c] The P-value for statistical significance of arterial function measure in Cox regression model

Table 2.3 Number of Cardiovascular Disease (CVD), Coronary Heart Disease (CHD), and Congestive Heart Failure (CHF) Events Among Multi-Ethnic Study of Atherosclerosis (MESA) Participants That Had Arterial Functional Measure Obtained, United States, 2000-2011

Population that had this arterial functional measure obtained	Total cardiovascular disease (CVD) events	Total coronary heart disease (CHD) events	Total congestive heart failure (CHF) events
C2	590	417	225
C1	590	417	225
Aortic Distensibility	301	220	112
Carotid Distensibility	616	435	233
Young's Modulus	616	435	233

Table 2.4 Hazard Ratio for All Cardiovascular Disease (CVD) Events by Standard Deviation of Arterial Function Measure for Multi-Ethnic Study of Atherosclerosis (MESA) Participants, United States, 2000-2011.

	Hazard Ratio per Standard Deviation of Measure		
	Estimate	95% CI	Two-sided P-value[c]
C2			
Minimally adjusted model [a] (n=6309)	0.68	0.60, 0.77	<0.001
Fully adjusted model [b] (n=6206)	0.75	0.66, 0.86	<0.001
C2*SVR			
Minimally adjusted model (n=6309)	0.75	0.67, 0.83	<0.001
Fully adjusted model (n=6242)	0.81	0.72, 0.90	<0.001
C1			
Minimally adjusted model (n=6309)	0.82	0.74, 0.92	<0.001
Fully adjusted model (n=6206)	0.97	0.87,1.08	0.534
C1*SVR			
Minimally adjusted model (n=6309)	0.91	0.83,1.00	0.048
Fully adjusted model (n=6242)	0.98	0.90, 1.07	0.631
Aortic Distensibility (AD)			
Minimally adjusted model (n=3660)	0.79	0.65, 0.96	0.020
Fully adjusted model (n=3612)	0.92	0.77, 1.09	0.324
Carotid Distensibility (CD)			
Minimally adjusted model (n=6501)	0.81	0.73, 0.91	<0.001
Fully adjusted model (n=6422)	0.93	0.83, 1.04	0.191
Young's modulus (YM)			
Minimally adjusted model (n=6498)	1.06	0.99,1.14	0.104
Fully adjusted model (n=6419)	1.00	0.92,1.07	0.903

Abbreviations: CI, confidence interval; SVR, systemic vascular resistance

[a] Minimally adjusted model: age, gender, clinical center site, and height; stratified by race/ethnicity

[b] Fully adjusted model: Minimally adjusted model covariates + heart rate (beats/minute) (C2, C1 only), mean arterial pressure (mmHguse of blood pressure medication, weight, smoking (never smoked, ever smoked, current smoker), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, use of cholesterol lowering medication, high-sensitivity C-reactive protein; stratified by race/ethnicity and diabetes

[c] The P-value for statistical significance of arterial function measure in Cox regression model <0.05.

Table 2.5 Hazard Ratio for Congestive Heart Failure (CHF) Events by Standard Deviation of Arterial Function Measure for Multi-Ethnic Study of Atherosclerosis (MESA) Participants, United States, 2000-2011.

	Hazard Ratio per Standard Deviation of Measure		
	Estimate	95% CI	Two-sided P-value [c]
C2			
Minimally adjusted model [a] (n=6308)	0.68	0.56, 0.84	<0.001
Fully adjusted model [b] (n=6203)	0.70	0.56, 0.88	0.002
C2*SVR			
Minimally adjusted model (n=6308)	0.74	0.62, 0.88	0.001
Fully adjusted model (n=6239)	0.79	0.65, 0.95	0.011
C1			
Minimally adjusted model (n=6308)	0.66	0.54, 0.80	<0.001
Fully adjusted model (n=6203)	0.77	0.62, 0.94	0.012
C1*SVR			
Minimally adjusted model (n=6308)	0.73	0.62, 0.87	0.001
Fully adjusted model (n=6239)	0.84	0.71, 0.99	0.037
Aortic Distensibility (AD)			
Minimally adjusted model (n=3659)	0.99	0.80, 1.22	0.890
Fully adjusted model (n=3610)	1.08	0.92, 1.26	0.341
Carotid Distensibility (CD)			
Minimally adjusted model (n=6500)	0.78	0.64, 0.95	0.013
Fully adjusted model (n=6419)	0.92	0.77, 1.11	0.398
Young's modulus (YM)			
Minimally adjusted model (n=6497)	1.07	0.96, 1.19	0.235
Fully adjusted model (n=6416)	1.00	0.89, 1.13	0.948

Abbreviations: CI, confidence interval; SVR, systemic vascular resistance

[a] Minimally adjusted model: age, gender, clinical center site, and height, race/ethnicity

[b] Fully adjusted model: Minimally adjusted model covariates + heart rate (beats/minute) (C2, C1 only), mean arterial pressure (mmHguse of blood pressure medication, weight, smoking (never smoked, ever smoked, current smoker), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, use of cholesterol lowering medication, high-sensitivity C-reactive protein, diabetes; stratified by total cholesterol (tertiles)

[c] The P-value for statistical significance of arterial function measure in Cox regression model.

Table 2.6 Hazard Ratio for Coronary Heart Disease (CHD) Events by Quartile[a] of Arterial Function Measure for Multi-Ethnic Study of Atherosclerosis (MESA) Participants, United States, 2000-2011.

	Quartile 3		Quartile 2		Quartile 1	
CHD Events	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
C2: Minimally adj.	1.75	1.26, 2.42	1.75	1.25, 2.45	2.35	1.67, 3.32
C2: Fully adj.	1.52	1.09, 2.12	1.50	1.06, 2.12	2.08	1.45, 3.00
C2*SVR: Minimally adj.	1.84	1.34, 2.53	1.95	1.42, 2.69	2.08	1.50, 2.89
C2*SVR: Fully adj.	1.63	1.18, 2.25	1.65	1.19, 2.28	1.80	1.29, 2.51
C1: Minimally adj.	1.18	0.87, 1.59	1.30	0.96, 1.76	1.57	1.14, 2.17
C1: Fully adj.	1.06	0.78, 1.44	1.09	0.80, 1.49	1.18	0.83, 1.68
C1*SVR: Minimally adj.	0.99	0.75, 1.32	1.05	0.78, 1.39	1.62	1.21, 2.16
C1*SVR: Fully adj.	0.92	0.69,1.22	0.92	0.69,1.23	1.35	1.01, 1.81
AD: Minimally adj.	1.93	1.23, 3.02	1.24	0.76, 2.02	1.58	0.98, 2.56
AD: Fully adj.	1.78	1.17, 2.91	1.11	0.68, 1.80	1.25	0.77, 2.04
CD: Minimally adj.	1.19	0.87, 1.62	1.18	0.86, 1.61	1.36	0.98, 1.87

CD: Fully adj.	1.11	0.81, 1.52	1.01	0.74, 1.40	1.07	0.76, 1.50
	Quartile 2		Quartile 3		Quartile 4	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
YM: Minimally adj.	1.02	0.78, 1.33	0.92	0.70, 1.21	0.94	0.71, 1.23
YM: Fully adj.	1.02	0.78,1.34	0.89	0.68, 1.18	0.86	0.65, 1.14

Abbreviations: CI, confidence interval; SVR, systemic vascular resistance; adj., adjusted

[a] With reference to Quartile 4 (most elastic) for C2, C2*SVR, C1, C1*SVR, AD, CD; Quartile 1 (least stiff) for YM

[b] Minimally adjusted model: age, gender, clinical center site, and height, race/ethnicity

[c] Fully adjusted model: Minimally adjusted model covariates + heart rate (beats/minute) (C2, C1 only), mean arterial pressure (mmHg), use of blood pressure medication, weight, smoking (never smoked, ever smoked, current smoker), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, use of cholesterol lowering medication, high-sensitivity C-reactive protein, stratified by diabetes

Table 2.7 Hazard Ratio for All Cardiovascular Disease (CVD) Events by Quartile [a] of Arterial Function Measure for Multi-Ethnic Study of Atherosclerosis (MESA) Participants, United States, 2000-2011.

	Quartile 3		Quartile 2		Quartile 1	
All CVD Events	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
C2: Minimally Adj.	1.87	1.41, 2.49	1.98	1.48, 2.65	2.42	1.79, 3.26
C2: Fully Adj.	1.61	1.21, 2.16	1.62	1.20, 2.18	1.97	1.43, 2.70
C2*SVR: Minimally Adj.	1.87	1.43, 2.46	1.95	1.48, 2.56	1.99	1.50, 2.63
C2*SVR: Fully Adj.	1.65	1.25, 2.17	1.62	1.23, 2.14	1.70	1.28, 2.26
C1: Minimally Adj.	1.16	0.90, 1.51	1.21	0.93, 1.58	1.73	1.32, 2.28
C1: Fully Adj.	1.01	0.77, 1.31	0.97	0.75, 1.28	1.10	0.81, 1.47
C1*SVR: Minimally Adj.	1.06	0.83, 1.35	1.16	0.91, 1.48	1.60	1.25, 2.06
C1*SVR: Fully Adj.	0.96	0.75, 1.23	1.01	0.79, 1.30	1.30	1.01, 1.68
AD: Minimally Adj.	1.69	1.13, 2.53	1.35	0.89, 2.06	1.81	1.20, 2.74
AD: Fully Adj.	1.54	1.02, 2.31	1.15	0.75, 1.75	1.33	0.87, 2.03

CD: Minimally Adj.	1.20	0.92, 1.58	1.22	0.92, 1.60	1.63	1.24, 2.15
CD: Fully Adj.	1.10	0.83, 1.45	1.03	0.78, 1.36	1.21	0.90, 1.61
	Quartile 2		Quartile 3		Quartile 4	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
YM: Minimally Adj.	1.06	0.84, 1.34	1.04	0.82, 1.31	1.12	0.89, 1.41
YM: Fully Adj.	1.06	0.84, 1.35	1.00	1.00, 1.27	0.97	0.77, 1.24

Abbreviations: CI, confidence interval; SVR, systemic vascular resistance; adj., adjusted

[a] With reference to Quartile 4 (most elastic) for C2, C2*SVR, C1, C1*SVR, AD, CD; Quartile 1 (least stiff) for YM

[b] Minimally adjusted model: age, gender, clinical center site, and height, stratified by race/ethnicity

[c] Fully adjusted model: Minimally adjusted model covariates + heart rate (beats/minute) (C2, C1 only), mean arterial pressure (mmHg), use of blood pressure medication, weight, smoking (never smoked, ever smoked, current smoker), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, use of cholesterol lowering medication, high-sensitivity C-reactive protein, stratified by diabetes

Table 2.8 Hazard Ratio for Congestive Heart Failure (CHF) Events by Quartile[a] of Arterial Function Measure for Multi-Ethnic Study of Atherosclerosis (MESA) Participants, United States, 2000-2011.

CHF Events	Quartile 3		Quartile 2		Quartile 1	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
C2: Minimally adj.	1.78	1.11, 2.85	1.79	1.11, 2.88	2.23	1.37, 3.62
C2: Fully adj.	1.55	0.97, 2.48	1.58	0.97, 2.57	2.08	1.25, 3.47
C2*SVR: Minimally adj.	2.10	1.32, 3.32	1.90	1.19, 3.03	2.28	1.43, 3.63
C2*SVR: Fully adj.	1.77	1.11, 2.81	1.56	0.98, 2.49	1.98	1.23, 3.17
C1: Minimally adj.	1.37	0.85, 2.20	2.08	1.32, 3.26	2.81	1.75, 4.53
C1: Fully adj.	1.20	0.74, 1.93	1.64	1.03, 2.59	1.96	1.18, 3.25
C1*SVR: Minimally adj.	1.65	1.08, 2.53	1.41	0.90, 2.21	2.98	1.94,4.57
C1*SVR: Fully adj.	1.49	0.97, 2.29	1.16	0.74,1.83	2.19	1.42, 3.38
AD: Minimally adj.	1.13	0.58,2.23	1.29	0.67, 2.47	1.06	0.54, 2.05
AD: Fully adj.	1.05	0.53, 2.06	0.97	0.50, 1.87	0.65	0.33, 1.29
CD: Minimally adj.	0.96	0.59, 1.57	1.24	0.78, 1.97	1.72	1.09, 2.72
CD: Fully adj.	0.92	0.56, 1.51	1.04	0.65,1.67	1.23	0.76,1.98
	Quartile 2		Quartile 3		Quartile 4	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
YM: Minimally adj.	1.21	0.81, 1.79	1.17	0.79, 1.73	1.23	0.84, 1.81
YM: Fully adj.	1.22	0.82 1.81	1.05	0.71, 1.56	1.03	0.69, 1.53

Abbreviations: CI, confidence interval; SVR, systemic vascular resistance; adj., adjusted

[a] With reference to Quartile 4 (most elastic) for C2, C2*SVR, C1, C1*SVR, AD, CD; Quartile 1 (least stiff) for YM
[b] Minimally adjusted model: age, gender, race/ethnicity, clinical center site, and height
[c] Fully adjusted model: Minimally adjusted model covariates + heart rate (beats/minute) (C2, C1 only), mean arterial pressure (mmHg), use of blood pressure medication, weight, smoking (never smoked, ever smoked, current smoker), high density lipoprotein (HDL) cholesterol, triglycerides, use of cholesterol lowering medication, high-sensitivity C-reactive protein, diabetes, stratified by tertiles of total cholesterol

Table 2.9 Comparison of receiver-operating characteristic curves for prediction of coronary heart disease (CHD) events for models with covariates only and covariates plus stiffness variable for Multi-Ethnic Study of Atherosclerosis (MESA) Participants, United States, 2000-2011.

	Receiver-operating characteristic area for CHD Events		
	Estimate	95% CI	Two-sided P-value [c]
Covariates only-Minimally adj. model [a]	0.693	0.669, 0.717	
Minimally adj. model with C2	0.706	0.682, 0.730	0.010
Minimally adj. model with C1	0.695	0.671, 0.719	0.432
Minimally adj. model with C2*SVR	0.706	0.682, 0.730	0.003
Minimally adj. model with C1*SVR	0.694	0.669, 0.718	0.579
Covariates only-Fully adj. [b]	0.736	0.713, 0.758	
Fully adj. with C2	0.743	0.720, 0.765	0.041
Fully adj. with C1	0.737	0.714, 0.759	0.386
Covariates only-Fully adj.	0.737	0.714, 0.759	
Fully adj. with C2*SVR	0.742	0.720, 0.765	0.050
Fully adj. with C1*SVR	0.737	0.714, 0.759	0.851
Covariates only- Minimally adj. model	0.706	0.674, 0.738	
Minimally adj. model with AD	0.715	0.684, 0.746	0.079
Covariates only- Fully adj.	0.750	0.719, 0.782	
Fully adj. with AD	0.755	0.724, 0.786	0.258
Covariates only- Minimally adj. model	0.694	0.670, 0.718	
Minimally adj. model with CD	0.694	0.670, 0.718	0.930
Minimally adj. model with YM	0.694	0.670, 0.717	0.580
Covariates only- Fully adj.	0.736	0.713, 0.759	
Fully adj. with CD	0.737	0.714, 0.760	0.220
Fully adj. with YM	0.737	0.715, 0.760	0.095

Abbreviations: CI, confidence interval; SVR, systemic vascular resistance; adj., adjusted

[a] Minimally adjusted model: age, gender, clinical center site, and height, race/ethnicity

[b] Fully adjusted model: Minimally adjusted model covariates + heart rate (beats/minute) (C2, C1 only), mean arterial pressure (mmHg), use of blood pressure medication, weight, smoking (never smoked, ever smoked, current smoker), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, use of cholesterol lowering medication, high-sensitivity C-reactive protein; stratified by diabetes

[c] The P-value for Chi-square test with null hypothesis that receiver-operating characteristic area with covariates only and model with covariates plus arterial stiffness measure are equal

Table 2.10 Percentage of Subjects in Low-, Medium-, and High-risk Categories for Coronary Heart Disease (CHD) Event in the Multi-Ethnic Study of Atherosclerosis Study in Most Fully Adjusted Model With and Without C2, United States, 2000-2011.

	Most Fully Adjusted [a] Model with CV risk factors						Most Fully Adjusted [a] with CV risk factors + C2				
	Non-event		Event				Non-event		Event		
Risk Category	N	%	N	%	Row Total		N	%	N	%	Row Total
0-6%	3612	62.13	113	27.36	3725		3658	62.92	114	27.6	3772
6-20%	2015	34.66	249	60.29	2264		1926	33.13	247	59.81	2173
>20%	187	3.22	51	12.35	238		230	3.96	52	12.59	282
Column Total	5814		413				5814		413		

Abbreviations: CHD, coronary heart disease; CV, cardiovascular

[a] Most fully adjusted model: age, gender, clinical center site, and height, race/ethnicity, heart rate (beats/minute) (C2, C1 only), mean arterial pressure (mmHg), use of blood pressure medication, weight, smoking (never smoked, ever smoked, current smoker), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, use of cholesterol lowering medication, high-sensitivity C-reactive protein, stratified by diabetes

Table 2.11 Hazard Ratio for Coronary Heart Disease (CHD) Events by Standard Deviation of Arterial Function Measure for Subjects with All Five Arterial Function Measures (C2, C1, AD, CD, YM) for Multi-Ethnic Study of Atherosclerosis (MESA) Participants, United States, 2000-2011.

	Hazard Ratio per Standard Deviation of Measure		
	Estimate	95% CI	Two-sided p-value [c]
C2			
Min. adjusted model [a] (n=3282)	0.72	0.58, 0.88	0.002
Fully adjusted model [b] (n=3222)	0.79	0.63,0.98	0.030
C2*SVR			
Min. adjusted model (n=3282)	0.74	0.61,0.89	0.001
Fully adjusted model (n=3247)	0.81	0.67, 0.98	0.029
C1			
Min.adjusted model (n=3282)	0.96	0.82, 1.12	0.574
Fully adjusted model (n=3222)	1.07	0.91, 1.26	0.408
C1*SVR			
Min. adjusted model (n=3282)	0.98	0.86, 1.13	0.810
Fully adjusted model (n=3247)	1.04	0.91, 1.19	0.535
Aortic Distensibility (AD)			
Min. adjusted model (n=3282)	0.80	0.63, 1.01	0.058
Fully adjusted model (n=3247)	0.88	0.71, 1.09	0.242
Carotid Distensibility (CD)			
Min. adjusted model (n=3282)	0.94	0.79, 1.11	0.469
Fully adjusted model (n=3247)	1.05	0.89, 1.25	0.534
Young's modulus (YM)			
Min. adjusted model (n=3282)	0.98	0.84 1.14	0.764
Fully adjusted model (n=3247)	0.92	0.78 1.08	0.295

Abbreviations: CI, confidence interval; SVR, systemic vascular resistance; Min., minimally

[a] Minimally adjusted model: age, gender, clinical center site, and height, race/ethnicity

[b] Fully adjusted model: Minimally adjusted model covariates + heart rate (beats/minute) (C2, C1 only), mean arterial pressure (mmHg), use of blood pressure medication, weight, smoking (never smoked, ever smoked, current smoker), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, use of cholesterol lowering medication, high-sensitivity C-reactive protein; stratified by diabetes

[c] The P-value for statistical significance of arterial function measure in Cox regression model <0.05.

Table 2.12 Comparison of receiver-operating characteristic curves for prediction of coronary heart disease (CHD) events for models with covariates only and covariates plus stiffness variable for subjects with all five arterial function measures (C2, C1, AD, CD, YM) for Multi-Ethnic Study of Atherosclerosis (MESA) Participants, United States, 2000-2011.

	Receiver-operating characteristic area for CHD Events		
	Estimate	95% CI	Two-sided P-value [c]
Covariates only-Min. adj. [a] model (n=3282)	0.716	0.683, 0.749	
Minimally adj. model with C2	0.725	0.692, 0.758	0.162
Minimally adj. model with C1	0.716	0.683, 0.749	0.770
Minimally adj. model with C2*SVR	0.725	0.692, 0.758	0.134
Minimally adj. model with C1*SVR	0.716	0.683, 0.749	0.970
Covariates only-Fully adj. [b] (n=3221)	0.757	0.726, 0.789	
Fully adj. with C2	0.760	0.728, 0.792	0.533
Fully adj. with C1	0.758	0.726, 0.789	0.768
Covariates only-Fully adj. (n=3221)	0.758	0.726, 0.790	
Fully adj. with C2*SVR	0.761	0.729, 0.792	0.419
Fully adj. with C1*SVR	0.759	0.727, 0.791	0.457
Covariates only- Minimally adj. model (n=3282)	0.716	0.683, 0.749	
Minimally adj. model with AD	0.720	0.688, 0.752	0.208
Covariates only- Fully adj. (n=3221)	0.758	0.726, 0.790	
Fully adj. with AD	0.760	0.728, 0.791	0.162
Covariates only- Minimally adj. model (n=3282)	0.716	0.683, 0.749	
Minimally adj. model with CD	0.716	0.683, 0.749	0.883
Minimally adj. model with YM	0.716	0.683, 0.749	0.454
Covariates only- Fully adj. (n=3221)	0.758	0.726, 0.790	
Fully adj. with CD	0.758	0.726, 0.790	0.776
Fully adj. with YM	0.759	0.728, 0.791	0.345

Abbreviations: CI, confidence interval; SVR, systemic vascular resistance; adj., adjusted

[a] Minimally adjusted model: age, gender, clinical center site, and height, race/ethnicity

[b] Fully adjusted model: Minimally adjusted model covariates + heart rate (beats/minute) (C2, C1 only), mean arterial pressure (mmHg), use of blood pressure medication, weight, smoking (never smoked, ever smoked, current smoker), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, use of cholesterol lowering medication, high-sensitivity C-reactive protein, stratified by diabetes

[c] P-value for Chi-square test with null hypothesis that receiver-operating characteristic area with covariates only and model with covariates plus arterial stiffness measure are equal

Table 2.13 Number of participants with missing covariate values by Arterial Functional Measure Group for Multi-Ethnic Study of Atherosclerosis (MESA) Participants at Baseline Exam, United States, 2000-2002.

Covariate	**C2** (total participants = 6,336)		**Aortic Distensibility (AD)** (total participants=3,677)		**Carotid distensibility (CD)** (total participants= 6,531)	
Variable	**Number missing**	**% Missing in Sample**	**Number missing**	**% Missing in Sample**	**Number missing**	**% Missing in Sample**
Cigarette smoking	14	0.22	14	0.38	19	0.29
Use of hypertension medication	3	0.05	3	0.08	3	0.05
Use of any lipid medication	3	0.05	3	0.08	3	0.05
Diabetes mellitus	19	0.3	10	0.27	18	0.28
Heart rate	36	0.57	32	0.87	47	0.72
Mean blood pressure	3	0.05	1	0.03	1	0.02
Total cholesterol	18	0.28	9	0.24	18	0.28
HDL cholesterol	21	0.33	11	0.3	21	0.32
Triglycerides	18	0.28	9	0.24	18	0.28
C-reactive protein	40	0.63	26	0.71	47	0.72

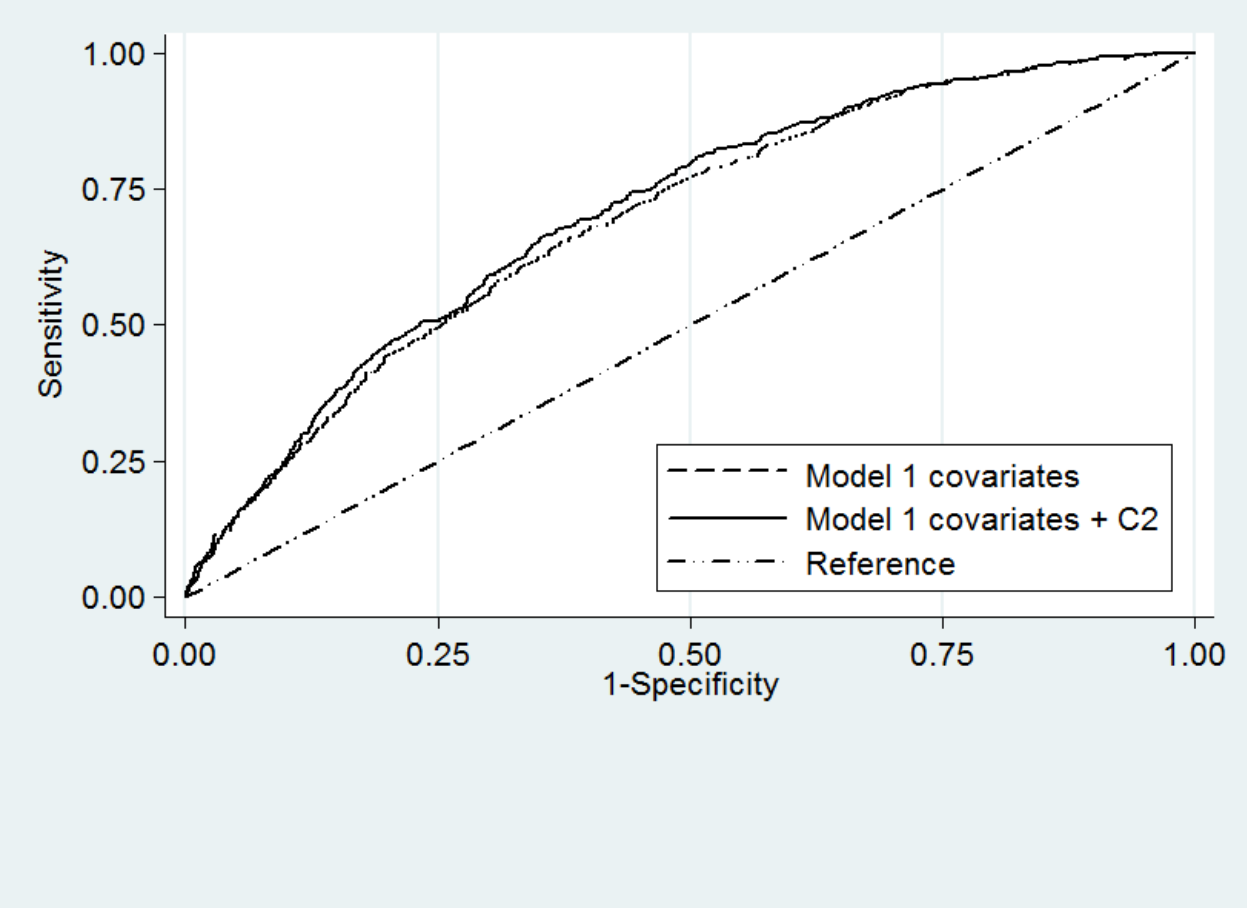

Figure 2.1 Receiver operator characteristic curves showing area under curve for risk prediction of incident coronary heart disease (CHD) with minimally adjusted model (Model 1) covariates and C2 for Multi-Ethnic Study of Atherosclerosis (MESA) participants, United States, 2000-2011. Model 1 is a Cox regression model includes age, gender, clinical center site, and height, and race/ethnicity.

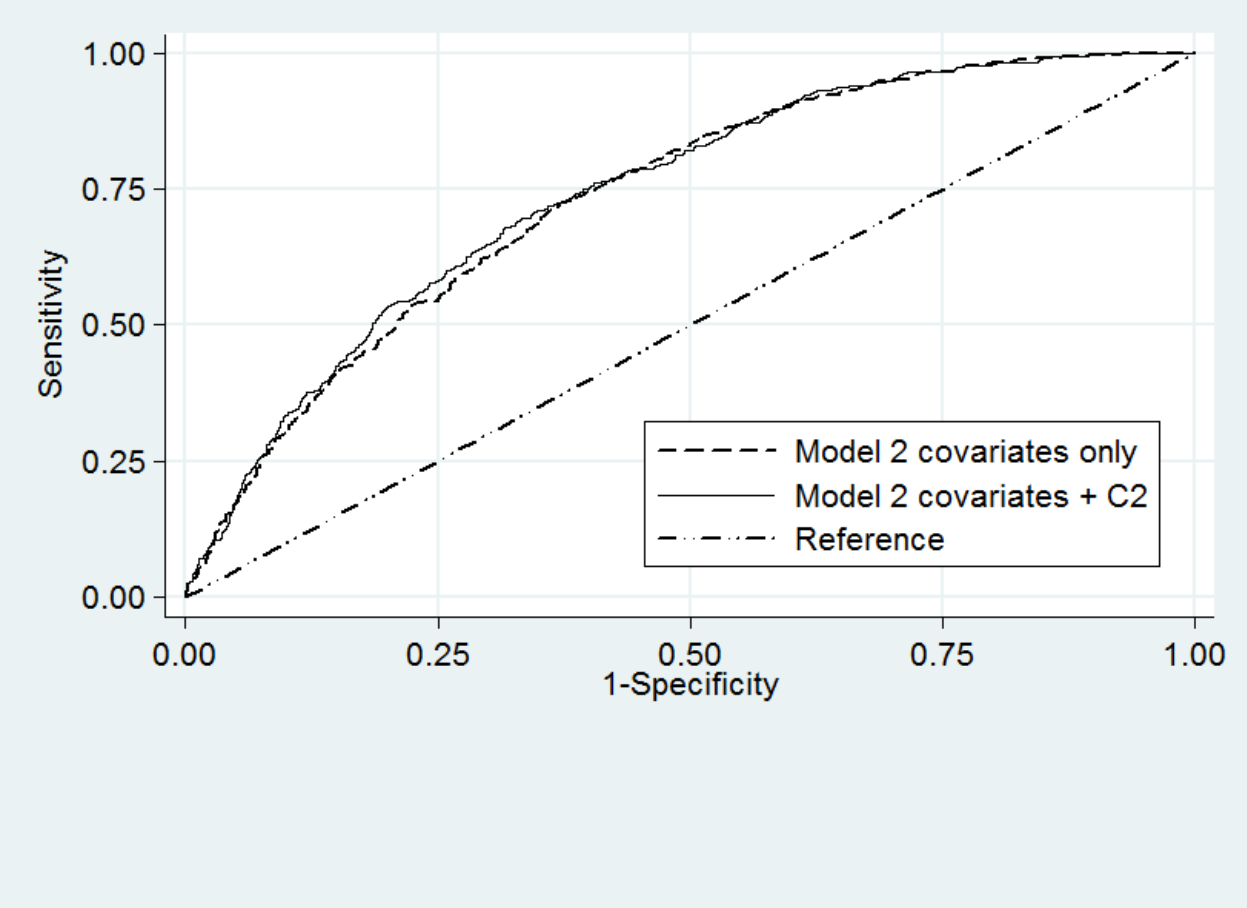

Figure 2.2 Receiver operator characteristic curves showing area under curve for risk prediction of incident coronary heart disease (CHD) with most fully adjusted model (Model 2) covariates and C2 for Multi-Ethnic Study of Atherosclerosis (MESA) participants, United States, 2000-2011. Model 2 adjusts for age, gender, clinical center site, and height, race/ethnicity, plus heart rate (beats/minute) (for C2, C1 only), mean arterial pressure (mmHg), use of blood pressure medication, weight, smoking (never smoked, ever smoked, current smoker), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, use of cholesterol lowering medication, high-sensitivity C-reactive protein. Model 2 is also stratified to allow for different baseline hazards by diabetes mellitus status (yes/no).

Chapter 3. Association of Cardiovascular Risk Factors with Longitudinal Change in Arterial Function Measures in the Multi-Ethnic Study of Atherosclerosis (MESA)

3.1 Abstract

Background and purpose: Arterial functional measures, including those considered measures of arterial elasticity, are associated with subsequent coronary heart disease and congestive heart failure events, independent of traditional cardiovascular risk factors. The degree to which traditional cardiovascular risk factors may influence decline in arterial elasticity in aging is not well understood. We examined the relationship between individual characteristics and changes over time in four different arterial stiffness measures, to better understand the functional pathways linking CV risk factors to cardiovascular disease events.

Methods and Results: Participants from the Multi-Ethnic Study of Atherosclerosis were assessed in 2000-2002 and again in 2010-2012. Pressure Time Constant 1 (PTC1) and 2 (PTC2) values, derived from the diastolic pressure decay waveform collected via radial tonometry, were measured in 3,545 participants, and distensibility coefficient (DC) and Young's Elastic Modulus (YEM) at the carotid artery, via carotid artery ultrasound, was measured in 2,593 participants. Determinants of arterial stiffness progression were examined using a linear mixed model. Arterial stiffness increased in all measures as anticipated over time, though different risk factors were associated with changes in specific arterial function measures: Being of male gender was associated with larger declines for PTC2. Higher heart rate was associated with smaller declines in PTC1. Higher BMI at baseline was associated with smaller declines in DC. Having diabetes at baseline was associated with larger increases in YEM. Increased age at baseline was associated with smaller declines in PTC1, PTC2, DC (deceleration of stiffening), but larger increases in

YEM (acceleration of stiffening) over follow-up. In addition, increased systolic arterial pressure (SBP) at baseline and as a time-varying variable were associated with smaller declines in PTC1, PTC2. However, higher mean arterial pressure (MAP) was associated with larger increases in YEM (acceleration of stiffening).

Conclusions: Higher mean arterial pressure (MAP), having diabetes at baseline, and increased age at baseline were associated with larger increases in YEM over follow-up. However, we observed blood pressure measures and baseline age having the opposite effects on progression of other arterial function measures. The different directions of the association between age with arterial stiffness progression and between blood pressure measures with arterial stiffness progression indicate complex relationships between CV risk factors and change in arterial stiffness in varying vascular beds over time. Some of these differences may be due to the different aspects of arterial stiffness being measured and how stiffness is calculated.

3.2 Introduction

Previous studies have shown association between arterial function measures, which includes arterial stiffness (or elasticity) measures, and risk of cardiovascular disease (CVD) events. Aortic pulse wave velocity (PWV) was highly correlated with actual cardiovascular disease outcomes independent of traditional risk factors in multiple studies.(Sutton-Tyrrell et al. 2005; Hansen et al. 2006a; T Shokawa et al. 2005; Meaume et al. 2001) In addition, C2, also called small artery elasticity (SAE), has been associated with physician-adjudicated CVD events (D A Duprez et al. 2011) and coronary heart disease events (Hom et al. 2016) after adjustment for traditional risk factors in the MESA cohort. Furthermore, C1, also called large artery elasticity (LAE), was

associated with congestive heart failure (CHF) events even following inclusion of classic cardiovascular risk factors in the model in the MESA cohort.

Several "traditional" cardiovascular risk factors are strongly and consistently associated with risk of CVD events. The Framingham Heart Study showed that smoking, unhealthy diet, physical inactivity, obesity, elevated blood cholesterol, elevated blood pressure, and diabetes are strong risk factors for CVD.(Mendis 2010) The associations between these risk factors and longitudinal change in measures of arterial stiffness are not well understood. If a CVD risk factor is strongly associated with longitudinal change in an arterial stiffness measure, this could suggest that the arterial stiffness measure may provide information on functional pathways linking the CVD risk factor to subsequent CVD events.

Past investigation has demonstrated there are differences in cross-sectional arterial stiffness (or elasticity) for various groups defined by traditional cardiovascular risk factors such as gender, race/ethnicity, age, hypertension, and HDL levels.(D A Duprez et al. 2009; Valappil et al. 2008; A A Malayeri et al. 2008b; A Redheuil et al. 2010) Relatively few studies have investigated the effects of cardiovascular risk factors on longitudinal change in arterial stiffness compared to cross-sectional studies. Several previous studies were of relatively short follow-up time.(Li et al. 2011a; van Dijk et al. 2000b) In addition, some of the past study populations were mostly ethnically homogenous(Koskinen et al. 2010; Li et al. 2011b; Koskinen et al. 2012) or young.(Koskinen et al. 2010; Koskinen et al. 2012)

We examined the correlates of longitudinal change in arterial stiffness in order to better understand how these measures may be on the biological pathway connecting traditional cardiovascular risk factors and CVD events. We examined the association between traditional CVD risk factors and longitudinal change in the following arterial function measures between Exam 1 (2000-2002) and Exam 5 (2010-2012) of the MESA study: 1) derivatives of the arterial blood pressure waveform measured at the radial artery: PTC1 and PTC2, and 2) derivatives of cross-sectional analysis of the carotid artery: distensibility coefficient of the carotid artery (DC), Young's elastic modulus at the carotid artery (YEM). This analysis was an opportunity to see how cardiovascular risk factors on longitudinal change in arterial stiffness in greater depth and in a standardized fashion among a wider range of stiffness measures in a large, ethnically diverse, older study population. To our knowledge, it is also the first published analysis of longitudinal change in two novel radial tonometry measures, PTC1 and PTC2.

3.3 Methods

3.3.1 Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is an ongoing longitudinal study funded by the National Heart Lung and Blood Institute.(Bild et al. 2002) The full MESA cohort contains 6,814 men and women between the ages of 45 to 84 years which participated in MESA's Exam 1 clinic visit. Participants did not have clinical CVD at enrollment and were recruited from six field centers in the United States. The initial baseline examination (Exam 1) was completed from July 2000 to August 2002. Follow-up data comes from the fifth exam (Exam 5), which was completed from April 2010 to February 2012. This study was approved by the Institutional Review Boards of all MESA study sites and all participants gave their informed consent.

There were 3,751 participants with both Exam 1 and Exam 5 radial tonometry measures. There were 2,582 participants with only Exam 1 radial tonometry measures. There were 254 participants with only Exam 5 radial tonometry measures. The following observations were included in our analysis: 3,577 participants had Exam 1 radial tonometry measures and all covariate data. 3,533 participants had Exam 1 and Exam 5 radial tonometry measures and all covariate data. 3,655 participants had Exam 5 radial tonometry and all covariate data. Because we limited our analysis to participants with both Exam 1 and Exam 5 covariate data, we had 3,799 unique participants in our analysis. (Figure 3.1)

There were 2,729 participants with both Exam 1 and Exam 5 carotid ultrasound measures. There were 144 participants with only Exam 1 carotid ultrasound measures. There were 490 participants with only Exam 5 carotid ultrasound measures. The following observations were included in our analysis: 2,719 participants had Exam 1 carotid ultrasound measures and all covariate data. 2,593 participants had Exam 1 and Exam 5 radial tonometry measures and all covariate data. 2,983 participants had Exam 5 radial tonometry and all covariate data. Because we limited our analysis to participants with both Exam 1 and Exam 5 covariate data, we had 3,115 unique participants in our analysis. (Figure 3.2)

In the Appendix chapter, there is additional explanation about the radial tonometry (Page 308) and carotid ultrasound participant groups (Page 308) included in our analyses.

3.3.2 Data collection and definitions of baseline cardiovascular risk factors

Age, race/ethnicity (Caucasian, African-American, Hispanic, Chinese-American), sex, and smoking status were obtained by self-report. Body mass index was calculated as weight (kg) divided by height squared (m^2). Resting seated systolic and diastolic blood pressure were measured three times using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida), with the average of the last 2 measurements used. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive medication. Heart rate (beats per minute) was monitored and recorded at the time of the magnetic resonance imaging (MRI) exam. Use of blood pressure medication and use of cholesterol lowering medication were assessed using standardized questionnaires and by examining medication containers.

A central laboratory (University of Vermont, Burlington) measured concentrations of total cholesterol, high density lipoprotein cholesterol, triglycerides, plasma glucose, and high-sensitivity C-reactive protein obtained after 12-hour fast. Diabetes was defined as having fasting plasma glucose greater or equal to 126 mg/dL (7.0 mmol/L) or a history of receiving medical treatment for diabetes.

3.3.3 Methods for calculating previous (C1, C2) and current (PTC1 and PTC2) arterial function measures derived from diastolic pulse contour analysis

The radial artery pressure waveform is a non-invasive method to measure blood pressure throughout the cardiac cycle.(Nichols, O'Rourke, and Vlachopoulos 2011b) We obtained the radial artery blood pressure waveform by applanation tonometry using HDI/PulseWave CR-2000 device (Hypertension Diagnostics, Inc., Eagan, Minnesota) during the baseline examination

(Exam 1) and using Millar Mikro-Tip Pulse Transducer (Millar Instruments, Houston, Texas) during Exam 5. For both Exams 1 and 5, a solid-state pressure transducer array, also called a radial tonometer, was placed over the radial artery of the dominant arm to record the pulse contour. A 30-second analog tracing of the radial waveform, constituting continuous pressure changes during diastole, was digitized at 200 samples per second. All cardiac cycles from each set of 30 seconds data collection were analyzed. In exam 1, only one set of waveforms was collected. For exam 5, two to three sets of waveforms were collected.

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In a previous analysis, MESA investigators utilized an algorithm included with software provided with the HDI/PulseWave CR-2000 device to generate two different measures of arterial function, C1 and C2. The HDI device fits a third-order Windkessel model to a subset of linearly calibrated "diastolic pulse contours" from the 30 seconds of radial artery blood pressure waveform collected at Exam 1. The HDI device's model contained a decaying exponential term and exponentially dampened cosine term. C1 and C2 are each the product of estimated systemic vascular resistance (SVR) and a function of modified third-order Windkessel model parameters in specific formulas. SVR is estimated from participant characteristics including age, mean arterial blood pressure, heart rate, height, and weight. Unfortunately, HDI's methods for calibration and selection of the subset of 30 seconds of waveform data (a subset of the waveforms corresponding to each heartbeat and a subset of each heartbeat waveform corresponding to diastole) are proprietary and not in the public domain. Estimates of C1 and C2 are sensitive to calibration and data selection and thus HDI/PulseWave CR-2000 device's C1 and C2 cannot be reproduced.

Therefore, MESA investigators developed several novel indices of radial pressure waveform by modeling the pressure decay, which included PTC1 and PTC2. The goal of these indices were to develop reproducible indices of arterial stiffness for exam 1 and exam 5 data. We did not model the "diastolic portion of the waveform," as the HDI device had done, because diastole in the waveform is not clearly defined. Instead, we modeled a portion of the waveform, beginning from the time of maximum pressure to the end of the waveform, since the time of maximum pressure for a waveform is clearly defined. Similar to the HDI device, we used standard nonlinear regression methods to fit a model to the pressure decay waveform occurring during each heartbeat. However, our model contained an intercept, in addition to the exponential term and exponentially dampened cosine term used by the HDI device's formula. The benefit of having an intercept is that the model fits the data better, and PTC1 and PTC2 are invariant to linear calibration of the waveform. We calculated values for PTC1 and PTC2 by utilizing coefficients from each fitted model. Another advantage is that PTC1 and PTC2 also did not require estimation of systemic vascular resistance. We included details on the HDI device's and our formulas in the Introduction chapter.(Page 32)

We calculated the weighted mean of all PTC1 and PTC2 values for one set in exam 1 for each participant. We also calculated the weighted means of all PTC1 and PTC2 values for two to three sets in exam 5 to produce PTC1 and PTC2 values for exam 5. Throughout the remainder of this paper, we refer to the weighted mean of PTC2 as "PTC2" and the weighted mean of PTC1 as "PTC1." The units for the weighted mean of PTC2 is $(\text{seconds}*100)^{-1}$. The units for the weighted mean of PTC1 is $(\text{seconds}*10)^{-1}$.

We wanted to know whether our novel arterial function indices, PTC2 and PTC1, were similar to the previous arterial function indices from the HDI device, C2 or small artery elasticity (SAE) and C1 or larger artery elasticity (LAE), respectively. We examined these particular pairings (PTC2 and C2; PTC1 and C1) because each pair is based on the same formula of coefficients. However, a key difference is that our formula contains an addition of an intercept term. PTC2 is of particular interest because C2 has been associated with cardiovascular disease independent of other cardiovascular risk factors (D A Duprez et al. 2011; Finkelstein and Cohn 1992), but has been difficult to estimate(Manning, Shykoff, and Izzo 2002). We calculated the correlation between PTC2 and C2*SVR and PTC1 and C1*SVR in order to evaluate the similarity between these sets of indexes of the radial artery waveform. C2*SVR and C1*SVR were used because these measures only include information based on the waveform and are not dependent on the calculation of SVR. The units for C2*SVR and C1*SVR were (seconds*10) and seconds, respectively. We also examined the association between PTC2 and PTC1 with the occurrence of coronary heart disease, cardiovascular disease, and congestive heart failure events. Cox proportional hazards regression was used to examine the associations between CHD with measures of arterial function from the current methodology: PTC2, PTC1, DC, YEM and previous methodology: C2, C2*SVR, C1, C1*SVR, CD, YM, using methods that we have previously described.(Hom et al. 2016)

We used these calculations to assess if the novel measures PTC2 and PTC1 displayed the same behavior as C2 and C1 in terms of prediction of cardiovascular disease events. If results were similar, this would provide evidence that PTC2 and PTC1 may be capturing the same arterial properties as C2 and C1.

3.3.4 Distensibility coefficient (DC) and Young's elastic modulus (YEM) of the right common carotid artery

Distensibility coefficient (DC) and Young's elastic modulus (YEM) were measured using B-mode ultrasound at the distal right common carotid artery with a Logiq 700 machine (General Electric Medical Systems, Milwaukee, WI). This method has been described previously.(Gepner et al. 2014) Repeated measures of the brachial blood pressure measurement was made on the right arm using the automated upper arm sphygmomanometer (Dinamap Pro 100; Critikon, Inc., Tampa, FL) after ten minutes of rest in the supine position and before the carotid artery ultrasound was acquired. The largest and smallest diameters during the cardiac cycle were classified as the systolic and diastolic diameters, respectively. Access Point Web version 3.0 (Freeland Systems, Westminster, CO) was used to measure internal and external artery diameters were measured. Distensibility coefficient was calculated by the relative change in the cross-sectional area of the carotid artery by the pulse pressure at the brachial artery. The units for DC were $(mmHg*1000)^{-1}$. Young's modulus was calculated by dividing circumferential stress by the circumferential strain on the arterial wall. The units for YEM were mmHg. Additional information on the acquisition and calculation of DC and YEM are in the Introduction chapter. (Page 35)

3.4 Statistical analysis

3.4.1 Linear mixed effects model

We utilized a linear mixed effects model to look at both cross-sectional and longitudinal associations between various cardiovascular risk factors and arterial stiffness measurements at Exam 1 and Exam 5.(Gassett et al. 2015) The first, cross-sectional term in the model uses baseline covariates (including cardiovascular risk factors) to estimate (or model) the arterial stiffness at Exam 1. The second, longitudinal term in the model estimates the change in stiffness

between Exams 1 and 5 utilizing baseline and time-varying covariates. We used a fixed slope, in which a coefficient for the average rate of change in arterial stiffness was used for all participants. We also used a participant-specific random intercept, in which each participant was allowed to have a different arterial stiffness value at baseline.

We centered all continuous variables by subtracting the mean value from all continuous covariates. Thus, the reference group were participants with mean age, heart rate, body mass index, total cholesterol, HDL cholesterol, triglycerides, CRP, SBP for radial tonometry measures and MAP for carotid ultrasound measures. In addition, the values of for categorical variables for the reference group include being female, White race/ethnicity, recruited at the Winston-Salem, North Carolina site (Wake Forest University), less than a high school graduate, never smoker and having less than $25,000 per year in gross annual income, no diabetes, and taking no lipid lowering medication or anti-hypertensive medication.

Here is the linear mixed effects model for a participant *"i"* at exam *"v"*, where v =1 for exam 1 and v=5 for exam 5*:*

$Y_{jv} = [\alpha_o + X_{io} * \alpha_1 + a_i] + [t * \beta_0 + t * W_{iv} * \beta_1] + [\varepsilon_{iv}]$

Where Y_{jv} = arterial stiffness measurement for participant *i* at exam *v*,

α_o = average arterial stiffness measurement at exam 1 for participants in reference group, which I described in the preceding paragraph.

X_{io} =cross-sectional confounders and cardiovascular risk factors at Exam 1 for participant *i* that are time-invariant (ie. CV risk factor at baseline)

α_1 = coefficients for associations between CV risk factors or confounders and arterial stiffness at exam 1

a_i = participant-specific random intercept

W_{iv} = possibly time-varying longitudinal confounders and risk factors for at exam *v* for participant *i*

t= time in years from Exam 1 for participant *i*

t=0 for arterial measures at Exam 1

t=time in years between Exam 1 and 5 radial tonometry exams for PTC2 and PTC1 arterial function measures or Exam 1 and 5 carotid ultrasound exams for DC and YEM arterial function measures

β_0= coefficient association between CV risk factor and annual rate of change in arterial function measures for participants in the reference group, which I described in the preceding paragraph.

β_1 = coefficients for association between CV risk factor and annual rate of change in arterial function measures.

In our analysis, β_1 is a vector containing a different coefficient of interest for each cardiovascular (CV) risk factor of interest. CV risk factors may change the slope for the annual rate of change in arterial stiffness in stiffness over time. Thus, these CV risk factors may act as effect modifiers.

ε_{iv} = error associated with Y_{iv}

The interpretation of β_1 depends on which arterial stiffness measure we are examining. With aging, we expect arterial elasticity to decrease and arterial stiffness to increase over the follow-up time. For PTC2, PTC1, and DC, we hypothesized a decline in these arterial elasticity measures over time (negative rate of change in arterial elasticity variable). Thus, a positive β_1 for PTC2, PTC1, and DC means that the change in elasticity has slowed or decelerated (smaller decline). A negative β_1 for PTC2, PTC1, and DC means that change in elasticity has been accelerated (larger decline). For YEM, we hypothesized an increase in this arterial stiffness measure over time (positive rate of change in arterial elasticity variable). A positive β_1 for YEM means that the change in stiffness has been accelerated (larger increase). A negative β_1 for YEM means that the change in stiffness has slowed or decelerated (smaller increase).

All models were adjusted for the sex, race/ethnicity, site, and age at baseline ("base model covariates").

In the minimally adjusted model, we adjusted for each CV risk factor, separately, in addition to the base model covariates ("univariate analysis.") These CV risk factors included the following variables at Exam 1: body mass index (BMI), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, diabetes mellitus status (yes/no), annual gross family income in the past 12 months, highest educational level completed, and high sensitivity c-reactive protein. The following variables were included as time-varying covariates for Exams 1 and 5: systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP), pulse pressure (PP), smoking status (never smoked, ever smoked, current smoker), use of blood pressure medication (yes/no), use of lipid lowering medication (yes/no), and heart rate. When examining the association between lipid levels (total cholesterol, HDL cholesterol, or triglycerides) at exam 1 and change in arterial stiffness, models were adjusted for use of lipid lowering medication at exam 1. When examining the association between blood pressure measures (time-varying SBP, DBP, MAP, PP) and change in stiffness, models were adjusted for use of blood pressure medication (time-varying).

In the fully adjusted model, we explored how various CV risk factors and distending pressure influence the stiffness of the artery. Previous researchers have observed that the elasticity (or stiffness) of an artery changes with distending pressure, which is the pressure felt inside of the artery due to blood flow.(Greenfield and Patel 1962) Others have observed that higher distending

pressure results in the recruitment of collagen fibers in the arterial wall and a reduction in arterial elasticity.(Bank et al. 1996) A priori we included mean arterial pressure (MAP), which estimates distending pressure, in the fully adjusted model for DC and YEM and systolic blood pressure (SBP) in the fully adjusted model for PTC1 and PTC2. SBP had a strong association with both C1 and C2 in a previous study, especially compared to DBP. C1 and C2 are arterial functional measures derived from the diastolic portion of the blood pressure waveform using a similar, yet still slightly different formula than that used to derive PTC1 and PTC2. More details on the relationship between C1 and C2 with PTC1 and PTC2 are in the Methods section of this chapter and Introduction chapter. As a sensitivity analysis, we also examined multivariate models using the other BP measures (DBP, MAP, PP for PTC1 and PTC2; SBP, DBP, PP for DC and YEM).

We also included all base model covariates and CV risk factors listed for the minimally adjusted model previously were adjusted for simultaneously ("multivariate" analysis.) Thus, the fully adjusted model included the following variables at Exam 1: sex, race/ethnicity, site, age, and BMI, total cholesterol, HDL cholesterol, triglycerides, diabetes mellitus status, annual gross family income, highest educational level completed, educational attainment and high sensitivity c-reactive protein. In addition, we examined smoking status, use of blood pressure medication, use of lipid lowering medication, and heart rate as time-varying covariates.

To explore the effects of baseline age and time-varying blood pressure further, we examined the multivariate model using categorical age and categorical blood pressure measures. We categorized age as: 1) 45-54 years old (reference group), 2) 55-64 years old, 3) 65-74 years old,

and 4) 75-84 years old. We divided mean arterial pressure into quartiles. We divided systolic blood pressure into the following categories: 1) <120mmHg, 2) 120-139 mmHg, 3) >=140 mmHg, which corresponds to normal, pre-hypertension, and hypertension according to the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.(Chobanian et al. 2003)

We also wanted to examine if taking blood pressure medication modified the relationship between blood pressure and longitudinal change. Thus, we included a "blood pressure medication * blood pressure measurement" interaction term in the multivariate model as a sensitivity analysis. The "blood pressure measurement" was SBP for PTC2 and PTC1, and MAP for DC and YEM.

3.4.2 Linear regression model (Sensitivity analysis)

As a sensitivity analysis, the association between cardiovascular risk factors and rate of change in arterial stiffness between Exams 1 to 5 was also examined using a linear regression model. The rate of change in arterial stiffness between Exams 1 to 5 was the outcome variable. All models were adjusted for "base model covariates": sex, race/ethnicity, site, and age at baseline. We have included additional information on this sensitivity analysis in the Appendix chapter.(Page 309)

3.5 Results

3.5.1 Descriptive analysis of participant characteristics

Table 3.1 shows the baseline characteristics of all MESA participants, participants with Exam 1 and 5 radial tonometry data plus all covariate data, participants with Exam 1 and 5 carotid ultrasound data plus all covariate data. Participants with Exam 1 and 5 radial tonometry and carotid ultrasound measures plus all covariate data compared to all MESA participants at Exam 1 were slightly younger, more educated, had higher annual gross family income, had lower use of anti-hypertension medication, lower prevalence of diabetes, lower proportion of current smokers, slightly lower SBP and MAP, and slightly lower triglycerides levels at baseline.

Participants with Exam 1 and 5 radial tonometry and carotid ultrasound measures compared to all MESA participants at Exam 1 also had similar height, heart rate, DBP, total cholesterol levels, HDL cholesterol levels, LDL cholesterol levels, CRP levels, as well as similar proportions of gender groups, race/ethnicity groups and those taking lipid medication at Exam 1.

3.5.2 Descriptive analysis of arterial function measures

Table 3.2 shows the descriptive characteristics of the arterial function measures in this analysis, including PTC2, PTC1, DC, and YEM. There were more PTC1 and PTC2 values available for Exam 1 compared to Exam 5. However, for DC and YEM, there were more Exam 5 compared to Exam 1 values. The mean values of PTC2, PTC1, and DC were higher at Exam 1 compared to Exam 5, indicating a drop in arterial elasticity over time, on average. The mean values of YEM were lower at exam 1 compared to exam 5, which describes an increase in arterial stiffness over time, on average. Yet, a notable percentage of participants actually showed no change or even a gain in elasticity (or loss in stiffness) between exams 1 and 5. Considering participants that had

both Exam 1 and 5 measures, 1,288 (34.3%) experienced an increase or no change in PTC2, 925 (24.7%) experienced an increase or no change in PTC1, 973 (35.7%) experienced no change or a gain in DC, 1,208 (44.2%) experienced no change or a loss in YEM (Table 3.8).

3.5.3 Comparing PTC1 and PTC2 with C1*SVR and C2*SVR

There was moderate correlation (0.61) between C2 and PTC2. There was low, negative correlation (-0.08) between C1 and PTC1. It appears the addition of the intercept to the model and the specific subset of waveform data that were modeled had a much bigger impact on the relationship between PTC1 and C1 than on the relationship between PTC2 and C2.

In the most fully adjusted model, higher PTC2 was strongly associated with lower risk of CHD, all CVD, and CHF events (Table 3.3, Table 3.9,Table 3.10). In this respect, PTC2 behaves very similarly to C2. In the fully adjusted model, PTC1 and C1 both showed no association with risk of CHD events (Table 3.3). In the fully adjusted model, higher C1 was strongly associated with lower risk of CHF events, but there was no association between PTC1 and CHF events (Table 3.10). In addition, for the fully adjusted model, higher PTC1 was strongly associated with lower risk of all CVD events, but there was no association between C1 and all CVD events (Table 3.9).

These findings suggests that PTC2 may capture similar properties in the arterial system as C2. However, PTC1 is likely measuring quite different properties of the arterial system than C1.

3.5.4 Association between CV risk factors and PTC2

The unadjusted annual rate of decline in PTC2 was -0.17 $(seconds*100)^{-1}$ per year (Table 3.2), before adjustment for cardiovascular risk factors. Using the linear mixed effects model, the mean annual change in PTC2 was -0.104 $(seconds*100)^{-1}$ per year using the minimally adjusted model and -0.108 $(seconds*100)^{-1}$ per year using the fully adjusted model.

Age, gender, and SBP were associated with change in PTC2 for both minimal and fully adjusted models (Table 3.4). Older age at Exam 1 was associated with a smaller decline in PTC2 for the minimal and fully adjusted models. There was a small, positive coefficient for age at Exam 1 applied to the average rate of decline in PTC2 over time. Being male compared to female was associated with a greater decline in PTC2 for the minimal and fully adjusted models. Increased SBP as a time-varying variable was associated with smaller declines in PTC2 in the minimal and fully adjusted model, even after adjustment by use of anti-hypertensive medication. In our sensitivity analyses, increased DBP, MAP, PP were also associated with smaller declines in PTC2 in the minimal and fully adjusted models (Table 3.11).

When we examined baseline age and time-varying SBP as categorical variables, we found confirmation that higher values of each of these risk factors resulted in deceleration of the overall average decline in PTC2 (Table 3.15). The older age category, 65-74, had a slightly larger deceleration (0.053) of the decline in PTC2 than the younger age category, 55-64, (deceleration = 0.041) compared to the reference age category, 45-54. In addition, the higher blood pressure category (>=140 mmHg) had a larger deceleration (0.106) of the decline in PTC2 than the lower

blood pressure category (120-139mmHg) (deceleration = 0.070) compared to the reference SBP category (<120mmHg).

Several risk factors were associated with only the minimally adjusted model: Being a participant of Black or Hispanic compared to White race/ethnicity groups were both associated with a smaller decline in PTC2. Increased HDL cholesterol, adjusted for lipid medication, was associated with greater declines in PTC2. Increased triglycerides, adjusted for lipid medication, was associated with smaller decreases in PTC2. Increased CRP was associated with a smaller decline in PTC2.

3.5.5 Association between CV risk factors and PTC1

The unadjusted annual rate of decline in PTC1 was -0.139 (seconds*10) $^{-1}$ per year (SD=0.25), before adjustment for cardiovascular risk factors (Table 3.2). Using the linear mixed effects model, the mean annual change in PTC1 was -0.17 $(seconds*10)^{-1}$ per year using the minimally adjusted model and -0.14 $(seconds*10)^{-1}$ per year using the fully adjusted model.

Age, SBP, and heart rate were associated with change in PTC1 for both minimal and fully adjusted models (Table 3.5). Increased age at Exam 1 was associated with smaller declines in PTC1 in the minimal and fully adjusted models. Higher SBP as a time-varying variable after adjustment by anti-hypertensive medication was associated with smaller decline in PTC1 in both models. In our sensitivity analyses, increased DBP, MAP, PP were also associated with smaller declines in PTC1 in the minimal and fully adjusted models (Table 3.12). Increased heart rate as a

time-varying variable was associated with smaller declines in PTC1 in both models (Table 3.5). Increased CRP was associated with smaller decline in PTC1 for the minimal model only (Table 3.5).

When we examined baseline age and time-varying SBP as categorical variables, we found confirmation that increases in both of these risk factors resulted in deceleration of the overall average decline in PTC1 (Table 3.17). The oldest age category, 75-84 years old, had a slightly larger deceleration (0.052) of the decline in PTC1 than the middle age category, 65-74 years old, (0.030) compared to the reference age category, 45-54 years old. The two higher blood pressure categories (>=140 mmHg, 120-139 mmHg) both showed decelerations (0.033 and 0.032, respectively) of the decline in PTC1 compared to the reference SBP category (<120mmHg).

3.5.6 Association between CV risk factors and DC

The unadjusted rate of decline was -0.041 $(mmHg*1000)^{-1}$ per year (SD=0.119), before adjustment for cardiovascular risk factors (Table 3.2). Using the linear mixed effects model, the mean annual change in DC was -0.056 $(mmHg*1000)^{-1}$ per year for the minimal model and -0.0650 $(mmHg*1000)^{-1}$ per year (SD=0.0105) for the fully adjusted model.

Age and BMI were associated with change in DC for both minimal and fully adjusted models. Increased age at Exam 1 was associated with a smaller decline in DC in the minimal and fully adjusted models. Increased BMI as a time-varying variable was associated with smaller decline in DC in the minimal and fully adjusted models. Increased CRP at Exam 1 was associated with

greater decline in DC for the fully adjusted model only. MAP, SBP, and PP were each not associated with change in DC in the fully adjusted models. In sensitivity analyses, increased DBP was associated with smaller decline in DC for the fully adjusted model.

When we examined baseline age and time-varying MAP as categorical variables, we observed both age and MAP were not influential on the overall average decline in DC (

Table 3.19).

Some CV risk factors were only associated with decline in DC for the minimally adjusted model (Table 3.6): Increased MAP as a time-varying variable was associated with a smaller decline in DC. Increased triglycerides were associated with a smaller decrease in DC. Use of blood pressure medication as a time-varying variable was associated with smaller declines in DC. Being a current or former smoker compared to a never smoker was associated with greater decline in DC.

3.5.7 Associations between CV risk factors and YEM

The unadjusted rate of increase in YEM was 18.33 $(mmHg)^{-1}$ per year, before adjustment by cardiovascular risk factors. Using the linear mixed effects model, the mean annual change in YEM was 16.58 $(mmHg)^{-1}$ per year using the minimally adjusted model and 37.20 $(mmHg)^{-1}$ per year using the fully adjusted model.

Age, MAP, and diabetes were associated with change in YEM for both minimal and fully adjusted models (Table 3.7). Increased age was associated with larger increases in YEM for the minimal and fully adjusted models. Increased MAP as a time-varying variable was associated with larger increases in YEM for the minimal and fully adjusted models, even after adjustment by use of anti-hypertension medication. Having diabetes compared to not having diabetes at Exam 1 was associated with larger increases in YEM for minimal and fully adjusted models.

When we examined baseline age and time-varying MAP as categorical variables, we found that increase in both risk factors resulted in acceleration of the overall average increase in YEM (Table 3.21). The oldest age category, 75-84, had a larger acceleration (42.95) of increase in YEM than the younger age categories, 65-74, (9.18) and 55-64 (8.81) compared to the reference age category, 45-54. In addition, the two higher blood pressure categories (3rd and 4th quartile of MAP) had larger accelerations of the increase in YEM compared to the reference, 1st quartile of MAP.

We did not find an interaction between SBP and the use of anti-hypertensive medication for PTC2 or PTC1 (Table 3.16, Table 3.18). Nor did we detect an interaction between MAP and the use of anti-hypertensive medication for DC or YEM (Table 3.20, Table 3.22).

There were minor differences between the results for the linear mixed effects model with modeled cross-sectional baseline value (primary analysis) and the linear regression model with

rate of change in arterial function as the outcome (secondary analysis). We have described these differences are described in Appendix chapter.

3.6 Discussion

We examined the association of cardiovascular risk factors with longitudinal change in four different arterial stiffness measures (PTC1, PTC2, DC, YEM) obtained via two different methods, radial tonometry and carotid ultrasound, in a large, multi-ethnic cohort of older individuals that did not have cardiovascular disease at baseline.

Baseline age and time-varying measures of blood pressure, including SBP and MAP, had differing effects on change in arterial stiffness measures over follow-up. Multivariate analysis showed that risk factors varied in predicting change in the different stiffness measures. For PTC2, we found that male participants had larger declines in arterial elasticity than female participants. For PTC1, we found that increased heart rate was associated with smaller decline in arterial elasticity. For DC, we found that increased CRP levels at baseline was associated with larger declines in arterial elasticity, while higher BMI was also associated with smaller declines in arterial elasticity. For YEM, having diabetes was associated with greater increases in arterial stiffness. These findings may reflect the different pathological and physiological underpinnings of each measure.

We were surprised to find that the direction of the association between blood pressure measures and the change in arterial stiffness measures differed by measure. Increasing SBP as a time-varying variable was associated with smaller declines in PTC1 and PTC2 (deceleration of decline in elasticity). Increasing MAP as a time-varying variable was associated with larger increases for YEM (acceleration of increase in stiffness). However, MAP was associated with change in DC for the minimally adjusted, but not the fully adjusted model.

The finding that higher MAP is associated with greater increases in arterial stiffness measured by YEM corresponds to the results of several other studies. Increased blood pressure over a 6-year follow up period was also associated with decreased common carotid distensibility among study participants in Finland.(Koskinen et al. 2012) Increases in blood pressure during adolescence have been associated with increased carotid distensibility and decreased Young's elastic modulus at the carotid artery in adulthood in a study conducted in Amsterdam.(Ferreira et al. 2012) Lin and colleagues found that increased baseline MAP was associated with increased progression rates for pulse wave velocity and elastic modulus of the common carotid artery in both hypertensive and normotensive subjects in Taiwan.(Lin et al. 2015)

The complexity of the relationship between blood pressure and arterial stiffness may help explain why the results from our analysis seem contradictory. The relationship between blood pressure and arterial stiffness may be bi-directional. On one hand, increased blood pressure has been linked to damage of the arterial wall, causing blood vessels to lose elasticity, resulting in greater conduit artery stiffness.(S Laurent et al. 2006) In the opposite direction, a longitudinal

analysis of data from the Framingham Offspring Study found that increased arterial stiffness at baseline was associated with increased pressure pulsatility in blood vessels and increased systolic blood pressure at follow-up.(Kaess et al. 2012) It has been theorized that blood vessels with reduced elasticity have more difficulty controlling blood pressure resulting in a vicious cycle of greater stiffness and greater blood pressure.(Lin et al. 2015) Thus, greater increases in YEM may reflect thickening and stiffening of the arterial wall in response to high blood pressure. However, it is still unclear why increased blood pressure at Exam 1 and as a time-varying variable was associated with smaller declines in PTC2 and PTC1.

We had theorized that perhaps the unusual relationship between increasing blood pressure and smaller declines in PTC2 and PTC1 over time were due to differences among those taking anti-hypertensive medication compared to those who were not. However, we did not find an interaction between SBP and anti-hypertensive medication for PTC2 or PTC1. Thus, this unusual finding and other possible reasons deserve further study.

Age was strongly associated with change in arterial stiffness for all the measures, but the direction of the association varied among measures. We found that increasing baseline age was associated with smaller declines in PTC1, PTC2, and DC (smaller decline in elasticity). But increasing baseline age was associated with larger increases in YEM (greater increase in stiffness).

The finding that there are smaller declines in PTC1 and PTC2 with older baseline age is similar to patterns that were observed for aortic distensibility assessed via MRI in the MESA study. Redheuil and colleagues found that for MESA participants that were <50 years and younger had a much steeper decline in aortic strain and distensibility than those that were 50 years and older.(A Redheuil et al. 2010) This finding suggests that vascular function, as represented by these arterial function measures, may undergo changes and decline in young adulthood. As Redheuil and colleagues have previously explained, that decline in vascular function at younger ages may be related to changes occurring in vascular structural matrix proteins, mitochondria, and inflammation in early life. Thus, one hypothesis is that by older age, the decline in vascular function measured by PTC1 and PTC2 slows down and is not as steep.

The result that those at who were older at baseline have less decline in arterial elasticity over follow-up might also be due to fact that all MESA participants were required to be free of overt CVD at baseline. Thus, older participants who did not have overt CVD at baseline may already have cardiovascular health promoting behaviors (ie. active, fitness regimen) compared than younger participants that do not have overt CVD, that have allowed them to stay healthy for so long. These same cardiovascular-promoting behaviors on older participants may also result in lower declines in arterial elasticity over follow-up.

There were greater increases in YEM with older baseline age (greater acceleration of increase in arterial stiffness), but smaller declines in DC with older baseline age (smaller declines in arterial elasticity). Our findings are in agreement with a previous analysis of MESA participants in

which Gepner and colleagues observed that the rate of YEM increase was steeper for subjects that were older than 75 years old.(Gepner et al. 2014) We agree with explanations previously provided by Gepner and colleagues: YEM may better detect negative changes in the artery wall because it includes a measurement of wall thickness in its calculation. In contrast, DC is based on the change in arterial diameter divided by the pulse pressure, and has no measurement of wall thickness. Thus, DC may encounter "floor effects," in which participants who were older at baseline began the study with the lowest DC values, corresponding to the stiffest arteries. Thus, older participants at baseline showed less decline in DC over time because their artery diameters could not get even larger and pulse pressures could not increase even higher due to constraints of physiology.(Gepner et al. 2014)

Our finding that higher baseline age was associated with greater increases in YEM increase were also in agreement with other studies. Aging was found to be associated with acceleration of increase in arterial stiffness measured by carotid stiffness (Lin et al. 2015), aortic PWV (Benetos et al. 2002), baPWV (Tomiyama et al. 2011). This may happen because as vascular aging occurs, there are changes in the arterial wall leading to increased arterial stiffness. This includes deposition of collagen in the arterial wall, fragmentation and loss of elastin in the arterial wall, and increased amounts of calcium in the medial layer of the arterial wall.(McEniery, Wilkinson, and Avolio 2007; Izzo and Shykoff 2001)

Higher CRP levels at baseline were associated with larger declines in DC (elasticity). There has been little study of the association of CRP with longitudinal change in arterial function measures.

However, several cross-sectional studies in apparently healthy individuals found that increased CRP was associated with increased arterial stiffness using a variety of different measures including aortic pulse wave velocity (aPWV), brachial PWV, AIx, pulse pressure, central (aortic) pulse pressure, carotid-femoral PWV, brachial-ankle pulse wave velocity.(Yasmin et al. 2004; Kullo et al. 2005; F. U. S. Mattace-Raso et al. 2004; Nagano et al. 2005) These different cross-sectional studies highlight that inflammation, as measured by CRP, may be linked to arterial stiffness. Higher CRP levels may also signify increased endothelial dysfunction and atherosclerosis that lead to decreased arterial elasticity.(D A Duprez et al. 2005)

Men had larger declines in PTC2 than women. Our findings are consistent with findings from a longitudinal analysis of PWV measurements among 354 male and 423 female participants in the Baltimore Study of Aging. Al-Ghatrif and colleagues also found that there was a steeper longitudinal increase in PWV during follow-up in men than in women (AlGhatrif et al. 2013). In that study, men had greater acceleration of PWV increase while women had slower rates of PWV increase with older ages. Al-Ghatrif and colleagues hypothesized that this might be related to differences in aortic remodeling by sex (Lam et al. 2010). Aortic dilation, like arterial stiffness, tends to increase as people increase in age. Past studies have shown that women have slower rates of aortic dilation with aging.

Increased heart rate was associated with a smaller decline in PTC1. Our results conflict with a previous longitudinal study, which found that increased heart rate, was associated with accelerated increase in stiffness. In a six-year study of 483 subjects attending health checkups

over a 6-year time period in France, Benetos and colleagues found that increased heart rate at baseline was associated with accelerated increases in PWV among participants being treated for hypertension (Benetos et al. 2002). In addition, in a cross-sectional study of 6484 participants who had B-mode ultrasound and 3512 participants with cardiac MRI from the MESA study, Whelton and colleagues found that increased mean resting rate was associated with decreased carotid distensibility and decreased aortic distensibility after controlling for physical activity and atrioventricular nodal blocking agents (Whelton et al. 2013). Increased heart rate may contribute to chronic hemodynamic stress, which has been associated with the arterial fatigue and to the formation of atherosclerotic lesions (Bassiouny et al. 1994). As heart rate increases, there may be progressively less time for the arterial wall to recover from expansion during the diastole and a higher number of pulsatile strain cycles on the arterial wall. This may lead to fatigue and fracture of the elastic fibers in arterial wall (Mangoni et al. 1996). Thus, reasons for our finding are unclear and deserve more study.

Increased BMI was found to be associated with smaller decline in DC. Our results were in contrast to several longitudinal studies that found increased obesity or adiposity were associated with greater increases in arterial stiffness. During a 6-year follow-up period in the Amsterdam Growth and Health Longitudinal Study of 207 healthy adults, Ferriera and colleagues found that increased waist circumference at baseline and increases in waist circumference during follow-up were associated with steeper increases in Young's elastic modulus during the follow-up period (Ferreira et al. 2012). In a 6-year study of 1,711 young Finnish adults, increased baseline waist circumference and increases in waist circumference during follow-up were associated with larger decreases in carotid artery distensibility over the follow-up period (Koskinen et al. 2012).

However, in one smaller, cross-sectional study of 24 subjects, which included 12 young, obese, normotensive subjects were matched in age and sex to 12 lean subjects (Mangoni et al. 1995), the results were closer to what we found. The obese subjects were found to have larger radial artery diameter and greater radial compliance values than lean subjects throughout the range of systolic and diastolic pressure ranges. Mangoni and colleagues hypothesized that since obesity is characterized by insulin resistance, there may be an increase of insulin in the blood stream. Insulin may cause arteriolar smooth muscle cells to relax and cause vasodilation in the large arteries (James et al. 1986; Anderson et al. 1991). Another explanation is that obesity may cause increased blood volume, cardiac output and peripheral blood flow. As flow increases, there may be increased secretion of endothelium-derived relaxing factors and nitric oxide. These factors may lead to greater arterial elasticity. And though increased compliance is usually a positive health outcome, Mangoni and colleagues suggest that the increase in radial artery compliance in obese, normotensive subjects may actually be similar to increased radial artery compliance in subjects with mild essential hypertension (S Laurent et al. 1993). This may mean that the increased arterial compliance resulting from obesity may then be followed by an increase in blood pressure and eventual negative cardiac effects and pathogenesis of heart disease.

Having diabetes mellitus (also known as type 2 diabetes) compared to not having diabetes was associated with larger increases in YEM, but was not associated with changes in DC. Our finding contrasted with the discovery that having diabetes mellitus was associated with an accelerated decrease in DC, but were not independent predictors of change in YEM in an analysis of carotid artery stiffness in 2,650 participants from the MESA study by Gepner and colleagues (Gepner et

al. 2014). One possible reason is a difference in statistical analysis. Gepner and colleagues used a multivariate ANCOVA regression model with adjustment for baseline stiffness measures were used to assess the association between cardiovascular risk factors and difference between baseline and follow-up carotid artery stiffness measurements. In contrast, this analysis used a linear mixed model and controlled for baseline carotid artery stiffness using a modeled variable based on cross-sectional covariate values.

The finding that diabetes is associated with accelerated stiffening of the arteries measured by YEM corresponds well to other population-based cohort studies. Other studies that have found that having type 2 diabetes was associated with increased carotid, femoral and brachial stiffness compared to having normal glucose metabolism (Henry et al. 2003) and increased central arterial stiffness as measured by total systemic arterial compliance, aortic pressure augmentation index, and carotid-femoral transit time (Schram et al. 2004). One possible mechanism by which diabetes affects arterial stiffness is through insulin resistance which precedes the development of type 2 diabetes.(Stehouwer, Henry, and Ferreira 2008) In insulin-resistant states such as type 2 diabetes, insulin no longer provides acute vasodilatory effects, which leads to decreased arterial distensibility. Another mechanism may be that diabetes results in the formation of advanced glycation end-products (AGEs) on the arterial wall, which cause cross-linking of collagen molecules. This may lead to loss of collagen elasticity and increased arterial stiffness (Airaksinen et al. 1993; Aronson 2003).

There were a few limitations in this study. Only two measurements were made. Thus, we did not have the ability to study non-linear relationships between cardiovascular risk factors and change in arterial stiffness. In addition, there might be selection bias because only participants with Exams 1 and 5 measurements were included in the rate of change analysis using linear regression and the part of the linear mixed model estimating change in stiffness over time. As shown in Table 3.1, participants that had radial tonometry and carotid ultrasound measurements at Exams 1 and 5 plus full covariate data had a lower proportion with hypertension medication use, lower proportion with diabetes mellitus, and lower proportion of current smokers at baseline compared to all participants at Exam 1.

However, there were several strengths in this study. The MESA cohort has had excellent data on both baseline and follow-up demographic and health characteristics for the cohort. This study features different arterial stiffness measures using two different methods, carotid ultrasound and radial tonometry, that may reflect different regions and properties of the arterial tree. In contrast, most previous studies have focused on only one method of measuring arterial stiffness, making comparisons between methods difficult. Thus, it is an opportunity to compare and contrast what types of cardiovascular risk factors impact changes in arterial stiffness in time. This paper would add to the growing, but still small number of published studies on the impact of cardiovascular risk factors on longitudinal change in arterial stiffness. A majority of studies exploring the relationship between cardiovascular risk factors and longitudinal change in arterial stiffness are cross-sectional. Another strength of this study is the use of linear mixed effects model with modeled cross-sectional value for baseline arterial stiffness using cross-sectional covariates. Though many studies control for baseline arterial stiffness directly, when the baseline outcome

variable is measured with error, the results of the analysis can have substantial bias (Yanez, Kronmal, and Shemanski 1998). The goal of using modeled baseline outcome is that the baseline outcome may be measured more precisely and result in less bias. In simulation studies, the linear mixed model with modeled baseline outcome showed less bias than a model using measured baseline outcome (Gassett et al. 2015).

3.7 Conclusion

We observed that higher mean arterial pressure, having diabetes at baseline, and increased baseline age were associated with larger increases in arterial stiffness, measured by YEM, over follow-up (acceleration of stiffening). Yet, we also found that older age at baseline and higher systolic blood pressure were associated with smaller declines in arterial elasticity, as measured by PTC2 and PTC1 (deceleration of elasticity loss). In addition, increased baseline age was associated with smaller declines in arterial elasticity, as measured by DC (deceleration of elasticity loss). These results indicate that age and blood pressure measures are key determinants of the change in the arterial stiffness measures examined in this study. These conflicting results also indicate that the relationships of age and MAP with arterial stiffness progression are complex and require a deeper understanding of the measures themselves and how they change over time.

Table 3.1 Participant characteristics at Exam 1 for All Participants and Selected Participants with Complete Covariate Data

	All participants		**Participants with Exam 1 and 5 radial tonometry[1]**		**Participants with Exam 1 and 5 carotid ultrasound[1]**	
N	N= 6,814		N=3,545		N=2,593	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Years between exams[2]	N/A	N/A	9.6	0.6	9.5	0.6
Age (years)	62.2	10.2	60.2	9.5	59.9	9.4
Weight (pounds)	173.4	38.2	173.6	37.7	170.4	36.4
Height (cm)	166.4	10.0	166.9	9.9	166.8	10.0
Heart rate (beats/min.)	63.1	9.7	62.5	9.2	62.3	9.0
Systolic blood pressure (mmHg)	126.6	21.5	124.1	20.1	123.3	20.0
Diastolic blood pressure (mmHg)	71.9	10.3	71.9	10.1	71.7	10.1
Mean arterial pressure (mmHg)	90.1	12.6	89.3	12.1	88.9	12.1
Cholesterol, exam 1 (mg/dL)	194.2	35.7	193.7	34.1	193.5	33.8

HDL cholesterol, exam 1 (mg/dL)	51.0	14.8	51.4	14.7	51.7	15.0
LDL cholesterol exam 1 (mg.dL)	117.2	31.5	117.3	31.1	117.2	30.6
Triglycerides, exam 1 (mg/dL)	131.6	88.8	125.3	64.6	122.6	63.0
C-reactive protein, exam 1 (mg/L)	3.8	5.9	3.4	4.9	3.3	5.1

	N	%	N	%	No.	%
Gender						
Female	3601	52.8	1873	52.8	1383	53.3
Male	3213	47.2	1672	47.2	1210	46.7
Race/Ethnicity						
White	2622	38.5	1419	40	1010	39
Chinese	804	11.8	450	12.7	375	14.5
Black	1892	27.8	904	25.5	649	25
Hispanic	1496	22	772	21.8	559	21.6
Metropolitan Area (Site) at Exam 1						

Forsyth County, North Carolina (WFU)	1077	15.8	576	16.2	446	17.2
New York, NY (COL)	1102	16.2	647	18.3	503	19.4
Baltimore, MD (JHU)	1086	15.9	397	11.2	238	9.2
St. Paul, MN (UMN)	1066	15.6	638	18	398	15.3
Chicago, IL (NWU)	1164	17.1	779	22	549	21.2
Los Angeles, CA (UCLA)	1319	19.4	508	14.3	459	17.7
Highest level of education completed at exam 1						
Less than high school	1225	18	480	13.5	355	13.7
High school graduate/GED	1236	18.2	583	16.4	440	17
Some college/2 year college degree	1937	28.5	1044	29.4	741	28.6
4 year college degree/more	2393	35.2	1438	40.6	1057	40.8
Anti-hypertensive medication at exam 1	2536	37.2	1192	33.6	841	32.4
Smoking status at exam 1						
Never	3418	50.3	1857	52.4	1384	53.4
Former	2487	36.6	1266	35.7	920	35.5

Current	887	13.1	422	11.9	289	11.1
Any lipid-lowering medication at Exam 1	1105	16.3	565	15.9	387	14.9
Has diabetes mellitus at exam 1[3]	859	12.7	340	9.6	218	8.4
Total gross annual family income at exam 1						
$0-$24,999	2060	31.5	873	24.6	644	24.8
25,000-49,999	1892	28.9	1048	29.6	776	29.9
50,000-74,999	1111	17	658	18.6	484	18.7
75,000+	1478	22.6	966	27.2	689	26.6

[1] These participants have complete covariate data for most fully adjusted model.

[2] Radial tonometry or carotid ultrasound depending on the group

[3] Based on 2003 ADA fasting criteria algorithm

Table 3.2 Descriptive characteristics of arterial function measures

Measure (units)	N (Observations)	Mean	Standard Deviation	Minimum value	Maximum value
Exam 1					
PTC2, weighted mean $(seconds*100)^{-1}$	6333	8.90	3.87	-1.80	46.70
PTC1, weighted mean $(seconds*10)^{-1}$	6333	3.47	2.22	-20.41	23.06
DC $(mmHg*1000)^{-1}$	2873	3.08	1.27	0.00	8.94
YEM (mmHg)	2872	1596.16	935.49	292.68	13592.84
Exam 5					
PTC2, weighted mean $(seconds*100)^{-1}$	4005	7.63	2.88	-2.10	40.20
PTC1, weighted mean $(seconds*10)^{-1}$	4005	2.31	1.05	-5.82	11.09
DC $(mmHg*1000)^{-1}$	3219	2.68	1.15	-0.69	11.25
YEM (mmHg)	3219	1772.57	1330.48	320.82	23134.58
Between exam 1 and 5					
Rate of change in PTC2, weighted mean $(seconds*100)^{-1}$ per year	3751	-0.17	0.40	-3.56	3.31
Rate of change in PTC1, weighted mean $(seconds*10)^{-1}$ per year	3751	-0.14	0.25	-2.14	1.81
Rate of change in DC $(mmHg*1000)^{-1}$ per year	2729	-0.04	0.12	-0.61	0.48
Rate of change in YEM (mmHg per year)	2729	18.33	134.86	-1003.61	2349.93

Table 3.3 Hazard Ratio for Coronary Heart Disease (CHD) Events by Standard Deviation of Arterial Function Measure for Multi-Ethnic Study of Atherosclerosis (MESA) Participants With Any Available Measure, United States, 2000-2011.

	Hazard Ratio per Standard Deviation of Measure[d]		
	Estimate	95% CI	Two-sided P-value [c]
C2 (Past)			
Minimally adjusted model [a] (n=6,308)	0.69	0.60, 0.80	<0.001
Fully adjusted model [b] (n=6,194)	0.73	0.63, 0.86	<0.001
C2*SVR (Past)			
Minimally adjusted model (n=6,308)	0.73	0.64, 0.83	<0.001
Fully adjusted model (n=6,194)	0.78	0.69, 0.90	<0.001
PTC2			
Minimally adjusted model (n=6,305)	0.72	0.63, 0.82	<0.001
Fully adjusted model (n=6,191)	0.76	0.67, 0.88	<0.001
C1 (Past)			
Minimally adjusted model (n=6,308)	0.87	0.77, 0.98	0.026
Fully adjusted model (n=6,194)	0.97	0.85, 1.10	0.636
C1*SVR (Past)			
Minimally adjusted model (n=6,308)	0.93	0.84,1.04	0.196
Fully adjusted model (n=6,194)	1.02	0.92,1.13	0.697
PTC1			
Minimally adjusted model (n=6,305)	0.83	0.74, 0.92	0.001
Fully adjusted model (n=6,191)	0.89	0.79, 1.01	0.060
Carotid Distensibility (CD) (Past)			
Minimally adjusted model (n=6,500)	0.89	0.79,1.01	0.074
Fully adjusted model (n=6,375)	0.98	0.87,1.11	0.843
Distensibility Coefficient at Carotid Artery (DC)			
Minimally adjusted model (n=2,871)	0.99	0.81, 1.21	0.952
Fully adjusted model (n=2,829)	1.15	0.93, 1.44	0.186
Young's modulus at carotid artery (YM) (Past)			
Minimally adjusted model (n=6,497)	1.03	0.94,1.12	0.585
Fully adjusted model (n=6,372)	0.98	0.89,1.08	0.736
Young's elastic modulus at carotid artery (YEM)			
Minimally adjusted model (n=2,870)	1.00	0.84,1.19	0.995
Fully adjusted model (n=2,828)	0.92	0.76, 1.10	0.342

Abbreviations: CI, confidence interval

[a] Minimally adjusted model: age, gender, clinical center site, and height, race/ethnicity

[b] Fully adjusted model: Minimally adjusted model covariates + heart rate (beats/minute), mean arterial pressure (mmHg), use of blood pressure medication, weight, smoking (never smoked, ever smoked, current smoker), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, use of cholesterol lowering medication, high-sensitivity C-reactive protein; stratified by diabetes

[c] The P-value for statistical significance of arterial function measure in Cox regression model

[d] Standard deviations for arterial function measures at Exam 1 are as follows:
C2: 2.8 mL/mmHg*100
C2*SVR: 0.3 seconds*10
PTC2: 3.87 $(\text{seconds}*100)^{-1}$
C1: 5.6 mL/mmHg*10
C1*SVR: 0.6 seconds
PTC1: 2.22 $(\text{seconds}*10)^{-1}$
CD: 1.11 $(\text{mmHg}*1000)^{-1}$
DC: 1.15 $(\text{mmHg}*1000)^{-1}$
YM: 645.8 mmHg/mm
YEM: 1330.5 mmHg

Table 3.4 Associations Between Cardiovascular Risk Factors and Annual Rate of Change in PTC2 Using Linear Mixed Models

	Minimally adjusted[1]					**Fully adjusted[2]**				
Risk Factors	Difference in Annual Rate of Change	Standard Error	95% CI LL	95% CI UL	p-value	Difference in Annual Rate of Change	Standard Error	95% CI LL	95% CI UL	p-value
Age[3], 10 years	**0.035**	**0.007**	**0.021**	**0.048**	**<0.001**	**0.020**	**0.008**	**0.004**	**0.035**	**0.013**
Gender (Reference: Female)	**-0.072**	**0.013**	**-0.097**	**-0.047**	**<0.001**	**-0.089**	**0.015**	**-0.119**	**-0.059**	**<0.001**
Race/Ethnicity (Reference: White)										
Chinese	0.038	0.024	-0.009	0.086	**0.001**	0.036	0.026	-0.015	0.086	0.160
Black	**0.053**	**0.017**	**0.019**	**0.087**		0.027	0.018	-0.009	0.063	
Hispanic	**0.066**	**0.020**	**0.027**	**0.105**		0.034	0.022	-0.009	0.076	
Site (Reference: Forysth County, North Carolina (WFU))										
New York, NY (COL)	**-0.051**	**0.024**	**-0.098**	**-0.005**	**<0.001**	-0.003	0.024	-0.050	0.044	**<0.001**
Baltimore, MD (JHU)	**-0.102**	**0.025**	**-0.150**	**-0.053**		**-0.075**	**0.025**	**-0.124**	**-0.027**	
St. Paul, MN (UMN)	**-0.200**	**0.024**	**-0.247**	**-0.154**		**-0.173**	**0.024**	**-0.221**	**-0.126**	
Chicago, IL (NWU)	0.043	0.022	0.000	0.087		**0.080**	**0.023**	**0.035**	**0.124**	
Los Angeles, CA (UCLA)	**-0.060**	**0.027**	**-0.113**	**-0.008**		-0.029	0.027	-0.082	0.023	

Total cholesterol[3,4], 10 mg/dL	0.000	0.002	-0.003	0.004	0.825	0.000	0.002	-0.004	0.004	0.874
HDL cholesterol[3,4], 10 mg/dL	**-0.010**	**0.005**	**-0.020**	**0.000**	**0.041**	-0.009	0.006	-0.020	0.002	0.100
Triglycerides[3,4], 10 mg/dL	**0.002**	**0.001**	**0.001**	**0.004**	**0.009**	0.001	0.001	-0.001	0.003	0.482
Any lipid lowering medication[5]	-0.015	0.017	-0.048	0.019	0.399	-0.021	0.018	-0.056	0.014	0.233
SBP[5,6], 10 mmHg	**0.028**	**0.005**	**0.019**	**0.037**	**<0.001**	**0.025**	**0.004**	**0.018**	**0.032**	**<0.001**
DBP[5,6], 10 mmHg	**0.038**	**0.009**	**0.020**	**0.056**	**<0.0001**					
MAP[5,6], 10 mmHg	**0.036**	**0.006**	**0.024**	**0.047**	**<0.0001**					
PP[5,6], 10 mmHg	**0.033**	**0.006**	**0.021**	**0.045**	**<0.0001**					
Use of blood pressure medication[5]	**0.038**	**0.015**	**0.009**	**0.067**	**0.010**	-0.006	0.016	-0.038	0.025	0.690

Cigarette smoking status[5] (Reference: Never smoker)										
Former	**0.031**	**0.015**	**0.002**	**0.059**	0.078	0.028	0.014	0.000	0.056	0.122
Current	0.032	0.024	-0.016	0.079		0.027	0.024	-0.021	0.074	
Diabetes[3,7] (Reference: No diabetes)	0.007	0.022	-0.036	0.051	0.740	0.004	0.023	-0.041	0.050	0.855
Annual Gross Family Income[3], (Reference: $0-24,999)										
$25,000-49,999	0.021	0.018	-0.015	0.057	0.470	0.033	0.019	-0.004	0.069	0.181
$50,000-74,999	0.024	0.021	-0.017	0.066		**0.044**	**0.022**	**0.002**	**0.087**	
$75,000+	0.003	0.021	-0.038	0.043		0.031	0.022	-0.012	0.074	
Highest educational level completed[3] (Reference: Less than high school)										
HS grad	-0.013	0.025	-0.061	0.036	0.159	-0.020	0.025	-0.068	0.029	0.283
Some/2 yr. college	-0.024	0.023	-0.069	0.021		-0.032	0.023	-0.077	0.014	
4 yr. college or more	**-0.046**	**0.023**	**-0.092**	**-0.001**		-0.046	0.025	-0.095	0.002	
Body Mass Index[3], 5 kg/m^2	0.012	0.007	-0.001	0.025	0.064	-0.005	0.007	-0.019	0.009	0.473

Heart Rate[5], 10 beats/minute	0.000	0.007	-0.015	0.014	0.979	-0.001	0.007	-0.020	0.009	0.437
C-Reactive Protein[3], 10 mg/L	**0.034**	**0.013**	**0.007**	**0.060**	**0.012**	0.024	0.014	0.003	0.051	0.085

[1]**Minimally adjusted model**: sex, race/ethnicity, site, and age at baseline

[2]**Fully adjusted model**: Minimally adjusted model covariates + following variables at Exam 1: body mass index (BMI), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, diabetes mellitus status (yes/no), annual gross family income in the past 12 months, highest educational level completed, and high sensitivity c-reactive protein + following time-varying covariates: systolic blood pressure (SBP) smoking status (never smoked, ever smoked, current smoker), use of blood pressure medication (yes/no), use of lipid lowering medication (yes/no), and heart rate

[3] At Exam 1

[4] Adjusted by lipid lowering medication

[5] Time-varying variable

[6] Adjusted by anti-hypertensive medication

[7] Based on 2003 American Diabetes Association fasting algorithm

Table 3.5: Associations Between Cardiovascular Risk Factors and Annual Rate of Change in of PTC1 using Linear Mixed Models

	Minimally adjusted[1]					**Fully adjusted model[2]**				
	Difference in Annual Rate of Change	Standard Error	95% CI LL	95% CI UL	p-value	Difference in Annual Rate of Change	Standard Error	95% CI LL	95% CI UL	p-value
Age[3], 10 years	**0.022**	**0.004**	**0.013**	**0.030**	**<0.001**	**0.016**	**0.005**	**0.006**	**0.025**	**0.001**
Gender (Reference: Female)	-0.007	0.008	-0.023	0.009	0.402	0.006	0.009	-0.012	0.025	0.492
Race/Ethnicity (Reference: White)										
Chinese	0.022	0.015	-0.008	0.051	0.089	0.010	0.016	-0.021	0.041	0.220
Black	-0.005	0.011	-0.026	0.015		-0.014	0.011	-0.036	0.009	
Hispanic	0.024	0.012	0.000	0.048		0.012	0.013	-0.014	0.039	
Site (Reference: Forysth County, North Carolina (WFU))										
New York, NY (COL)	0.042	0.015	0.013	0.071	**<0.001**	0.048	0.015	0.019	0.077	**<0.001**
Baltimore, MD (JHU)	0.015	0.015	-0.015	0.045		0.027	0.015	-0.003	0.057	

St. Paul, MN (UMN)	-0.059	0.015	-0.088	-0.030		-0.052	0.015	-0.082	-0.023	
Chicago, IL (NWU)	0.090	0.014	0.062	0.117		0.094	0.014	0.066	0.121	
Los Angeles, CA (UCLA)	0.088	0.017	0.056	0.121		0.091	0.017	0.058	0.124	
Total cholesterol[3,4], 10 mg/dL	0.002	0.001	0.000	0.004	0.084	0.001	0.001	0.000	0.000	0.324
HDL cholesterol[3,4], 10 mg/dL	0.002	0.003	-0.004	0.008	0.461	0.002	0.004	-0.005	0.009	0.576
Triglycerides[3,4], 10 mg/dL	0.000	0.001	-0.001	0.001	0.599	0.000	0.001	-0.002	0.001	0.452
Any lipid lowering medication[5]	0.010	0.010	-0.010	0.030	0.343	0.007	0.011	-0.014	0.027	0.532
SBP[5,6], 10 mmHg	**0.013**	**0.003**	**0.007**	**0.018**	**<0.001**	**0.008**	**0.002**	**0.004**	**0.013**	**<0.001**
DBP[5,6], 10 mmHg	**0.016**	**0.004**	**0.009**	**0.023**	**<0.001**					
MAP[5,6], 10 mmHg	**0.019**	**0.006**	**0.008**	**0.030**	**<0.001**					
PP[5,6], 10 mmHg	**0.014**	**0.004**	**0.007**	**0.022**	**<0.001**					
Use of blood pressure medication[5]	0.006	0.009	-0.011	0.024	0.490	-0.003	0.009	-0.021	0.016	0.779
Cigarette smoking status[5] (Reference: Never smoker)										

Former	-0.015	0.009	-0.032	0.003	0.253	-0.015	0.009	-0.032	0.003	0.247
Current	-0.007	0.015	-0.036	0.022		-0.002	0.015	-0.031	0.027	
Diabetes[3,7] (Reference: No diabetes)	0.018	0.014	-0.009	0.046	0.184	0.009	0.014	-0.019	0.037	0.537
Annual Gross Family Income[3], (Reference: 0-24999)										
25000-49999	-0.001	0.011	-0.023	0.021	0.460	0.004	0.012	-0.019	0.026	0.695
50000-74999	-0.019	0.013	-0.044	0.007		-0.010	0.014	-0.037	0.016	
75000+	-0.007	0.013	-0.033	0.018		0.000	0.014	-0.027	0.027	
Highest educational level completed[3] (Reference: Less than high school)										
HS grad	-0.017	0.015	-0.047	0.013	0.148	-0.017	0.015	-0.047	0.013	0.455
some/2 yr. college	-0.027	0.014	-0.055	0.000		-0.022	0.014	-0.050	0.006	
4 yr college+	**-0.032**	**0.015**	**-0.061**	**-0.004**		-0.025	0.015	-0.055	0.005	
Body Mass Index[3], 5 kg/m^2	0.004	0.004	-0.004	0.012	0.384	-0.004	0.005	-0.013	0.005	0.382
Heart Rate[5], 10 beats/minute	**0.015**	**0.004**	**0.007**	**0.024**	**<0.001**	**0.013**	**0.004**	**0.004**	**0.021**	**0.005**
C-Reactive Protein[3], 10 mg/L	**0.002**	**0.001**	**0.000**	**0.004**	**0.025**	0.001	0.001	0.000	0.003	0.136

[1]**Minimally adjusted model**: sex, race/ethnicity, site, and age at baseline

[2]**Fully adjusted model**: Minimally adjusted model covariates + following variables at Exam 1: body mass index (BMI), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, diabetes mellitus status (yes/no), annual gross family income in the past 12 months, highest educational level completed, and high sensitivity c-reactive protein + following time-varying covariates: systolic blood pressure (SBP) smoking status (never smoked, ever smoked, current smoker), use of blood pressure medication (yes/no), use of lipid lowering medication (yes/no), and heart rate

[3] At Exam 1

[4] Adjusted by lipid lowering medication

[5] Time-varying variable

[6] Adjusted by anti-hypertensive medication

[7] Based on 2003 American Diabetes Association fasting algorithm

Table 3.6: Associations Between Cardiovascular Risk Factors and change in DC using Linear Mixed Models

	Minimally Adjusted[1]					**Fully adjusted model[2]**				
Risk Factors	Difference in Annual Rate of Change	Standard Error	95% CI LL	95% CI UL	p-value	Difference in Annual Rate of Change	Standard Error	95% CI LL	95% CI UL	p-value
Age[3], 10 years	**0.009**	**0.002**	**0.005**	**0.014**	**<0.001**	**0.006**	**0.003**	**0.001**	**0.011**	**0.020**
Gender (Reference: Female)	-0.001	0.005	-0.010	0.008	0.822	-0.006	0.005	-0.016	0.005	0.294
Race/Ethnicity (Reference: White)										
Chinese	0.003	0.008	-0.013	0.018	0.188	0.001	0.008	-0.015	0.018	0.451
Black	**0.012**	**0.006**	**0.000**	**0.024**		0.010	0.006	-0.003	0.022	
Hispanic	0.000	0.007	-0.014	0.013		0.004	0.007	-0.011	0.018	
Site (Reference: Forysth County, North Carolina (WFU))										
New York, NY (COL)	**0.022**	**0.008**	**0.007**	**0.038**	**<0.001**	**0.039**	**0.008**	**0.023**	**0.055**	**<0.001**
Baltimore, MD (JHU)	-0.009	0.009	-0.027	0.008		0.003	0.009	-0.014	0.020	
St. Paul, MN (UMN)	**0.030**	**0.009**	**0.013**	**0.047**		**0.037**	**0.008**	**0.020**	**0.053**	

Chicago, IL (NWU)	0.007	0.008	-0.009	0.022		0.014	0.008	-0.001	0.029	
Los Angeles, CA (UCLA)	0.013	0.009	-0.004	0.030		**0.020**	**0.009**	**0.004**	**0.037**	
Total cholesterol[3,4], 10 mg/dL	0.000	0.001	-0.001	0.002	0.513	0.000	0.000	0.000	0.000	0.465
HDL cholesterol[3,4], 10 mg/dL	0.000	0.000	0.000	0.000	0.972	0.000	0.000	0.000	0.001	0.272
Triglycerides[3,4], 10 mg/dL	**0.001**	**0.000**	**0.000**	**0.001**	**0.044**	0.000	0.000	0.000	0.000	0.208
Any lipid lowering medication[5]	0.012	0.006	0.000	0.024	0.052	0.004	0.006	-0.008	0.017	0.496
MAP[5,6], 10 mmHg	**0.005**	**0.002**	**0.001**	**0.009**	**0.015**	0.003	0.002	-0.001	0.007	0.126
SBP[5,6], 10 mmHg	**0.003**	**0.001**	**0.000**	**0.006**	**0.023**					
DBP[5,6], 10 mmHg	**0.008**	**0.002**	**0.003**	**0.012**	**0.002**					
PP[5,6], 10 mmHg	0.002	0.002	-0.002	0.005	0.275					
Use of blood pressure medication[5]	**0.018**	**0.005**	**0.008**	**0.029**	**0.001**	-0.002	0.005	-0.012	0.009	0.764

Cigarette smoking status[5] (Reference: Never smoker)										
Former	-0.007	0.005	-0.017	0.003	**0.030**	-0.008	0.005	-0.017	0.002	0.197
Current	**-0.021**	**0.009**	**-0.038**	**-0.004**		-0.011	0.008	-0.027	0.006	
Diabetes[3,7] (Reference: No diabetes)	0.001	0.008	-0.014	0.016	0.879	0.007	0.069	-0.128	0.143	0.918
Annual Gross Family Income[3], (Reference: 0-24999)										
25000-49999	0.001	0.006	-0.011	0.014	0.176	-0.003	0.006	-0.015	0.009	0.193
50000-74999	0.014	0.007	0.000	0.028		0.008	0.007	-0.006	0.022	
75000+	0.005	0.007	-0.010	0.019		-0.004	0.007	-0.018	0.011	
Highest educational level completed[3] (Reference: <high school)										
HS grad.	0.007	0.009	-0.010	0.024	0.459	0.006	0.008	-0.010	0.023	0.489

some/2 yr. college	0.012	0.008	-0.004	0.028		0.011	0.008	-0.004	0.027	
4 yr. college+	0.011	0.008	-0.005	0.027		0.012	0.008	-0.004	0.028	
BMI[3], 5 kg/m^2	**0.010**	**0.002**	**0.005**	**0.014**	**<0.001**	**0.007**	**0.003**	**0.002**	**0.012**	**0.010**
Heart Rate[5], 10 beats/minute	0.002	0.003	-0.003	0.007	0.355	0.001	0.003	-0.004	0.006	0.730
CRP[3], 10 mg/L	-0.006	0.005	-0.015	0.003	0.161	**-0.013**	**0.005**	**-0.022**	**-0.004**	**0.003**

[1]**Minimally adjusted model**: Sex, race/ethnicity, site, and age at baseline

[2]**Fully adjusted model**: Minimally adjusted model covariates + following variables at Exam 1: body mass index (BMI), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, diabetes mellitus status (yes/no), annual gross family income in the past 12 months, highest educational level completed, and high sensitivity c-reactive protein + following time-varying covariates: systolic blood pressure (SBP) smoking status (never smoked, ever smoked, current smoker), use of blood pressure medication (yes/no), use of lipid lowering medication (yes/no), and heart rate

[3] At Exam 1

[4] Adjusted by lipid lowering medication

[5] Time-varying variable

[6] Adjusted by anti-hypertensive medication

[7] Based on 2003 American Diabetes Association fasting algorithm

Table 3.7: Associations Between Cardiovascular Risk Factors and Change in YEM using Linear Mixed Models

	Minimally Adjusted					**Fully adjusted model**				
Risk Factors	Difference in Annual Rate of Change	Standard Error	95% CI LL	95% CI UL	p-value	Difference in Annual Rate of Change	Standard Error	95% CI LL	95% CI UL	p-value
Age[3], 10 years	**10.58**	**2.70**	**5.28**	**15.87**	**<0.001**	**11.27**	**2.98**	**5.43**	**17.11**	**<0.001**
Gender (Reference: Female)	-0.59	5.05	-10.48	9.30	0.91	3.76	5.97	-7.95	15.46	0.53
Race/Ethnicity (Reference: White)										
Chinese	5.65	9.01	-12.00	23.31	0.78	-1.20	9.49	-19.81	17.41	0.67
Black	5.76	6.75	-7.47	18.99		0.38	7.21	-13.75	14.50	
Hispanic	2.27	7.73	-12.88	17.41		-8.84	8.41	-25.33	7.65	
Site (Reference: Forysth County, North Carolina (WFU))										
New York, NY (COL)	-4.06	9.08	-21.85	13.73	0.22	-15.28	9.08	-33.07	2.51	0.08
Baltimore, MD (JHU)	14.32	9.97	-5.24	33.87		7.76	9.86	-11.58	27.09	
St. Paul, MN (UMN)	-11.11	9.55	-29.82	7.61		-13.52	9.59	-32.32	5.28	
Chicago, IL (NWU)	6.64	8.78	-10.56	23.85		7.00	8.88	-10.41	24.41	

Los Angeles, CA (UCLA)	-6.95	9.84	-26.24	12.34		-10.46	9.78	-29.64	8.72	
Total cholesterol[3,4], 10 mg/dL	-0.33	0.75	-1.80	1.14	0.66	-0.52	0.82	-2.13	1.09	0.53
HDL cholesterol[3,4], 10 mg/dL	-0.29	1.89	-4.00	3.42	0.88	1.09	2.17	-3.16	5.33	0.62
Triglycerides[3,4], 10 mg/dL	0.15	0.34	-0.52	0.83	0.66	0.33	0.40	-0.45	1.12	0.41
Any lipid lowering medication[2]	-9.66	6.86	-23.10	3.77	0.16	-6.14	7.04	-19.94	7.67	0.38
Mean Arterial Pressure (MAP)[5,6], 10 mmHg	**6.84**	**2.35**	**2.23**	**11.45**	**<0.01**	**7.29**	**2.37**	**2.63**	**11.94**	**<0.01**
SBP[5,6], 10 mmHg	**3.85**	**1.46**	**0.99**	**6.71**	**0.01**					
DBP[5,6], 10 mmHg	**8.57**	**2.71**	**3.25**	**13.88**	**<0.01**					
PP[5,6], 10 mmHg	**4.04**	**1.98**	**0.16**	**7.91**	**0.04**					
Use of blood pressure medication[5]	-5.11	5.85	-16.57	6.36	0.38	0.69	6.17	-11.40	12.78	0.91
Cigarette smoking status[5] (Reference: Never smoker)										
Former	-5.67	5.69	-16.83	5.49	0.32	-6.20	5.61	-17.19	4.79	0.48

Current	4.59	9.64	-14.31	23.49		-4.71	9.60	-23.52	14.10	
Diabetes[3,7] (Reference: No diabetes)	**21.63**	**8.99**	**4.01**	**39.25**	**0.02**	**22.10**	**9.21**	**4.04**	**40.16**	**0.02**
Annual Gross Family Income[3] (Reference: $0-24,999)										
$25,000-49,999	-0.37	7.06	-14.21	13.48	0.47	3.78	7.05	-10.04	17.60	0.82
$50,000-74,999	-5.35	8.19	-21.41	10.71		0.69	8.26	-15.50	16.88	
$75,000+	-11.59	8.12	-27.51	4.33		-1.39	8.50	-18.05	15.26	
Highest educational level completed[3] (Reference: Less than high school)										
HS grad	-17.05	9.59	-35.84	1.74	0.12	-15.57	9.45	-34.10	2.96	0.17
Some/2 yr. college	-11.31	8.95	-28.85	6.23		-8.84	8.95	-26.38	8.70	
4 yr. college or more	**-20.24**	**9.15**	**-38.17**	**-2.31**		-18.40	9.45	-36.92	0.12	
Body Mass Index[3], 5 kg/m^2	-2.79	2.70	-8.09	2.50	0.30	-2.16	2.91	-7.88	3.55	0.46
Heart Rate[3], 10 beats/minute	5.21	2.88	-0.43	10.86	0.07	3.57	2.95	-2.22	9.35	0.23

C-Reactive Protein[3], 10 mg/L	2.19	5.11	-7.83	12.20	0.67	4.59	5.21	-5.62	14.80	0.38

[1]**Minimally adjusted model**: sex, race/ethnicity, site, and age at baseline

[2]**Fully adjusted model**: Minimally adjusted model covariates + following variables at Exam 1: body mass index (BMI), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, diabetes mellitus status (yes/no), annual gross family income in the past 12 months, highest educational level completed, and high sensitivity c-reactive protein + following time-varying covariates: systolic blood pressure (SBP) smoking status (never smoked, ever smoked, current smoker), use of blood pressure medication (yes/no), use of lipid lowering medication (yes/no), and heart rate

[3] At Exam 1

[4] Adjusted by lipid lowering medication

[5] Time-varying variable

[6] Adjusted by anti-hypertensive medication

[7] Based on 2003 American Diabetes Association fasting algorithm

Table 3.8 Descriptive characteristics of difference in arterial function measures between Exams 1 and 5

Measure (Units)	N	Percentage	Mean	Standard Deviation	Minimum value	Maximum value
Difference in PTC2, weighted mean (seconds*100)$^{-1}$	3,751		-1.62	3.86	-37.80	30.20
No difference or gain in PTC2, weighted mean	1,288	34.3%	1.98	2.01	0.00	30.20
Loss in PTC2, weighted mean (more stiff)	2,463	65.7%	-3.50	3.20	-37.80	-0.10
Difference in PTC1, weighted mean (seconds*10)$^{-1}$	3,751		-1.33	2.43	-21.51	19.07
No difference or gain in PTC1, weighted mean	925	24.7%	1.08	1.62	0.00	19.07
Loss in PTC1, weighted mean (more stiff)	2,826	75.3%	-2.12	2.11	-21.51	-0.01
Difference in DC (mmHg*1000)$^{-1}$	2,729		-0.40	1.13	-5.77	5.03
No difference or gain in DC	973	35.7%	0.74	0.65	0.00	5.03
Loss in DC (more stiff)	1,756	64.3%	-1.03	0.80	-5.77	0.00
Difference in YEM (mmHg)	2,729		174.4	1,274.9	-11,073.3	21,360.1
No difference or loss in YEM	1,208	44.3%	-596.4	761.1	-11,073.3	-0.1
Gain in YEM (more stiff)	1,521	55.7%	786.5	1,268.9	0.4	21,360.1

Table 3.9: Hazard Ratio for All Cardiovascular Disease (CVD) Events by Standard Deviation of Arterial Function Measure for Multi-Ethnic Study of Atherosclerosis (MESA) Participants With Any Available Measure, United States, 2000-2011.

	Hazard Ratio per Standard Deviation of Measure[d]		
	Estimate	95% CI	Two-sided P-value[c]
C2 (Past)			
Minimally adjusted model [a] (n=6,309)	0.68	0.60, 0.77	<0.001
Fully adjusted model [b] (n=6,206)	0.75	0.66, 0.86	<0.001
C2*SVR (Past)			
Minimally adjusted model (n=6,309)	0.75	0.67, 0.83	<0.001
Fully adjusted model (n=6,242)	0.81	0.72, 0.90	<0.001
PTC2			
Minimally adjusted model (n=6,306)	0.67	0.22, 0.81	<0.001
Fully adjusted model (n=6,226)	0.71	0.58, 0.86	<0.001
C1 (Past)			
Minimally adjusted model (n=6,309)	0.82	0.74, 0.92	<0.001
Fully adjusted model (n=6,206)	0.97	0.87,1.08	0.534
C1*SVR (Past)			
Minimally adjusted model (n=6,309)	0.91	0.83,1.00	0.048
Fully adjusted model (n=6,242)	0.98	0.90, 1.07	0.631
PTC1			
Minimally adjusted model (n=6,306)	0.82	0.75,0.90	<0.001
Fully adjusted model (n=6,226)	0.89	0.80, 0.99	0.029
Aortic Distensibility (AD)			
Minimally adjusted model (n=3,660)	0.79	0.65, 0.96	0.02
Fully adjusted model (n=3,612)	0.92	0.77, 1.09	0.324
Carotid Distensibility (CD) (Past)			

Minimally adjusted model (n=6,501)	0.81	0.73, 0.91	<0.001
Fully adjusted model (n=6,422)	0.93	0.83, 1.04	0.191
Distensibility Coefficient at Carotid Artery (DC)			
Minimally adjusted model (n=2,871)	0.94	0.79,1.12	0.473
Fully adjusted model (n=2,843)	1.11	0.92,1.35	0.278
Young's modulus (YM) (Past)			
Minimally adjusted model (n=6,498)	1.06	0.99,1.14	0.104
Fully adjusted model (n=6,419)	1.00	0.92,1.07	0.903
Young's elastic modulus at carotid artery (YEM)			
Minimally adjusted model (n=2,870)	1.03	0.89,1.19	0.682
Fully adjusted model (n=2,842)	0.93	0.80, 1.08	0.346

Abbreviations: CI, confidence interval; SVR, systemic vascular resistance

[a] Minimally adjusted model: age, gender, clinical center site, and height; stratified by race/ethnicity

[b] Fully adjusted model: Minimally adjusted model covariates + heart rate (beats/minute) (C2, C1 only), mean arterial pressure (mmHg), use of blood pressure medication, weight, smoking (never smoked, ever smoked, current smoker), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, use of cholesterol lowering medication, high-sensitivity C-reactive protein; stratified by race/ethnicity and diabetes

[c] The P-value for statistical significance of arterial function measure in Cox regression model

[d] Standard deviations for arterial function measures at Exam 1 are as follows:

C2: 2.8 mL/mmHg*100

C2*SVR: 0.3 seconds*10

PTC2: 3.87 $(\text{seconds}*100)^{-1}$

C1: 5.6 mL/mmHg*10

C1*SVR: 0.6 seconds

PTC1: 2.22 $(\text{seconds}*10)^{-1}$

CD: 1.11 $(\text{mmHg}*1000)^{-1}$

DC: 1.15 $(\text{mmHg}*1000)^{-1}$

YM: 645.8 mmHg/mm

YEM: 1330.5 mmHg

Table 3.10 Hazard Ratio for Congestive Heart Failure (CHF) Events by Standard Deviation of Arterial Function Measure for Multi-Ethnic Study of Atherosclerosis (MESA) Participants With Any Available Measure, United States, 2000-2011.

	Hazard Ratio per Standard Deviation of Measure[d]		
	Estimate	95% CI	Two-sided P-value [c]
C2 (Past)			
Minimally adjusted model [a] (n=6,308)	0.68	0.56, 0.84	<0.001
Fully adjusted model [b] (n=6,203)	0.7	0.56, 0.88	0.002
C2*SVR (Past)			
Minimally adjusted model (n=6,308)	0.74	0.62, 0.88	0.001
Fully adjusted model (n=6,239)	0.79	0.65, 0.95	0.011
PTC2			
Minimally adjusted model (n=6,305)	0.67	0.55, 0.81	<0.001
Fully adjusted model (n=6,225)	0.72	0.59, 0.88	<0.001
C1 (Past)			
Minimally adjusted model (n=6,308)	0.66	0.54, 0.80	<0.001
Fully adjusted model (n=6,203)	0.77	0.62, 0.94	0.012
C1*SVR (Past)			
Minimally adjusted model (n=6,308)	0.73	0.62, 0.87	0.001
Fully adjusted model (n=6,239)	0.84	0.71, 0.99	0.037
PTC1			
Minimally adjusted model (n=6,305)	0.88	0.74, 1.04	0.126
Fully adjusted model (n=6,225)	1.02	0.86,1.22	0.802
Aortic Distensibility (AD)			
Minimally adjusted model (n=3,659)	0.99	0.80, 1.22	0.89
Fully adjusted model (n=3,610)	1.08	0.92, 1.26	0.341
Carotid Distensibility (CD) (Past)			
Minimally adjusted model (n=6,500)	0.78	0.64, 0.95	0.013

Fully adjusted model (n=6,419)	0.92	0.77, 1.11	0.398
Distensibility Coefficient at Carotid Artery (DC)			
Minimally adjusted model (n=2,871)	0.55	0.37,0.84	0.004
Fully adjusted model (n=2,843)	0.69	0.44,1.06	0.092
Young's modulus (YM) (Past)			
Minimally adjusted model (n=6,497)	1.07	0.96, 1.19	0.235
Fully adjusted model (n=6,416)	1.00	0.89, 1.13	0.948
Young's elastic modulus at carotid artery (YEM)			
Minimally adjusted model (n=2,870)	1.17	0.95,1.44	0.132
Fully adjusted model (n=2,842)	1.03	0.82,1.33	0.762

Abbreviations: CI, confidence interval; SVR, systemic vascular resistance

[a] Minimally adjusted model: age, gender, clinical center site, and height, race/ethnicity

[b] Fully adjusted model: Minimally adjusted model covariates + heart rate (beats/minute) (C2, C1 only), mean arterial pressure (mmHg), use of blood pressure medication, weight, smoking (never smoked, ever smoked, current smoker), high density lipoprotein (HDL) cholesterol, triglycerides, use of cholesterol lowering medication, high-sensitivity C-reactive protein, diabetes; stratified by total cholesterol (tertiles)

[d] Standard deviations for arterial function measures at Exam 1 are as follows:
C2: 2.8 mL/mmHg*100
C2*SVR: 0.3 seconds*10
PTC2: 3.87 $(\text{seconds}*100)^{-1}$
C1: 5.6 mL/mmHg*10
C1*SVR: 0.6 seconds
PTC1: 2.22 $(\text{seconds}*10)^{-1}$
CD: 1.11 $(\text{mmHg}*1000)^{-1}$
DC: 1.15 $(\text{mmHg}*1000)^{-1}$
YM: 645.8 mmHg/mm
YEM: 1330.5 mmHg

Table 3.11: Associations Between Cardiovascular Risk Factors and Change in Weighted Mean of PTC2 Using Fully Adjusted Linear Mixed Models For Different Blood Pressure Measures

Blood pressure measure	**SBP**			**MAP**			**DBP**			**PP**		
CV risk factor	Coeff.[1]	95% CI LL	95% CI UL	Coeff.[1]	95% CI LL	95% CI UL	Coeff.[1]	95% CI LL	95% CI UL	Coeff.[1]	95% CI LL	95% CI UL
Time between exams (years)	**-0.108**	**-0.168**	**-0.047**	**-0.098**	**-0.159**	**-0.038**	**-0.087**	**-0.163**	**-0.010**	**-0.121**	**-0.182**	**-0.060**
Age (years)[2]	**0.002**	**0.000**	**0.004**	**0.003**	**0.001**	**0.004**	**0.003**	**0.002**	**0.005**	**0.002**	**0.000**	**0.003**
Gender[3]	**-0.089**	**-0.119**	**-0.059**	**-0.106**	**-0.136**	**-0.076**	**-0.113**	**-0.145**	**-0.081**	**-0.065**	**-0.096**	**-0.035**
Race/Ethnicity[4]												
Chinese	0.036	-0.015	0.086	0.033	-0.018	0.083	0.036	-0.015	0.088	0.045	-0.006	0.095
Black	0.027	-0.009	0.063	0.022	-0.014	0.059	0.025	-0.012	0.062	**0.039**	**0.003**	**0.076**
Hispanic	0.034	-0.009	0.076	0.032	-0.011	0.075	0.035	-0.008	0.078	0.042	0.000	0.085
Site[5]												
COL	-0.003	-0.050	0.044	-0.010	-0.057	0.037	-0.028	-0.076	0.019	-0.011	-0.058	0.037
JHU	**-0.075**	**-0.124**	**-0.027**	**-0.076**	**-0.125**	**-0.028**	**-0.085**	**-0.134**	**-0.036**	**-0.083**	**-0.131**	**-0.034**
UMN	**-0.173**	**-0.221**	**-0.126**	**-0.174**	**-0.222**	**-0.127**	**-0.187**	**-0.235**	**-0.140**	**-0.186**	**-0.234**	**-0.138**
NWU	**0.080**	**0.035**	**0.124**	**0.078**	**0.033**	**0.122**	**0.068**	**0.023**	**0.113**	**0.072**	**0.028**	**0.117**
UCLA	-0.029	-0.082	0.023	-0.030	-0.083	0.023	-0.040	-0.093	0.013	-0.038	-0.091	0.014
Total cholesterol[2] (mg/dL)	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

HDL cholesterol[2] (mg/dL)	-0.001	-0.002	0.000	-0.001	-0.002	0.000	-0.001	-0.002	0.000	-0.001	-0.002	0.000
Triglycerides[2] (mg/dL)	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Any lipid lowering medication	-0.021	-0.056	0.014	-0.021	-0.056	0.014	-0.021	-0.056	0.015	-0.024	-0.059	0.011
BP Measure[5] (mmHg)	**0.002**	**0.002**	**0.003**	**0.004**	**0.003**	**0.005**	**0.004**	**0.002**	**0.005**	**0.003**	**0.002**	**0.004**
Use of blood pressure medication[5]	-0.006	-0.038	0.025	-0.003	-0.034	0.028	0.011	-0.020	0.042	0.006	-0.025	0.037
Cigarette smoking status[2,6]												
Former	0.028	0.000	0.056	0.028	0.000	0.056	**0.029**	**0.000**	**0.058**	**0.029**	**0.000**	**0.057**
Current	0.027	-0.021	0.074	0.027	-0.021	0.074	0.027	-0.022	0.075	0.028	-0.020	0.075
Diabetes[2,7]	0.004	-0.041	0.050	0.006	-0.040	0.051	-0.007	-0.054	0.039	-0.001	-0.047	0.044
Annual Gross Family Income[2,8]												
$25,000-49,999	0.033	-0.004	0.069	0.032	-0.004	0.068	0.033	-0.004	0.070	0.033	-0.003	0.070
$50,000-74,999	**0.044**	**0.002**	**0.087**	0.040	-0.003	0.083	0.037	-0.006	0.080	**0.048**	**0.005**	**0.090**

$75,000+	0.031	-0.012	0.074	0.028	-0.015	0.072	0.027	-0.017	0.070	0.033	-0.011	0.076
Highest educational level[9]												
HS grad.	-0.020	-0.068	0.029	-0.020	-0.069	0.028	-0.019	-0.068	0.030	-0.019	-0.068	0.030
Some/2 yr. college	-0.032	-0.077	0.014	-0.032	-0.078	0.013	-0.031	-0.077	0.015	-0.033	-0.079	0.013
4 yr. college+	-0.046	-0.095	0.002	-0.047	-0.095	0.001	-0.047	-0.096	0.001	-0.047	-0.096	0.001
BMI[2] (kg/m^2)	-0.001	-0.004	0.002	-0.001	-0.003	0.002	0.000	-0.003	0.003	-0.001	-0.004	0.002
Heart Rate[5] (beats/min.)	-0.001	-0.002	0.001	-0.001	-0.002	0.000	-0.001	-0.003	0.000	0.000	-0.001	0.001
CRP[2] (mg/L)	0.002	0.000	0.005	0.003	0.000	0.005	**0.003**	**0.000**	**0.006**	0.002	-0.001	0.005

[1] Coefficient for difference in annual rate of PTC2 change per unit change in CV risk factor

[2] At Exam 1

[2] Reference: Female

[3] Reference: White

[4] WFU as reference

[5] Time-varying

[6] Reference: Never smoker

[7] Reference: no diabetes, based on 2003 ADA fasting algorithm

[8] For past 12 months; Reference: $0-24,999

[9] Completed at Exam 1; Reference: Less than high school

Table 3.12: Associations Between Cardiovascular Risk Factors and Change in Weighted Mean of PTC1 Using Fully Adjusted Linear Mixed Models For Different Blood Pressure Measures

Blood Pressure Measure	**SBP**			**MAP**			**DBP**			**PP**		
CV risk factor	Coefficient[1]	95% CI LL	95% CI UL	Coefficient[1]	95% CI LL	95% CI UL	Coefficient[1]	95% CI LL	95% CI UL	Coefficient[1]	95% CI LL	95% CI UL
Time between exams (years)	**-0.143**	**-0.180**	**-0.105**	**-0.140**	**-0.177**	**-0.102**	**-0.125**	**-0.172**	**-0.078**	**-0.147**	**-0.185**	**-0.109**
Age (years)[2]	**0.002**	**0.001**	**0.003**	**0.002**	**0.001**	**0.003**	**0.002**	**0.001**	**0.003**	**0.001**	**0.000**	**0.002**
Gender[3]	0.006	-0.012	0.025	0.002	-0.017	0.021	0.001	-0.018	0.021	0.014	-0.005	0.033
Race/Ethnicity[4]												
Chinese	0.010	-0.021	0.041	0.010	-0.022	0.041	0.009	-0.022	0.041	0.012	-0.019	0.044
Black	-0.014	-0.036	0.009	-0.014	-0.037	0.008	-0.013	-0.036	0.010	-0.010	-0.032	0.012
Hispanic	0.012	-0.014	0.039	0.012	-0.014	0.039	0.013	-0.013	0.040	0.014	-0.012	0.040
Site[5]												
COL	**0.048**	**0.019**	**0.077**	**0.044**	**0.015**	**0.073**	**0.037**	**0.007**	**0.066**	**0.049**	**0.019**	**0.078**
JHU	0.027	-0.003	0.057	0.026	-0.004	0.056	0.024	-0.007	0.054	0.026	-0.003	0.056
UMN	**-0.052**	**-0.082**	**-0.023**	**-0.055**	**-0.084**	**-0.025**	**-0.061**	**-0.091**	**-0.031**	**-0.054**	**-0.084**	**-0.025**
NWU	**0.094**	**0.066**	**0.121**	**0.092**	**0.064**	**0.119**	**0.087**	**0.058**	**0.115**	**0.093**	**0.065**	**0.121**
UCLA	**0.091**	**0.058**	**0.124**	**0.090**	**0.057**	**0.123**	**0.086**	**0.053**	**0.120**	**0.089**	**0.056**	**0.122**
Total cholesterol[2] (mg/dL)	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
HDL cholesterol[2] (mg/dL)	0.000	0.000	0.001	0.000	0.000	0.001	0.000	0.000	0.001	0.000	-0.001	0.001
Triglycerides[2] (mg/dL)	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Any lipid lowering medication	0.007	-0.014	0.027	0.007	-0.014	0.028	0.007	-0.014	0.028	0.006	-0.015	0.026
BP Measure[5] (mmHg)	**0.0008**	**0.0004**	**0.0013**	**0.0012**	**0.0005**	**0.0019**	**0.0011**	**0.0003**	**0.0020**	**0.0011**	**0.0005**	**0.0017**
Use of blood pressure medication[5]	-0.003	-0.021	0.016	0.000	-0.019	0.018	0.003	-0.015	0.022	-0.002	-0.020	0.017
Cigarette smoking status[2,6]												
Former	-0.015	-0.032	0.003	-0.015	-0.032	0.003	-0.015	-0.032	0.003	-0.015	-0.032	0.003
Current	-0.002	-0.031	0.027	-0.002	-0.031	0.027	-0.002	-0.032	0.027	-0.002	-0.031	0.027
Diabetes[2,7]	0.009	-0.019	0.037	0.010	-0.018	0.038	-0.013	-0.041	0.016	0.008	-0.021	0.036
Gross Family Income[2,8]												
$25,000-49,999	0.004	-0.019	0.026	0.004	-0.019	0.026	0.004	-0.019	0.027	0.004	-0.019	0.026
$50,000-74,999	-0.010	-0.037	0.016	-0.011	-0.038	0.015	-0.011	-0.038	0.015	-0.009	-0.036	0.018
$75,000+	0.000	-0.027	0.027	0.000	-0.027	0.026	-0.001	-0.028	0.027	0.001	-0.026	0.028
Highest educational level[9]												
HS grad.	-0.017	-0.047	0.013	-0.017	-0.048	0.013	-0.017	-0.047	0.014	-0.017	-0.047	0.014
Some/2 yr. college	-0.022	-0.050	0.006	-0.022	-0.051	0.006	-0.022	-0.051	0.006	-0.022	-0.050	0.006
4 yr. college+	-0.025	-0.055	0.005	-0.025	-0.055	0.005	-0.025	-0.055	0.005	-0.025	-0.055	0.005

BMI[2] (kg/m[2])	-0.001	-0.003	0.001	-0.001	-0.002	0.001	0.000	-0.002	0.001	-0.001	-0.003	0.001
Heart Rate[5] (beats/min.)	**0.0013**	**0.0004**	**0.0021**	**0.0012**	**0.0003**	**0.0020**	**0.0012**	**0.0003**	**0.0021**	**0.0014**	**0.0006**	**0.0023**
CRP[2] (mg/L)	0.001	0.000	0.003	0.001	0.000	0.003	0.001	0.000	0.003	0.001	0.000	0.003

[1] Coefficient for difference in annual rate of PTC1 change per unit change in CV risk factor

[2] At Exam 1

[2] Reference: Female

[3] Reference: White Race

[4] WFU as reference

[5] Time-varying

[6] Reference: Never smoker

[7] Reference: no diabetes, based on 2003 ADA fasting algorithm

[8] For past 12 months; Reference: $0-24,999

[9] Completed at Exam 1; Reference: Less than high school

Table 3.13: Associations Between Cardiovascular Risk Factors and Change in Weighted Mean of DC Using Fully Adjusted Linear Mixed Models For Different Blood Pressure Measures

Blood pressure measure	**SBP**			**MAP**			**DBP**			**PP**		
CV risk factor	Coeff.[1]	95% CI LL	95% CI UL	Coeff.[1]	95% CI LL	95% CI UL	Coeff.[1]	95% CI LL	95% CI UL	Coeff.[1]	95% CI LL	95% CI UL
Time between exams (years)	**-0.064**	**-0.085**	**-0.043**	**-0.066**	**-0.086**	**-0.045**	**-0.088**	**-0.108**	**-0.067**	**-0.067**	**-0.088**	**-0.046**
Age (years)[2]	**0.001**	**0.000**	**0.001**	**0.001**	**0.000**	**0.001**	**-0.001**	**-0.002**	**-0.001**	**0.001**	**0.000**	**0.002**
Gender[3]	-0.003	-0.013	0.007	-0.006	-0.016	0.005	**0.029**	**0.019**	**0.040**	-0.001	-0.011	0.010
Race/Ethnicity[4]												
Chinese	0.003	-0.014	0.019	0.001	-0.015	0.018	0.016	0.000	0.032	0.005	-0.011	0.022
Black	0.011	-0.001	0.023	0.010	-0.003	0.022	**0.017**	**0.005**	**0.029**	**0.013**	**0.000**	**0.025**
Hispanic	0.005	-0.010	0.019	0.004	-0.011	0.018	0.011	-0.003	0.025	0.007	-0.008	0.022
Site[5]												
COL	**0.039**	**0.023**	**0.055**	**0.039**	**0.023**	**0.055**	**0.026**	**0.011**	**0.042**	**0.033**	**0.017**	**0.049**
JHU	0.004	-0.013	0.021	0.003	-0.014	0.020	-0.004	-0.021	0.013	0.002	-0.015	0.019
UMN	**0.034**	**0.017**	**0.050**	**0.037**	**0.020**	**0.053**	**0.028**	**0.012**	**0.044**	**0.027**	**0.010**	**0.044**
NWU	0.013	-0.002	0.028	0.014	-0.001	0.029	0.013	-0.002	0.028	0.009	-0.007	0.024
UCLA	**0.020**	**0.003**	**0.037**	0.020	0.004	0.037	0.007	-0.009	0.024	0.018	**0.001**	**0.034**
Total cholesterol[2] (mg/dL)	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

HDL cholesterol[2] (mg/dL)	0.000	0.000	0.001	0.000	0.000	0.001	0.000	0.000	0.001	0.000	0.000	0.001
Triglycerides[2] (mg/dL)	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Any lipid lowering medication	0.004	-0.008	0.017	0.004	-0.008	0.017	0.003	-0.009	0.015	0.005	-0.008	0.017
BP Measure[5] (mmHg)	0.0002	-0.0001	0.0004	0.004	-0.008	0.017	**0.0010**	**0.0005**	**0.0015**	0.0000	-0.0003	0.0004
Use of blood pressure medication[5]	0.000	-0.011	0.010	0.000	0.000	0.001	0.000	-0.011	0.010	0.006	-0.005	0.017
Cigarette smoking status[2,6]												
Former	-0.008	-0.017	0.002	-0.008	-0.017	0.002	-0.004	-0.014	0.006	-0.007	-0.017	0.002
Current	-0.010	-0.027	0.007	-0.011	-0.027	0.006	-0.006	-0.023	0.010	-0.009	-0.026	0.007
Diabetes[2,7]	-0.008	-0.024	0.008	-0.010	-0.026	0.006	**-0.025**	**-0.041**	**-0.009**	-0.008	-0.024	0.008
Annual Gross Family Income[2,8]												
$25,000-49,999	-0.003	-0.015	0.009	-0.003	-0.015	0.009	-0.002	-0.014	0.010	-0.003	-0.015	0.010

$50,000-74,999	0.008	-0.006	0.023	0.008	-0.006	0.022	0.013	-0.001	0.027	0.009	-0.005	0.024
$75,000+	-0.004	-0.019	0.011	-0.004	-0.018	0.011	-0.001	-0.015	0.014	-0.004	-0.019	0.011
Highest educational level[9]												
HS grad.	0.007	-0.010	0.023	0.006	-0.010	0.023	0.008	-0.008	0.025	0.007	-0.010	0.023
Some/2 yr. college	0.011	-0.005	0.026	0.011	-0.004	0.027	0.015	-0.001	0.030	0.010	-0.005	0.026
4 yr. college+	0.012	-0.005	0.028	0.012	-0.004	0.028	**0.019**	**0.003**	**0.035**	0.012	-0.005	0.028
BMI[2] (kg/m^2)	**0.001**	**0.000**	**0.002**	**0.001**	**0.000**	**0.002**	0.000	-0.001	0.001	**0.001**	**0.000**	**0.002**
Heart Rate[5] (beats/min.)	0.000	0.000	0.001	0.000	0.000	0.001	**0.001**	**0.000**	**0.001**	0.000	0.000	0.001
CRP[2] (mg/L)	**-0.001**	**-0.002**	**-0.001**	**-0.001**	**-0.002**	**0.000**	**-0.002**	**-0.003**	**-0.001**	-0.001	-0.002	-0.001

[1] Coefficient for change in annual average progression rate per unit change in variable

[2] At Exam 1

[2] Reference: Female

[3] Reference: White

[4] WFU as reference

[5] Time-varying

[6] Reference: Never smoker

[7] Reference: no diabetes, based on 2003 ADA fasting algorithm

[8] For past 12 months; Reference: $0-24,999

[9] Completed at Exam 1; Reference: Less than high school

Table 3.14: Associations Between Cardiovascular Risk Factors and Change in Weighted Mean of YEM Using Fully Adjusted Linear Mixed Models For Different Blood Pressure Measures

Blood pressure measure	**SBP**			**MAP**			**DBP**			**PP**		
CV risk factor	Coeff.[1]	95% CI LL	95% CI UL	Coeff.[1]	95% CI LL	95% CI UL	Coeff.[1]	95% CI LL	95% CI UL	Coeff.[1]	95% CI LL	95% CI UL
Time between exams (years)	**35.10**	**11.53**	**58.67**	**37.92**	**14.40**	**61.44**	**51.53**	**27.82**	**75.25**	**35.64**	**11.87**	**59.41**
Age (years)[2]	**0.84**	**0.24**	**1.44**	**1.12**	**0.54**	**1.71**	**2.41**	**1.78**	**3.03**	0.62	-0.02	1.27
Gender[3]	6.08	-5.45	17.61	3.65	-8.09	15.39	**-17.30**	**-29.27**	**-5.32**	7.62	-4.19	19.43
Race/Ethnicity[4]												
Chinese	-1.44	-20.06	17.19	-1.20	-19.81	17.41	-9.15	-27.87	9.57	-2.27	-20.99	16.46
Black	0.79	-13.29	14.88	0.38	-13.75	14.50	-3.78	-17.95	10.38	1.72	-12.40	15.84
Hispanic	-9.51	-26.02	7.00	-8.84	-25.33	7.65	-12.45	-29.03	4.12	-10.54	-27.15	6.07
Site[5]												
COL	-13.88	-31.74	3.99	-15.28	-33.07	2.51	-9.75	-27.58	8.08	-9.95	-27.96	8.06
JHU	6.80	-12.56	26.16	7.76	-11.58	27.09	11.63	-7.77	31.03	7.05	-12.41	26.50
UMN	-10.90	-29.76	7.95	-13.52	-32.32	5.28	-10.59	-29.39	8.22	-7.46	-26.41	11.49
NWU	8.24	-9.22	25.70	7.00	-10.41	24.41	6.63	-10.85	24.10	10.54	-7.02	28.10
UCLA	-10.50	-29.71	8.71	-10.46	-29.64	8.72	-3.97	-23.21	15.27	-9.99	-29.29	9.31

Total cholesterol[2] (mg/dL)	-0.06	-0.22	0.10	-0.05	-0.21	0.11	-0.04	-0.20	0.12	-0.05	-0.21	0.11
HDL cholesterol[2] (mg/dL)	0.11	-0.31	0.54	0.11	-0.32	0.53	0.05	-0.38	0.48	0.07	-0.36	0.50
Triglycerides[2] (mg/dL)	0.03	-0.05	0.11	0.03	-0.05	0.11	0.04	-0.04	0.11	0.02	-0.05	0.10
Any lipid lowering medication	-6.83	-20.63	6.97	-6.14	-19.94	7.67	-5.14	-19.00	8.71	-8.34	-22.20	5.53
BP Measure[5] (mmHg)	**0.43**	**0.14**	**0.72**	**0.73**	**0.26**	**1.19**	**0.54**	**0.00**	**1.07**	**0.48**	**0.09**	**0.87**
Use of blood pressure medication[5]	-0.46	-12.59	11.66	0.69	-11.40	12.78	0.84	-11.16	12.83	-3.15	-15.27	8.97
Cigarette smoking status[2,6]												
Former	-6.11	-17.13	4.90	-6.20	-17.19	4.79	-8.28	-19.34	2.78	-6.49	-17.57	4.59
Current	-5.02	-23.85	13.82	-4.71	-23.52	14.10	-7.11	-26.01	11.80	-5.64	-24.59	13.31
Diabetes[2,7]	**18.89**	**0.80**	**36.99**	**22.10**	**4.04**	**40.16**	**32.26**	**14.09**	**50.44**	18.11	-0.16	36.37

Annual Gross Family Income[2,8]												
$25,000-49,999	3.48	-10.36	17.33	3.78	-10.04	17.60	2.91	-11.00	16.81	2.86	-11.07	16.78
$50,000-74,999	0.65	-15.57	16.87	0.69	-15.50	16.88	-2.17	-18.46	14.12	-0.08	-16.40	16.24
$75,000+	-0.77	-17.46	15.92	-1.39	-18.05	15.26	-3.65	-20.40	13.10	-1.08	-17.88	15.71
Highest educational level[9]												
HS grad.	-15.98	-34.54	2.58	-15.57	-34.10	2.96	-16.69	-35.33	1.96	-16.54	-35.21	2.12
Some/2 yr. college	-8.46	-26.03	9.11	-8.84	-26.38	8.70	-11.08	-28.72	6.56	-8.77	-26.45	8.90
4 yr. college+	-18.16	-36.72	0.40	-18.40	-36.92	0.12	**-22.72**	**-41.36**	**-4.07**	-18.58	-37.26	0.10
BMI[2] (kg/m[2])	-0.48	-1.63	0.67	-0.43	-1.58	0.71	0.07	-1.08	1.23	-0.58	-1.74	0.57
Heart Rate[5] (beats/min.)	0.42	-0.15	1.00	0.36	-0.22	0.94	-0.16	-0.74	0.43	0.47	-0.11	1.05
CRP[2] (mg/L)	0.45	-0.57	1.47	0.46	-0.56	1.48	0.67	-0.35	1.70	0.47	-0.56	1.50

[1] Coefficient for change in annual average progression rate per unit change in variable

[2] At Exam 1

[2] Reference: Female

[3] Reference: White

[4] WFU as reference

[5] Time-varying

[6] Reference: Never smoker

[7] Reference: no diabetes, based on 2003 ADA fasting algorithm

[8] For past 12 months; Reference: $0-24,999

[9] Completed at Exam 1; Reference: Less than high school

Table 3.15: Association between categorical age and categorical SBP with Change in Weighted Mean of PTC2

	Difference in Annual Average Rate of Change[1]	Standard Error	95% CI LL	95% CI UL	P-value
Age (Reference: 45-54 years old)					
Age 55-64	**0.041**	**0.017**	**0.008**	**0.073**	**0.020**
Age 65-74	**0.053**	**0.018**	**0.016**	**0.089**	
Age 75-84	0.051	0.028	-0.004	0.106	
Systolic blood pressure (Reference: Less than 120 mmHg)					
120-139 mmHg	**0.070**	**0.017**	**0.036**	**0.103**	**<0.001**
>=140 mmHg	**0.106**	**0.020**	**0.067**	**0.145**	

[1] Fully adjusted, linear mixed model that adjusts for age at Exam 1, gender, race/ethnicity, site, total cholesterol, HDL cholesterol, triglycerides, use of any lipid lowering medication (time-varying), use of blood pressure medication (time-varying), cigarette smoking status, diabetes, gross annual family income, highest educational level completed, BMI, heart rate, CRP

Table 3.16 Association between Selected Risk Factors and Interaction between SBP and BP medication With Change in Weighted Mean of PTC2

	Difference in Annual Average Rate of Change[1]	Standard Error	95% CI LL	95% CI UL	p-value
Age	**0.002**	**0.001**	**0.001**	**0.004**	**0.005**
Systolic blood pressure (Reference: Less than 120 mmHg)					
120-139 mmHg	**0.046**	**0.023**	**0.001**	**0.092**	**<0.001**
>=140 mmHg	**0.098**	**0.029**	**0.042**	**0.154**	
Anti-hypertension medication	-0.008	0.024	-0.055	0.039	0.742
Interaction: Systolic blood pressure * Anti-hypertension medication					
120-139 mmHg*Anti-hypertension medication	0.189	0.256	-0.313	0.690	0.692
>=140 mmHg*Anti-hypertension medication	0.363	0.287	-0.198	0.925	

[1] Fully adjusted, linear mixed model that adjusts for age at Exam 1, gender, race/ethnicity, site, total cholesterol, HDL cholesterol, triglycerides, use of any lipid lowering medication (time-varying), use of blood pressure medication (time-varying), cigarette smoking status, diabetes, gross annual family income, highest educational level completed, BMI, heart rate, CRP

Table 3.17: Association Between Categorical Age and Categorical SBP With Change in Weighted Mean of PTC1 Using Fully Adjusted, Linear Mixed Models

	Difference in Annual Average Rate of Change[1]	Standard Error	95% CI LL	95% CI UL	p-value
Age (Reference: 45-54 years old)					
Age 55-64 years old	0.017	0.010	-0.004	0.037	**0.002**
Age 65-74 years old	**0.030**	**0.011**	**0.007**	**0.052**	
Age 75-84 years old	**0.052**	**0.017**	**0.018**	**0.086**	
Systolic Blood Pressure (Reference: Less than 120 mmHg)					
120-139 mmHg	**0.033**	**0.010**	**0.014**	**0.052**	**0.007**
>=140 mmHg	**0.032**	**0.012**	**0.010**	**0.055**	

[1] For fully adjusted, linear mixed model that adjusts for age at Exam 1, gender, race/ethnicity, site, total cholesterol, HDL cholesterol, triglycerides, use of any lipid lowering medication (time-varying), use of blood pressure medication (time-varying), cigarette smoking status, diabetes, gross annual family income, highest educational level completed, BMI, heart rate, CRP

Table 3.18: Association between Selected Risk Factors and Interaction between SBP and BP medication With Weighted Mean of PTC1

	Difference in Annual Average Rate of Change[1]	Standard Error	95% CI LL	95% CI UL	p-value
Age	**0.002**	**4.938E-04**	**0.001**	**0.003**	**0.001**
Systolic blood pressure (Reference: Less than 120 mmHg)					
120-139 mmHg	**0.031**	**0.013**	**0.005**	**0.058**	**0.005**
>=140 mmHg	0.029	0.017	-0.004	0.061	
Anti-hypertension medication	-0.002	0.014	-0.030	0.026	0.897
Interaction: Systolic blood pressure * Anti-hypertensive medication					
120-139 mmHg*anti-hypertension medication	-0.004	0.020	-0.044	0.036	0.937
>=140 mmHg*anti-hypertension medication	0.004	0.023	-0.041	0.050	

[1] For fully adjusted, linear mixed model that adjusts for age at Exam 1, gender, race/ethnicity, site, total cholesterol, HDL cholesterol, triglycerides, use of any lipid lowering medication (time-varying), use of blood pressure medication (time-varying), cigarette smoking status, diabetes, gross annual family income, highest educational level completed, BMI, heart rate, CRP

Table 3.19 Association Between Categorical Age and Categorical MAP measures with Change in DC

	Difference in Annual Average Rate of Change[1]	Standard Error	95% CI LL	95% CI UL	p-value
Age (Reference: 45-54 years old)					
Age 55-64 years old	0.009	0.005	-0.002	0.020	0.178
Age 65-74 years old	0.014	0.006	0.003	0.026	
Age 75-84 years old	0.012	0.010	-0.006	0.031	
Mean Arterial Pressure (Reference: 1st quartile of MAP)[2]					
2nd quartile of MAP	0.007	0.007	-0.007	0.021	0.562
3rd quartile of MAP	0.004	0.007	-0.010	0.018	
4th quartile of MAP	0.010	0.007	-0.004	0.025	

[1] For fully adjusted, linear mixed model that adjusts for age at Exam 1, gender, race/ethnicity, site, total cholesterol, HDL cholesterol, triglycerides, use of any lipid lowering medication (time-varying), use of blood pressure medication (time-varying), cigarette smoking status, diabetes, gross annual family income, highest educational level completed, BMI, heart rate, CRP

[2]Quartiles of MAP: 49.5-81.5 mmHg, 78.8-89.3 mmHg, 86-98 mmHg, 94.3, 154.7 mmHg

Table 3.20: Association between Selected Risk Factors and Interaction Between MAP and BP medication with Change in DC

	Difference in Annual Average Rate of Change[1]	Standard Error	95% CI LL	95% CI UL	p-value
Age	0.001	2.623E-04	1.290E-04	0.001	0.014
Mean Arterial Pressure (Reference: 1st quartile of MAP)[2]					
2nd quartile of MAP	-0.001	0.009	-0.019	0.017	0.550
3rd quartile of MAP	4.859E-04	0.009	-0.018	0.019	
4th quartile of MAP	0.004	0.010	-0.015	0.023	
Anti-hypertension medication	-0.010	0.011	-0.032	0.012	0.385
Interaction: Mean arterial pressure * Anti-hypertensive medication					
2nd quartile of MAP*anti-hypertension medication	-0.054	0.115	-0.279	0.171	0.682
3rd quartile of MAP*anti-hypertension medication	0.012	0.113	-0.210	0.234	
4th quartile of MAP*anti-hypertension medication	-0.022	0.115	-0.248	0.203	

[1] For fully adjusted, linear mixed model that adjusts for age at Exam 1, gender, race/ethnicity, site, total cholesterol, HDL cholesterol, triglycerides, use of any lipid lowering medication (time-varying), use of blood pressure medication (time-varying), cigarette smoking status, diabetes, gross annual family income, highest educational level completed, BMI, heart rate, CRP

[2]Quartiles of MAP: 49.5-81.5 mmHg, 78.8-89.3 mmHg, 86-98 mmHg, 94.3, 154.7 mmHg

Table 3.21: Association Between Categorical Age and Categorical MAP with Change in YEM

	Difference in Annual Average Rate of Change[1]	Standard Error	95% CI LL	95% CI UL	p-value
Age (Reference: 45-54 years old)					
Age 55-64 years old	8.807	6.283	-3.507	21.122	**<0.001**
Age 65-74 years old	9.179	6.896	-4.338	22.696	
Age 75-84 years old	42.953	10.913	21.564	64.343	
Mean Arterial Pressure (Reference: 1st quartile of MAP)[2]					
2nd quartile of MAP	0.632	7.896	-14.845	16.108	**0.029**
3rd quartile of MAP	7.530	7.983	-8.117	23.177	
4th quartile of MAP	21.740	8.254	5.561	37.918	

[1] For fully adjusted, linear mixed model that adjusts for age at Exam 1, gender, race/ethnicity, site, total cholesterol, HDL cholesterol, triglycerides, use of any lipid lowering medication (time-varying), use of blood pressure medication (time-varying), cigarette smoking status, diabetes, gross annual family income, highest educational level completed, BMI, heart rate, CRP

[2]Quartiles of MAP: 49.5-81.5 mmHg, 78.8-89.3 mmHg, 86-98 mmHg, 94.3, 154.7 mmHg

Table 3.22: Association between Selected Risk Factors and Interaction Between MAP measures and BP medication with Change in YEM

	Difference in Annual Average Rate of Change[1]	Standard Error	95% CI LL	95% CI UL	p-value
Age	1.094	0.300	0.506	1.681	**<0.001**
Mean Arterial Pressure (Reference: 1st quartile of MAP)[2]					
2nd quartile of MAP	6.723	10.175	-13.220	26.666	**0.040**
3rd quartile of MAP	6.920	10.470	-13.601	27.440	
4th quartile of MAP	12.442	11.073	-9.261	34.144	
Anti-hypertension medication	-7.296	12.663	-32.115	17.524	0.565
Interaction: Mean Arterial Pressure * Anti-hypertensive medication					
2nd quartile of MAP*anti-hypertension medication	-126.967	127.471	-376.810	122.876	0.440
3rd quartile of MAP*anti-hypertension medication	-84.759	125.794	-331.316	161.797	
4th quartile of MAP*anti-hypertension medication	-112.937	127.718	-363.264	137.390	

[1] For fully adjusted, linear mixed model that adjusts for age at Exam 1, gender, race/ethnicity, site, total cholesterol, HDL cholesterol, triglycerides, use of any lipid lowering medication (time-varying), use of blood pressure medication (time-varying), cigarette smoking status, diabetes, gross annual family income, highest educational level completed, BMI, heart rate, CRP

[2]Quartiles of MAP: 49.5-81.5 mmHg, 78.8-89.3 mmHg, 86-98 mmHg, 94.3, 154.7 mmHg

Table 3.23: Sensitivity analysis of univariate association between cardiovascular risk factors and change in PTC2 comparing rate of change versus linear mixed model

	Rate of Change model				**Linear mixed model**				
Risk Factor	Difference in Annual Rate of Change[1]	95% CI LL	95% CI UL	p-value	Risk Factor	Difference in Annual Rate of Change[1]	95% CI LL	95% CI UL	p-value
Age[2] (years)	**0.003**	**0.002**	**0.005**	**<0.001**	Age[2] (years)	**0.003**	**0.002**	**0.005**	**<0.001**
Gender (Reference: Female)	**-0.071**	**-0.096**	**-0.046**	**<0.001**	Gender (Reference: Female)	**-0.072**	**-0.097**	**-0.047**	**<0.001**
Race/Ethnicity (Reference: White)					Race/Ethnicity (Reference: White)				
Chinese	0.041	-0.006	0.089	0.090	Chinese	0.038	-0.009	0.086	**0.001**
Black	**0.049**	**0.016**	**0.082**	**0.004**	Black	**0.053**	**0.019**	**0.087**	
Hispanic	**0.067**	**0.029**	**0.106**	**0.001**	Hispanic	**0.066**	**0.027**	**0.105**	
Site (Reference: Forysth County, North Carolina (WFU))					Site (Reference: Forysth County, North Carolina (WFU))				
New York, NY (COL)	**-0.056**	**-0.102**	**-0.011**	**0.016**	New York, NY (COL)	**-0.051**	**-0.098**	**-0.005**	**<0.0001**
Baltimore, MD (JHU)	**-0.097**	**-0.144**	**-0.049**	**<0.001**	Baltimore, MD (JHU)	**-0.102**	**-0.150**	**-0.053**	
St. Paul, MN (UMN)	**-0.209**	**-0.256**	**-0.163**	**<0.001**	St. Paul, MN (UMN)	**-0.200**	**-0.247**	**-0.154**	

Chicago, IL (NWU)	0.043	0.001	0.086	0.047	Chicago, IL (NWU)	0.043	0.000	0.087	
Los Angeles, CA (UCLA)	**-0.075**	**-0.127**	**-0.023**	**0.005**	Los Angeles, CA (UCLA)	**-0.060**	**-0.113**	**-0.008**	
Total cholesterol[2]	0.000	0.000	0.000	0.594	Total cholesterol[2]	0.000	0.000	0.000	0.533
Total cholesterol[2,3]	0.000	0.000	0.000	0.583	Total cholesterol[2,3]	0.000	0.000	0.000	0.825
HDL cholesterol[2]	**-0.001**	**-0.002**	**0.000**	**0.008**	HDL cholesterol[2]	**-0.001**	**-0.002**	**0.000**	**0.042**
HDL cholesterol[2,3]	**-0.001**	**-0.002**	**0.000**	**0.007**	HDL cholesterol[2,3]	**-0.001**	**-0.002**	**0.000**	**0.041**
Triglycerides[2]	**0.000**	**0.000**	**0.000**	**0.008**	Triglycerides[2]	**0.000**	**0.000**	**0.000**	**0.009**
Triglycerides[2,3]	**0.000**	**0.000**	**0.000**	**0.006**	Triglycerides[2,3]	**0.000**	**0.000**	**0.000**	**0.009**
Any lipid lowering medication[2]	-0.006	-0.041	0.029	0.734	Any lipid lowering medication[2]	-0.006	-0.041	0.029	0.747
SBP[4] (mmHg)	**0.003**	**0.002**	**0.004**	**<0.001**	SBP[4] (mmHg)	**0.003**	**0.002**	**0.004**	**<0.001**
SBP[4,5](mmHg)	**0.003**	**0.002**	**0.004**	**<0.001**	SBP[4,5](mmHg)	**0.003**	**0.002**	**0.004**	**<0.001**
MAP[1] (mmHg)	**0.005**	**0.004**	**0.006**	**<0.0001**	MAP[4] (mmHg)	**0.004**	**0.002**	**0.005**	**<0.001**
MAP[4,5](mmHg)	**0.005**	**0.003**	**0.006**	**<0.0001**	MAP[4,5] (mmHg)	**0.004**	**0.002**	**0.005**	**<0.001**
Use of blood pressure medication[2]	0.022	-0.005	0.050	0.115	Use of blood pressure medication[2]	0.020	-0.009	0.048	0.171
Cigarette smoking status[2] (Reference: Never smoker)					Cigarette smoking status[2] (Reference: Never smoker)				
Former	**0.043**	**0.015**	**0.071**	**0.003**	Former	**0.031**	**0.002**	**0.059**	0.078
Current	**0.058**	**0.017**	**0.098**	**0.006**	Current	0.032	-0.016	0.079	

Diabetes[2] (Reference: No diabetes, based on 2003 ADA fasting algorithm)	-0.003	-0.046	0.039	0.876	Diabetes[2] (Reference: No diabetes, based on 2003 ADA fasting algorithm)	0.007	-0.036	0.051	0.740
Annual Gross Family Income[2] (Reference: $0-24,999)					Annual Gross Family Income[2] (Reference: $0-24,999)				
$25,000-$49,999	0.020	-0.016	0.056	0.276	$25,000-$49,999	0.021	-0.015	0.057	0.470
$50,000-$74,999	0.019	-0.023	0.061	0.380	$50,000-$74,999	0.024	-0.017	0.066	
$75,000+	0.001	-0.040	0.042	0.964	$75,000+	0.003	-0.038	0.043	
Highest educational level completed[2] (Reference: Less than high school)					Highest educational level completed[2] (Reference: Less than high school)				
HS grad.	0.020	-0.016	0.056	0.276	HS grad.	-0.013	-0.061	0.036	0.159
Some/2 yr. college	0.019	-0.023	0.061	0.380	some/2 yr. college	-0.024	-0.069	0.021	
4 yr. college+	0.001	-0.040	0.042	0.964	4 yr. college+	**-0.046**	**-0.092**	**-0.001**	
BMI[2] (kg/m[2])	0.002	0.000	0.005	0.100	BMI[2] (kg/m[2])	0.002	0.000	0.005	0.064
Heart Rate[2](beats/min.)	0.000	-0.001	0.002	0.689	Heart Rate[2] (beats/min.)	0.000	-0.001	0.002	0.522
CRP[2] (mg/L)	**0.003**	**0.000**	**0.006**	**0.027**	CRP[2] (mg/L)	**0.003**	**0.001**	**0.006**	**0.012**

[1] Adjusting for base model covariates: age at Exam 1, sex, race/ethnicity, site

[2] At Exam 1

[3] Adjusted by lipid medication at Exam 1

[4] Time-varying variable

[5] Adjusted by anti-hypertensive medication at Exam 1

Table 3.24 Sensitivity analysis of multivariate association between cardiovascular risk factors and decline in PTC2 comparing rate of change versus linear mixed model

Rate of Change Model					**Linear mixed model**					
Risk Factor	Difference in Annual Rate of Change	Standard error	95% confidence interval	p-value		Difference in Annual Rate of Change	Standard Error	95% CI LL	95% CI UL	p-value
Age[1]	**0.002**	**0.001**	**0.000,0.003**	**0.029**	Age[1]	**0.002**	**0.001**	**0.000**	**0.004**	**0.013**
Gender (Reference: Female)	**-0.093**	**0.015**	**-0.123,-0.063**	**0.000**	Gender (Reference: Female)	**-0.089**	**0.015**	**-0.119**	**-0.059**	**<0.0001**
Race (Reference: White Race)					Race (Reference: White Race)					
Chinese	0.043	0.026	-0.008,0.093	0.100	Chinese	0.036	0.026	-0.015	0.086	0.160
Black	0.023	0.019	-0.014,0.059	0.222	Black	0.027	0.018	-0.009	0.063	
Hispanic	0.038	0.022	-0.004,0.081	0.079	Hispanic	0.034	0.022	-0.009	0.076	
Site (WFU as reference)					Site (WFU as reference)					
COL	-0.010	0.024	-0.058,0.038	0.687	COL	-0.003	0.024	-0.050	0.044	**<0.0001**
JHU	**-0.075**	**0.025**	**-0.125,-0.026**	**0.003**	JHU	**-0.075**	**0.025**	**-0.124**	**-0.027**	
UMN	**-0.187**	**0.025**	**-0.235,-0.138**	**0.000**	UMN	**-0.173**	**0.024**	**-0.221**	**-0.126**	
NWU	**0.075**	**0.023**	**0.030,0.120**	**0.001**	NWU	**0.080**	**0.023**	**0.035**	**0.124**	
UCLA	-0.043	0.027	-0.096,0.010	0.114	UCLA	-0.029	0.027	-0.082	0.023	
Total cholesterol[1]	0.000	0.000	-0.000,0.000	0.932	Total cholesterol[1]	0.000	0.000	0.000	0.000	0.874
HDL cholesterol[1]	-0.001	0.001	-0.002,0.000	0.120	HDL cholesterol[1]	-0.001	0.001	-0.002	0.000	0.100
Triglycerides[1]	0.000	0.000	-0.000,0.000	0.475	Triglycerides[1]	0.000	0.000	0.000	0.000	0.482

Any lipid lowering medication[1]	-0.007	0.019	-0.044,0.030	0.708	Any lipid lowering medication[2]	-0.021	0.018	-0.056	0.014	0.233
SBP[1]	**0.003**	**0.000**	**0.002,0.004**	**0.000**	SBP[2]	**0.002**	**0.000**	**0.002**	**0.003**	**<0.0001**
Use of blood pressure medication[1]	-0.009	0.015	-0.039,0.021	0.550	Use of blood pressure medication[2]	-0.006	0.016	-0.038	0.025	0.690
Cigarette smoking status[1] (Reference: Never smoker)					Cigarette smoking status[1] (Reference: Never smoker)					
Former	**0.036**	**0.015**	**0.008,0.065**	**0.013**	Former	0.028	0.014	0.000	0.056	0.122
Current	**0.048**	**0.021**	**0.006,0.090**	**0.025**	Current	0.027	0.024	-0.021	0.074	
Diabetes[1] (Reference: No diabetes, based on 2003 ADA fasting algorithm)	-0.011	0.023	-0.056,0.034	0.633	Diabetes[1] (Reference: No diabetes, based on 2003 ADA fasting algorithm)	0.004	0.023	-0.041	0.050	0.855
Annual Gross Family Income[1] (Reference: $0-24,999)					Annual Gross Family Income[1] (Reference: $0-24,999)					
25000-49999	0.032	0.019	-0.005,0.068	0.089	25000-49999	0.033	0.019	-0.004	0.069	0.181
50000-74999	0.044	0.022	0.000,0.087	0.048	50000-74999	**0.044**	**0.022**	**0.002**	**0.087**	
75000+	0.032	0.022	-0.011,0.076	0.148	75000+	0.031	0.022	-0.012	0.074	

Highest educational level completed[1] (Reference: Less than high school)					Highest educational level completed[1] (Reference: Less than high school)					
HS grad	-0.014	0.025	-0.063,0.034	0.566	HS grad	-0.020	0.025	-0.068	0.029	0.283
some/2 yr. college	-0.018	0.023	-0.064,0.027	0.434	some/2 yr. college	-0.032	0.023	-0.077	0.014	
4 yr. college+	-0.035	0.025	-0.083,0.013	0.156	4 yr. college+	-0.046	0.025	-0.095	0.002	
BMI[1]	-0.001	0.001	-0.004,0.002	0.587	BMI[1]	-0.001	0.001	-0.004	0.002	0.473
Heart Rate[1]	0.000	0.001	-0.002,0.001	0.605	Heart Rate[2]	-0.001	0.001	-0.002	0.001	0.437
CRP[1]	0.002	0.001	-0.001,0.005	0.191	CRP[1]	0.002	0.001	0.000	0.005	0.085

[1] At Exam 1

[2] Time-varying variable

Table 3.25 : Sensitivity analysis of univariate association between cardiovascular risk factors and change in PTC1 comparing rate of change versus linear mixed model

	Rate of change model				**Linear mixed model**				
Risk Factor	Difference in Annual Rate of Change	95% CI	p-value		Difference in Annual Rate of Change	Standard Error	95% CI LL	95% CI UL	p-value
Age[1]	**0.002**	**0.001,0.003**	**0.000**	Age[1]	**0.002**	**0.000**	**0.001**	**0.003**	**0.000**
Gender (Reference: Female)	-0.007	-0.023,0.009	0.369	Gender (Reference: Female)	-0.007	0.008	-0.023	0.009	0.402
Race (Reference: White Race)				Race (Reference: White Race)					
Chinese	0.026	-0.004,0.056	0.088	Chinese	0.022	0.015	-0.008	0.051	0.089
Black	0.001	-0.020,0.021	0.961	Black	-0.005	0.011	-0.026	0.015	
Hispanic	**0.026**	**0.002,0.050**	**0.035**	Hispanic	0.024	0.012	0.000	0.048	
Site (WFU as reference)				Site (WFU as reference)					
COL	**0.042**	**0.013,0.071**	**0.004**	COL	**0.042**	**0.015**	**0.013**	**0.071**	**<0.0001**
JHU	0.020	-0.010,0.050	0.201	JHU	0.015	0.015	-0.015	0.045	
UMN	**-0.066**	**-0.095,-0.036**	**0.000**	UMN	**-0.059**	**0.015**	**-0.088**	**-0.030**	
NWU	**0.089**	**0.062,0.116**	**<0.0001**	NWU	**0.090**	**0.014**	**0.062**	**0.117**	
UCLA	**0.086**	**0.053,0.119**	**0.000**	UCLA	**0.088**	**0.017**	**0.056**	**0.121**	
Total cholesterol[1]	0.000	-0.0001,0.0003	0.341	Total cholesterol [1]	0.000	0.000	0.000	0.000	0.195

Total cholesterol[1,2]	0.000	-0.0001,0.0004	0.301	Total cholesterol[1,2]	0.000	0.000	0.000	0.000	0.084
HDL cholesterol[1]	0.000	-0.0006,0.0006	0.949	HDL cholesterol[1]	0.000	0.000	0.000	0.001	0.471
HDL cholesterol[1,2]	0.000	-0.0006,0.0006	0.916	HDL cholesterol[1,2]	0.000	0.000	0.000	0.001	0.461
Triglycerides[1]	**0.000**	**0.00006,0.0004**	**0.008**	Triglycerides[1]	0.000	0.000	0.000	0.000	0.591
Triglycerides[1,2]	0.000	-0.00006,0.0001	0.435	Triglycerides[1,2]	0.000	0.000	0.000	0.000	0.599
Any lipid lowering medication[1]	0.007	-0.015,0.0284	0.552	Any lipid lowering medication[1]	0.008	0.011	-0.014	0.030	0.475
SBP[1]	**0.001**	**0.0007,0.002**	**0.000**	SBP[1]	**0.001**	**0.000**	**0.001**	**0.002**	**0.000**
SBP[1,3]	**0.001**	**0.0007,0.002**	**0.000**	SBP[1,3]	**0.001**	**0.000**	**0.001**	**0.002**	**0.000**
MAP[1]	**0.002**	**0.0009,0.002**	**0.000**	MAP[1]	**0.004**	**0.001**	**0.002**	**0.005**	**0.000**
MAP[1,3]	**0.002**	**0.0009,0.002**	**0.000**	MAP[1,3]	**0.004**	**0.001**	**0.002**	**0.005**	**0.000**
Use of blood pressure medication[1]	0.002	-0.016,0.019	0.852	Use of blood pressure medication[4]	0.003	0.009	-0.014	0.021	0.722
Cigarette smoking status[1] (Reference: Never smoker)				Cigarette smoking status[1] (Reference: Never smoker)					
Former	-0.012	-0.029,0.006	0.196	Former	-0.015	0.009	-0.032	0.003	0.253
Current	0.010	-0.015,0.036	0.435	Current	-0.007	0.015	-0.036	0.022	

Diabetes[1] (Reference: No diabetes, based on 2003 ADA fasting algorithm)	0.024	-0.002,0.051	0.074	Diabetes[1] (Reference: No diabetes, based on 2003 ADA fasting algorithm)	0.018	0.014	-0.009	0.046	0.184
Annual Gross Family Income[1] (Reference: $0-24,999)				Annual Gross Family Income[1] (Reference: $0-24,999)					
25000-49999	0.000	-0.023,0.023	0.999	25000-49999	-0.001	0.011	-0.023	0.021	0.460
50000-74999	-0.017	-0.043,0.009	0.207	50000-74999	-0.019	0.013	-0.044	0.007	
75000+	-0.012	-0.038,0.014	0.362	75000+	-0.007	0.013	-0.033	0.018	
Highest educational level completed[1] (Reference: Less than high school)				Highest educational level completed[1] (Reference: Less than high school)					
HS grad	-0.007	-0.036,0.023	0.651	HS grad	-0.017	0.015	-0.047	0.013	0.148
some/2 yr. college	-0.023	-0.051,0.004	0.100	some/2 yr. college	-0.027	0.014	-0.055	0.000	
4 yr. college+	-0.027	-0.055,0.001	0.058	4 yr. college+	**-0.032**	**0.015**	**-0.061**	**-0.004**	
BMI[1]	0.001	-0.0006,0.003	0.235	BMI[1]	0.001	0.001	-0.001	0.002	0.384
Heart Rate[1]	**0.002**	**0.002,0.003**	**<0.001**	Heart Rate[1]	**0.003**	**0.000**	**0.002**	**0.003**	**0.000**

CRP[1]	**0.002**	**0.0006,0.004**	**0.009**	CRP[1]	**0.002**	**0.001**	**0.000**	**0.004**	**0.025**

[1] At Exam 1
[2] Adjusted by lipid medication at Exam 1
[3] Adjusted by anti-hypertensive medication at Exam 1
[4] Time-varying variable

Table 3.26 Sensitivity analysis of multivariate association between cardiovascular risk factors and change in PTC1 comparing rate of change versus linear mixed model

Rate of Change Model					**Linear mixed effects model**					
Risk Factor	Difference in Annual Rate of Change	Standard error	95% confidence interval	p-value		Difference in Annual Rate of Change	Standard Error	95% CI LL	95% CI UL	p-value
Age[1]	**0.001**	**0.001**	**0.000,0.002**	**0.004**	Age[1]	**0.002**	**0.000**	**0.001**	**0.003**	**0.001**
Gender (Reference: Female)	0.006	0.010	-0.013,0.024	0.563	Gender (Reference: Female)	0.006	0.009	-0.012	0.025	0.492
Race (Reference: White Race)					Race (Reference: White Race)					
Chinese	0.015	0.016	-0.017,0.047	0.356	Chinese	0.010	0.016	-0.021	0.041	0.220
Black	-0.010	0.012	-0.033,0.013	0.375	Black	-0.014	0.011	-0.036	0.009	
Hispanic	0.009	0.014	-0.018,0.036	0.519	Hispanic	0.012	0.013	-0.014	0.039	
Site (WFU as reference)					Site (WFU as reference)					
COL	**0.052**	**0.015**	**0.021,0.082**	**0.001**	COL	**0.048**	**0.015**	**0.019**	**0.077**	**<0.0001**
JHU	0.026	0.016	-0.005,0.057	0.104	JHU	0.027	0.015	-0.003	0.057	
UMN	**-0.055**	**0.016**	**-0.085,-0.024**	**0.000**	UMN	**-0.052**	**0.015**	**-0.082**	**-0.023**	
NWU	**0.099**	**0.014**	**0.071,0.128**	**0.000**	NWU	**0.094**	**0.014**	**0.066**	**0.121**	

UCLA	**0.094**	**0.017**	**0.060,0.128**	**0.000**	UCLA	**0.091**	**0.017**	**0.058**	**0.124**	
Total cholesterol[1]	0.000	0.000	-0.000,0.000	0.601	Total cholesterol[1]	0.000	0.000	0.000	0.000	0.324
HDL cholesterol[1]	0.000	0.000	-0.001,0.001	0.695	HDL cholesterol[1]	0.000	0.000	0.000	0.001	0.576
Triglycerides[1]	0.000	0.000	-0.000,0.000	0.545	Triglycerides[1]	0.000	0.000	0.000	0.000	0.452
Any lipid lowering medication[1]	0.008	0.012	-0.015,0.031	0.505	Any lipid lowering medication[2]	0.007	0.011	-0.014	0.027	0.532
SBP[1]	**0.001**	**0.000**	**0.001,0.001**	**0.000**	SBP[2]	**0.001**	**0.000**	**0.000**	**0.001**	**0.000**
Use of blood pressure medication[1]	-0.009	0.010	-0.028,0.010	0.377	Use of blood pressure medication[2]	-0.003	0.009	-0.021	0.016	0.779
Cigarette smoking status[1] (Reference: Never smoker)					Cigarette smoking status[2] (Reference: Never smoker)					
Former	-0.014	0.009	-0.032,0.004	0.120	Former	-0.015	0.009	-0.032	0.003	0.247
Current	-0.002	0.013	-0.028,0.025	0.892	Current	-0.002	0.015	-0.031	0.027	
Diabetes[1] (Reference: No diabetes, based on 2003 ADA	0.006	0.015	-0.023,0.034	0.692	Diabetes[1] (Reference: No diabetes, based on 2003	0.009	0.014	-0.019	0.037	0.537

fasting algorithm)					ADA fasting algorithm)					
Annual Gross Family Income[1] (Reference: $0-24,999)					Annual Gross Family Income[1] (Reference: $0-24,999)					
25000-49999	0.004	0.012	-0.019,0.028	0.708	25000-49999	0.004	0.012	-0.019	0.026	0.695
50000-74999	-0.007	0.014	-0.034,0.020	0.605	50000-74999	-0.010	0.014	-0.037	0.016	
75000+	0.003	0.014	-0.025,0.031	0.838	75000+	0.000	0.014	-0.027	0.027	
Highest educational level completed[1] (Reference: Less than high school)					Highest educational level completed[1] (Reference: Less than high school)					
HS grad	-0.014	0.016	-0.045,0.017	0.373	HS grad	-0.017	0.015	-0.047	0.013	0.455
some/2 yr college	-0.021	0.015	-0.050,0.008	0.158	some/2 yr college	-0.022	0.014	-0.050	0.006	
4 yr college+	-0.023	0.016	-0.054,0.008	0.139	4 yr college+	-0.025	0.015	-0.055	0.005	
BMI[1]	-0.001	0.001	-0.002,0.001	0.496	BMI[1]	-0.001	0.001	-0.003	0.001	0.382
Heart Rate[1]	**0.002**	**0.000**	**0.001,0.003**	**0.000**	Heart Rate[2]	**0.001**	**0.000**	**0.000**	**0.002**	**0.005**

CRP[1]	0.001	0.001	-0.001,0.003	0.172	CRP[1]	0.001	0.001	0.000	0.003	0.136

[1] At Exam 1
[2] Time-varying variable

Table 3.27 Sensitivity analysis of multivariate association between cardiovascular risk factors and change in DC comparing rate of change versus linear mixed model

	Rate of Change model				**Linear mixed model**			
Risk Factor	Difference in Annual Rate of Change	95% CI	p-value	Risk Factor	Difference in Annual Rate of Change	Standard Error	95% CI LL	p-value
Age[1]	**0.001**	**0.0003,0.001**	**0.001**	Age[1]	**0.001**	**0.000**	**0.000**	**0.000**
Gender (Reference: Female)	-0.002	-0.011,0.007	0.608	Gender (Reference: Female)	-0.001	0.005	-0.010	0.822
Race (Reference: White Race)				Race (Reference: White Race)				
Chinese	0.005	-0.011,0.020	0.579	Chinese	0.003	0.008	-0.013	0.188
Black	**0.014**	**0.003,0.026**	**0.017**	Black	**0.012**	**0.006**	**0.000**	
Hispanic	0.000	-0.014,0.014	0.993	Hispanic	0.000	0.007	-0.014	
Site (WFU as reference)				Site (WFU as reference)				
COL	0.026	0.010,0.041	0.001	COL	**0.022**	**0.008**	**0.007**	0.000
JHU	-0.014	-0.032,0.004	0.126	JHU	-0.009	0.009	-0.027	
UMN	**0.033**	**0.016,0.049**	**0.000**	UMN	**0.030**	**0.009**	**0.013**	
NWU	0.007	-0.008,0.022	0.365	NWU	0.007	0.008	-0.009	
UCLA	0.014	-0.004,0.031	0.123	UCLA	0.013	0.009	-0.004	
Total cholesterol[1]	0.000	-0.00004,0.0002	0.175	Total cholesterol[1]	0.000	0.000	0.000	0.513
Total cholesterol[1,2]	0.000	-0.0004,0.0003	0.678	Total cholesterol[1, 2]	0.000	0.000	0.000	0.972
HDL cholesterol[1]	0.000	-0.00001,0.0001	0.109	HDL cholesterol[1]	**0.000**	**0.000**	**0.000**	**0.044**

HDL cholesterol[1,2]	0.003	-0.001,0.015	0.679	HDL cholesterol[1,2]	0.008	0.006	-0.004	0.194
MAP[1]	**0.002**	**0.001,0.002**	**<0.0001**	MAP[1]	**0.002**	**0.000**	**0.001**	**0.000**
MAP[1,3]	**0.002**	**0.001,0.002**	**<0.0001**	MAP[1,3]	**0.001**	**0.000**	**0.001**	**0.000**
				MAP[4]	**0.001**	**0.000**	**0.000**	**0.013**
				MAP[3,4]	**0.001**	**0.000**	**0.000**	**0.015**
Use of blood pressure medication[1]	0.006	-0.004,0.016	0.246	Use of blood pressure medication[2]	0.009	0.005	0.000	0.061
Cigarette smoking status[1] (Reference: Never smoker)				Cigarette smoking status[2] (Reference: Never smoker)				
Former	-0.008	-0.018,0.001	0.093	Former	-0.007	0.005	-0.017	0.176
Current	**-0.021**	**-0.036,-0.006**	**0.005**	Current	**-0.021**	**0.009**	**-0.038**	
Diabetes[1] (Reference: No diabetes, based on 2003 ADA fasting algorithm)	-0.010	-0.026,0.006	0.219	Diabetes[1] (Reference: No diabetes, based on 2003 ADA fasting algorithm)	-0.006	0.008	-0.022	0.461
Annual Gross Family Income[1] (Reference: $0-24,999)				Annual Gross Family Income[1] (Reference: $0-24,999)				
25000-49999	0.003	-0.010,0.015	0.683	25000-49999	0.001	0.006	-0.011	0.459

50000-74999	**0.016**	**0.0008,0.030**	**0.038**	50000-74999	0.014	0.007	0.000	
75000+	0.006	-0.009,0.020	0.445	75000+	0.005	0.007	-0.010	
Highest educational level completed[1] (Reference: Less than high school)				Highest educational level completed[1] (Reference: Less than high school)				
HS grad	0.006	-0.011,0.023	0.481	HS grad	0.007	0.009	-0.010	0.400
some/2 yr college	0.011	-0.005,0.026	0.178	some/2 yr college	0.012	0.008	-0.004	0.136
4 yr college+	0.013	-0.003,0.029	0.121	4 yr college+	0.011	0.008	-0.005	0.163
BMI[1]	**0.002**	**0.0006,0.002**	**0.001**	BMI[1]	**0.002**	**0.000**	**0.001**	**0.000**
Heart Rate[1]	**0.001**	**0.0007,0.001**	**0.000**	Heart Rate[2]	**0.001**	**0.000**	**0.001**	**0.000**
CRP[1]	-0.001	-0.0014,0.0004	0.269	CRP[1]	-0.001	0.000	-0.002	0.161

[1] At Exam 1
[2] Adjusted by lipid medication at Exam 1
[3] Adjusted by anti-hypertensive medication at Exam 1

Table 3.28 Sensitivity analysis of multivariate association between cardiovascular risk factors and change in DC comparing rate of change versus linear mixed model

Rate of Change Model					**Linear mixed model**					
Risk Factor	Difference in Annual Rate of Change	Standard error	95% CI	p-value		Difference in Annual Rate of Change	Standard Error	95% CI LL	95% CI UL	p-value
Age[1]	**0.001**	**0.000**	**0.000,0.001**	**0.014**	Age[1]	**0.001**	**0.000**	**0.000**	**0.001**	**0.020**
Gender (Reference: Female)	-0.007	0.006	-0.018,0.004	0.221	Gender (Reference: Female)	-0.006	0.005	-0.016	0.005	0.294
Race (Reference: White Race)					Race (Reference: White Race)					
Chinese	0.004	0.009	-0.013,0.021	0.680	Chinese	0.001	0.008	-0.015	0.018	0.451
Black	0.010	0.007	-0.003,0.023	0.146	Black	0.010	0.006	-0.003	0.022	
Hispanic	0.001	0.008	-0.014,0.016	0.881	Hispanic	0.004	0.007	-0.011	0.018	
Site (WFU as reference)					Site (WFU as reference)					
COL	**0.033**	**0.008**	**0.017,0.050**	**0.000**	COL	**0.039**	**0.008**	**0.023**	**0.055**	0.000
JHU	-0.006	0.009	-0.025,0.012	0.498	JHU	0.003	0.009	-0.014	0.020	
UMN	**0.038**	**0.009**	**0.021,0.056**	**0.000**	UMN	**0.037**	**0.008**	**0.020**	**0.053**	
NWU	0.011	0.008	-0.005,0.027	0.182	NWU	0.014	0.008	-0.001	0.029	
UCLA	**0.023**	**0.009**	**0.005,0.040**	**0.012**	UCLA	**0.020**	**0.009**	**0.004**	**0.037**	
Total cholesterol[1]	0.000	0.000	-0.000,0.000	0.977	Total cholesterol[1]	0.000	0.000	0.000	0.000	0.465
HDL cholesterol[1]	0.000	0.000	-0.000,0.001	0.552	HDL cholesterol[1]	0.000	0.000	0.000	0.001	0.272

Triglycerides[1]	0.000	0.000	-0.000,0.000	0.239	Triglycerides[1]	0.000	0.000	0.000	0.000	0.208
Any lipid lowering medication[1]	0.002	0.007	-0.011,0.015	0.771	Any lipid lowering medication[2]	0.004	0.006	-0.008	0.017	0.496
MAP[2]	**0.001**	**0.000**	**0.001,0.002**	**0.000**	MAP[2]	0.000	0.000	0.000	0.001	0.126
Use of blood pressure medication[1]	-0.002	0.005	-0.012,0.009	0.746	Use of blood pressure medication[2]	-0.002	0.005	-0.012	0.009	0.764
Cigarette smoking status[1] (Reference: Never smoker)					Cigarette smoking status[2] (Reference: Never smoker)					
Former	-0.006	0.005	-0.016,0.004	0.237	Former	-0.008	0.005	-0.017	0.002	0.197
Current	**-0.020**	**0.008**	**-0.035,-0.005**	**0.011**	Current	-0.011	0.008	-0.027	0.006	
Diabetes[1] (Reference: No diabetes, based on 2003 ADA fasting algorithm)	-0.016	0.009	-0.033,0.001	0.061	Diabetes[1] (Reference: No diabetes, based on 2003 ADA fasting algorithm)	-0.010	0.008	-0.026	0.006	0.217
Annual Gross Family Income[1] (Reference: $0-24,999)					Annual Gross Family Income[1] (Reference: $0-24,999)					
25000-49999	0.000	0.006	-0.013,0.013	0.987	25000-49999	-0.003	0.006	-0.015	0.009	0.193
50000-74999	0.011	0.008	-0.004,0.026	0.142	50000-74999	0.008	0.007	-0.006	0.022	
75000+	0.004	0.008	-0.012,0.019	0.644	75000+	-0.004	0.007	-0.018	0.011	
Highest educational level completed[1] (Reference: Less than high school)					Highest educational level completed[1] (Reference: Less than high school)					
HS grad	0.008	0.009	-0.009,0.025	0.366	HS grad	0.006	0.008	-0.010	0.023	0.489

some/2 yr college	0.013	0.008	-0.003,0.029	0.111	some/2 yr college	0.011	0.008	-0.004	0.027	
4 yr college+	0.012	0.009	-0.005,0.029	0.161	4 yr college+	0.012	0.008	-0.004	0.028	
BMI[1]	**0.001**	**0.001**	**0.000,0.002**	**0.031**	BMI[1]	**0.001**	**0.001**	**0.000**	**0.002**	**0.010**
Heart Rate[1]	**-0.001**	**0.000**	**-0.002,-0.000**	**0.011**	Heart Rate[2]	0.000	0.000	0.000	0.001	0.730
CRP[1]	**0.001**	**0.000**	**0.000,0.001**	**0.000**	CRP[1]	**-0.001**	**0.000**	**-0.002**	**0.000**	**0.003**

[1] At Exam 1

[2] Time-varying variable

Table 3.29: Sensitivity analysis of univariate association between cardiovascular risk factors and change in YEM comparing rate of change versus linear mixed model

	Rate of Change Model			**Linear mixed model**					
Risk Factor	Difference in Annual Rate of Change	95% CI	p-value		Difference in Annual Rate of Change	Standard Error	95% CI LL	95% CI UL	p-value
Age	**1.392**	**0.854,1.931**	**0.000**	Age	**1.058**	**0.270**	**0.528**	**1.587**	**0.000**
Gender (Reference: Female)	-1.488	-11.606,8.631	0.773	Gender (Reference: Female)	-0.590	5.046	-10.480	9.300	0.907
Race (Reference: White Race)				Race (Reference: White Race)					
Chinese	6.742	-11.440,24.925	0.467	Chinese	5.654	9.009	-12.003	23.312	0.782
Black	3.537	-9.880,16.955	0.605	Black	5.760	6.749	-7.467	18.988	
Hispanic	1.605	-13.938,17.147	0.840	Hispanic	2.265	7.727	-12.880	17.411	
Site (WFU as reference)				Site (WFU as reference)					
COL	-14.478	-32.283,3.328	0.111	COL	-4.059	9.078	-21.852	13.734	0.221
JHU	12.963	-7.421,33.347	0.213	JHU	14.315	9.975	-5.236	33.866	
UMN	-17.108	-36.026,1.8105	0.076	UMN	-11.109	9.548	-29.823	7.606	
NWU	1.075	-16.261,18.41	0.903	NWU	6.644	8.777	-10.558	23.846	
UCLA	-15.217	-34.848,4.414	0.129	UCLA	-6.948	9.842	-26.238	12.341	
Total cholesterol[1,2]	-0.098	-0.249,0.052	0.199	Total cholesterol[1,2]	-0.033	0.075	-0.180	0.114	0.659
HDL cholesterol[1,2]	-0.016	-0.390,0.358	0.932	HDL cholesterol[1,2]	-0.029	0.189	-0.400	0.342	0.878

Triglycerides[1,2]	0.017	-0.048,0.081	0.613	Triglycerides[1,2]	0.015	0.034	-0.052	0.083	0.656
Any lipid lowering medication[1]	-0.399	-14.840,14.04	0.957	Any lipid lowering medication[1]	-6.142	7.108	-20.074	7.790	0.388
MAP[1]	**-0.535**	**-0.975,-0.096**	**0.017**	MAP[1]	-0.425	0.220	-0.856	0.005	0.053
MAP[1,3]	**-0.638**	**-1.086,-0.190**	**0.005**	MAP[1,3]	-0.400	0.233	-0.857	0.057	0.086
				MAP[4]	**0.687**	**0.231**	**0.233**	**1.140**	**0.003**
				MAP[3,4]	**0.684**	**0.235**	**0.223**	**1.145**	**0.004**
Cigarette smoking status[1] (Reference: Never smoker)				Cigarette smoking status[2] (Reference: Never smoker)					
Former	-4.930	-16.250,6.390	0.393	Former	-5.673	5.693	-16.831	5.485	0.119
Current	0.519	-16.403,17.441	0.952	Current	4.590	9.641	-14.307	23.487	
Diabetes[1] (Reference: No diabetes, based on 2003 ADA fasting algorithm)	**21.394**	**3.288,39.500**	**0.021**	Diabetes[1] (Reference: No diabetes, based on 2003 ADA fasting algorithm)	**21.627**	**8.989**	**4.009**	**39.245**	**0.016**
Highest educational level completed[1] (Reference: Less than high school)				Highest educational level completed[1] (Reference: Less than high school)					
HS grad	**-22.977**	**-42.042,-3.913**	**0.018**	HS grad	-17.053	9.586	-35.842	1.736	0.473

some/2 yr college	-14.665	-32.502,3.172	0.107	some/2 yr college	-11.312	8.948	-28.849	6.225	
4 yr college+	**-26.579**	**-44.768,-8.389**	**0.004**	4 yr college+	**-20.236**	**9.148**	**-38.166**	**-2.306**	
Annual Gross Family Income[1] (Reference: $0-24,999)				Annual Gross Family Income[1] (Reference: $0-24,999)					
25000-49999	0.618	-13.585,14.821	0.932	25000-49999	-0.367	7.064	-14.213	13.479	0.959
50000-74999	-4.865	-21.407,11.676	0.564	50000-74999	-5.352	8.195	-21.413	10.710	0.514
75000+	-12.548	-28.927,3.830	0.133	75000+	-11.591	8.124	-27.515	4.333	0.154
BMI[1]	-0.494	-1.593,0.604	0.378	BMI[1]	-0.559	0.540	-1.617	0.500	0.301
Heart Rate[1]	-0.348	-0.914,0.218	0.228	Heart Rate[2]	-0.233	0.281	-0.783	0.318	0.407
CRP[1]	-0.102	-1.123,0.920	0.845	CRP[1]	0.219	0.511	-0.783	1.220	0.669

[1] At Exam 1

[2] Adjusted by lipid medication at Exam 1

[3] Adjusted by anti-hypertensive medication at Exam 1

[4] Time-varying variable

Table 3.30 Sensitivity analysis of multivariate association between cardiovascular risk factors and change in YEM comparing rate of change versus linear mixed model

Rate of change model

Most fully adjusted	Difference in Annual Rate of Change	Standard error	95% confidence interval	p-value
Age[1]	**1.118**	**0.312**	**0.506,1.730**	**0.000**
Gender (Reference: Female)	3.719	6.327	-8.688,16.126	0.557
Race (Reference: White Race)				
Chinese	-1.656	9.982	-21.230,17.918	0.868
Black	0.511	7.585	-14.362,15.385	0.946
Hispanic	-8.247	8.841	-25.583,9.090	0.351
Site (WFU as reference)				
COL	-14.946	9.518	-33.610,3.717	0.116
JHU	13.701	10.743	-7.363,34.77	0.202
UMN	-16.691	10.094	-36.484,3.103	0.098
NWU	8.461	9.302	-9.779,26.701	0.363
UCLA	-16.154	10.300	-36.352,4.044	0.117
Total cholesterol[1]	-0.117	0.086	-0.286,0.053	0.176
HDL cholesterol[1]	0.176	0.227	-0.269,0.621	0.439
Triglycerides[1]	0.029	0.043	-0.055,0.113	0.494

Linear mixed model

	Difference in Annual Rate of Change	Standard Error	95% CI LL	95% CI UL	p-value
Age[1]	**1.127**	**0.298**	**0.543**	**1.711**	**0.000**
Gender (Reference: Female)	3.758	5.973	-7.949	15.465	0.529
Race (Reference: White Race)					
Chinese	-1.196	9.494	-19.805	17.413	0.667
Black	0.376	7.208	-13.751	14.503	
Hispanic	-8.840	8.413	-25.329	7.649	
Site (WFU as reference)					
COL	-15.280	9.075	-33.068	2.507	0.078
JHU	7.756	9.863	-11.576	27.087	
UMN	-13.521	9.591	-32.321	5.278	
NWU	7.003	8.883	-10.407	24.413	
UCLA	-10.461	9.785	-29.640	8.717	
Total cholesterol[1]	-0.052	0.082	-0.213	0.109	0.526
HDL cholesterol[1]	0.109	0.217	-0.316	0.533	0.615
Triglycerides[1]	0.033	0.040	-0.045	0.112	0.406

Any lipid lowering medication[1]	-2.774	7.748	-17.966,12.418	0.720	Any lipid lowering medication[2]	-6.137	7.043	-19.940	7.667	0.384
MAP[1]	**-0.526**	**0.237**	**-0.991,-0.060**	**0.027**	MAP[2]	**0.729**	**0.237**	**0.263**	**1.194**	**0.002**
Use of blood pressure medication[1]	11.122	6.185	-1.006,23.251	0.072	Use of blood pressure medication[2]	0.688	6.168	-11.400	12.776	0.911
Cigarette smoking status[1] (Reference: Never smoker)					Cigarette smoking status[2] (Reference: Never smoker)					
Former	-6.609	5.889	-18.156,4.939	0.262	Former	-6.201	5.609	-17.195	4.792	0.477
Current	-0.081	8.837	-17.409,17.247	0.993	Current	-4.710	9.596	-23.519	14.098	
Diabetes[1] (Reference: No diabetes, based on 2003 ADA fasting algorithm)	16.784	9.839	-2.509,36.078	0.088	Diabetes[1] (Reference: No diabetes, based on 2003 ADA fasting algorithm)	**22.103**	**9.215**	**4.042**	**40.164**	**0.017**
Annual Gross Family Income[1] (Reference: $0-24,999)					Annual Gross Family Income[1] (Reference: $0-24,999)					
25000-49999	2.707	7.439	-11.881,17.295	0.716	25000-49999	3.780	7.050	-10.039	17.599	0.818

50000-74999	-1.636	8.744	-18.782,15.509	0.852	50000-74999	0.688	8.260	-15.500	16.877	
75000+	-9.338	8.960	-26.908,8.232	0.297	75000+	-1.395	8.497	-18.049	15.260	
Highest educational level completed[1] (Reference: Less than high school)					Highest educational level completed[1] (Reference: Less than high school)					
HS grad	**-21.589**	**9.966**	**-41.131,-2.048**	**0.030**	HS grad	-15.569	9.454	-34.098	2.960	0.170
some/2 yr. college	-13.068	9.450	-31.599,5.463	0.167	some/2 yr. college	-8.840	8.948	-26.378	8.697	
4 yr. college+	**-22.153**	**9.955**	**-41.673,-2.632**	**0.026**	4 yr. college+	-18.399	9.449	-36.919	0.122	
BMI[1]	-0.443	0.627	-1.673,0.786	0.480	BMI[1]	-0.433	0.583	-1.575	0.710	0.458
Heart Rate[1]	-0.395	0.303	-0.988,0.198	0.192	Heart Rate[2]	0.357	0.295	-0.222	0.935	0.227
CRP[1]	0.057	0.550	-1.021,1.135	0.917	CRP[1]	0.459	0.521	-0.562	1.480	0.378

[1] At Exam 1

[2] Time-varying variable

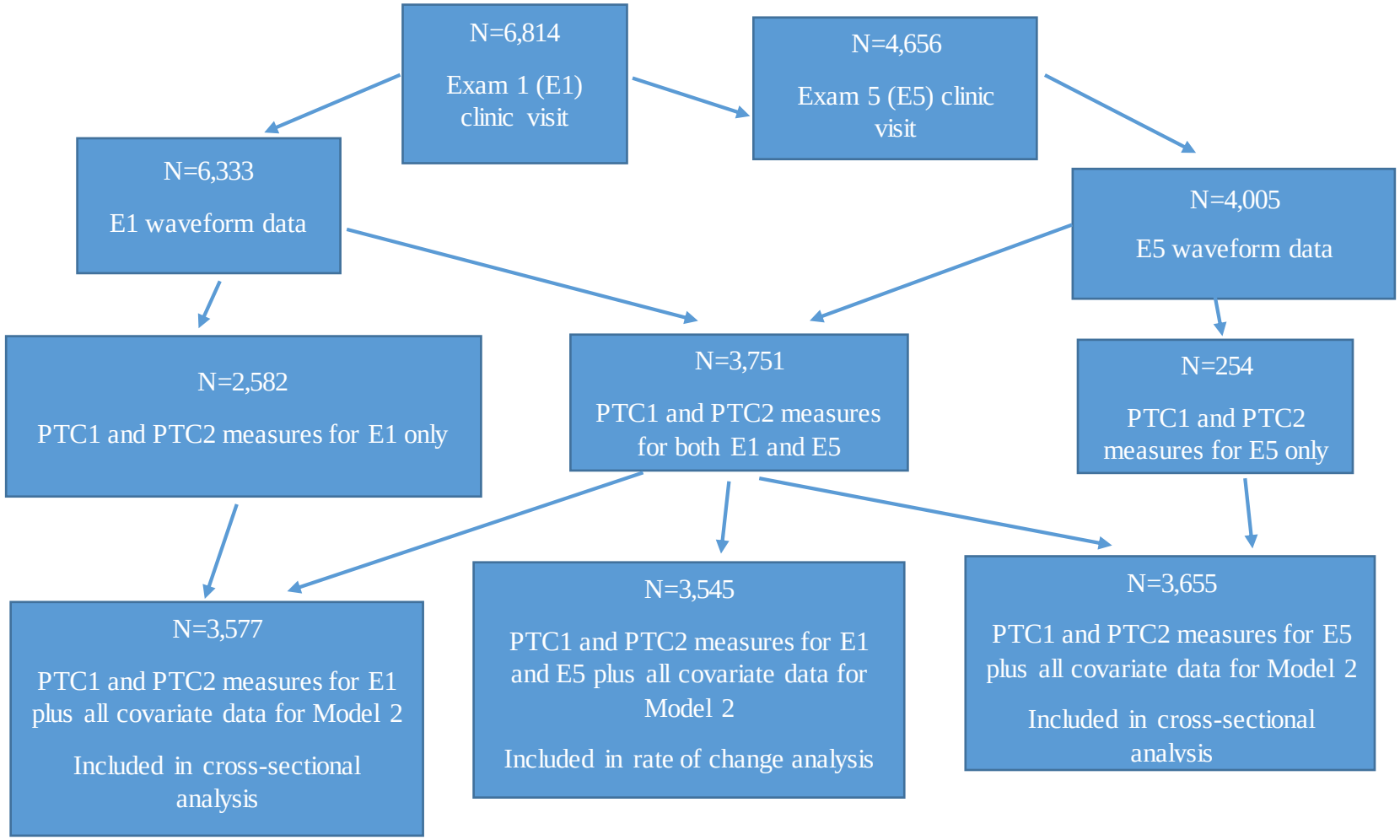

Figure 3.1 How many participants were included in the analysis of correlates of cross-sectional measurement and longitudinal change in radial tonometry measures, PTC1 and PTC2

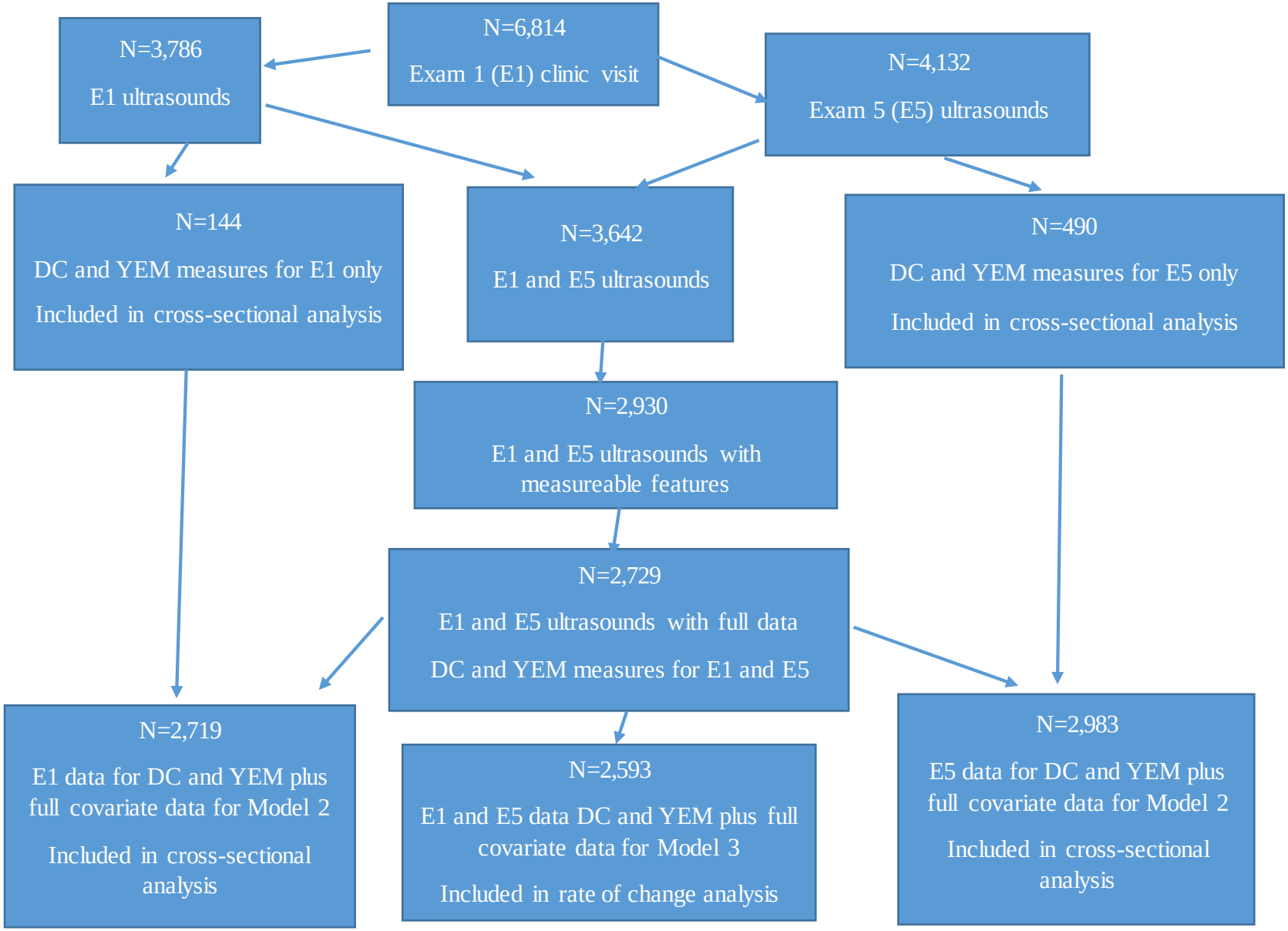
N=6,814
Exam 1 (E1) clinic visit
N=3,786
E1 ultrasounds
N=4,132
Exam 5 (E5) ultrasounds
N=144
DC and YEM measures for E1 only
Included in cross-sectional analysis
N=3,642
E1 and E5 ultrasounds
N=490
DC and YEM measures for E5 only
Included in cross-sectional analysis
N=2,930
E1 and E5 ultrasounds with measureable features
N=2,729
E1 and E5 ultrasounds with full data
DC and YEM measures for E1 and E5
N=2,719
E1 data for DC and YEM plus full covariate data for Model 2
Included in cross-sectional analysis
N=2,593
E1 and E5 data DC and YEM plus full covariate data for Model 3
Included in rate of change analysis
N=2,983
E5 data for DC and YEM plus full covariate data for Model 2
Included in cross-sectional analysis

Figure 3.2 How many participants were included in the analysis of correlates of cross-sectional measurement and longitudinal change in carotid ultrasound measures, DC and YEM

Chapter 4. Association of Short and Long Term Air Pollution with Cross-sectional Measurements and Longitudinal Change in Arterial Function Measures in the Multi-Ethnic Study of Atherosclerosis (MESA)

4.1 Abstract

Background and purpose: Many studies have shown an association between $PM_{2.5}$, particulate matter with diameter of less than 2.5 micrometers in aerodynamic diameter, and CVD events. However, there is gap in understanding the biological mechanisms by which air pollution affects the cardiovascular system. Detrimental changes in arterial function may be part of a biological mechanism linking air pollution and CVD events. Arterial functional measures are relevant subclinical measures of cardiovascular health because increased arterial stiffness has been associated with greater mortality and CVD events in healthy adults after controlling for traditional cardiovascular risk factors. This study analyzes the association between assessment of short-term and long-term air pollutant exposures and measurements of arterial function at baseline and after about 10 years of follow-up in the Multi-Ethnic Study of Atherosclerosis (MESA), a cohort initially free of clinical CVD.

Methods and Results: Arterial function measures from participants from the Multi-Ethnic Study of Atherosclerosis were assessed in 2000-2002 (Exam 1) and again in 2010-2012 (Exam 5). Arterial function measures included Pressure Time Constant 1 (PTC1) and 2 (PTC2) values, derived from the diastolic pressure decay waveform collected via radial tonometry, and distensibility coefficient (DC) and Young's Elastic Modulus (YEM) at the carotid artery, collected via carotid artery ultrasound. We used a linear mixed model to measure 1) the

association between long-term air pollution at Exam 1 with cross-sectional measurements of arterial function at Exams 1 and 5, and 1) the association between long-term air pollution during the follow-up period and rate of change in arterial function between Exams 1 and 5. We used a linear mixed model to examine the association between short-term air pollution (on the day of, one day before, and two days before the measurement of arterial function) and cross-sectional measurements of arterial function at Exams 1 and 5.

We found that a one interquartile (IQR) increase in annual average exposure to NOx during year 2000 (IQR= 44.5 ppb) was associated with a 0.220 $(seconds*10)^{-1}$ decrease in PTC1 (95% confidence interval (CI): -0.437 to -0.003) measured at Exam 1 (less arterial elasticity). There were no statistically significant associations between long-term air pollutant exposures and the rate of change in any of the arterial function measures. We also found associations between increased short-term air pollution exposure with smaller cross-sectional measurements of arterial elasticity, assessed by PTC2 and DC, and with larger cross-sectional measurements of arterial stiffness, assessed by YEM.

Conclusions: We found evidence that greater long-term traffic related air pollution measured at the baseline exam was associated with less arterial elasticity based on cross-sectional measurement of PTC1 at baseline. However, these findings do not support our original hypothesis that long-term air pollution is associated with rate of change in arterial function measures. We also found evidence that increased acute exposure to fine particulate air pollution, ranging from the day of, one day before, or two days before cross-sectional measurements of

arterial function at both exams, was associated a reduction in arterial elasticity and an increase in arterial stiffness. Future research using estimates of indoor exposure to air pollution and other arterial stiffness measures that have a stronger association with the occurrence of clinical CVD events, such as aortic pulse wave velocity, can help provide additional information on how arterial stiffness may be mechanism for the association between air pollution and CVD events.

4.2 Introduction

Many studies have shown an association between $PM_{2.5}$, particulate matter with diameter of less than 2.5 micrometers in aerodynamic diameter, and CVD events (Dockery et al. 1993; Miller et al. 2007; Pope 3rd et al. 2004). However, the exact biological mechanism linking particulate matter exposure to CVD events remains unclear.

Altered arterial function, assessed via arterial stiffness or arterial elasticity, may be part of the mechanism linking air pollution to CVD events. Previous research studies found that increased arterial stiffness is an independent predictor of mortality and cardiovascular disease events in hypertensive (S Laurent et al. 2003) and healthy adult populations (F. U. Mattace-Raso et al. 2006; Charalambos Vlachopoulos, Aznaouridis, and Stefanadis 2010). Cross-sectional studies have found that increased short-term air pollution exposure is associated with increased arterial stiffness. The lag time between exposure and measurement of stiffness has varied from 10 minutes (Lundback et al. 2009), to several hours (Fang et al. 2008; C. Wu et al. 2010), and even the next day after air pollution exposure is measured (Fang et al. 2008; C.-F. Wu et al. 2016; Mehta et al. 2013). Results from studies evaluating the association of increased long-term air

pollution with arterial stiffness have been mixed (Iannuzzi et al. 2010; Lenters et al. 2010; Jiang et al. 2016; M S O'Neill et al. 2011).

Our study, nested within the Multi-Ethnic Study of Atherosclerosis (MESA), provides additional data on the relationship between long-term exposure to $PM_{2.5}$ and NO_X with arterial function using an improved air pollution exposure model compared to previous studies. A previous study of air pollution and arterial function measures from MESA study participants utilized a space-time exposure model incorporating levels of various different pollutants, temperature and airport visibility data, and population density data.(Marie S. O'Neill et al. 2011) Our spatio-temporal exposure model utilizes cohort-specific fixed and individual-level monitoring data, in addition to a large set of geographic covariates to improve prediction of exposure to $PM_{2.5}$ and NO_x. The same previous study examined the effects of long-term air pollution on C1 and C2, which are measures of systemic arterial elasticity collected via radial tonometry, and carotid distensibility (CD) and Young's modulus (YM) at the carotid artery collected via carotid ultrasound. Our study also includes four different arterial function measures to capture varied aspects of the arterial system potentially affected by air pollution: Pressure Time Constant 1 (PTC1) and Pressure Time Constant 2 (PTC2), measures of systemic arterial elasticity, which were collected via radial tonometry, and Distensibility Constant (DC) and Young's Elastic Modulus (YEM) at the carotid artery, measures of local elasticity, collected via carotid ultrasound. This is the first study that we know of that has examined the association between air pollution with PTC1 and PTC2. Details on the advantages of PTC1 and PTC2 compared to C1 and C2 are explained in the Introduction chapter.(Page 33)

Another important feature of the MESA study is that we have arterial function data at two different time points, the baseline exam and a follow-up exam roughly ten years later. This data allows us to examine the association between long-term air pollution and rates of longitudinal change in arterial function measures. To our knowledge, no previous study has examined the association between long-term air pollution and longitudinal change in arterial function measures. We believe that exploring the connection between air pollution and rate of change in arterial stiffness can provide key insights on potential mechanisms that air pollution is leading to greater risk of CV events.

4.3 Methods

4.3.1 Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is an ongoing longitudinal study funded by the National Heart Lung and Blood Institute (Bild et al. 2002). Participants did not have clinical CVD at enrollment and were recruited from six field centers in the United States. 6,814 men and women between the ages of 45 to 84 years participated in MESA's initial clinic visit (Exam 1), which was completed from July 2000 to August 2002. Follow-up data comes from the fifth exam (Exam 5), which was completed from April 2010 to February 2012. This study was approved by the Institutional Review Boards of all MESA study sites and all participants gave their informed consent.

Of 6,587 participants with radial tonometry measures from either Exam 1, Exam 5 or both Exam 1 and 5, only 2,841 unique participants had baseline and longitudinal measures of long-term $PM_{2.5}$ pollution and covariate data for the most fully adjusted model (Model 3). Of 3,363 participants with carotid ultrasound measures from either Exam 1, Exam 5 or both Exam 1 and 5,

only 2,971 unique participants had baseline and longitudinal measures of long-term $PM_{2.5}$ pollution and covariate data for the most fully adjusted model (Model 3).

The proportion of MESA Exam 1 participants with radial tonometry raw waveform data, and those with carotid ultrasound imaging data were similar for NOx air pollution analyses. The Appendix chapter contains details on the participants included in the $PM_{2.5}$ and NOx air pollution analyses for the radial tonometry and carotid ultrasound populations.(Page 312)

4.3.2 Data collection

Age, race/ethnicity (Caucasian, African-American, Hispanic, Chinese-American), sex, and smoking status were obtained by self-report. Weight and height was measured during the exam. Body mass index was calculated as weight (kg) divided by height squared (m^2). Resting seated systolic and diastolic blood pressure were measured three times using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida), with the average of the last 2 measurements used for all analyses. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive medication. Heart rate (beats per minute) was monitored and recorded at the time of the magnetic resonance imaging (MRI) exam. Use of blood pressure medication and use of cholesterol lowering medication were assessed using standardized questionnaires and by examining medication containers.

A central laboratory (University of Vermont, Burlington) measured concentrations of total cholesterol, high density lipoprotein cholesterol, triglycerides, plasma glucose, and high-sensitivity C-reactive protein obtained after 12-hours of fasting. Diabetes was defined as having fasting plasma glucose greater or equal to 126 mg/dL (7.0 mmol/L) based on the 2003 American Diabetes Association criteria for diagnosis of diabetes(S Genuth et al. 2003).

4.3.3 Diastolic pulse contour analysis (PTC1 and PTC2)

Pressure time constant 1 and 2 (PTC1 and PTC2) were calculated from the radial artery blood pressure waveform. The radial artery pressure waveform is a non-invasive method to measure blood pressure throughout the cardiac cycle (Nichols, O'Rourke, and Vlachopoulos 2011b). We obtained the radial artery blood pressure waveform by applanation tonometry using HDI/PulseWave CR-2000 (Hypertension Diagnostics, Inc., Eagan, Minnesota) during the baseline examination (Exam 1) and using Millar Mikro-Tip Pulse Transducer (Millar Instruments, Houston, Texas) during Exam 5. For both Exams 1 and 5, a solid-state pressure transducer array, also called a radial tonometer, was placed over the radial artery of the dominant arm to record the pulse contour. A 30-second analog tracing of the radial waveform, constituting continuous pressure changes during diastole, was digitized at 200 samples per second. All cardiac cycles from each set of 30 seconds data collection were analyzed. In Exam 1, only one set of waveforms was collected. For Exam 5, two to three sets of waveforms were collected.

We analyzed a portion of the waveform, beginning from the time of maximum pressure to the end of the waveform. We used standard nonlinear regression methods to fit a model to the

pressure decay waveform occurring during each heartbeat. Our model contained an intercept, an exponential term, and a exponentially dampened cosine term.

We calculated the weighted mean of all PTC1 and PTC2 values for one set of waveforms during Exam 1 for each participant. We also calculated the weighted means of all PTC1 and PTC2 values for two to three sets of waveforms during Exam 5 to produce PTC1 and PTC2 values for each participant. Throughout the remainder of this paper, we refer to the weighted mean of PTC2 as "PTC2" and the weighted mean of PTC1 as "PTC1." The units for the weighted mean of PTC2 is $(seconds*100)^{-1}$. The units for the weighted mean of PTC1 is $(seconds*10)^{-1}$.

4.3.4 Distensibility coefficient (DC) and Young's elastic modulus (YEM) of the right common carotid artery

Distensibility coefficient (DC) and Young's elastic modulus (YEM) were measured using B-mode ultrasound at the distal right common carotid artery with a Logiq 700 machine (General Electric Medical Systems, Milwaukee, WI). This method has been described previously (Gepner et al. 2014). Repeated measures of the brachial blood pressure measurement were made on the right arm using the automated upper arm sphygmomanometer (Dinamap Pro 100; Critikon, Inc., Tampa, FL) after ten minutes of rest in the supine position and before the carotid artery ultrasound was acquired. The largest and smallest diameters during the cardiac cycle were classified as the systolic and diastolic diameters, respectively. Access Point Web version 3.0 (Freeland Systems, Westminster, CO) was used to measure internal and external artery diameters. Distensibility coefficient (DC) at the carotid artery was calculated as the relative change in the cross-sectional area of the carotid artery divided by the pulse pressure at the

brachial artery [$(mmHg*1000)^{-1}$]. Young's elastic modulus (YEM) at the carotid artery was calculated as circumferential stress divided by the circumferential strain on the arterial wall (mmHg).

4.3.5 Air pollution exposure model

Researchers at the MESA Air Pollution study (MESA Air) designed spatiotemporal air pollution exposure models to estimate outdoor $PM_{2.5}$ ($\mu g/m^3$) and NOx concentrations (ppb). Models were developed for each of the six metropolitan areas in the MESA Air study to predict pollutant concentrations from 1999 to 2012 in two-week averages (Keller et al. 2015). The exposure models utilized air quality monitoring data from the U.S. Environmental Protection Agency (EPA) Air Quality System (AQS). The exposure models also included data from three different types of supplementary air monitoring conducted by the MESA Air Study: 1) participants' homes for one to three times during different seasons, 2) fixed sites in the MESA Air Study cities during a four-year sampling period, 3) "snapshot sites" in MESA Air cities which were often located near sources of air pollution such as major roadways during three 2-week time periods during different seasons. This model also incorporated key geographic covariates such as proximity measures (ie. distance to nearest major road) and buffer measures (ie. land use category, population density, and emission sources). MESA Air utilized likelihood-based statistical methods to adapt to the irregular nature of the monitoring data (ie. different time periods and spatial locations) and to utilize all available monitoring results.

Keller and colleagues found that the predictive accuracy of the spatiotemporal models for all six metropolitan areas for both $PM_{2.5}$ and NOx were good to excellent (Keller et al. 2015). This

study defined good accuracy to a cross-validation R^2 greater than 0.8 and excellent accuracy to be cross-validation R^2 of greater than 0.9. For home sites, this study used 10-fold cross-validation, which involved leaving one-tenth of the data out for each round. For AQS and fixed sites, this study used leave-one-out cross-validation. For snapshot sites, this study used 10-fold cross-validation, in which monitors from the same cluster were left out together. This study compared the predictions of pollutant concentrations generated from models utilizing the left-in data with the pollutant concentrations measured at the left-out monitoring sites.

4.3.6 Long-term air pollution variables

Outdoor $PM_{2.5}$ and NOx exposure estimates for the year 2000 at participants' addresses at baseline were calculated by averaging 2-week estimates over the year 2000. Year 2000 estimates may reflect chronic, long-term exposure before the start of the study, especially if the participant has rarely moved. About 65% of MESA participants did not move from the beginning of 1990, which was roughly 10 years prior to the start of the MESA study.

We also estimated average outdoor $PM_{2.5}$ and NOx exposure between Exams 1 and 5 at the MESA participant's address(es) by averaging the 2-week estimates between Exam 1 (approximately year 2000) and Exam 5 (approximately year 2010). We considered this exposure estimate to be "longitudinal" $PM_{2.5}$ and NOx exposure representing a participant's exposure during follow-up.

4.3.7 Short-term air pollution exposure

Short-term $PM_{2.5}$ pollutant exposures were based on data collected by Air Quality System (AQS) monitors in each city. We did not use estimates from the spatiotemporal model because the smallest time resolution for this model was two weeks. The average daily exposure to $PM_{2.5}$ was calculated for the day of, one day before, and two days before the Exam 1 or Exam 5 radial tonometry or carotid ultrasound exam. For our analysis, we used residuals of the short-term $PM_{2.5}$ exposure that were pre-adjusted for seasonal variability. We conducted this pre-adjustment to ensure that effects we saw on arterial stiffness were related to $PM_{2.5}$ exposure and not other factors such as temperature or humidity (Szpiro et al. 2014). To generate these pre-adjusted $PM_{2.5}$ exposures, we created a prediction model that included basis splines (b-splines) for temperature, humidity (6 degrees of freedom per year for each variable), and calendar time (12 degrees of freedom per year), and with categorical adjustment for day of week.

We evaluated pre-adjusted $PM_{2.5}$ exposure on the day of the exam, one day before the exam, and two days before the exam.

4.3.8 Statistical analysis

4.3.8.1 Linear mixed effects model: long-term air pollution and arterial stiffness

We utilized a linear mixed effects model to look at the association between long-term air pollution variables with cross-sectional measurements of arterial function and change in arterial function between Exam 1 and Exam 5 (Gassett et al. 2015).

Here is the linear mixed effects model for participant *"i"* at exam *"v"*,:

$Y_{jv} = [\alpha_o + X_{io} * \alpha_1 + a_i] + [t * \beta_0 + t * W_{iv} * \beta_1] + [\varepsilon_{iv}]$

Where Y_{jv} = arterial stiffness measurement for participant *i* at exam *v*.

α_o = average arterial stiffness measurement at exam 1 for participants in reference group, which I described in the preceding paragraph.

X_{io} =cross-sectional confounders and cardiovascular risk factors at Exam 1 for participant *i* that are time-invariant. These include annual average air pollution exposure during year 2000.

α_1 = coefficient for association between CV risk factor or confounder and arterial stiffness at exam 1 (including annual average air pollution exposure during year 2000)

a_i = participant-specific random intercept

W_{iv} = possibly time-varying longitudinal confounders and risk factors at exam *v* for participant *i*. These include annual average air pollution exposure during the time period between Exams 1 and 5, rounded to the nearest whole year.

t= time in years from Exam 1 for participant *i*

t=0 for arterial measures at Exam 1

t=time in years between Exam 1 and 5 radial tonometry exams for PTC2 and PTC1 measures or Exam 1 and 5 carotid ultrasound exams for DC and YEM measures

β_0= coefficient for association between CV risk factor and annual rate of change in arterial function measures for participants in the reference group, which I described later in this section.

β_1 = coefficients for association between CV risk factor (such as annual average air pollution between Exams 1 and 5) and annual rate of change in arterial function measures.

ε_{iv} = error associated with Y_{iv}

The first term in the model used baseline $PM_{2.5}$ exposure and baseline cardiovascular risk factors to estimate the arterial function at Exam 1. Thus, this first term examines the cross-sectional relationships between baseline $PM_{2.5}$ exposure and arterial function at Exam 1.

The second term in the model uses longitudinal $PM_{2.5}$ exposure, baseline cardiovascular risk factors, and time-varying cardiovascular risk factors to estimate the change in arterial function between Exams 1 and 5. We used a fixed slope, in which a coefficient for the average rate of

change in arterial stiffness was the same for all participants. We also used a participant-specific random intercept, in which each participant was allowed to have a different arterial stiffness value at baseline. With this second term, we examined the relationship between longitudinal $PM_{2.5}$ exposure, quantified by annual average $PM_{2.5}$ exposure between Exams 1 and 5, and rate of change in arterial function between Exams 1 and 5. We were interested in seeing if annual average $PM_{2.5}$ exposure between Exams 1 and 5 affected the rate of change in arterial function measures over the follow-up period between Exams 1 and 5.

These analyses were also repeated using annual average exposure to NOx during year 2000 for the first term and annual average exposure to NOx between Exams 1 and 5 as the second term in the same linear mixed effects model.

As a sensitivity analysis, we also examined if baseline $PM_{2.5}$ exposure, quantified by annual average exposure to $PM_{2.5}$ during year 2000, was associated with rate of change in arterial function between Exams 1 and 5. We also repeated this analysis using baseline NOx exposure, quantified by annual average exposure to NOx during year 2000, was associated with rate of change in arterial function between Exams 1 and 5.

We centered all continuous variables by subtracting the mean value of each variable. Thus, the reference group were participants with mean age, heart rate, body mass index, total cholesterol, HDL cholesterol, triglycerides, CRP, SBP for radial tonometry measures and MAP for carotid ultrasound measures.

Interpretation of β_1 depends on the arterial stiffness measure being examined. With aging, we expect arterial elasticity to decrease and arterial stiffness to increase over the follow-up time. For PTC2, PTC1, and DC, we hypothesized a decline in these arterial elasticity measures over time (negative rate of change in arterial elasticity variable). Thus, a positive β_1 for PTC2, PTC1, and DC means that the change in elasticity has slowed or decelerated (smaller decline). A negative β_1 for PTC2, PTC1, and DC means that change in elasticity has been accelerated (larger decline). For YEM, we hypothesized an increase in this arterial stiffness measure over time (positive rate of change in arterial elasticity variable). A positive β_1 for YEM means that the change in stiffness has been accelerated (larger increase). A negative β_1 for YEM means that the change in stiffness has slowed or decelerated (smaller increase).

Three separate analyses for each air pollution and outcome measure were completed. In the first, we adjusted for time-varying age, sex, race/ethnicity, site (one of the six metropolitan areas in MESA Air). In the second, our primary analysis model, we adjusted for the covariates in Model 1 plus the following variables at Exam 1: body mass index (BMI), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, diabetes mellitus status (yes/no), annual gross family income in the past 12 months, highest educational level completed, and high sensitivity c-reactive protein. Model 2 also adjusted for the following variables as time-varying covariates for Exams 1 and 5: smoking status (never smoked, ever smoked, current smoker), use of lipid lowering medication (yes/no), and heart rate. We also completed a third exploratory analysis adjusted for the covariates in Model 2 plus the following variables as time-varying covariates: systolic blood pressure (SBP) for PTC2 and PTC1, mean arterial pressure (MAP) for DC and

YEM, use of blood pressure medication (yes/no). The third model is exploratory because we were concerned that blood pressure measures and use of blood pressure medication variables might be mediating variables in the association between air pollution and arterial stiffness. Thus, adjusting for blood pressure measures and use of blood pressure medication variables might eliminate a valid association between air pollution and arterial function measures.

4.3.8.2 Linear mixed effects model: short-term air pollution and arterial stiffness

We utilized a linear mixed effects model to look at the association between short-term air pollution variables and cross-sectional measurements of arterial function at Exams 1 and 5.

Here is the linear mixed effects model for participant *"i"* at exam *"v"*:

$$Y_{jv} = \alpha_o + [X_{io} * \alpha_1 + a_i] + [\varepsilon_{iv}]$$

Where Y_{jv} = arterial stiffness measurement for participant *i* at exam *v*,

α_o = average arterial stiffness measurement at Exam 1 for participants in reference group, which I describe later in this section.

X_{io} =cross-sectional and time-varying confounders and cardiovascular risk factors at exam *v* for participant *i*. These include daily average $PM_{2.5}$ exposure on the day of, one day before, or two days before exam *v*.

α_1 = coefficient for association between CV risk factor or confounder and arterial stiffness at exam *v* (including daily average $PM_{2.5}$ exposure on the day of, one day before, or two days before exam v)

a_i = participant-specific random intercept

ε_{iv} = error associated with Y_{iv}

The first term in the model is the average arterial stiffness measurement at Exam 1 for participants in the reference group. We centered all continuous variables by subtracting the mean value of each variable. Thus, the reference group was participants with mean age, heart rate, body mass index, total cholesterol, HDL cholesterol, triglycerides, CRP, SBP for radial tonometry measures and MAP for carotid ultrasound measures.

The second term in the model uses short-term $PM_{2.5}$, baseline cardiovascular risk factors, and time-varying cardiovascular risk factors to estimate the arterial function measures at Exams 1 and 5. We used a fixed slope, in which a coefficient for the average change in arterial stiffness

was the same for all participants. We also used a participant-specific random intercept, in which each participant was allowed to have a different arterial stiffness value at baseline. With this second term, we examined the relationship between short-term $PM_{2.5}$ exposure and cross-sectional measurements of arterial function at Exams 1 and 5.

Interpretation of α_1 depends on the arterial stiffness measure being examined. With aging, we expect arterial elasticity to decrease and arterial stiffness to increase over the follow-up time. For PTC2, PTC1, and DC, a positive α_1 for PTC2, PTC1, and DC means that the arterial elasticity has increased (lower stiffness). A negative α_1 for PTC2, PTC1, and DC means that arterial elasticity has decreased (higher stiffness). For YEM, a positive α_1 for YEM means arterial stiffness has increased (lower elasticity). A negative β_1 for YEM means that arterial stiffness has decreased (higher elasticity).

Three separate analyses for each short-term air pollution and arterial function measure were completed. In the first model, we adjusted for time-varying age, sex, race/ethnicity, site (one of the six metropolitan areas in MESA Air). In the second, our primary analysis model, we adjusted for the covariates in Model 1 plus the following variables at Exam 1: body mass index (BMI), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, diabetes mellitus status (yes/no), annual gross family income in the past 12 months, highest educational level completed, and high sensitivity c-reactive protein. Model 2 also adjusted for the following variables as time-varying covariates for Exams 1 and 5: smoking status (never smoked, ever smoked, current smoker), use of lipid lowering medication (yes/no), and heart rate. In the third,

exploratory analysis, we adjusted for the covariates in Model 2 plus the following variables as time-varying covariates: systolic blood pressure (SBP) for PTC2 and PTC1, mean arterial pressure (MAP) for DC and YEM, use of blood pressure medication (yes/no). Our reasoning for adjusted for blood pressure measures and blood pressure medication in the exploratory model was the same as the reasoning followed in the long-term air pollution analyses.

4.4 Results

4.4.1 Participant characteristics

Table 4.1 shows the baseline characteristics of: 1) all MESA participants; 2) participants included in Model 3 analysis of long-term $PM_{2.5}$ air pollution with radial tonometry measures (PTC2 and PTC1); 3) participants included in Model 3 analysis of long-term $PM_{2.5}$ air pollution with carotid ultrasound measures (DC and YEM).

The average time in between Exams 1 and 5 was similar for participants included in the analyses of $PM_{2.5}$ pollution with radial tonometry measures and carotid ultrasound measures. Participants included in the analyses of $PM_{2.5}$ with radial tonometry and carotid ultrasound measures compared to all MESA participants at Exam 1 also had similar BMI, heart rate, DBP, MAP, total cholesterol, HDL cholesterol, and c-reactive protein. These groups also had similar proportions of gender groups and proportion of those taking lipid-lowering medication at baseline.

However, participants included in the analyses of long-term $PM_{2.5}$ with radial tonometry and carotid ultrasound measures compared to all MESA participants at Exam 1 were slightly

younger, more educated, had higher annual gross family income, had slightly lower baseline SBP, had a lower prevalence of anti-hypertension medication use, had a lower prevalence of diabetes, were less likely to be current smokers, and had slightly lower triglycerides levels at baseline. Compared to all MESA participants, participants included in the analyses of long-term $PM_{2.5}$ exposure with radial tonometry and carotid ultrasound arterial function measures were slightly more likely to be Chinese and less likely to be Hispanic. Participants included in the analyses of long-term $PM_{2.5}$ exposure with radial tonometry and carotid ultrasound arterial function measures also tended to be located in New York, NY and Chicago IL, with a lower proportion of participants being from Baltimore, MD and Los Angeles, CA.

Baseline characteristics for MESA participants included in the analyses of long-term $PM_{2.5}$, long-term NOx, and short-term $PM_{2.5}$ exposure with radial tonometry and carotid ultrasound measures were generally similar to each other (Table 4.7,

Table 4.8, Table 4.9). Compared to all MESA participants, participants included in analyses of short-term $PM_{2.5}$ exposure with radial tonometry and carotid ultrasound measures had slightly larger proportions of participants who were Chinese and Hispanic.

4.4.2 Arterial function and air pollution measures

Table 4.2 shows the descriptive characteristics of the arterial function measures in this analysis, including PTC2, PTC1, DC, and YEM. The mean values of PTC2, PTC1, and DC were higher at

Exam 1 compared to Exam 5, indicating a drop in arterial elasticity over time. The mean values of YEM were lower at Exam 1 compared to Exam 5, which indicates an increase in arterial stiffness over time.

Table 4.3 shows the annual average $PM_{2.5}$ and NOx concentrations for year 2000 and between Exams 1 and 5 (roughly between years 2000 and 2010) for MESA participants which had radial tonometry measures for Exams 1 and 5. Table 4.12 is the corresponding table for MESA participants that had carotid ultrasound measures for Exams 1 and 5.

Table 4.6 shows the characteristics of the short-term $PM_{2.5}$ concentrations for MESA participants that had radial tonometry measures at Exams 1 and/or 5. Table 4.13 is the corresponding table for MESA participants that had carotid ultrasound measures for Exams 1 and/or 5.

4.4.3 Association between long-term air pollution and arterial stiffness

In the cross-sectional portion of our linear effects model, adjusting for Model 2 covariates, we did not find any association between annual average $PM_{2.5}$ exposure for year 2000 and any of our arterial stiffness measures at Exam 1 (PTC1, PTC2, DC, YEM) (Table 4.4). For the rate of change portion of our linear mixed effects model, adjusting for Model 2 covariates, we also found no association between annual average $PM_{2.5}$ exposure between Exams 1 and 5 and the rate of change between Exams 1 and 5 in any of our arterial stiffness measures (Table 4.4).

In the cross-sectional portion of our linear effects model, we did not find any association between annual average NOx exposure for year 2000 and three of our arterial stiffness measures at Exam 1 (PTC2, DC, YEM) (Table 4.5). However, we found that an IQR change in outdoor NOx in year 2000 (IQR=44.5 ppb) was associated with a 0.220 $(seconds*10)^{-1}$ decrease in PTC1 at Exams 1 or 5 (95% CI: -0.437, -0.003). For the rate of change model, we also found no association between annual average NOx exposure between Exams 1 and 5 and the rate of change between Exams 1 and 5 in any of our arterial stiffness measures (PTC1, PTC2, DC, YEM).

The results for the association between outdoor $PM_{2.5}$ and NOx air pollution with arterial stiffness measures at Exams 1 and 5 using additional covariate adjustment models (Models 1 and 3) are found in Table 4.14 (PTC2), Table 4.15 (PTC1), Table 4.16 (DC) and

Table 4.17 (YEM).

In our sensitivity analyses, we found no associations between baseline $PM_{2.5}$ exposure and rate of change between Exams 1 and 5 in any of our arterial stiffness measures (PTC1, PTC2, DC, and YEM; Data not shown). We also did not find any associations between baseline NOx exposure

and rate of change between Exams 1 and 5 in any of our arterial stiffness measures (Data not shown).

4.4.4 Short-term air pollution and arterial stiffness

We found that a 5 microgram/m^3 increase in daily average $PM_{2.5}$ exposure one day before the radial tonometry exam was associated with a -0.068 $(seconds*100)^{-1}$ decrease in PTC2 (95% CI: -0.134, -0.002) at Exams 1 and 5 (

Table 4.7). We also found an association between increased daily average $PM_{2.5}$ exposure two days before the radial tonometry exam and decreased PTC2 at Exams 1 and 5. A 5 microgram/m^3 increase in daily average $PM_{2.5}$ exposure two days before the carotid ultrasound exam was associated with a -0.030 $(mmHg*1000)^{-1}$ decrease in DC (95% CI: -0.055, -0.004) at Exams 1 and 5. For reference, we observed a 0.04 $(mmHg*1000)^{-1}$ per year decrease in DC for MESA participants before adjustment for cardiovascular risk factors. For YEM, we observed consistent associations between increased daily average exposure to $PM_{2.5}$ on the day of, one day before, and two days before the carotid ultrasound exam with increases in YEM at Exams 1 and 5. For example, we observed that a 5 microgram/m^3 increase in daily average $PM_{2.5}$ exposure on the day of the carotid ultrasound exam was associated with a 30.30 mmHg increase in YEM (95% CI: 2.74, 57.85) at Exams 1 and 5. However, we did not find any associations between daily average exposure to $PM_{2.5}$ and PTC1 at Exams 1 and 5.

The results for the association between short-term daily average outdoor $PM_{2.5}$ air pollution with arterial function measures at Exams 1 and 5 using additional covariate adjustment models (Models 1 and 3) are found in Table 4.18 (PTC2), Table 4.19 (PTC1), Table 4.20 (DC) and Table 4.21 (YEM).

4.5 Discussion

We had a rare opportunity to study potential effects of long-term air pollution on arterial function in a multi-ethnic population of older adults over a follow-up time of about ten years. To our knowledge, there have been no previous studies published on the association between air pollution and rate of change in arterial function measures (stiffness or elasticity). We did not find an association between annual average exposure to $PM_{2.5}$ between Exams 1 and 5 with rate of change in any of the arterial function measures. In addition, there was no association between annual average exposure to NOx between Exams 1 and 5 with rate of change in any of the arterial function measures. We did, however, find that increased annual average exposure to NOx during the year 2000 was associated with lower arterial elasticity, assessed by measuring PTC1 at Exam 1. The NOx concentration during year 2000 represents traffic-related air pollution at the baseline exam. For the 65% of MESA participants that did not move between 1990 and 2000, NOx concentration during year 2000 may also represent chronic exposure to traffic-related air pollution before the MESA study began.

Similar to our finding that increased NOx was associated with decreased PTC1 (arterial elasticity) in our cross-sectional analysis, other studies have also found associations between increased long-term air pollution and decreased arterial elasticity (or increased arterial stiffness).

Iannuzi and colleagues observed that closer residential proximity to major roadway was associated with increased carotid arterial stiffness in a cross-sectional study (n=52) of children in a small Italian town(Iannuzzi et al. 2010) . Lenters and colleagues found that increased long-term exposure to gaseous pollutants, NO_2 and SO_2, was associated with increased aortic PWV (increased arterial stiffness, n=524) and increased AIx (indirect measure of arterial stiffness, n=729) in participants from the Atherosclerosis Risk in Young Adults study, a prospective cohort study in the Netherlands(Lenters et al. 2010) . In a cross-sectional study in Shanghai (n=371), Jiang and colleagues also observed that participants living closer to a major road had higher average personal $PM_{2.5}$ exposure levels and higher augmentation index measurement (AIx) than other participants living farther away from the major road.(Jiang et al. 2016)

The lack of association between $PM_{2.5}$ and the various measures of arterial function (PTC2, PTC1, DC, and YEM) is consistent with some other studies. Among participants of the Atherosclerosis Risk in Young Adults study, Lenters and colleagues did not find an association between long-term $PM_{2.5}$ exposure and aortic PWV or augmentation index(Lenters et al. 2010) . In a previous study of MESA participants, O'Neill and colleagues found no association between long-term $PM_{2.5}$ exposure and two different measures of arterial elasticity: C1, also called large artery elasticity and C2, also called small artery elasticity(Marie S. O'Neill et al. 2011) .

Our measurement of NOx, as compared to $PM_{2.5}$, may have better characterized traffic-related air pollution. The mixture of pollutants associated with traffic related air pollution and quantified by NOx may specifically affect arterial function, as measured by PTC1. Ambient NOx itself does

not appear to have adverse effects, but the $PM_{2.5}$ near roads, which may be measured by traffic-related air pollutants, may be at higher concentrations or may be more toxic than ambient $PM_{2.5}$ (Ayres 1998; Sanderson et al. 2005). NO_x has been established as a particularly good proxy for traffic-related air pollutants in various settings and may better capture intraurban variability in exposure than ambient $PM_{2.5}$(Singer et al. 2004; Minguillón et al. 2012).

These findings show some support for the hypothesis that long-term traffic-related air pollution decreases arterial elasticity. The association between increased annual average concentration of NOx in year 2000 and decreased PTC1 may reflect the effect of traffic-related air pollution on overall elasticity in the arterial system. In our previous chapter, we found that decreased PTC1 was associated with increased risk of all CVD events among MESA participants during follow-up. Therefore, we hypothesize that decreased PTC1 might be part of a biological pathway by which traffic-related air pollution increases risk of all CVD events. We were surprised that we found no association between NOx and PTC2, since increased PTC2 is associated with lower risk of all CVD, CHF, and CHD events. Perhaps, there was no association between NOx with DC and YEM because those carotid ultrasound measures are capturing only local arterial stiffness effects at the carotid artery. In the previous chapter of this dissertation, we did not find an association between decreased DC and increased risk of CVD events, nor did we find an association between increased YEM and increased risk of CVD events.

In our analysis of the effects of short-term air pollution exposure on arterial function, we did not find any associations between short-term $PM_{2.5}$ measurements and cross-sectional measurements

of PTC1. However, we observed several different associations between short-term $PM_{2.5}$ measurements and cross-sectional measurements of PTC2, DC and YEM. We found associations between increased daily average $PM_{2.5}$ concentration one day before the radial tonometry exam and decreased PTC2 measured at Exams 1 and 5. We also saw increased daily average $PM_{2.5}$ exposure two days before the carotid ultrasound exam associated with decreased DC (lower arterial elasticity) measured at Exams 1 and 5. We observed increased daily average $PM_{2.5}$ exposure on the day, one day before, and two days before the carotid ultrasound exam and increased YEM (higher arterial stiffness) measured at Exams 1 and 5.

These results provide some evidence that acute exposure to particulate air pollution was associated with reduction in arterial elasticity (PTC2 and DC) and increase in arterial stiffness (YEM). We found it interesting that daily average $PM_{2.5}$ concentrations were associated with measures characterizing systemic arterial elasticity (PTC2) and two measures characterizing local arterial elasticity (DC) and local arterial stiffness (YEM) at the carotid artery. Perhaps each of these measures are capturing specific aspects of systemic and local elasticity affected by air pollution that PTC1 does not have. Of the two radial tonometry measures, PTC2 may more strongly reflect the behavior of the small arteries, since it is more strongly correlated with C2. Among the two carotid ultrasound measures, DC may show more of the elastic behavior of the carotid artery. DC represents change in cross-sectional area given pressure change during cardiac cycle of the carotid artery. YEM reflects the composition and quality of the arterial wall material in the carotid artery itself. YEM measures how stiff and resistant the arterial wall material is to expanding the artery's lumen (circular cross-section) in response to blood flow through the carotid artery.

There are previous studies that also show relationships between short-term air pollution exposures and subsequent changes in measures correlated with greater arterial stiffness. In a panel study (n=26), Fang and colleagues found that among welders that were exposed to 2 consecutive days of welding fumes, measured levels of $PM_{2.5}$ from the welding fumes were associated with increased greater augmentation index during the afternoon after their second day of exposure(Fang et al. 2008). In a small study of healthy volunteers (n=12), Lundbaeck and colleagues observed that participants exposed to diesel exhaust showed increases in augmentation pressure and augmentation index ten minutes after exposure to diesel exhaust compared to those only exposed to filtered air (Lundback et al. 2009). Augmentation pressure and augmentation index are two measures reflecting the effects of arterial stiffness. In a small study of mail carriers in Taiwan (n=17), Wu and colleagues found that increases in the interquartile region of personal exposure to particulate matter measured by personal samplers carried while delivering mail outdoors was associated with increases in cardio-ankle vascular index (CAVI), a measure of arterial stiffness (C. Wu et al. 2010).

The associations between increased daily average exposure of $PM_{2.5}$ one to two days before the measurement of arterial function and lower arterial elasticity measured by PTC2, DC, and YEM in our analysis were similar to other studies looking at lag times between air pollution exposure and measurement of arterial stiffness (or its correlates). In a study of participants from the Veterans Affairs Normative Aging Study which includes elderly men in Boston, Massachusetts (n=370), increases in the interquartile range (IQR) of the 3-day average exposures to $PM_{2.5}$ were associated with increases in augmentation index and augmentation pressure.(Mehta et al. 2013)

In a study of healthy adults working at a bank in Taiwan (n=89), Wu and colleagues also found that increases in $PM_{2.5}$ exposure were associated with increases in brachial-ankle pulse wave velocity (baPWV) with 0-day and 1-day lags between exposure and PWV measurement.(C.-F. Wu et al. 2016). In this study conducted in Taiwan, $PM_{2.5}$ exposure was assessed via land use regression models or land use regression models plus indoor air sampling.

There are significant limitations to comparing results from our analysis to previous studies using different arterial function measures. For example, augmentation pressure and augmentation index show the effects of arterial stiffness, but are not direct measures of arterial stiffness. The stiffening of arteries causes forward and reflected waves to have increased velocity. Thus, the reflected wave to arrive at the central aorta earlier. Augmentation pressure is the difference between first and second systolic peaks measured in mmHg(Lundbäck et al. 2009). Augmentation index is augmentation pressure as a percentage of pulse pressure. Early reflection of the waves, and thus increased arterial stiffness, results in an increase in augmentation index and augmentation pressure. In addition, brachial ankle pulse wave velocity and cardio-ankle vascular index both are measures of arterial stiffness that focus on specific areas of the arterial system. Cardio-ankle vascular index (CAVI) represents the stiffness of the aorta, femoral artery and tibial artery.(Shirai et al. 2006) CAVI is also designed to be independent of blood pressure. Brachial-ankle pulse wave velocity (baPWV) measures the speed of the pulse wave in the brachial-ankle segment of the arterial system.(Tsuchikura et al. 2010) Greater baPWV signifies greater arterial stiffness. Greater baPWV has been correlated with greater aortic (carotid-femoral) PWV, which represents central arterial stiffness and is considered the "gold standard" measure of arterial stiffness.(Sugawara et al. 2005)

We saw cross-sectional associations between long-term exposure to NOx and PTC1 at Exam 1, as well as short-term exposure to $PM_{2.5}$ with PTC2, DC, and YEM. However, we saw no association between long-term exposure to $PM_{2.5}$ or NOx air pollution with longitudinal change in arterial function. These differences may provide clues about how arterial functional measures fit into proposed pathways connecting air pollution and CVD events. First, arterial function measures appear to be more transient and variable over time than other measures of subclinical CVD such as coronary artery calcification (CAC). We expected almost all participants to show an increase in arterial stiffness over time due to aging. Instead, a notable proportion of all four arterial function measures, ranging from 24.7% for PTC1 to 44.2% for YEM either had no change or a decrease in arterial stiffness during follow-up. Because arterial stiffness can more easily change over time, it may be more susceptible to the acute effects of air pollution.

Since arterial stiffness varies quite a bit over time, the effects of air pollution on arterial stiffness may also be more transient. Consequently, there may not be long term effects of air pollution on stiffness that are readily apparent. Instead, arterial function measures may be involved in biological pathways for associations between short-term air pollution concentrations and the triggering of CVD events. Several time-series studies have documented that short-term air pollution such as ozone, particulate matter less than 10 micrometers in aerodynamic diameter (PM_{10}), NO_2, CO, and SO_2 were associated with the triggering of myocardial infarction and ischemic stroke.(Ruidavets et al. 2005; Wellenius, Schwartz, and Mittleman 2005; Tsai et al. 2003)

Acute exposure to $PM_{2.5}$ located near roads may trigger systemic inflammation and oxidative stress, down-regulation of nitric oxide synthase, and release of endothelins(Glantz 2002; Bouthillier et al. 1998). These processes may trigger endothelial dysfunction, vasoconstriction, decreased heart rate variability, ventricular remodeling, and increased blood pressure(Robert D. Brook et al. 2002; Gold et al. 2000; Ying et al. 2009; Sørensen et al. 2003). Mixed hypertension, which is elevation in both systolic and diastolic blood pressure, elevated pulse pressure, which is the difference between systolic and diastolic blood pressure, and adverse ventricular remodeling are associated with increased arterial stiffness.

Increased arterial stiffness can have several downstream effects on the cardiovascular system that ultimately result in the cardiovascular disease events. First, increased arterial stiffness results in decreased cushioning in the arteries. As a result, there is increased systolic blood pressure and decreased diastolic blood pressure, and thus increased pulse pressure. There is minimal, reduced flow from the peripheral arteries during diastole. This leads to increased systolic blood pressure, decreased blood pressure and increased pulse pressure. Decreased diastolic blood pressure results in reduction of aortic pressure during diastole. This can lead to decreased coronary perfusion pressure and myocardial ischemia.(Michael F O'Rourke 2008) Increased pulse pressure can also lead to more turbulent blood flow and disturbances to the vessel walls. This can cause a variety of cardiovascular disease events.

Secondly, increased arterial stiffness also causes incident and reflected pulse waves to travel with greater speed. As a result, the aortic pressure and pressure to the left ventricle increases during systole(Adji, Rourke, and Namasivayam 2011). This process causes increased load to the left ventricle, and left ventricle hypertrophy. Left ventricular hypertrophy is associated with increased coronary ischemia and decreased ischemic threshold(Roman and Devereux 2006). The overworked left ventricle muscle weakens and does not pump as well. Eventually, this can lead to congestive heart failure.

Third, increased arterial stiffness also affects microvascular flow, affecting the flow to highly perfused vascular beds like those in the brain or kidney(Adji, Rourke, and Namasivayam 2011). Flow to the highly perfused vascular beds tend to be highly pulsatile. When arterial stiffness of the microvasculature increases, there is a loss in ability to cushion pulsatility of blood flow. This can predispose a person to rupture of arterial walls, micro-hemorrhages, thrombotic obstruction of tiny arteries, and microinfarcts (Michael F O'Rourke and Safar 2005). These processes can lead to greater risk of stroke.

Our study has some weaknesses. We examined two different exposures, $PM_{2.5}$ and NOx, as well as four different measures of arterial stiffness, PTC1, PTC2, DC and YEM. Thus, there is the possibility of increasing the likelihood of false positives because we are examining so many different relationships. However, we decided a priori to investigate the effects of specific risk factors, including air pollution with respect to different arterial function measures. We planned these particular comparisons before investigating the data. We also acknowledge that by using a

p-value of 0.05 or lower to establish statistical significance that we expect 5% of the values to be significant even if there is no association. This is also called having a 5% risk of false positives. Yet, since our arterial function measures are correlated, we consider this 5% risk of false positives to be very conservative and likely an overestimation of our risk of false positives. Another limitation is that we used different arterial function measures that ranged in the strength of association with clinical CVD events. Notably, DC and YEM did not show association with any of the composite CVD outcomes that we analyzed in a previous chapter. In the future, a study of long-term air pollution with aortic pulse wave velocity, which is often considered the "gold standard" or large artery stiffness, may yield results that are more informative.

We also examined the outdoor concentration of $PM_{2.5}$ and NOx as our exposure variables, instead of estimates of air pollution exposure indoors. The use of the outdoor concentration might be considered a weakness because most participants probably spend most of their time indoors (Klepeis et al. 2001). Ambient air pollution, which originates from outdoor sources, tends to be reduced as it moves indoors (Ryan Allen et al. 2003; Wallace and Williams 2005). Thus, our use of outdoor air pollution concentrations may have led to a slight overestimate of the air pollution that participants were actually exposed to. This may have led to a systematic overestimate of the effects of air pollution on arterial function measures. As part of the MESA Air study, extensive work was done to explore the calculation of an indoor air pollution exposure that would draw upon participants' time location patterns and calculation of infiltration of air pollutants into homes. It makes sense for future analyses to examine the association between indoor estimates of long-term exposure to PM2.5 and NOx and arterial function measures.

Our study has some key strengths. The MESA study includes comprehensive data important cardiovascular risk factors, allowing us to adjust for any potential confounding effects. This study also utilized a carefully designed air pollution exposure model that takes into account key sources of exposure variability (Cohen et al. 2009). It has included spatial and temporal variations in ambient concentrations and characterized within-city variability in air pollution concentrations. It incorporated data from cohort-specific exposure modeling. It has aimed to reflect traffic generated air pollutants and geographic predictors of air pollution. This approach is a marked improvement to assigning large groups of participants the same exposure based on measurements from air pollution regulatory monitors or using residential proximity to major roads as a measure of air pollution metric as has been the case in many previous studies.

4.6 Conclusion

We found no evidence that long-term air pollution affects rate of change in arterial function. However, we did observe that long-term traffic-related air pollution at the baseline exam, as measured by outdoor annual average NOx concentration in the year 2000, was associated with cross-sectional measurements of lower arterial elasticity, as measured by PTC1 at Exams 1 and 5. We also found evidence that short-term air pollution, as measured by daily average $PM_{2.5}$ concentrations, was associated with lower arterial elasticity ($PM_{2.5}$ one day before exam, PTC2; $PM_{2.5}$ two days before exam, DC) and higher arterial stiffness ($PM_{2.5}$ on the day of, one day before, and two days before exam, YEM). These results provide evidence that long-term traffic related air pollution and short-term particulate air pollution are associated with detrimental changes in arterial function.

Table 4.1 Participant characteristics at Exam 1 for all participants and participants included in analysis of long-term $PM_{2.5}$ air pollution exposure data with radial tonometry and carotid ultrasound measures

	All participants		**Participants with long-term $PM_{2.5}$ and radial tonometry measures data[1]**		**Participants with long-term $PM_{2.5}$ and carotid ultrasound measures data[1]**	
N	N= 6,814		N=2,870		N=2,934	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Years between exams[2]	N/A	N/A	9.6	0.6	9.5	0.6
Age (years)	62.2	10.2	60.6	9.5	60.4	9.4
BMI (kg/m^2)	28.3	5.5	28.2	5.3	27.9	5.1
Weight (pounds)	173.4	38.2	173.8	37.8	173.9	37.9
Height (cm)	166.4	10.0	166.9	10.0	166.9	10.0
Heart rate (beats/min)	63.1	9.7	62.6	9.2	62.5	9.0
Systolic blood pressure (mmHg)	126.6	21.5	124.8	20.1	124.5	20.2
Diastolic blood pressure (mmHg)	71.9	10.3	72.0	10.0	71.9	10.1
Mean arterial pressure (mmHg)	90.1	12.6	89.6	12.1	89.2	12.2
Total cholesterol, exam 1 (mg/dl)	194.2	35.7	194.0	34.8	194.3	35.1
HDL cholesterol, exam 1 (mg/dl)	51.0	14.8	51.2	14.8	51.1	14.9

Triglycerides, exam 1 (mg/dl)	131.6	88.8	126.7	73.6	128.2	75.8
C-reactive protein, exam 1 (mg/L)	3.8	5.9	3.4	4.7	3.4	5.0

	N	%	N	%	N	%
Gender						
Female	3,601	52.8	1,526	53.2	1,559	53.1
Male	3,213	47.2	1,344	46.8	1,375	46.9
Race/Ethnicity						
White	2,622	38.5	1,127	39.3	1,155	39.4
Chinese	804	11.8	372	13	374	12.7
Black	1,892	27.8	777	27.1	777	26.5
Hispanic	1,496	22	594	20.7	628	21.4
Metropolitan Area (Site) at Exam 1						
Forsyth County, North Carolina (WFU)	1,077	15.8	476	16.6	486	16.6
New York, NY (COL)	1,102	16.2	542	18.9	549	18.7
Baltimore, MD (JHU)	1,086	15.9	334	11.6	363	12.4

St. Paul, MN (UMN)	1,066	15.6	475	16.6	457	15.6
Chicago, IL (NWU)	1,164	17.1	661	23	593	20.2
Los Angeles, CA (UCLA)	1,319	19.4	382	13.3	486	16.6
Highest level of education completed at exam 1						
Less than high school	1,225	18	387	13.5	399	13.6
High school graduate/GED	1,236	18.2	485	16.9	514	17.5
Some college/2 year college degree	1,937	28.5	839	29.2	858	29.3
4 year college degree/more	2,393	35.2	1,159	40.4	1,158	39.5
Anti-hypertensive medication at exam 1	2,536	37.2	972	35.5	873	34.1
Smoking status at exam 1						
Never	3,418	50.3	1,435	52.4	1,340	52.4
Former	2,487	36.6	995	36.4	926	36.2
Current	887	13.1	306	11.2	292	11.4

Any lipid-lowering medication at Exam 1	1,105	16.3	448	16.4	401	15.7
Has diabetes mellitus at exam 1[3]	859	12.7	272	9.9	240	9.4
Total gross annual family income at exam 1						
$0-$24,999	2,060	31.5	687	24.6	711	24.9
$25,000-$49,999	1,892	28.9	830	29.7	868	30.4
$50,000-$74,999	1,111	17	528	18.9	540	18.9
$75,000+	1,478	22.6	749	26.8	736	25.8

[1] These participants have Exam 1 and/or 5 data for arterial function measure and covariate data for full adjusted model (years between exams 1 and 5; at exam 1: gender, race, site, BMI, total cholesterol, HDL cholesterol, triglycerides, cigarette smoking status, diabetes, annual gross household income, highest educational level completed; at exams 1 and 5: age, use of lipid-lowering medication, SBP, DBP, MAP, use of anti-hypertension medication, heart rate.

[2] Radial tonometry or carotid ultrasound depending on the group

[3] Based on 2003 ADA fasting criteria algorithm

Table 4.2 Descriptive characteristics of arterial function measures overall and by clinical site

Arterial stiffness measure (Units)	Overall	Winston-Salem, NC	New York City, NY	Baltimore, MD	St. Paul, MN	Chicago, IL	Los Angeles County, CA
		WFU	COL	JHU	UMN	NWU	UCLA
PTC2 at Exam 1 (seconds*100)$^{-1}$							
N	6333	1049	1024	867	1000	1111	1282
Mean	8.9	8.1	8.7	8.9	10.5	8.6	8.7
SD	3.9	3.5	3.7	3.6	4.4	3.8	3.7
PTC2 at Exam 5 (seconds*100)$^{-1}$							
N	4005	665	728	533	710	831	538
Mean	7.6	7.3	7.6	7.2	7.6	8.2	7.6
SD	2.9	3.0	2.7	2.7	2.7	3.1	2.8

Annual rate of PTC2 change (seconds*100)$^{-1}$per year							
N	3751	650	677	428	675	796	525
Mean	-0.17	-0.12	-0.14	-0.22	-0.33	-0.07	-0.17
SD	0.40	0.41	0.35	0.42	0.41	0.40	0.36
PTC1 at Exam 1 (seconds*10)$^{-1}$							
N	6333	1049	1024	867	1000	1111	1282
Mean	3.5	3.6	3.4	3.4	4.3	3.1	3.1
SD	2.2	2.1	2.0	2.2	2.7	2.5	1.4
PTC1 at Exam 5 (seconds*10)$^{-1}$							
N	4005	665	728	533	710	831	538
Mean	2.3	2.1	2.4	2.1	2.2	2.5	2.6
SD	1.0	1.0	1.1	1.0	1.0	1.1	1.0
Annual rate of PTC1 change (seconds*10)$^{-1}$ per year							
N	3751	650	677	428	675	796	525
Mean	-0.14	-0.18	-0.12	-0.16	-0.23	-0.08	-0.07
SD	0.25	0.25	0.21	0.25	0.31	0.26	0.16

DC at Exam 1 (mmHg*1000)$^{-1}$							
N	2873	530	536	287	432	591	497
Mean	3.1	3.1	2.8	3.2	3.3	3.2	3.0
SD	1.3	1.3	1.1	1.2	1.3	1.3	1.3
DC at Exam 5 (mmHg*1000)$^{-1}$							
N	3219	532	615	385	515	629	543
Mean	2.7	2.6	2.5	2.6	3.0	2.8	2.6
SD	1.1	1.0	1.1	1.1	1.3	1.2	1.1
Annual rate of DC change (mmHg*1000)$^{-1}$ per year							
N	2729	498	524	250	419	561	477
Mean	-0.04	-0.05	-0.03	-0.07	-0.03	-0.05	-0.04
SD	0.12	0.12	0.11	0.11	0.12	0.13	0.12
YEM at Exam 1 (mmHg)							
N	2872	529	536	287	432	591	497

Mean	1596.2	1533.1	1758.3	1518.8	1513.2	1508.2	1709.7
SD	935.5	816.9	1012.6	1035.4	851.4	749.3	1126.5
YEM at Exam 5 (mmHg)							
N	3219	532	615	385	515	629	543
Mean	1775.4	1739.0	1892.9	1847.8	1566.3	1758.0	1845.4
SD	1330.5	1600.0	1402.3	1329.8	910.6	1375.4	1214.7
Annual rate of YEM change (mmHg per year)							
N	2729	498	524	250	419	561	477
Mean	18.3	24.4	10.5	37.0	4.5	27.4	12.3
SD	134.9	165.8	130.0	99.9	103.3	147.8	126.8

Table 4.3: Descriptive characteristics of long-term $PM_{2.5}$ and NOx air pollution concentrations for radial tonometry participants

	Overall	Winston-Salem, NC	New York City, NY	Baltimore, MD	St. Paul, MN	Chicago, IL	Los Angeles County, CA
Average annual outdoor $PM_{2.5}$ concentration during year 2000 (micrograms/m^3)							
N	3,624	617	667	419	647	782	492
Mean	16.4	16.2	16.4	15.9	12.9	16.5	21.6
Standard Deviation (SD)	2.7	0.7	1.6	0.8	0.7	1.3	1.1
Minimum	10.9	11.3	10.9	13.6	11.4	12.6	19.0
25^{th} percentile	15.1	15.8	15.4	15.3	12.4	15.8	21.0
50^{th} percentile	16.1	16.2	16.2	15.7	12.9	16.3	21.6
75^{th} percentile	17.3	16.7	17.1	16.3	13.4	17.3	22.3
Maximum	27.9	18.3	24.6	18.3	20.0	27.9	25.9
Interquartile (IQR)	2.2	0.9	1.7	1.0	1.0	1.5	1.3

Average annual outdoor $PM_{2.5}$ concentration between Exams 1 and 5 radial tonometry exams (about years 2000-2010) (micrograms/m^3)							
N	3,489	611	623	404	630	745	476
Mean	13.4	13.0	14.5	13.1	10.1	13.6	16.7
Standard Deviation (SD)	2.1	0.3	1.5	0.8	0.6	0.9	1.0
Minimum	8.6	11.6	9.9	10.8	8.6	10.5	11.7
25^{th} percentile	12.6	12.8	13.6	12.6	9.7	13.0	16.2
50^{th} percentile	13.2	13.0	14.4	13.0	10.1	13.5	16.8
75^{th} percentile	14.5	13.2	15.3	13.6	10.5	14.2	17.3
Maximum	22.1	14.2	22.1	15.5	13.4	18.5	19.4
Interquartile (IQR)	1.9	0.4	1.7	1.0	0.9	1.2	1.1
Average annual outdoor NOx concentration during year 2000 (ppb)							
N	3,614	615	667	419	644	782	487

Mean	48.3	22.4	81.7	40.9	24.1	43.8	80.9
Standard Deviation (SD)	27.1	6.4	15.5	12.6	5.8	8.3	22.4
Minimum	8.7	12.5	30.9	10.7	8.7	22.6	15.9
25th percentile	24.8	18.0	73.1	34.7	21.0	39.3	68.4
50th percentile	41.2	21.1	81.4	38.7	23.6	43.1	79.3
75th percentile	69.4	25.2	88.4	47.3	26.3	47.3	96.9
Maximum	174.5	49.8	174.5	82.7	93.2	69.8	136.3
Interquartile (IQR)	44.5	7.2	15.3	12.7	5.2	8.0	28.5
Average annual outdoor NOx concentration between Exams 1 and 5 radial tonometry exams (about years 2000-2010) (ppb)							
N	3,467	605	623	402	625	745	467
Mean	35.2	13.9	65.9	27.7	20.0	33.2	52.2
Standard Deviation (SD)	20.2	4.7	12.6	9.0	4.5	6.5	11.8
Minimum	6.6	6.6	21.7	7.5	6.8	17.3	14.4
25th percentile	18.9	10.8	58.5	22.7	17.4	29.6	45.0

50th percentile	30.5	12.8	65.9	26.2	19.7	33.3	51.8
75th percentile	49.7	16.2	71.2	32.5	22.3	36.6	59.5
Maximum	133.1	34.7	133.1	57.9	38.1	52.7	84.8
Interquartile (IQR)	30.8	5.3	12.6	9.8	4.9	7.0	14.4

Table 4.4 Association between interquartile region (IQR) of annual average $PM_{2.5}$ pollution for year 2000 and between Exams 1 and 5 with various arterial functional measures adjusted by cardiovascular risk factors for primary analysis model (Model 2)

	Cross-sectional estimate[1]						Rate of change estimate[2]				
Model 2[3] (units of arterial function measure)	Estimate	Std. Error	95%LL	95%UL	P-value		Estimate	Std. Error	95%LL	95%UL	P-value
PTC2[4,6] (seconds*100)$^{-1}$	0.137	0.118	-0.094	0.368	0.245		-0.008	0.014	-0.035	0.019	0.551
PTC1[4,6] (seconds*10)$^{-1}$	-0.026	0.060	-0.144	0.092	0.669		0.001	0.008	-0.014	0.017	0.869
DC[5,7] (mmHg*1000)$^{-1}$	0.002	0.041	-0.078	0.081	0.966		0.004	0.005	-0.005	0.014	0.335
YEM[5,7] (mmHg)	-23.484	43.039	-107.840	60.872	0.585		0.307	5.274	-10.031	10.645	0.954

[1] Cross-sectional estimate: Association of annual average PM2.5 exposure during year 2000 (baseline exam) with arterial function measure at exam 1

[2] Rate of change estimate: Association of annual average PM2.5 exposure between exams 1 and 5 (roughly 2000-2010) with rate of change of arterial function measure between exams 1 and 5

[3] Model 2: Adjusted for time-varying age, smoking, lipid lowering medication, heart rate; baseline gender, race/ethnicity, site, education, income, BMI, total cholesterol, HDL cholesterol, triglycerides, diabetes, CRP

[4] IQR for annual average PM2.5 exposure for baseline year 2000 for radial tonometry participants = 2.2 micrograms/m^3

[5] IQR for annual average PM2.5 exposure for baseline year 2000 for carotid ultrasound participants= 2.4 micrograms/m^3

[6] IQR for annual average PM2.5 exposure between Exams 1 and 5 (2000-2010) for radial tonometry participants=1.94 micrograms/m^3

[7] IQR for annual average PM2.5 exposure between Exams 1 and 5 (2000-2010) for carotid ultrasound participants= 1.92 micrograms/m^3

Table 4.5 Association between interquartile region (IQR) of annual average NOx pollution for year 2000 and between Exams 1 and 5 with various arterial functional measures adjusted by cardiovascular risk factors for primary analysis model (Model 2)

	Cross-sectional estimate[1]						Rate of change estimate[2]				
Model 2[3] (units of arterial function measure)	Estimate	Std. Error	95%LL	95%UL	P-value		Estimate	Std. Error	95%LL	95%UL	P-value
PTC2[4,6] (seconds*100)$^{-1}$	-0.149	0.216	-0.571	0.274	0.491		0.012	0.025	-0.037	0.060	0.638
PTC1[4,6] (seconds*10)$^{-1}$	**-0.220**	**0.111**	**-0.437**	**-0.003**	**0.047**		0.020	0.014	-0.008	0.048	0.161
DC[5,7] (mmHg*1000)$^{-1}$	-0.063	0.073	-0.206	0.081	0.391		0.004	0.008	-0.011	0.020	0.578
YEM[5,7] (mmHg)	51.60	78.20	-101.67	204.88	0.51		3.96	9.07	-13.82	21.75	0.66

[1] Cross-sectional estimate: Association of annual average PM2.5 exposure during year 2000 (baseline exam) with arterial function measure at exam 1

[2] Rate of change estimate: Association of annual average PM2.5 exposure between exams 1 and 5 (roughly 2000-2010) with rate of change of arterial function measure between exams 1 and 5

[3] Model 2: Adjusted for time-varying age, smoking, lipid lowering medication, heart rate; baseline gender, race/ethnicity, site, education, income, BMI, total cholesterol, HDL cholesterol, triglycerides, diabetes, CRP

[4] IQR for annual average NOx exposure for baseline year 2000 for radial tonometry participants = 44.5 ppb

[5] IQR for annual average NOx exposure for baseline year 2000 for carotid ultrasound participants= 48.4 ppb

[6] IQR for annual average NOx exposure between Exams 1 and 5 (2000-2010) for radial tonometry participants=30.8 ppb

[7] IQR for annual average NOx exposure between Exams 1 and 5 (2000-2010) for carotid ultrasound participants= 32.7 ppb

Table 4.6: Descriptive characteristics of short-term $PM_{2.5}$ air pollution concentrations for radial tonometry participants

	Overall	Winston-Salem, NC	New York City, NY	Baltimore, MD	St. Paul, MN	Chicago, IL	Los Angeles County, CA
Outdoor $PM_{2.5}$ concentration on day of radial tonometry Exam 1 (micrograms/m^3)							
N	3432	598	633	383	589	707	522
Mean	16.8	16.2	16.3	17.3	11.5	19.1	21.0
Standard Deviation (SD)	9.8	8.1	9.0	10.2	6.9	9.2	12.4
Minimum	1	2.9	3.6	4.8	1	3	3.9
25th percentile	9.8	10.6	9.7	9.8	6.5	11.8	13
50th percentile	14.7	14	14.3	15	9.7	18	17.9
75th percentile	21.6	20.7	20.1	22.1	15.9	24.8	25
Maximum	85.1	69.7	47.9	56.7	47.9	56.4	85.1
Interquartile (IQR)	11.8	10.1	10.4	12.3	9.4	13	12
Outdoor $PM_{2.5}$ one day before radial tonometry Exam 1 (micrograms/m^3)							

N	3486	608	650	391	600	713	524
Mean	16.3	15.5	15.4	16.5	11.0	18.8	20.6
Standard Deviation (SD)	9.7	7.9	8.6	10.2	7.0	9.3	11.9
Minimum	1	2	3.8	4	1	3	4.3
25th percentile	9.3	9.65	8.8	9.2	6.2	11.3	13.1
50th percentile	14.2	13.8	13.8	13.7	9.55	17.8	17.5
75th percentile	21	19.3	19.2	21.5	14.85	24.3	24.15
Maximum	70.4	49.4	55.3	70.4	42.2	52.9	69.6
Interquartile (IQR)	11.7	9.65	10.4	12.3	8.65	13	11.05
Outdoor $PM_{2.5}$ two days before radial tonometry Exam 1 (micrograms/m^3)							
N	3335	587	636	370	553	666	523
Mean	16.1	15.1	15.2	15.8	11.0	18.5	20.6
Standard Deviation (SD)	8.7	7.2	7.5	8.6	6.1	8.3	11.0
Minimum	1.0	3.7	4.0	4.8	1.0	4.1	4.4
25th percentile	9.9	9.9	9.9	10.0	7.0	11.9	13.7
50th percentile	14.1	13.6	13.3	13.4	9.7	17.3	18.3
75th percentile	20.1	18.6	19.1	19.1	13.6	23.6	24.6
Maximum	64.2	47.9	47.1	58.5	39.7	54.7	64.2

Interquartile (IQR)	10.2	8.7	9.2	9.1	6.6	11.7	10.9
Outdoor $PM_{2.5}$ concentration <u>on day of</u> radial tonometry Exam 5 (micrograms/m^3)							
N	3542	597	661	308	667	788	521
Mean	10.8	10.3	10.5	10.4	8.8	12.5	11.8
Standard Deviation (SD)	6.1	4.7	6.1	5.2	5.1	7.5	5.6
Minimum	1	1	2.4	2.4	1	1	3
25th percentile	6.3	6.8	5.8	6.65	5.2	6.4	8
50th percentile	9.6	9.8	9.4	9.1	7.7	10.8	10.9
75th percentile	13.8	13.4	13.5	13.4	11.4	16.95	13.6
Maximum	46.6	26.5	41.1	31.9	29	39.9	46.6
Interquartile (IQR)	7.5	6.6	7.7	6.75	6.2	10.55	5.6
Outdoor $PM_{2.5}$ <u>one day before</u> radial tonometry Exam 5 (micrograms/m^3)							
N	3546	601	663	321	667	774	520
Mean	10.6	10.0	10.2	10.4	8.7	12.4	11.4
Standard Deviation (SD)	6.0	4.6	5.8	5.4	4.8	7.5	5.8
Minimum	1.0	1.0	2.4	1.0	1.0	1.0	3.0
25th percentile	6.2	6.5	5.7	6.7	5.2	6.3	7.9

50th percentile	9.4	9.6	8.8	9.2	7.7	10.9	10.4
75th percentile	13.1	13.0	13.2	12.3	10.9	16.6	13.0
Maximum	46.6	26.5	41.1	31.9	26.2	39.9	46.6
Interquartile (IQR)	6.9	6.5	7.5	5.6	5.7	10.3	5.1
Outdoor $PM_{2.5}$ two days before radial tonometry Exam 5 (micrograms/m^3)							
N	3440	582	655	271	661	752	519
Mean	10.7	10.1	10.3	10.4	8.9	12.7	11.3
Standard Deviation (SD)	5.4	4.1	5.1	4.8	4.4	6.7	5.2
Minimum	1.7	2.5	3.1	1.7	2.3	1.7	4.5
25th percentile	6.9	6.9	6.5	7.0	5.7	7.5	7.8
50th percentile	9.8	9.7	9.4	9.6	8.1	11.2	10.2
75th percentile	13.4	12.4	13.1	13.0	11.0	17.2	13.5
Maximum	39.3	22.0	33.4	26.0	22.0	39.3	35.9
Interquartile (IQR)	6.5	5.5	6.6	6.0	5.3	9.8	5.7

Table 4.7: Association between 5 micrograms/m^3 of daily average $PM_{2.5}$ pollution with various arterial stiffness measures from Exams 1 and 5 adjusted by cardiovascular risk factors for primary analysis model (Model 2)

Model 2[1]	Residuals of PM2.5 on day of exam[2]	Residuals of PM2.5 ONE DAY BEFORE exam[2]	Residuals of PM2.5 TWO DAYS BEFORE of exam[2]
PTC2 (seconds*100)$^{-1}$			
Coefficient	-0.012	**-0.068**	**-0.078**
Standard Error	0.036	**0.034**	**0.037**
95% Lower Limit	-0.084	**-0.134**	**-0.151**
95% Upper Limit	0.059	**-0.002**	**-0.004**
P-value	0.731	**0.044**	**0.038**
PTC1 (seconds*10)$^{-1}$			
Coefficient	0.024	-0.005	-0.023
Standard Error	0.020	0.018	0.020
95% Lower Limit	-0.014	-0.040	-0.063
95% Upper Limit	0.063	0.031	0.016
P-value	0.213	0.789	0.246
DC (mmHg*1000)$^{-1}$			
Coefficient	-0.001	-0.011	**-0.030**
Standard Error	0.012	0.012	**0.013**

95% Lower Limit	-0.025	-0.034	**-0.055**
95% Upper Limit	0.023	0.012	**-0.004**
P-value	0.937	0.341	**0.022**
YEM (mmHg)			
Coefficient	**30.30**	**33.60**	**34.72**
Standard Error	**14.06**	**13.15**	**14.74**
95% Lower Limit	**2.74**	**7.83**	**5.84**
95% Upper Limit	**57.85**	**59.36**	**63.61**
P-value	**0.03**	**0.01**	**0.02**

[1] Model 2: Adjusted for time-varying age, smoking, lipid lowering medication, heart rate; baseline gender, race/ethnicity, site, highest educational level attained, income, BMI, total cholesterol, HDL cholesterol, triglycerides, diabetes, CRP

[2] Radial tonometry exam for PTC2 and PTC1; Carotid ultrasound exam for DC and YEM

Table 4.8: Participant characteristics at Exam 1 for all participants and participants included in analysis of long-term NOx air pollution exposure data with radial tonometry and carotid ultrasound measures

	All participants		**Participants with long-term NOx data and radial tonometry measures data[1]**		**Participants with long-term NOx data and carotid ultrasound measures data[1]**	
N	N= 6,814		N=2,831		N=2,917	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Years between exams[2]	N/A	N/A	9.6	0.6	9.5	0.6
Age (years)	62.2	10.2	60.7	9.5	60.4	9.4
BMI (kg/m^2)	28.3	5.5	28.2	5.3	27.9	5.1
Weight (pounds)	173.4	38.2	173.8	37.8	174.0	37.9
Height (cm)	166.4	10.0	166.9	10.0	166.9	10.0
Heart rate (beats/min)	63.1	9.7	62.5	9.2	62.5	9.0
Systolic blood pressure (mmHg)	126.6	21.5	124.8	20.1	124.5	20.2
Diastolic blood pressure (mmHg)	71.9	10.3	72.0	10.0	71.9	10.2
Mean arterial pressure (mmHg)	90.1	12.6	89.6	12.1	89.2	12.2

Cholesterol, exam 1 (mg/dl)	194.2	35.7	193.5	34.0	194.3	35.1
HDL cholesterol, exam 1 (mg/dl)	51.0	14.8	51.3	14.7	51.1	14.8
Triglycerides, exam 1 (mg/dl)	131.6	88.8	123.3	62.9	128.1	75.9
C-reactive protein, exam 1 (mg/L)	3.8	5.9	3.4	4.7	3.4	5.0

	N	%	No.	%	No.	%
Gender						
Female	3,601	52.8	1,504	53.1	1,547	53.0
Male	3,213	47.2	1,327	46.9	1,370	47.0
Race/Ethnicity						
White	2,622	38.5	1,116	39.4	1,155	39.6
Chinese	804	11.8	364	12.9	370	12.7
Black	1,892	27.8	770	27.2	771	26.4
Hispanic	1,496	22	581	20.5	621	21.3
Metropolitan Area (Site) at Exam 1						

Forsyth County, North Carolina (WFU)	1,077	15.8	471	16.6	483	16.6
New York, NY (COL)	1,102	16.2	540	19.1	549	18.8
Baltimore, MD (JHU)	1,086	15.9	334	11.8	363	12.4
St. Paul, MN (UMN)	1,066	15.6	462	16.3	453	15.5
Chicago, IL (NWU)	1,164	17.1	659	23.3	593	20.3
Los Angeles, CA (UCLA)	1,319	19.4	365	12.9	476	16.3
Highest level of education completed at exam 1						
Less than high school	1,225	18	376	13.3	391	13.4
High school graduate/GED	1,236	18.2	478	16.9	513	17.6
Some college/2 year college degree	1,937	28.5	829	29.3	855	29.4
4 year college degree/more	2,393	35.2	1,148	40.6	1,153	39.6
Anti-hypertensive medication at exam 1	2,536	37.2	954	35.4	867	34.1

Smoking status at exam 1						
Never	3,418	50.3	1,414	52.4	1,331	52.3
Former	2,487	36.6	987	36.6	924	36.3
Current	887	13.1	297	11	289	11.4
Any lipid-lowering medication at Exam 1	1,105	16.3	442	16.4	400	15.7
Has diabetes mellitus at exam 1[3]	859	12.7	265	9.8	238	9.4
Total gross annual household income at exam 1						
$0-$24,999	2,060	31.5	673	24.4	703	24.8
25,000-49,999	1,892	28.9	815	29.6	861	30.3
50,000-74,999	1,111	17	521	18.9	538	19.0
75,000+	1,478	22.6	746	27.1	736	25.9

[1] These participants have Exam 1 and/or 5 data for arterial function measure and covariate data for model 3: years between exams 1 and 5; at exam 1: gender, race, site, BMI, total cholesterol, HDL cholesterol, triglycerides, cigarette smoking status,

diabetes, annual gross household income, highest educational level completed; at exams 1 and 5: age, use of lipid-lowering medication, SBP, DBP, MAP, use of anti-hypertension medication, heart rate.

[2] Radial tonometry or carotid ultrasound depending on the group

[3] Based on 2003 ADA fasting criteria algorithm

Table 4.9: Participant characteristics at Exam 1 for all participants included in analysis of short-term $PM_{2.5}$ air pollution exposure data with radial tonometry and carotid ultrasound arterial function measures

	All participants		**Participants with short-term $PM_{2.5}$ data and radial tonometry measures data[1]**		**Participants with short-term $PM_{2.5}$ data and carotid ultrasound measures data[1]**	
N	N= 6,814		N=3,558		N=2,960	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Years between exams[2]	N/A	N/A	9.6	0.6	9.5	0.6
Age (years)	62.2	10.2	60.3	9.5	60.3	9.4
BMI (kg/m^2)	28.3	5.5	28.1	5.3	27.7	4.9
Weight (pounds)	173.4	38.2	173.1	37.5	172.6	37.0
Height (cm)	166.4	10.0	166.8	9.9	166.7	10.0
Heart rate (beats/min)	63.1	9.7	62.6	9.2	62.2	9.0
Systolic blood pressure (mmHg)	126.6	21.5	124.1	20.3	124.3	20.4
Diastolic blood pressure (mmHg)	71.9	10.3	71.8	10.1	71.9	10.2
Mean arterial pressure (mmHg)	90.1	12.6	89.5	12.3	89.5	12.4

Cholesterol, exam 1 (mg/dl)	194.2	35.7	194.2	34.9	193.9	34.8
HDL cholesterol, exam 1 (mg/dl)	51.0	14.8	51.3	14.8	51.1	15.0
Triglycerides, exam 1 (mg/dl)	131.6	88.8	129.4	80.2	129.2	77.5
C-reactive protein, exam 1 (mg/L)	3.8	5.9	3.4	4.8	3.4	5.1

	N	%	N	%	N	%
Gender						
Female	3,601	52.8	1,883	52.9	1,550	52.4
Male	3,213	47.2	1,675	47.1	1,410	47.6
Race/Ethnicity						
White	2,622	38.5	1,416	39.8	1,101	37.2
Chinese	804	11.8	459	12.9	405	13.7
Black	1,892	27.8	885	24.9	755	25.5
Hispanic	1,496	22	798	22.4	699	23.6
Metropolitan Area (Site) at Exam 1						

Forsyth County, North Carolina (WFU)	1,077	15.8	554	15.6	495	16.7
New York, NY (COL)	1,102	16.2	685	19.3	593	20
Baltimore, MD (JHU)	1,086	15.9	346	9.7	242	8.2
St. Paul, MN (UMN)	1,066	15.6	668	18.8	490	16.6
Chicago, IL (NWU)	1,164	17.1	774	21.8	587	19.8
Los Angeles, CA (UCLA)	1,319	19.4	531	14.9	553	18.7
Highest level of education completed at exam 1						
Less than high school	1,225	18	497	14	436	14.7
High school graduate/GED	1,236	18.2	590	16.6	517	17.5
Some college/2 year college degree	1,937	28.5	1,044	29.3	857	29
4 year college degree/more	2,393	35.2	1,427	40.1	1,147	38.8
Anti-hypertensive medication at exam 1	2,536	37.2	924	34.5	739	34.6

Smoking status at exam 1						
Never	3,418	50.3	1,407	52.6	1,144	53.5
Former	2,487	36.6	956	35.7	755	35.3
Current	887	13.1	312	11.7	238	11.1
Any lipid-lowering medication at Exam 1	1,105	16.3	436	16.3	328	15.3
Has diabetes mellitus at exam 1[3]	859	12.7	269	10.1	219	10.2
Total gross annual household income at exam 1						
$0-$24,999	2,060	31.5	892	25.1	751	26.1
25,000-49,999	1,892	28.9	1,062	29.8	885	30.7
50,000-74,999	1,111	17	655	18.4	527	18.3
75,000+	1,478	22.6	949	26.7	718	24.9

[1] These participants have Exam 1 and/or 5 data for arterial function measure and covariate data for Model 3:years between exams 1 and 5; at exam 1: gender, race, site, BMI, total cholesterol, HDL cholesterol, triglycerides, cigarette smoking status, diabetes, annual gross household income, highest educational level completed; at exams 1 and 5: age, use of lipid-lowering medication, SBP, DBP, MAP, use of anti-hypertension medication, heart rate.

[2] Radial tonometry or carotid ultrasound depending on the group

[3] Based on 2003 ADA fasting criteria algorithm

Table 4.10: Distribution of participants included in linear mixed effects analyses of association between air pollution and arterial function measures by how many arterial function measures they had

	Radial tonometry measures (PTC1, PTC2)			Carotid ultrasound (DC, YEM)		
	Long-term PM2.5	Long-term NOx	Short-term PM2.5	Long-term PM2.5	Long-term NOx	Short-term PM2.5
Total included in linear mixed effects analysis	2,870	2,831	3,358	2,934	2,917	2,960
Both Exam 1 and Exam 5 measures	2,696	2,658	2,219	2,412	2,398	1,733
Exam 1 measures only	40	40	456	148	148	405
Exam 5 measures only	134	133	883	374	371	822

Table 4.11: Descriptive characteristics of difference in arterial function measures between exams 1 and 5

Measure (Units)	N (obs)	Mean	Standard Deviation	Minimum value	Maximum value
Difference in PTC2, weighted mean (seconds*100)$^{-1}$	3,751	-1.62	3.86	-37.80	30.20
No difference or gain in PTC2, weighted mean	1,288	1.98	2.01	0.00	30.20
Loss in PTC2, weighted mean (more stiff)	2,463	-3.50	3.20	-37.80	-0.10
Difference in PTC1, weighted mean (seconds*10)$^{-1}$	3,751	-1.33	2.43	-21.51	19.07
No difference or gain in PTC1, weighted mean	925	1.08	1.62	0.00	19.07
Loss in PTC1, weighted mean (more stiff)	2,826	-2.12	2.11	-21.51	-0.01
Difference in DC (mmHg*1000)$^{-1}$	2,729	-0.40	1.13	-5.77	5.03
No difference or gain in DC	973	0.74	0.65	0.00	5.03
Loss in DC (more stiff)	1,756	-1.03	0.80	-5.77	0.00
Difference in YEM (mmHg)	2,729	174.4	1,274.9	-11,073.3	21,360.1
No difference or loss in YEM	1,208	-596.4	761.1	-11,073.3	-0.1
Gain in YEM (more stiff)	1,521	786.5	1,268.9	0.4	21,360.1

Table 4.12: Descriptive characteristics of long-term $PM_{2.5}$ and NOx air pollution concentrations for carotid ultrasound participants

	Overall	Winston-Salem, NC	New York City, NY	Baltimore, MD	St. Paul, MN	Chicago, IL	Los Angeles County, CA
Average annual outdoor $PM_{2.5}$ concentration during year 2000 (micrograms/m^3)							
N	2,636	476	517	247	404	550	442
Mean	16.7	16.2	16.4	15.8	12.9	16.5	21.6
Standard Deviation (SD)	2.8	0.7	1.6	0.8	0.8	1.2	1.2
Minimum	10.9	11.3	10.9	13.6	11.4	12.6	18.6
25^{th} percentile	15.2	15.8	15.4	15.3	12.4	15.8	20.9
50^{th} percentile	16.2	16.2	16.2	15.7	12.9	16.3	21.5
75^{th} percentile	17.6	16.7	17.0	16.2	13.4	17.3	22.3
Maximum	25.9	18.3	24.6	18.2	20.0	22.4	25.9
Interquartile (IQR)	2.4	0.9	1.6	0.9	1.1	1.6	1.4

Average annual outdoor $PM_{2.5}$ concentration between Exams 1 and 5 radial tonometry exams (about years 2000-2010) (micrograms/m^3)							
N	2,320	432	464	207	372	513	332
Mean	13.5	13.1	14.5	13.1	10.1	13.6	16.6
Standard Deviation (SD)	2.1	0.3	1.5	0.8	0.6	1.0	1.0
Minimum	8.6	11.6	10.6	11.2	8.6	10.5	11.7
25^{th} percentile	12.7	12.9	13.6	12.5	9.6	13.0	16.2
50^{th} percentile	13.3	13.0	14.4	13.0	10.1	13.4	16.8
75^{th} percentile	14.6	13.2	15.2	13.6	10.6	14.2	17.2
Maximum	22.1	14.2	22.1	15.5	11.7	18.5	19.4
Interquartile (IQR)	1.9	0.4	1.6	1.1	0.9	1.2	1.1

Average annual outdoor NOx concentration during year 2000 (ppb)							
N	2,628	475	517	247	402	550	437
Mean	49.9	22.5	81.7	40.6	24.0	43.7	79.1
SD	27.8	6.7	15.1	12.0	6.3	8.7	23.1
min	8.7	12.5	30.9	11.4	8.7	22.6	15.9
p25	25.2	18.0	73.5	33.2	20.9	39.1	67.6
p50	42.4	21.2	81.4	38.5	23.5	43.1	78.8
p75	73.6	25.5	88.1	45.8	26.4	47.3	95.2
max	174.5	49.8	174.5	78.1	93.2	69.8	134.9
iqr	48.4	7.5	14.6	12.6	5.5	8.2	27.6
Average annual outdoor NOx concentration between Exams 1 and 5 radial tonometry exams (about years 2000-2010) (ppb)							

N	2,304	426	464	206	370	513	325
Mean	36.1	14.1	65.8	27.4	19.8	33.0	51.6
Standard Deviation (SD)	20.7	4.9	12.4	8.8	4.5	6.9	11.6
Minimum	6.6	6.6	29.6	7.7	6.8	17.5	14.4
25th percentile	19.0	10.8	58.7	21.9	17.1	28.8	44.9
50th percentile	31.3	13.0	65.9	26.0	19.5	33.2	51.1
75th percentile	51.7	16.2	71.1	31.2	22.3	36.6	58.8
Maximum	133.1	34.7	133.1	57.3	37.2	52.7	81.1
Interquartile (IQR)	32.7	5.4	12.4	9.3	5.2	7.7	13.9

Table 4.13: Descriptive characteristics of short-term $PM_{2.5}$ air pollution concentrations for carotid ultrasound participants

	Overall	Winston-Salem, NC	New York City, NY	Baltimore, MD	St. Paul, MN	Chicago, IL	Los Angeles County, CA
Outdoor $PM_{2.5}$ concentration on day of carotid ultrasound Exam 1 (micrograms/m^3)							
N	2518	458	492	227	371	497	473
Mean	17.2	16.1	16.5	17.3	11.7	18.7	21.6
Standard Deviation (SD)	10.3	7.9	9.6	10.3	7.3	9.6	12.9
Minimum	1	2.9	3.6	4.6	1	3.8	3.9
25th percentile	9.8	10.6	9.4	9.8	6.5	11.4	12.9
50th percentile	14.8	14.05	14.1	14.7	9.7	17.4	18.5
75th percentile	21.9	20.7	20.9	21.9	16.3	23.7	26.4
Maximum	85.1	49.4	55.3	56.7	47.9	56.4	85.1
Interquartile (IQR)	12.1	10.1	11.5	12.1	9.8	12.3	13.5
Outdoor $PM_{2.5}$ one day before carotid ultrasound Exam 1 (micrograms/m^3)							
N	2545	469	500	230	370	499	477

Mean	16.5	15.6	14.8	16.5	11.3	18.1	21.5
Standard Deviation (SD)	9.9	7.9	8.1	9.0	7.5	9.3	13.0
Minimum	1	2	3.6	4	1	2.5	4.3
25th percentile	9.5	9.8	8.9	9.4	5.9	11	13.1
50th percentile	14.4	13.9	13.45	14.7	9.55	16.9	17.6
75th percentile	21.1	19.5	17.9	21.6	15.1	23	25.2
Maximum	85.1	46.4	55.3	56.7	42.2	56.4	85.1
Interquartile (IQR)	11.6	9.7	9	12.2	9.2	12	12.1
Outdoor $PM_{2.5}$ two days before carotid ultrasound Exam 1 (micrograms/m^3)							
N	2432	453	491	221	333	458	476
Mean	16.3	15.5	14.6	16.1	11.0	17.7	21.4
Standard Deviation (SD)	9.0	7.2	6.9	7.9	6.5	8.3	11.9
Minimum	1.0	3.7	4.1	4.8	1.0	4.1	4.4
25th percentile	10.1	10.0	9.8	10.5	6.8	11.2	13.8
50th percentile	14.2	14.0	12.9	13.7	9.6	16.3	18.6
75th percentile	20.3	19.0	18.4	20.2	13.3	22.4	25.2
Maximum	77.4	42.0	47.1	50.0	39.7	54.7	77.4
Interquartile (IQR)	10.3	9.1	8.6	9.7	6.5	11.2	11.4

Outdoor $PM_{2.5}$ concentration on day of carotid ultrasound Exam 5 (micrograms/m^3)							
N	2581	453	515	179	412	553	469
Mean	10.7	10.2	10.9	11.2	8.6	11.6	11.3
Standard Deviation (SD)	5.7	4.9	6.2	6.2	4.7	6.5	4.8
Minimum	1.0	1.0	2.5	3.1	1.0	1.0	3.0
25th percentile	6.5	6.4	5.9	6.5	5.1	7.1	8.0
50th percentile	9.7	9.6	9.6	9.2	7.6	10.6	10.9
75th percentile	13.5	13.3	14.4	14.3	10.8	14.6	13.0
Maximum	46.6	25.3	41.1	32.1	24.5	39.9	46.6
Interquartile (IQR)	7.0	6.9	8.5	7.8	5.7	7.5	5.0
Outdoor $PM_{2.5}$ one day before carotid ultrasound Exam 5 (micrograms/m^3)							
N	2574	459	517	175	411	544	468
Mean	10.6	10.2	10.6	11.5	8.5	11.9	11.0
Standard Deviation (SD)	5.7	4.9	5.9	6.2	4.9	6.9	4.6
Minimum	1.0	1.0	2.4	2.4	1.0	1.0	3.0
25th percentile	6.4	6.5	6.3	6.7	5.1	6.7	8.0
50th percentile	9.6	9.7	9.5	10.0	7.4	10.7	10.6

75th percentile	13.1	13.1	12.8	14.8	10.3	14.9	13.0
Maximum	41.1	33.5	41.1	31.9	29.0	39.9	39.0
Interquartile (IQR)	6.7	6.6	6.5	8.1	5.2	8.2	5.0
Outdoor $PM_{2.5}$ two days before radial tonometry Exam 5 (micrograms/m^3)							
N	2507	442	508	151	405	534	467
Mean	10.6	10.2	10.5	11.6	8.6	12.0	11.0
Standard Deviation (SD)	5.1	4.3	5.2	5.5	4.4	6.1	4.3
Minimum	1.0	1.0	3.1	2.2	2.3	1.6	4.5
25th percentile	7.0	7.2	6.8	7.1	5.6	7.1	8.1
50th percentile	9.8	9.6	9.7	10.4	7.7	10.7	10.6
75th percentile	13.2	12.7	12.4	15.7	10.8	15.9	12.7
Maximum	36.0	25.0	33.4	26.4	26.6	36.0	35.9
Interquartile (IQR)	6.2	5.5	5.7	8.6	5.2	8.8	4.7

Table 4.14: Association between interquartile region (IQR) of annual average $PM_{2.5}$ and NOx pollution for year 2000 and between Exams 1 and 5 with PTC2 with three staged models

	Cross-sectional estimate[1]						Rate of change estimate[2]				
	Estimate	Std. Error	95%L L	95%U L	P-value		Estimate	Std. Error	95%L L	95%U L	P-value
Model 1[3]											
Outdoor $PM_{2.5}$	0.09	0.12	-0.14	0.32	0.46		-0.01	0.01	-0.04	0.02	0.48
Outdoor NOx	-0.27	0.21	-0.69	0.15	0.21		0.00	0.02	-0.04	0.05	0.85
Model 2[4]											
Outdoor $PM_{2.5}$	0.14	0.12	-0.09	0.37	0.25		-0.01	0.01	-0.04	0.02	0.55
Outdoor NOx	-0.15	0.22	-0.57	0.27	0.49		0.01	0.02	-0.04	0.06	0.64
Model 3[5]											

Outdoor $PM_{2.5}$	0.11	0.12	-0.11	0.34	0.33		-0.01	0.01	-0.03	0.02	0.63
Outdoor NOx	-0.11	0.21	-0.52	0.31	0.61		0.01	0.02	-0.04	0.06	0.68

[1] Air pollution exposure for cross-sectional estimate: Association of annual average PM2.5 exposure during year 2000 (baseline exam) with arterial function at exams 1 and 5

[2] Air pollution exposure for rate of change estimate: Association of annual average PM2.5 exposure between Exams 1 and 5 (roughly 2000-2010) with rate of change of arterial function measure between exams 1 and 5

[3] Model 1: Adjusted for time-varying age; baseline gender, race/ethnicity, site

[4] Model 2: Adjusted for Model 1 covariates plus time-varying smoking, lipid lowering medication, heart rate; baseline highest educational level attained, income, BMI, total cholesterol, HDL cholesterol, triglycerides, diabetes, CRP

[5]Model 3: Adjusted for Model 2 covariates plus time-varying SBP, anti-hypertensive medication

Table 4.15: Association between interquartile region (IQR) of annual average $PM_{2.5}$ and NOx pollution for year 2000 and between Exams 1 and 5 with PTC1 with three staged models

	Cross-sectional estimate[1]						Rate of change estimate[2]				
	Estimate	Std. Error	95%LL	95%UL	P-value		Estimate	Std. Error	95%LL	95%UL	P-value
Model 1[3]											
Outdoor PM2.5	-0.06	0.06	-0.18	0.06	0.31		0.00	0.01	-0.01	0.02	0.73
Outdoor NOx	**-0.37**	**0.11**	**-0.59**	**-0.15**	**0.001**		0.02	0.01	0.00	0.05	0.08
Model 2[4]											
Outdoor PM2.5	-0.03	0.06	-0.14	0.09	0.67		0.00	0.01	-0.01	0.02	0.87
Outdoor NOx	**-0.22**	**0.11**	**-0.44**	**0.00**	**0.05**		0.02	0.01	-0.01	0.05	0.16
Model 3[5]											
Outdoor PM2.5	-0.03	0.06	-0.15	0.09	0.59		0.00	0.01	-0.01	0.02	0.82

Outdoor NOx	-0.21	0.11	-0.43	0.01	0.06		0.02	0.01	-0.01	0.05	0.18

[1] Air pollution exposure for cross-sectional estimate: Association of annual average PM2.5 exposure during year 2000 (baseline exam) with arterial function at exams 1 and 5

[2] Air pollution exposure for rate of change estimate: Association of annual average PM2.5 exposure between Exams 1 and 5 (roughly 2000-2010) with rate of change of arterial function measure between exams 1 and 5

[3] Model 1: Adjusted for time-varying age; baseline gender, race/ethnicity, site

[4] Model 2: Adjusted for Model 1 covariates plus time-varying smoking, lipid lowering medication, heart rate; baseline highest educational level attained, income, BMI, total cholesterol, HDL cholesterol, triglycerides, diabetes, CRP

[5] Model 3: Adjusted for Model 2 covariates plus time-varying SBP, anti-hypertensive medication

Table 4.16: Association between interquartile region (IQR) of annual average $PM_{2.5}$ and NOx pollution for year 2000 and between Exams 1 and 5 with DC with three staged models

	Cross-sectional estimate[1]						Rate of change estimate[2]				
	Estimate	Std. Error	95%LL	95%UL	P-value		Estimate	Std. Error	95%LL	95%UL	P-value
Model 1[3]											
Outdoor $PM_{2.5}$	-0.02	0.04	-0.10	0.06	0.66		0.00	0.00	0.00	0.01	0.32
Outdoor NOx	**-0.15**	**0.07**	**-0.30**	**0.00**	**0.04**		0.00	0.01	-0.01	0.02	0.64
Model 2[4]											
Outdoor $PM_{2.5}$	0.00	0.04	-0.08	0.08	0.97		0.00	0.00	0.00	0.01	0.33
Outdoor NOx	-0.06	0.07	-0.21	0.08	0.39		0.00	0.01	-0.01	0.02	0.58
Model 3[5]											

Outdoor $PM_{2.5}$	0.00	0.04	-0.08	0.08	0.99		0.00	0.00	0.00	0.01	0.28
Outdoor NOx	-0.04	0.07	-0.18	0.10	0.56		0.00	0.01	-0.01	0.02	0.60

[1] Air pollution exposure for cross-sectional estimate: Association of annual average PM2.5 exposure during year 2000 (baseline exam) with arterial function at exams 1 and 5

[2] Air pollution exposure for rate of change estimate: Association of annual average PM2.5 exposure between Exams 1 and 5 (roughly 2000-2010) with rate of change of arterial function measure between exams 1 and 5

[3] Model 1: Adjusted for time-varying age; baseline gender, race/ethnicity, site

[4] Model 2: Adjusted for Model 1 covariates plus time-varying smoking, lipid lowering medication, heart rate; baseline highest educational level attained, income, BMI, total cholesterol, HDL cholesterol, triglycerides, diabetes, CRP

[5] Model 3: Adjusted for Model 2 covariates plus time-varying SBP, anti-hypertensive medication

Table 4.17: Association between interquartile region (IQR) of annual average $PM_{2.5}$ and NOx pollution for year 2000 and between Exams 1 and 5 with YEM with three staged models

	Cross-sectional estimate[1]						Rate of change estimate[2]				
	Estimate	Std. Error	95%LL	95%UL	P-value		Estimate	Std. Error	95%LL	95%UL	P-value
Model 1[3]	3.42	43.65	-82.14	88.98	0.94		0.52	5.29	-9.85	10.89	0.92
Outdoor $PM_{2.5}$	136.95	78.00	-15.94	289.83	0.08		6.87	8.95	-10.67	24.41	0.44
Outdoor NOx											
Model 2[4]	-23.48	43.04	-107.84	60.87	0.59		0.31	5.27	-10.03	10.65	0.95
Outdoor $PM_{2.5}$	51.60	78.20	-101.67	204.88	0.51		3.96	9.07	-13.82	21.75	0.66
Outdoor NOx											
Model 3[5]	-24.23	42.28	-107.10	58.64	0.57		-0.13	5.19	-10.31	10.04	0.98
Outdoor $PM_{2.5}$	34.71	76.84	-115.91	185.32	0.65		3.76	8.93	-13.76	21.27	0.67

Outdoor NOx	3.42	43.65	-82.14	88.98	0.94		0.52	5.29	-9.85	10.89	0.92

[1] Air pollution exposure for cross-sectional estimate: Association of annual average PM2.5 exposure during year 2000 (baseline exam) with arterial function at exams 1 and 5

[2] Air pollution exposure for rate of change estimate: Association of annual average PM2.5 exposure between Exams 1 and 5 (roughly 2000-2010) with rate of change of arterial function measure between exams 1 and 5

[3] Model 1: Adjusted for time-varying age; baseline gender, race/ethnicity, site

[4] Model 2: Adjusted for Model 1 covariates plus time-varying smoking, lipid lowering medication, heart rate; baseline highest educational level attained, income, BMI, total cholesterol, HDL cholesterol, triglycerides, diabetes, CRP

[5] Model 3: Adjusted for Model 2 covariates plus time-varying SBP, anti-hypertensive medication

Table 4.18: Association between 5 micrograms/m^3 of daily average $PM_{2.5}$ pollution with respect to day of exam[1] with PTC2 at Exams 1 and 5 with three staged models

	PTC2				
	Coef.	Std. err.	95% LL	95% UL	P-value
Model 1[2]					
Residuals of $PM_{2.5}$ on day of exam	-0.006	0.037	-0.078	0.066	0.877
Residuals of $PM_{2.5}$ ONE DAY BEFORE of exam	**-0.067**	**0.034**	**-0.133**	**0.000**	**0.049**
Residuals of $PM_{2.5}$ TWO DAYS BEFORE of exam	**-0.078**	**0.038**	**-0.152**	**-0.004**	**0.039**
Model 2[3]					
Residuals of $PM_{2.5}$ on day of exam	-0.012	0.036	-0.084	0.059	0.731
Residuals of $PM_{2.5}$ ONE DAY BEFORE of exam	**-0.068**	**0.034**	**-0.134**	**-0.002**	**0.044**
Residuals of $PM_{2.5}$ TWO DAYS BEFORE of exam	**-0.078**	**0.037**	**-0.151**	**-0.004**	**0.038**
Model 3[4]					
Residuals of $PM_{2.5}$ on day of exam	-0.013	0.036	-0.083	0.058	0.721
Residuals of $PM_{2.5}$ ONE DAY BEFORE of exam	**-0.067**	**0.033**	**-0.132**	**-0.001**	**0.045**
Residuals of $PM_{2.5}$ TWO DAYS BEFORE of exam	**-0.074**	**0.037**	**-0.146**	**-0.001**	**0.047**

[1] Radial tonometry exam for PTC1 and PTC2

[2] Model 1: Adjusted for time-varying age; baseline gender, race/ethnicity, site

[3] Model 2: Adjusted for Model 1 covariates plus time-varying smoking, lipid lowering medication, heart rate; baseline highest educational level attained, income, BMI, total cholesterol, HDL cholesterol, triglycerides, diabetes, CRP

[4] Model 3: Adjusted for Model 2 covariates plus time-varying SBP, anti-hypertensive medication

Table 4.19: Association between 5 micrograms/m^3 of daily average $PM_{2.5}$ pollution with respect to day of exam[1] with PTC1 at Exams 1 and 5 with three staged models

	PTC1				
	Coef.	Std. err.	95% LL	95% UL	P-value
Model 1[2]					
Residuals of $PM_{2.5}$ on day of exam	0.022	0.020	-0.017	0.062	0.270
Residuals of $PM_{2.5}$ ONE DAY BEFORE of exam	-0.010	0.019	-0.047	0.027	0.589
Residuals of $PM_{2.5}$ TWO DAYS BEFORE of exam	-0.024	0.021	-0.065	0.017	0.253
Model 2[3]					
Residuals of $PM_{2.5}$ on day of exam	0.024	0.020	-0.014	0.063	0.213
Residuals of $PM_{2.5}$ ONE DAY BEFORE of exam	-0.005	0.018	-0.040	0.031	0.789
Residuals of $PM_{2.5}$ TWO DAYS BEFORE of exam	-0.023	0.020	-0.063	0.016	0.246
Model 3[4]					
Residuals of $PM_{2.5}$ on day of exam	0.024	0.019	-0.014	0.063	0.211
Residuals of $PM_{2.5}$ ONE DAY BEFORE of exam	-0.005	0.018	-0.040	0.030	0.783
Residuals of $PM_{2.5}$ TWO DAYS BEFORE of exam	-0.023	0.020	-0.062	0.017	0.258

[1] Radial tonometry exam for PTC1 and PTC2

[2] Model 1: Adjusted for time-varying age; baseline gender, race/ethnicity, site

[3] Model 2: Adjusted for Model 1 covariates plus time-varying smoking, lipid lowering medication, heart rate; baseline highest educational level attained, income, BMI, total cholesterol, HDL cholesterol, triglycerides, diabetes, CRP

[4] Model 3: Adjusted for Model 2 covariates plus time-varying SBP, anti-hypertensive medication

Table 4.20: Association between 5 micrograms/m^3 of daily average $PM_{2.5}$ pollution with respect to day of exam[1] with DC at Exams 1 and 5 with three staged models

	DC				
	Coef.	Std. err.	95% LL	95% UL	P-value
Model 1[2]					
Residuals of $PM_{2.5}$ on day of exam	0.002	0.013	-0.023	0.027	0.893
Residuals of $PM_{2.5}$ ONE DAY BEFORE of exam	-0.014	0.012	-0.037	0.010	0.257
Residuals of $PM_{2.5}$ TWO DAYS BEFORE of exam	**-0.031**	**0.013**	**-0.057**	**-0.005**	**0.021**
Model 2[3]					
Residuals of $PM_{2.5}$ on day of exam	-0.001	0.012	-0.025	0.023	0.937
Residuals of $PM_{2.5}$ ONE DAY BEFORE of exam	-0.011	0.012	-0.034	0.012	0.341
Residuals of $PM_{2.5}$ TWO DAYS BEFORE of exam	**-0.030**	**0.013**	**-0.055**	**-0.004**	**0.022**
Model 3[4]					
Residuals of $PM_{2.5}$ on day of exam	0.001	0.012	-0.022	0.025	0.901
Residuals of $PM_{2.5}$ ONE DAY BEFORE of exam	-0.007	0.011	-0.029	0.015	0.506
Residuals of $PM_{2.5}$ TWO DAYS BEFORE of exam	-0.023	0.013	-0.048	0.001	0.064

[1] Carotid ultrasound exam for DC and YEM

[2] Model 1: Adjusted for time-varying age; baseline gender, race/ethnicity, site

[3] Model 2: Adjusted for Model 1 covariates plus time-varying smoking, lipid lowering medication, heart rate; baseline highest educational level attained, income, BMI, total cholesterol, HDL cholesterol, triglycerides, diabetes, CRP

[4] Model 3: Adjusted for Model 2 covariates plus time-varying MAP, anti-hypertensive medication

Table 4.21: Association between 5 micrograms/m^3 of daily average $PM_{2.5}$ pollution with respect to day of exam[1] with YEM at Exams 1 and 5 with three staged models

	YEM				
	Coef.	Std. err.	95% LL	95% UL	P-value
Model 1[2]					
Residuals of $PM_{2.5}$ on day of exam	**28.388**	**14.265**	**0.428**	**56.348**	**0.047**
Residuals of $PM_{2.5}$ ONE DAY BEFORE of exam	**35.000**	**13.331**	**8.871**	**61.130**	**0.009**
Residuals of $PM_{2.5}$ TWO DAYS BEFORE of exam	**35.105**	**14.957**	**5.790**	**64.420**	**0.019**
Model 2[3]					
Residuals of $PM_{2.5}$ on day of exam	**30.295**	**14.058**	**2.742**	**57.849**	**0.031**
Residuals of $PM_{2.5}$ ONE DAY BEFORE of exam	**33.596**	**13.145**	**7.832**	**59.361**	**0.011**
Residuals of $PM_{2.5}$ TWO DAYS BEFORE of exam	**34.721**	**14.737**	**5.836**	**63.606**	**0.019**
Model 3[4]					
Residuals of $PM_{2.5}$ on day of exam	**28.318**	**13.841**	**1.189**	**55.447**	**0.041**
Residuals of $PM_{2.5}$ ONE DAY BEFORE of exam	**31.109**	**12.942**	**5.743**	**56.476**	**0.016**
Residuals of $PM_{2.5}$ TWO DAYS BEFORE of exam	**30.086**	**14.513**	**1.639**	**58.532**	**0.038**

[1] Carotid ultrasound exam for DC and YEM

[2] Model 1: Adjusted for time-varying age; baseline gender, race/ethnicity, site

[3] Model 2: Adjusted for Model 1 covariates plus time-varying smoking, lipid lowering medication, heart rate; baseline highest educational level attained, income, BMI, total cholesterol, HDL cholesterol, triglycerides, diabetes, CRP

[4] Model 3: Adjusted for Model 2 covariates plus time-varying MAP, anti-hypertensive medication

Chapter 5. Conclusions and Recommendations for Future Research

The overall objective of this dissertation was to better understand how arterial function measures may be on biological pathways between increased exposure to air pollution and greater risk of CVD events. Limited research has been done to examine how predictive a wide range of arterial stiffness measures is of CVD events in a single cohort. Thus, we examined how five different arterial function measures, assessing arterial stiffness or elasticity, predict subsequent cardiovascular disease (CVD) events in the Multi-Ethnic Study of Atherosclerosis (MESA) during about 10 years of follow-up. Few studies have examined determinants of longitudinal change in arterial stiffness measures. Thus, we also investigated how traditional cardiovascular risk factors were associated with longitudinal change in arterial stiffness measures. Some studies examining the association between air pollution and subclinical measures of CVD have used relatively crude measures of exposure. Consequently, we utilized more highly refined estimates of outdoor ambient exposure to fine particulate matter ($PM_{2.5}$) and oxides of nitrogen (NOx) from a spatiotemporal model developed by the MESA Air study.

We observed several interesting relationships between arterial functional measures, that assessed the elasticity (or stiffness) of the arteries, and the risk of CVD events and between traditional CVD risk factors and longitudinal change in arterial function measures. First, we identified that higher C2, also known as small artery elasticity, at the baseline exam (Exam 1) was associated with increased risk of coronary heart disease events during follow-up. In addition, we found that C2 provided additional discrimination for the prediction of CHD events, when examining the area under the receiver-operating characteristic (ROC) curve. Next, we found that having higher

mean arterial pressure (MAP), having diabetes at baseline, and having increased age at baseline were associated with larger increases in YEM over follow-up. However, we observed that higher systolic blood pressure (SBP) was associated with smaller declines in PTC1 and PTC2. In addition, increased age at baseline was associated with smaller declines in PTC1, PTC2, and DC over follow-up. The different directions of the association of age with arterial stiffness progression and between blood pressure measures with arterial stiffness progression indicate complex relationships between those risk factors and change in arterial stiffness in different areas of the arterial system. Finally, we observed that greater long-term traffic related air pollution, as assessed by annual average exposure to NOx during the year 2000, was associated with less arterial elasticity based on measurements of PTC1, in a cross-sectional manner. We also observed that increased acute exposure to particulate air pollution, ranging from the day of, one day before, or two days before cross-sectional measurements of arterial elasticity at both exams, was associated with a reduction in arterial elasticity, assessed by PTC2 and DC, and an increase in arterial stiffness, assessed by YEM. However, we did not see a relationship between long-term air pollution exposure and rate of change in any of the arterial function measures we studied.

These findings are important because they can help form the basis for standard-setting for clean air. The United States Environmental Protection Agency (EPA) is required to set National Ambient Air Quality Standards (NAAQS) for six different criteria air pollutants by the Clean Air Act of 1970, which was amended in 1977 and 1990. These pollutants include ozone, particulate matter, carbon monoxide, lead, sulfur dioxide, and nitrogen dioxide.(United States Environmental Protection Agency 2017) The EPA must use scientific evidence on the public health and environmental health impacts of air pollution to set these standards. One of the

criticisms of the standards for criteria air pollutants is that there is a lack of data on the biological mechanisms linking air pollution and cardiovascular disease events. (Moolgavkar 2005) The results from this project provides more evidence for short-term effects of air pollution on arterial function, as opposed to long-term effects of air pollution on arterial function. These results suggest that air pollution may have transient effects on arterial elasticity and stiffness. These findings give additional support for the association between increased acute exposure to air pollution and the triggering of cardiovascular disease events.

Results from our analysis suggest that arterial function seems to be more variable and more easily changed or altered than other subclinical measures of cardiovascular disease, such as coronary artery calcification (CAC). We expected arterial stiffness to increase over time, with aging. However, for those with Exam 1 and 5 arterial function measures, a sizable percentage of participants either had no change or actually had decreased arterial stiffness (or increased arterial elasticity) over time. This was true for 34.3% of those with both PTC2 measures, 24.7% of those with both PTC1 measures, 35.7% of those with both DC measures, 44.2% of those with both YEM measures. It appears that these measures of arterial function have a much more important transient aspect, and hence are more easily reversible than the more chronically progressing changes in coronary artery calcification. This may be one reason that these measures arterial function are not as easily used as a measures of long-term effects of air pollution. In contrast, coronary artery calcification tends to get progressively worse, unless medical intervention such as surgery is undertaken.

One limitation of our analysis is that we used a set of arterial function measures with varying degrees of association with CVD events after adjustment for common cardiovascular risk factors. We found that increased baseline C2 and PTC2 was associated with decreased risk of all CVD, CHD, and CHF events. In our analysis, increased baseline C1 was associated with decreased risk of CHF events. We also observed that increased baseline PTC1 was associated with decreased risk of all CVD events. However, increases in baseline DC, CD, YM, and YEM did not show association with any of the composite CVD outcomes that we looked at. Thus, one possibility is that we failed to see associations between increased long-term air pollution and rate of change in increased arterial stiffness because the measures of arterial stiffness we examined were not very good predictors of CVD events. Therefore, these measures may not have been the best choice to measure damage to the cardiovascular system. If this is indeed the case, perhaps a future study of long-term air pollution and arterial function should consider aortic pulse wave velocity, often considered the most robust assessment of arterial stiffness, at least for large vessel stiffness. Increased aortic pulse wave velocity, not measured in MESA, at baseline has been strongly associated with the risk of CVD events in numerous studies.(C Vlachopoulos, Aznaouridis, and Stefanadis 2010)

We were also limited in our analysis by only having arterial function measures at Exam 1 and Exam 5. Therefore, we could not assess if the trajectory of the change between Exam 1 and 5 was non-linear. Particularly for the individuals that showed no change or gain in arterial elasticity (or loss in arterial stiffness) over follow-up, it would be interesting to see if there were changes in arterial function in the opposite direction between Exams 1 and 5 that we could not

detect. In future studies of longitudinal change in arterial function, it would be advantageous to have at least three, if not more, measurements of arterial function over time.

An additional limitation of our analysis was that we used residential outdoor air pollutant concentrations to estimate individual exposure to pollutants of ambient origin. This approach does not take into account more detailed micro-environmental contributions. For example, since most participants spend most of their time indoors, the indoor concentrations may be more directly relevant. The MESA study made great efforts to document individual participants' time-activity patterns. The MESA study also estimated how much ambient air pollution infiltrates from the outdoor environment into the indoor space where most people are a majority of their time. Future analyses could compare our results from the outdoor air pollutant concentrations with estimates of indoor air pollution concentrations as a sensitivity analysis.

A separate limitation is that the air pollution concentrations studied in this analysis are relatively low compared to those in rapidly industrializing countries. Thus, we may have seen very limited effects of long-term air pollution on arterial function because concentrations were too low to have biological effects on arterial function. Studies of air pollution and longitudinal change in arterial function in other countries with higher air pollution concentrations than the United States may yield different results.

Another limitation is that we were unable to distinguish if the short-term effects of $PM_{2.5}$ were due to a certain time interval between exposure and measurement of arterial function. For

example, there were positive associations between daily average $PM_{2.5}$ exposure on the day of the exam, one day before the exam, and two days before the exam with measurements of YEM from the carotid ultrasound exam. It is unclear whether these effects on YEM were primarily driven by only one particular time interval or if all of the time intervals. Therefore, in the future, it would be useful to use a distributed lag effects model in which we examined the effects of short-term $PM_{2.5}$ on the day of the exam, one day before the exam, and two days before the exam simultaneously in the same model.

Despite these limitations, this study has several strengths. To our knowledge, this is the first study to examine the association between air pollution and longitudinal change in arterial stiffness. This research adds important knowledge that there does not appear to be an association between long-term air pollution and rate of change in the arterial function measures that we studied. Our study population was an ethnically diverse (White, Black, Chinese, and Hispanic) group of older adults (aged 45-84 at baseline) in the United States. Thus, our findings are applicable to a variety of different racial/ethnic groups, as opposed to studies that have been conducted in a more ethnically homogenous population. In addition, we also were able to look at a variety of different arterial function measures that represent different aspects of the arterial system, such as systemic arterial system versus local arterial stiffness in the carotid artery. This enabled us to see the potential effects of air pollution on different vascular beds in the arterial system.

In summary, findings from these analyses improve our understanding on the predictive value of several arterial function measures for CVD events. We also examined the relationship between cardiovascular risk factors and longitudinal change in arterial function measures. While there are many studies of cardiovascular risk factors and cross-sectional measurements of arterial function measures, there are few looking at the determinants of longitudinal change in arterial function measures. Our analyses also added to the current state of knowledge regarding the effects of short-term and long-term air pollution on arterial function measures. The use of a linear mixed effects model enabled us to examine both effects of long-term air pollution on cross-sectional measurements of arterial function at Exams 1 and 5 and effects of long-term air pollution on longitudinal change of arterial function between Exams 1 and 5 simultaneously. We found transient, short-term effects of air pollution on arterial stiffness, but did not see long-term effects of air pollution on longitudinal change in arterial stiffness. These results suggest that future studies of short-term effects of air pollution and arterial function measures may be useful to help us better understand the biological mechanisms by which air pollution is connected with cardiovascular disease events.

Chapter 6. Appendix

6.1 Cardiovascular risk factors and arterial function measures analysis

6.1.1 Radial tonometry study population for cardiovascular risk factors analysis

Percentage of those with MESA Exam 1 data that were included in radial tonometry analysis:

3,545 participants included in analysis/6,814 participants with MESA Exam 1 data =52.0%

Percentage of those with MESA radial tonometry raw waveform data for Exam 1 and 5 that were included in radial tonometry analysis: 3,545 participants included in analysis/4,005 participants with Exam 1 and 5 radial tonometry data=88.5%

6.1.2 Carotid ultrasound study population for cardiovascular risk factors analysis

Percentage of those with MESA Exam 1 data that were included in carotid ultrasound analysis:

2,593 included in analysis/ 6,814 participants with MESA Exam 1 data = 38.1%

Percentage of those with MESA with carotid ultrasound imaging data for Exam 1 and 5: 2,593 included in analysis/ 3,642 participants with Exam 1 and 5 carotid ultrasound data=71.2%

6.1.3 Comparing distensibility coefficient (DC) at carotid artery and carotid distensibility (CD) as well as Young's Elastic Modulus (YEM) at carotid artery and Young's Modulus (YM) at carotid artery for cardiovascular risk factors analysis

At Exam 1, there was moderate correlation (0.58) between DC and CD. For Exam 1, there was also moderate correlation (0.45) between YEM and YM. It appears the methodology to calculate carotid distensibility (DC) and Young's modulus (YEM) for Exams 1 and 5 were slightly different, but not a huge departure from the prior methods to calculate these measures (CD and YM) at Exam 1.

We also found that baseline CD and DC measurements had the same qualitative associations with risk of subsequent CHD, CVD, and CHF events using a Cox proportional hazards model. In addition, YEM and YM had the same has the same qualitative associations with risk of CHD, CVD, and CHF events using a Cox proportional hazards model. This suggests that while CD and DC, and YEM and YM have only moderate correlation, they may capture the similar properties of the arterial system with respect to prediction of CVD event risk.

6.1.4 Sensitivity analysis comparing rate of change linear regression and linear mixed effects models for cardiovascular risk factors and arterial function measures analysis

6.1.4.1 Description of rate of change linear regression models (secondary analysis)

For the minimally adjusted model, we examined the association between each CV risk factor variable separately and rate of change in arterial stiffness, controlling for "base model covariates." The CV risk factors included these variables at Exam 1: BMI, total cholesterol, HDL cholesterol, triglycerides, diabetes mellitus status, annual gross family income, highest educational level completed, SBP for PTC2 and PTC1, MAP for DC and YEM, smoking status, use of blood pressure medication, use of lipid lowering medication, heart rate, and high-sensitivity c-reactive protein. When examining the association between lipid levels (total cholesterol, HDL cholesterol, or triglycerides) at exam 1 and change in arterial stiffness, models were also adjusted for use of lipid lowering medication at exam 1. When examining the association between blood pressure measures (SBP or MAP) at Exam 1 and change in stiffness, models were adjusted for use of blood pressure medication at exam 1.

For the fully adjusted model, all "base model covariates" and additional cardiovascular risk factors are controlled for simultaneously rather than separately. These additional cardiovascular risk factors included these variables at Exam 1: BMI, total cholesterol, HDL cholesterol, triglycerides, diabetes mellitus status, annual gross family income, highest educational level completed, SBP for PTC2 and PTC1, MAP for DC and YEM, smoking status, use of blood pressure medication, use of lipid lowering medication, heart rate, and high-sensitivity c-reactive protein.

6.1.4.2 PTC2 results comparing models for risk factors analysis

The sensitivity analyses of the association between cardiovascular risk factors and PTC2 showed that the rate of change model yielded similar results to the linear mixed model for the univariate (Table 3.23) and multivariate (Table 3.24) associations. However, for univariate and multivariate associations, being a current smoker compared to never smoker was associated with a smaller decline in PTC2 using the rate of change model only.

6.1.4.3 PTC1 results comparing models for risk factors analysis

The sensitivity analyses of the associations between cardiovascular risk factors and PTC1 showed a few differences between the rate of change model and linear mixed model for the univariate association (Table 3.25). For the univariate association, being Hispanic race/ethnicity versus White was associated with a smaller decline in PTC1 for the rate of change model only. Having increased triglycerides at baseline was associated with lower decline in PTC1 for the rate of change model only for the univariate association. For the linear mixed model only, having 4-

year college degree or more education (compared to less than high school degree) was associated with greater decline in PTC1 in the linear mixed model only for the univariate association. There were no differences between the rate of change model and linear mixed model for the multivariate association (Table 3.26).

6.1.4.4 DC results comparing models for risk factors analysis

The sensitivity analysis of the univariate and multivariate associations between CV risk factors and DC showed a few differences between the rate of change and linear mixed models (Table 3.27, Table 3.28). Increased triglycerides were associated with smaller declines in DC for the univariate association with linear mixed model only. Having annual gross family income of $50,000-$74,599 compared to <$25,000 at exam 1 was associated with a smaller decline in DC for univariate association with the rate of change model only. For the multivariate association, increased MAP at Exam 1 was associated with a smaller decline in DC for the rate of change model. But MAP as a time-varying variable was not associated with change in DC for the linear mixed model. Being a current smoker compared to never smoker was associated with a larger decline in DC for the rate of change model only for the multivariate association. Increased heart rate at exam 1 was associated with larger decline in DC for the rate of change model for the multivariate association. However, heart rate as a time-varying variable is not associated with change in DC in the linear mixed model.

6.1.4.5 YEM results comparing models for risk factors analysis

Sensitivity analyses of the association between cardiovascular risk factors and YEM increase showed that the rate of change model and linear mixed model results were mostly similar for

univariate (Table 3.29) and multivariate (Table 3.30) associations. However, there were a few differences: For both univariate and multivariate associations, being a HS graduate compared to less than HS education was associated with smaller increases in YEM for the rate of change model only. Having a 4-year college degree or more compared to less than HS graduation were associated with smaller increases in YEM for the multivariate association in the rate of change model only. For the multivariate model, having diabetes at Exam 1 compared to having no diabetes was associated with a larger increase in YEM for the linear mixed model only.

6.1.5 Air pollution analysis study populations

6.1.5.1 Radial tonometry study population for $PM_{2.5}$ air pollution analysis

There were 3,751 participants with both Exam 1 and Exam 5 radial tonometry measures. There were 2,582 participants with only Exam 1 radial tonometry measures. There were 254 participants with only Exam 5 radial tonometry measures. There were 6,575 participants with baseline year 2000 $PM_{2.5}$ data and 3,317 participants with longitudinal $PM_{2.5}$ data.

The following observations were included in our analysis: 2,736 participants had Exam 1 radial tonometry measures, baseline and longitudinal $PM_{2.5}$ data, and all covariate data for the most fully adjusted model (Model 3). 2,696 participants had Exam 1 and Exam 5 radial tonometry measures, baseline and longitudinal $PM_{2.5}$ data, and all covariate data for the most fully adjusted model (Model 3). 2,830 participants had Exam 5 radial tonometry, baseline and longitudinal $PM_{2.5}$ data, and all covariate data for the most fully adjusted model (Model 3). Because we limited our analysis to participants with both Exam 1 and Exam 5 covariate data, and baseline and longitudinal $PM_{2.5}$ data we had 2,870 unique participants in our analysis.

2,870 participants had either Exam 1 only, Exam 5 only, or both Exam 1 and 5 data for radial tonometry measures, plus data for the annual average exposure to $PM_{2.5}$ during year 2000 and the annual average exposure to $PM_{2.5}$ between Exams 1 and 5 (roughly between years 2000-2010), and covariate data for fully adjusted model (Model 3).

Percentage of those with MESA Exam 1 data that were included in radial tonometry and long-term $PM_{2.5}$ pollution analysis: 2,870 participants included in analysis/6,814 participants with MESA Exam 1 data =42.5%

Percentage of those with MESA participants with radial tonometry raw waveform data for Exam 1 and 5 that were included in radial tonometry and long-term $PM_{2.5}$ pollution analysis: 2,870 participants included in analysis/4,005 participants with MESA Exam 1 and Exam 5 radial tonometry raw waveform data =71.7%

6.1.5.2 Radial tonometry study population for NOx air pollution analysis

There were 6,557 participants with baseline year 2000 NOx data and 3,729 participants with longitudinal NOx data.

The following observations were included in our analysis: 2,698 participants had Exam 1 radial tonometry measures, baseline and longitudinal NOx data, and all covariate data for the most fully adjusted model (Model 3). 2,658 participants had Exam 1 and Exam 5 radial tonometry measures, baseline and longitudinal NOx data, and all covariate data for the most fully adjusted model (Model 3). 2,791 participants had Exam 5 radial tonometry, baseline and longitudinal

NOx data, and all covariate data for the most fully adjusted model (Model 3). Because we limited our analysis to participants with both Exam 1 and Exam 5 covariate data, and baseline and longitudinal NOx data we had 2,870 unique participants in our analysis.

2,831 participants had either Exam 1 only, Exam 5 only, or both Exam 1 and 5 data for radial tonometry measures, plus data for the annual average exposure to NOx during year 2000 and the annual average exposure to NOx between Exams 1 and 5 (roughly between years 2000-2010), and covariate data for fully adjusted model (Model 3).

Percentage of those with MESA Exam 1 data that were included in radial tonometry and long-term NOx pollution analysis: 2,831 participants included in analysis/6,814 participants with MESA Exam 1 data =41.5%

Percentage of those with MESA participants with radial tonometry raw waveform data for Exam 1 and 5 that were included in radial tonometry and long-term NOx pollution analysis: 2,831 participants included in analysis/4,005 participants with MESA Exam 1 and Exam 5 radial tonometry raw waveform data =70.7%

6.1.5.3 Carotid ultrasound study population for $PM_{2.5}$ air pollution analysis

There were 2,729 participants with both Exam 1 and Exam 5 carotid ultrasound measures. There were 144 participants with only Exam 1 carotid ultrasound measures. There were 490 participants with only Exam 5 carotid ultrasound measures. There were 6,575 carotid ultrasound

participants with baseline year 2000 $PM_{2.5}$ data and 3,317 carotid ultrasound participants with longitudinal $PM_{2.5}$ data.

The following observations were included in our analysis: 2,560 participants had Exam 1 carotid ultrasound measures, baseline and longitudinal $PM_{2.5}$ data, and all covariate data for the most fully adjusted model (Model 3). 2,412 participants had Exam 1 and Exam 5 carotid ultrasound measures, baseline and longitudinal $PM_{2.5}$ data, and all covariate data for the most fully adjusted model (Model 3). 2,786 participants had Exam 5 radial tonometry, baseline and longitudinal $PM_{2.5}$ data, and all covariate data for the most fully adjusted model (Model 3). Because we limited our analysis to participants with both Exam 1 and Exam 5 covariate data, and baseline and longitudinal $PM_{2.5}$ data we had 2,934 unique participants in our analysis.

2,934 participants had either Exam 1 only, Exam 5 only, or both Exam 1 and 5 data for carotid ultrasound measures, plus data for the annual average exposure to $PM_{2.5}$ during year 2000 and the annual average exposure to $PM_{2.5}$ between Exams 1 and 5 (roughly between years 2000-2010), and covariate data for fully adjusted model (Model 3).

Percentage of those with MESA Exam 1 data that were included in carotid and long-term $PM_{2.5}$ pollution analysis: 2,934 participants included in analysis/6,814 participants with MESA Exam 1 data =43.1%

Percentage of those with MESA participants with carotid ultrasound data for Exam 1 and 5 that were included in carotid ultrasound and long-term $PM_{2.5}$ pollution analysis: 2,934 participants included in analysis/3,642 participants with MESA Exam 1 and 5 carotid ultrasound data =80.6%

6.1.5.4 Carotid ultrasound study population for NOx air pollution analysis

There were 6,557 participants with baseline year 2000 NOx data and 3,729 participants with longitudinal NOx data.

The following observations were included in our analysis: 2,546 participants had Exam 1 carotid ultrasound measures, baseline and longitudinal NOx data, and all covariate data for the most fully adjusted model (Model 3). 2,398 participants had Exam 1 and Exam 5 radial tonometry measures, baseline and longitudinal NOx data, and all covariate data for the most fully adjusted model (Model 3). 2,769 participants had Exam 5 radial tonometry, baseline and longitudinal NOx data, and all covariate data for the most fully adjusted model (Model 3). Because we limited our analysis to participants with both Exam 1 and Exam 5 covariate data, and baseline and longitudinal NOx data we had 2,917 unique participants in our analysis.

2,917 participants had either Exam 1 only, Exam 5 only, or both Exam 1 and 5 data for carotid ultrasound measures, plus data for the annual average exposure to NOx during year 2000 and the annual average exposure to NOx between Exams 1 and 5 (roughly between years 2000-2010), and covariate data for fully adjusted model (Model 3).

Percentage of those with MESA Exam 1 data that were included in carotid ultrasound and long-term NOx pollution analysis: 2,917 participants included in analysis/6,814 participants with MESA Exam 1 data =42.8%

Percentage of those with MESA participants with carotid ultrasound data for Exam 1 and 5 that were included in carotid ultrasound and long-term NOx pollution analysis: 2,917 participants included in analysis/3,642 participants with MESA Exam 1 and 5 carotid ultrasound data =80.1%

Chapter 7. References

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