

ARTERIAL STIFFNESS AND PERIPHERAL ARTERIAL DISEASE AS INDICATORS OF
ABDOMINAL AORTA DIAMETERS: THE ATHEROSCLEROSIS AND RISK IN
COMMUNITIES STUDY

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

Chapel Hill
2016

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ABSTRACT

Ada Al-Qunaibet: Arterial Stiffness and Peripheral Arterial Disease as Indicators of Abdominal Aorta Diameters: The Atherosclerosis and Risk in Communities Study
(Under the direction of Gerardo Heiss)

Background: Abdominal aorta (AA) dilatation (AAD) and aneurysms result from remodeling that includes atherosclerotic and arteriosclerotic components. The latter frequently coexist across different arterial territories. Peripheral arterial disease (PAD) is an ischemic manifestation of atherosclerosis, while arterial stiffening (AS) primarily reflects arteriosclerosis. Our aim was to examine PAD and AS as potential indicators of AAD. Methods: Cross-sectional analysis of data from the 5th examination of the Atherosclerosis Risk in Communities cohort (2011-2013). 4,802 participants 70-89 years were included to examine the association between PAD and AAD, and 4,224 participants were included to examine the association between AS and AAD. The anterior-posterior (AP) diameter of the AA was quantified by b-mode ultrasound at the proximal, mid-, and distal locations. The ankle-brachial index (ABI) and pulse wave velocity (PWV) were used to evaluate PAD and AS (central and peripheral), respectively. Heart-carotid (hc) and carotid-femoral (cf) PWV were used to quantify central AS, and femoral-ankle (fa) PWV was used to measure peripheral AS. ABI and PWV measurements were performed using an automated non-invasive waveform analyzer.

Results: Sixty percent of examinees were women, ~22% were black, and the mean age was 75.3 ± 5.1 years. The mean AP diameters and confidence intervals (CIs) for proximal, mid-, and distal diameters were; 1.95 ± 0.32 cm, 1.81 ± 0.33 cm, and 1.70 ± 0.35 cm, respectively. The mean value and CI for the lowest ABI of the right and left leg was 1.10 ± 0.14 . The mean values and CIs for hcPWV, cfPWV, right faPWV, and left faPWV were $1,132.8 \pm 344.5$ cm/s, $1,159.5 \pm 302.7$ cm/s, $1,099.2 \pm 180.8$ cm/s, and $1,067.8 \pm 174.8$ cm/s, re-

spectively. A U-shaped association between ABI and AAD was observed at all three levels of the AA. A positive, linear association between hcPWV was observed at all the levels of the aorta as the only measure of AS exhibiting a consistent and statistically significant association with AAD.

Conclusions: In older adults AAD is associated with PAD and with central AS. Although statistically significant, these associations are of small magnitude and have little practical applicability as indicators of AA dilatation.

Dedicated to my family, friends, mentors, and teachers.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my advisor Prof. Gerardo Heiss for his support, patience, and unparalleled dedication. He has shaped my work and pushed me to be a better scientist.

Many thanks to Dr. Bill Miller for his mentorship and guidance. His support has helped me through the first few years of this program. I am also, deeply thankful to Dr. Laura Loehr for the time and effort that she has dedicated in reviewing my dissertation and related work. She was always generous with her time and assistance. My sincere thanks also goes to Dr. Alan Hinderliter and Dr. David Couper for being part of my dissertation committee and for providing me with valuable feedback throughout the process of completing my dissertation work.

Thanks to the staff at the University of North Carolina at Chapel Hill particularly; Carmen Woody, Valerie Hudock, and Jennifer Moore. I am forever grateful to Nancy Colvin for her help, guidance, and love. She has provided me with invaluable support and assistance through many of the challenges I faced during the program. I am also thankful for all the exceptional friendships that I have made during my time at UNC-CH. Their support and care helped through some challenging times.

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022. I am grateful to have worked with the ARIC data and I am thankful to the cohort participants and the ARIC staff that have made this possible.

Most importantly, my accomplishment was made possible due to the love and support of my family. Therefore, I would like to express my eternal gratitude and appreciation to my amazing family: my parents, sister, brother, husband, and daughters. They always believed in me and encouraged me throughout my journey. I dedicate this dissertation to my mother who has worried about me throughout this endeavor. Finally, a special and warm thanks to my daughters; Jena and Judy who have been the sunshine in my life and the source of my happiness.

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LIST OF ABBREVIATIONS

AAD	abdominal aorta diameter
AAA	abdominal aortic aneurysm
AHA	American Heart Association
ABI	ankle-brachial index
AP	anterior-posterior
AUC	area under the curve
ARIC	Atherosclerosis and Risk in Communities
AS	arterial stiffness
cfPWV	carotid-femoral pulse wave velocity
CIMT	carotid intima-media thickness
CIHD	chronic ischemic heart disease
CT	computed tomography
CAC	coronary artery calcification
CARDIA	Coronary Artery Risk Development in Young Adults
CHD	coronary heart disease
CAD	coronary artery disease
DALY's	disability-adjusted life years
ECG	electrocardiogram
faPWV	femoral-ankle pulse wave velocity
FHS	Framingham Heart Study
hcPWV	heart-carotid pulse wave velocity
ICC	intra-class correlation coefficient
IHD	ischemic heart disease
MRA	magnetic resonance arteriogram
MRI	magnetic resonance imaging

MDC ₉₅	minimal detectable change
MESA	Multi-Ethnic Study of Atherosclerosis
MI	myocardial infarction
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NRI	net reclassification improvement
PAD	peripheral artery disease
PWV	pulse wave velocity
QC	quality control
RAS	renal artery stenosis
SEM	standard error of measurement
US	ultrasonography

INTRODUCTION

The proposed doctoral research related the main features of atherosclerosis, namely atherosclerosis and sclerosis, to abdominal aorta diameters and aortic aneurysms in a biracial cohort of 6,538 men and women aged 72-84 years. The atherotic component was indexed by the presence of lumen-occupying atherosclerotic lesions in the lower extremities, identified non-invasively by a reduced ankle-brachial index (ABI). The sclerotic element was measured by pulse wave velocity (PWV) in the central and peripheral arterial territories. The abdominal aorta diameter (AAD) that served as the dependent variable was statistically predicted cross-sectionally from the above-referenced measurements.

The dissertation focused on abdominal aorta diameters measured by abdominal ultrasound as the dependent variable. The first aim characterized the relationship between peripheral artery disease (PAD) measured by ABI and diameters of the abdominal aorta at proximal, mid-, and distal locations. A second aim characterized the relation between central arterial stiffness (measured by heart-carotid pulse wave velocity), peripheral arterial stiffness (measured by femoral-ankle pulse wave velocity), and the diameters of the abdominal aorta at a proximal, mid-aorta, and distal locations. The third aim was to develop and evaluate a statistical predictive model that utilizes ABI and PWV to classify AAD at clinically meaningful levels.

The clinical entities pertinent to the measurements mentioned above were abdominal aortic dilatation and aneurysms diagnosed by abdominal ultrasound, PAD diagnosed by ABI, and central and peripheral arterial stiffness measured by heart-carotid pulse wave velocity (hcPWV) and femoral-ankle pulse wave velocity (faPWV), respectively.

The associations hypothesized under each aim were characterized across the full spectrum of the study measurements and we considered pre-defined clinical cut points as secondary aims in order to quantify subclinical processes and to describe the pathways that lead to clinical disease.

CHAPTER 1: BACKGROUND

1.1. Atherosclerosis

1.1.1. Pathophysiology of atherosclerosis

Structural components of the wall of medium and large arteries

The arterial wall is made up by three main layers (figure 1); tunica intima, tunica media, and tunica adventitia from the lumen outward (Lâevy & Tedgui, 1999; Lusis, 2000; Safar, Levy, & Struijker-Boudier, 2003). The biological mechanisms of atherosclerosis are caused by molecular and cellular processes that mainly affect the intimal layer of arterial vessels (Stary et al., 1992). The tunica intima is the innermost layer that is adjacent to the arterial lumen. It is separated from the adjacent tunica media by the internal elastic lamina.

Tunica intima: The tunica intima is composed of two layers; the innermost layer is comprised of connective tissue called proteoglycan, and the outer layer is comprised of smooth muscle cells and elastic fibers. Variations in blood flow strength and wall tension affect the tunica intima, resulting in physiological changes that cause thickening of this structure (Stary et al., 1992). Therefore, the arterial segments with disturbed blood flow and abnormal laminar shear stress, such as branching points and bifurcations in the arterial tree, are more prone to develop atherosclerosis (Libby, 2000; Stary et al., 1992).

The endothelial cells that form the endothelium are the innermost layer of the tunica intima, which is adjacent to the arterial lumen (Stary et al., 1992). Normally endothelial cells do not promote the adherence of platelets or leucocytes, nor do they facilitate thrombosis (Stary et al., 1992). On the contrary, normal endothelium exerts the first protective anti-atherogenic process (Gouverneur, Berg, Nieuwdorp, Stroes, & Vink, 2006; Lusis, 2000; Stary et al., 1992).

Tunica media: The tunica media constitutes the thickest layer, and its constituents are smooth muscle cells that secrete elastin and collagen proteins. The ratio of elastin to collagen varies along the arterial tree (Lâevy & Tedgui, 1999). Large elastic arteries more proximal to the heart contain more elastin compared to collagen, while more distal to the heart the ratio is reversed. A threshold point in this respect is found near the diaphragm where the abdominal aorta begins (Safar et al., 2003). The tunica media of muscular arteries is predominantly made up of smooth muscle cells with less elastin and connective tissue. Therefore, medium muscular arteries are capable of changing their diameter under neuro-humoral stimulation (Lâevy & Tedgui, 1999).

Tunica adventitia: The tunica adventitia is primarily made up of connective tissue that contains collagenous fibers, elastic fibers, fibroblasts, and macrophages. From the luminal side, the tunica adventitia is lined by the external elastic lamina; the lateral side is less defined and is in conjunction with the perivascular connective tissue (Lâevy & Tedgui, 1999). The adventitia is made of fibroblasts and few elastic fibers. The adventitia contains the vasa vasorum, which supplies nutrients and oxygen to the tunica adventitia and tunica media. In addition, the tunica adventitia contains a lymphatic and nervous system that supplies both tunica adventitia and media (Lâevy & Tedgui, 1999).

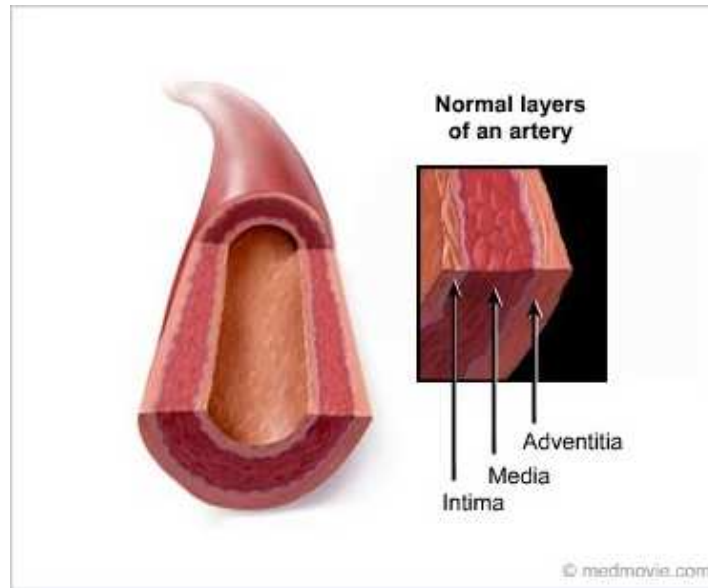


Figure 1. Arterial wall structure.

Source:<http://www.hwcr.org/Health/illustrations%20of%20human%20anatomy/Photos/arterial%20anatomy.jpg>

Definition of atherosclerosis

Atherosclerosis is defined as a systemic disease process, and inflammatory changes are part of its pathophysiology. Fatty deposits, inflammatory cells, and scar tissue build up within the sub-intimal space of arteries (Libby, 2000; Ross, 1999). Atherosclerotic changes affect primarily large and medium-sized elastic and muscular arteries (Ross, 1999). Inflammatory, molecular, and cellular processes that mainly affect the intimal layer of arterial vessels are involved in the biological mechanisms of atherosclerosis (Ross, 1999; Stary et al., 1992). Worldwide, cardiovascular morbidity and mortality are predominantly attributed to the sequelae of atherosclerosis (Go et al., 2013).

Below we combine the typology of the levels of atherosclerosis with the description of the dynamic process involved in atherogenesis.

Stages and types of atherosclerosis

Atherosclerosis starts in the peripubertal life epoch and progresses through stages, typically identified as initiation, progression, and complication (Libby, 2000; Scott, 2002; Stary et al., 1994). Atherosclerotic lesions have been systematized according to their cellular components and pathophysiological progression of the disease into six types. The initial and intermediate lesions include types I, II, and III. Advanced atherosclerotic lesions are subdivided into 3 types: IV, V, and VI (Stary et al., 1992; Stary et al., 1995; Stary et al., 1994). Of the aforementioned, types I and II are the only two that can exist in children (Stary et al., 1994).

Initial and intermediate atherosclerotic lesions: Type I (fatty streaks) — Fatty streaks are microscopic lipid deposits in the intimal layer that represent adaptive changes rather than an atherosclerotic transformation. Lipid is deposited in macrophages in an isolated manner forming foam cells (macrophages that contain lipid molecules). This type of lesion is common among children and young adults (Stary, 1994; Stary et al., 1994).

Type II — Type II lesions contain more abundant foam cells that are arranged in a stratified manner, and they are sub-grouped according to their progression into advanced lesions into type IIa (advanced-lesion prone) and type IIb (advanced-lesion resistant). Type II lesions contain some isolated mast cells, T lymphocytes, and small quantities of lipid droplets in extracellular spaces. However, the number of mast cells and T lymphocytes is less than the number of macrophages (Katsuda, Boyd, Fligner, Ross, & Gown, 1992; Munro, van der Walt, Munro, Chalmers, & Cox, 1987; Stary, 1990, 1994; Stary et al., 1994). Type II lesions involve deposition of lipid droplets in macrophages and smooth muscle cells, as compared to type I lesions which only involve lipid droplets in macrophages. Type II lesions may be visible as yellow spots or patches when they contain fatty streaks. Most of the lipid is deposited in foam cells, and small amounts are deposited in the extracellular space. Around three quarters of the lipid molecules in type II lesions are cholesterol esters. Development

and progression of type II lesions usually occurs in commonly susceptible parts of the arterial tree. Mechanical forces in these susceptible parts of the tree cause an influx of plasma lipoproteins (Cornhill, Herderick, & Sary, 1990; Glagov, Zarins, Giddens, & Ku, 1988; Sary et al., 1994). Common locations for type II lesions include: coronary arteries, aortic arch, descending thoracic aorta, and abdominal aorta. Only a small subgroup of type II (progression-prone IIa) lesions progress to type III lesions in the absence of elevated harmful lipoproteins. Conversely, progression of type IIb (progression-resistant) lesions may not occur, and it takes a longer lag time and higher levels of harmful lipoproteins to occur. In the aorta, the progression of type II lesions commonly occurs in the posterolateral walls (left and right) and at common iliac arteries bifurcation (Sary et al., 1994).

Type III —Type III lesions are the intermediate lesions between type II and atheroma; they are also called transitional lesions. Histologically, type III lesions exhibit the presence of extra-cellular lipid droplets infiltrating the layers of smooth muscle cells. This infiltration interrupts the unity of the smooth muscle cells present in the intimal layer (Sary et al., 1994).

Advanced atherosclerotic lesions: Based on histological characteristics, advanced atherosclerotic lesions are subdivided into three types; IV, V, and VI. Atherosclerosis morbidity and mortality is mostly due to complicated type IV and type V lesions, transforming them into type VI lesions. Changes in advanced atherosclerotic lesions cause disfiguration of the arterial wall due to intimal thickening and repair. These changes will consequently cause narrowing of the arterial lumen (Sary et al., 1995).

Type IV (atheroma) — Type IV atherosclerotic lesions are also known as atheroma. Lipid accumulation in type IV lesions can be recognized microscopically as a distinct area within the tunica intima, which is called a lipid core, and this causes intimal disarrangement (figure 2). The lipid core is separated from the arterial lumen predominately by a normal intimal endothelial surface. Type IV lesions develop where eccentric adaptive intimal thicken-

ing commonly occurs. Therefore, atheroma originally exists as an eccentric lesion (Stary et al., 1992; Stary et al., 1995), and at this stage the arterial lumen is preserved with no evident stenosis (Glagov, Weisenberg, Zarins, Stankunavicius, & Kolettis, 1987; Stary et al., 1992). Cellular and morphologic changes that occur include: elongation of smooth muscle cells, thickening of their basement membranes, and calcium deposits. In addition, there is new capillary formation, proteoglycans, foam cells, and macrophages primarily at the lipid core margins. Type IV lesions, compared to type V lesions, contain less collagen and fibrous tissue (Stary et al., 1995).

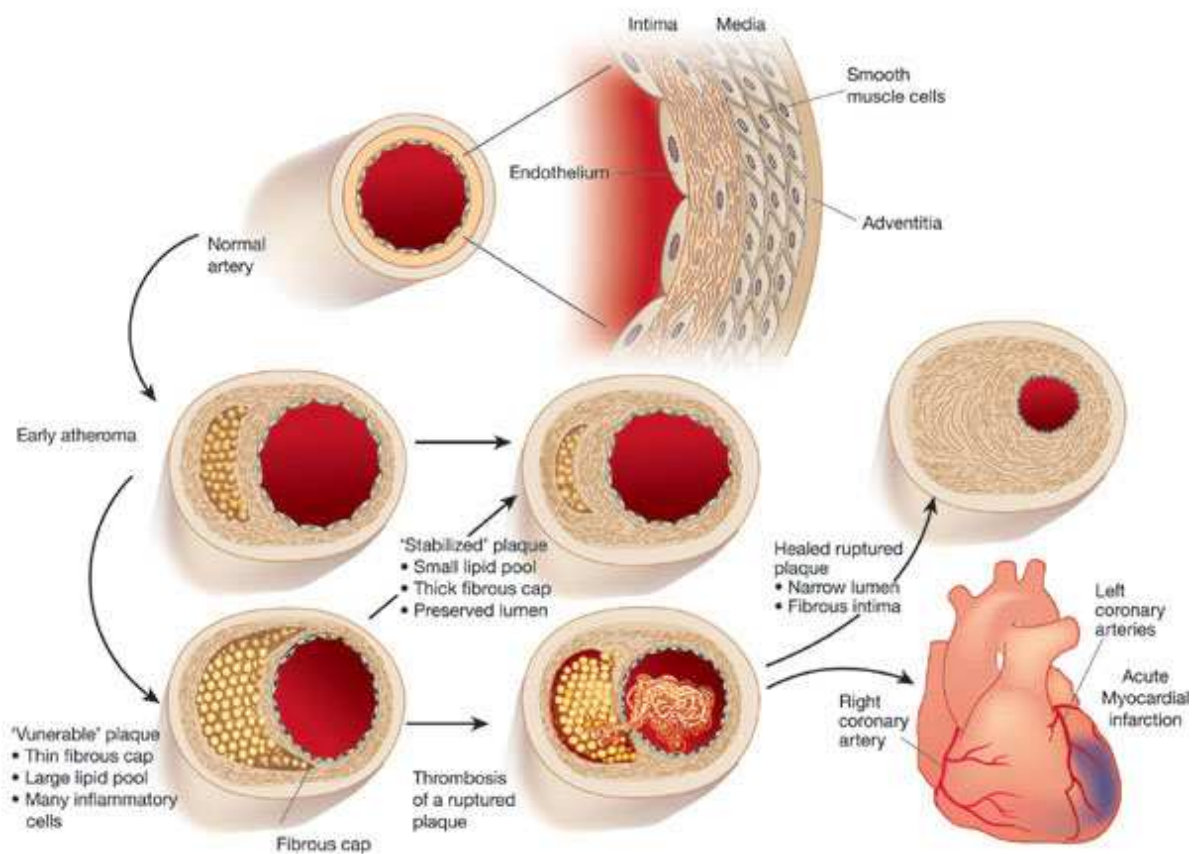


Figure 2. Atheroma formation and complications.

Source: <http://www.rayur.com/wp-content/uploads/2012/06/Atheroma.jpg>

Type V — In type V lesions there is additional fibrous connective tissue formation, which causes more evident narrowing of the arterial lumen. Cellular and morphologic changes that occur include: collagen accumulation, smooth muscle cells containing rough-surfaced endoplasmic reticulum, and larger and more numerous capillaries. In this advanced type of atherosclerotic lesion, there is involvement of the tunica media and adventitia in the form of accrual of foam cells, macrophages, and lymphocytes. Type V lesions are prone to complications that include hematoma, fissures, and/or thrombus formation. Type V lesions are further subdivided by cellular variations into types Va, Vb, and Vc (Stary et al., 1995).

Type Va is also called a fibroatheroma; it may be multi-layered, containing more than one lipid core that may form in more than one dimension. The multi-directional lipid core formation causes narrowing of the arterial lumen. Commonly the lipid core furthest from the tunica intima will form first. Multiple lipid core formations and fibrosis can be the result of a complicated initial lipid core caused by hematoma, fissure formation, or thrombosis followed by fibroses and further accumulation of foam cells and lipids (Stary et al., 1995). Type Vb is similar to Va, however it contains more calcification and mineral deposition. Type Vc contains more fibrotic tissue, and in this subtype fibrotic connective tissue replaces the normal tunica intima (Stary et al., 1995).

Type VI (complicated lesions) — Hematoma, fissures, and/or thrombosis are complications that occur in type IV and type V, changing them into type VI lesions, and they are subdivided depending on the complications that occur. Type VIa, is a complicated lesion due to fissure formation, ulcer formation, or discontinuity of the surface of the atherosclerotic lesions. Type VIb is an atherosclerotic lesion that developed hematoma or hemorrhage. Type VIc is a thrombotic atherosclerotic lesion. The coexistence of all of these three complications is called type VIabc atherosclerotic lesion (Stary et al., 1995).

Natural history of atherosclerosis: As mentioned previously, atheromatous lesions may develop morphological complications that include hematomas, fissures, ulcers, and thrombosis (Stary et al., 1995). Complicated atherosclerotic changes lead to subclinical central changes, most commonly coronary artery calcification (CAC) and carotid intima-media thickening (CIMT). Other lesions include renal artery stenosis (RAS) and peripheral artery disease (PAD). Atherosclerosis is a progressive disease that commonly affects various arterial beds. Therefore the aforementioned subclinical atherosclerotic manifestations frequently coincide (Go et al., 2013; Imori et al., 2014). The progression and complications of atherosclerosis depend on the severity and location of the lesion and trigger factors.

1.1.2. Clinical implications of atherosclerosis

Clinical manifestations

The main clinical manifestations of atherosclerosis include coronary heart disease (CHD), myocardial infarction (MI), and stroke.

Methods to assess acute, clinical manifestations atherosclerosis

Clinical signs and symptoms are commonly used to assess clinical manifestations of atherosclerosis, with the aid of a number of methods used to confirm the diagnosis. The latter include electrocardiogram (ECG), cardiac biomarkers, computed tomography (CT), and magnetic resonance imaging (MRI) (Anderson et al., 2011). The clinical manifestations of atherosclerosis and their measurement in different arterial territories and target organs are outside the scope of this research and will not be developed here.

Epidemiology

Population distribution of atherosclerosis

Atherosclerosis is a chronic process that starts early in life. The coexistence of more than one atherosclerotic manifestation is not uncommon. The abdominal aorta, coronary arteries, internal carotid, and popliteal arteries are sites of predilection for atherosclerosis. Ma-

major complications due to atherosclerotic changes in the aforementioned arterial territories include CHD, MI, stroke, PAD, and abdominal aortic aneurysms (AAAs) (Go et al., 2014).

It is estimated that at least one in three Americans has one type of cardiovascular disease, and a little over half of the cases affect adults sixty years of age or older (Go et al., 2014). Age-standardized death rates due to cardiovascular disease are estimated to have decreased by 1.1% per year for males and 1.25% per year for females during the last two decades, although due to an aging population the total number of deaths is projected to increase by 6.6 million from 2002 to 2030. In 2002, ischemic heart disease (IHD) and cerebrovascular disease were ranked as the first and second leading causes of death and the sixth and seventh leading causes of disability-adjusted life years (DALY's) globally. They are projected to remain the first two leading causes of death in 2030, and to move up to the third and sixth leading causes of DALY's globally (Mathers & Loncar, 2006).

Coronary heart disease (CHD)

The overall prevalence of CHD in U.S. adults twenty years or older is 6.4%, extrapolated from the National Health and Nutrition Examination Survey (NHANES) 2007-2010 data (NHLBI tabulation), and CHD prevalence is projected to increase 18% by 2030 (Heidenreich et al., 2011). In 2010 alone, the prevalence of CHD was estimated to be 15.4 million, and in 2014 it is estimated that 620,000 Americans will have a new coronary attack (Go et al., 2014).

Myocardial infarction (MI)

The overall prevalence of MI in U.S. adults twenty years or older is 2.9% (extrapolated from NHANES (2007-2010 data, NHLBI tabulation) (Heidenreich et al., 2011). It is estimated that the prevalence of MI was 7.6 million in 2010 and the American Heart Association (AHA) estimates that in 2014 one American will have an attack of MI every forty four seconds (Go et al., 2014).

Stroke

The prevalence of stroke in the United States is estimated at 2.8% (using NHANES data 2007-2010) (Go et al., 2014). The AHA projects an overall increase of 20% in the prevalence of stroke by the year 2030 (Ovbiagele et al., 2013). The projected increase is foreseen to affect men, women, and all ethnic groups (Ovbiagele et al., 2013). Approximately 795,000 individuals experience a stroke; 76.7% are a first attack, 23.3% are a recurrent attack, and 87% of strokes are due to ischemia (Go et al., 2013). The population distribution of stroke is affected by gender, age, and ethnicity (Go et al., 2013).

Risk factors

Atherosclerosis is a multifactorial disease, and various risk factors are involved to varying degrees in its development and complications. Well-established and widely replicated risk factors for atherosclerosis include both modifiable and non-modifiable factors. Modifiable risk factors include elevated blood pressure, cigarette smoking, diabetes mellitus, and abnormal lipid levels. Non-modifiable risk factors include aging, gender, and family history (Go et al., 2014).

Elevated blood pressure

It is estimated that almost eighty million Americans suffer from elevated blood pressure (Go et al., 2014). It is significantly associated with atherosclerotic lesions (Solberg & Strong, 1983) and is a strong determinant of stroke (Go et al., 2014). According to estimates from a number of NHLBI studies, around three quarters of first stroke attacks occur in individuals with blood pressure levels over 140/90 mmHg (Go et al., 2014).

Cigarette smoking

Cigarette smoking is positively and significantly associated with atherosclerotic lesions (especially in the aorta and peripheral arteries) (Solberg & Strong, 1983; Zieske, Malcom, & Strong, 2002). The association is dose-response in nature, and it is estimated

that the risk of stroke in current smokers is 2-4 times the risk of stroke in non-smokers and quitters (Bhat et al., 2008; Goldstein et al., 2011; R. S. Shah & Cole, 2010).

Diabetes mellitus

Diabetes mellitus is a strong risk factor for atherosclerosis. There is a parallel increase between the increase in diabetes prevalence and cardiovascular morbidity and mortality (Go et al., 2013; Wilsgaard & Jacobsen, 2007). Diabetic adults have 2-4 times the rate of developing heart disease compared to non-diabetics, and they have higher morbidity and mortality due to cardiovascular disease (US Department of Health and Human Services, Centers for Disease Control and Prevention; 2011) (Donahoe et al., 2007).

Hyperlipidemia

Hypercholesterolemia is the more prominent component of hyperlipidemia affecting atherosclerosis. The degree and level of association of HDL, total cholesterol, and triglyceride are inconsistent (de Boer et al., 2011; Go et al., 2013; Solberg & Strong, 1983; Zieske et al., 2002).

Gender

Atherosclerotic changes and manifestations are generally more common in men (Go et al., 2014). An example of subclinical atherosclerosis difference due to gender is that seen in CAC prevalence. The prevalence of CAC among women and men between 33 and 45 years of age is 5.1% and 15%, respectively (Loria et al., 2007). The prevalence is reported to be much higher in cohorts that include older ages, reaching 32% for women and 52.9% for men (Hoffmann, Massaro, Fox, Manders, & O'Donnell, 2008). CHD and MI prevalence are higher in men. CHD prevalence in U.S. adults is 5.1% in women and 7.9% in men, and the prevalence of MI is 1.7% in women and 4.2% in men (Go et al., 2014).

Family history

Family history of atherosclerotic cardiovascular disease reflects the interplay between biologically similar genetics and/or similar unhealthy environmental attributes. Both may act synergistically in increasing the risk of atherosclerotic morbidity and mortality. Capturing genotype and phenotype links using genome-wide association has been able to elicit small effects (Go et al., 2014).

In the U.S., positive family history for heart attack or angina is approximately 12.6%, with the highest reported prevalence seen in non-Hispanic white males and females (Go et al., 2014). A history of MI in parents increases the odds of having an MI: A history of MI in a single parent 50 years or older increases the odds of having an MI to 1.67 compared to those without parental history. Having a positive family history of MI in both parents at the age of 50 years or older increases the odds ratio to 2.36, and the odds ratio more than doubles if both parents had an MI before the age of fifty years (Chow et al., 2011).

1.1.3. Subclinical atherosclerosis

Topographical distribution of atherosclerosis

CAC, CIMT, RAS, and PAD have been identified as topographical manifestations of atherosclerosis.

Coronary artery calcification

Calcium deposits are integral to the atherosclerotic process, and artery calcification is pathognomonic of atherosclerosis. Calcific deposits in the coronary arteries can be seen using electron beam and/or helical computed tomography (CT) (Wexler et al., 1996). Calcification offsets arterial enlargement of the atherosclerotic coronary arteries (Clarkson, Prichard, Morgan, Petrick, & Klein, 1994). CAC in itself is not evident clinically, and it is a weak predictor of plaque rupture (Richardson, Davies, & Born, 1989). The portion of the CAC lesion most vulnerable to rupture is the connecting shoulder between the calcific cap

and the intima. Clinical manifestations occur due to plaque rupture or severe coronary artery narrowing (Wexler et al., 1996).

Carotid intima media thickening

Because of ease of accessibility, CIMT is commonly used to quantify atherosclerotic burden and to measure the progression of atherosclerosis. CIMT is believed to develop before CAC lesions (Go et al., 2013; Hodis et al., 1998). CIMT is commonly measured using B-mode ultrasound, which measures the tunica intima and tunica media layers of the carotid arteries (Go et al., 2013).

Methods to assess subclinical atherosclerosis

Non-invasive measures are used to visualize atherosclerosis that is subclinical or did not yet manifest. Computed tomography of the chest and B-mode ultrasound are used to assess CAC and CIMT, respectively (Go et al., 2014).

Epidemiology

Prevalence of subclinical atherosclerosis

The chronicity of atherosclerosis development and the advancement in imaging technology has promoted the examination of the level of atherosclerotic changes in the arterial systems to assess the burden of subclinical atherosclerosis. CAC and CIMT represent central subclinical atherosclerosis, and they are evaluated using chest computed tomography and B-mode ultrasound, respectively.

Coronary artery calcification

The prevalence and progression of CAC have been examined in populations of varying demographics. The prevalence of CAC varied according to age, gender, ethnicity, and cardiovascular risk factors, and it progressed more slowly with a healthy life style (Ahmed et al., 2013; Budoff et al., 2013). The prevalence of CAC in the Coronary Artery Risk Development in Young Adults (CARDIA) study, a U.S.-based cohort of young adults, was reported to be 9.6% in adults, three times the prevalence in men compared to women, one-and-a-half

times the prevalence in whites compared to African Americans, and twice the prevalence in adults between the ages of forty and forty five years compared to adults between the ages of thirty three and thirty nine years of age (Loria et al., 2007).

Carotid intima-media thickening

CIMT is the measurement of the intima and media layers of the carotid arterial wall. It is commonly measured with B-mode ultrasound, which also can assess arterial narrowing and plaque formation (Go et al., 2014). B-mode ultrasound is a reliable and valid tool ("High-resolution B-mode ultrasound scanning methods in the Atherosclerosis Risk in Communities Study (ARIC). The ARIC Study Group," 1991) that has been used by large U.S. observational studies to quantify CIMT (Bots, Vanmeurs, & Grobbee, 1991; Budoff et al., 2013; Chambless et al., 1997; Heiss et al., 1991). CIMT is a surrogate for and indicator of generalized atherosclerosis (Bots et al., 1991), and it is considered a predictor of CAD (Chambless et al., 1997).

The Bogalusa Heart Study (S. Li et al., 2003; Urbina et al., 2002) and the NHLBI's Cardiovascular Heart Study (O'Leary et al., 1999) are just two of the studies that have examined the prevalence of CIMT. In these studies it has been observed that CIMT is more severe in the presence of cardiovascular risk factors. According to epidemiological studies, CIMT is considered high-risk if the thickness equals or exceeds 1 mm or if it lies in the highest quartile or quintile according to age and gender (Go et al., 2014).

Risk factors

Subclinical and clinical atherosclerosis have common predisposing risk factors, and they are mentioned above in sections B.1.2. and B.1.3. Early exposure to modifiable risk factors increases the risk of subclinical atherosclerosis and consequent development of clinical complications (Berry et al., 2009; Loria et al., 2007).

1.2. Peripheral arterial disease

PAD involves atherosclerotic changes of the wall of arteries supplying the visceral organs and limbs (Hirsch et al., 2006). The presence of atherosclerotic changes in one segment of the arterial system is likely associated with atherosclerotic changes in other parts of the arterial tree. Therefore, individuals with PAD have a higher risk of developing ischemic events resulting in higher morbidity and mortality (Hirsch et al., 2006).

PAD is defined as insufficient arterial flow to the periphery due to atherosclerotic occlusive disease (Schirmang, Ahn, Murphy, Dubel, & Soares, 2009). Being affected with PAD reduces the quality of life, and studies have shown that modifying risk factors improves morbidity and mortality due to PAD (Abdulhannan, Russell, & Homer-Vanniasinkam, 2012). Intermittent claudication is muscular pain and/or cramps triggered by an increase in oxygen demand at the extremities that exceeds the available oxygen response and represents the hallmark of PAD manifestations (Abdulhannan et al., 2012). Intermittent claudication is insensitive as a tool to identify PAD in populations at higher risk for PAD, e.g., older populations and those with an elevated burden of risk factors (such as smoking and diabetes mellitus). Approximately 48% of newly diagnosed PAD individuals do not report leg pain, 46% report atypical leg pain, and only 5.5% report classic claudication; it is estimated that 85-95% of PAD cases would be missed if clinicians mainly relied on clinical symptoms (Hirsch et al., 2001; McDermott et al., 2001).

The first line to establish a diagnosis of PAD is commonly the ankle-brachial index (described below). However, duplex ultrasound is the recommended diagnostic tool to establish the need for intervention (Layden, Michaels, Bermingham, Higgins, & Guideline Development, 2012).

1.2.1. Methods to measure peripheral artery disease

A number of diagnostic tools are available to measure PAD, including invasive and noninvasive tools, as shown in Appendix 1.

Ankle-brachial index

Ankle brachial index—the ratio of the ankle over the brachial systolic pressures—is a non-invasive measurement of documented high sensitivity and validity in the assessment of peripheral arterial occlusive disease. Lower levels of ABI also are associated with central atherosclerotic changes, including subclinical atherosclerosis in other vascular territories such as coronary artery disease, incident ischemic strokes, and recurrent strokes (Feringa et al., 2007; A. J. Lee et al., 2004; McDermott et al., 2005; Otah et al., 2004; Papamichael et al., 2000; Resnick et al., 2004; Tsai, Folsom, Rosamond, & Jones, 2001; Zheng et al., 1997). A strong inverse association between ABI categories and ischemic strokes exists. However, the strength of association is driven by the presence of common cardiovascular risk factors (Tsai et al., 2001). Furthermore, ABI has been shown to aid in identifying persons with moderate to high cardiovascular risk and to be a predictor of cardiovascular morbidity and mortality (A. J. Lee et al., 2004; Papamichael et al., 2000; Resnick et al., 2004).

Definition and values

The systolic blood pressure progressively increases as the blood flows distally from the heart, resulting in a higher systolic blood pressure level at the ankle than that measured in the brachial artery. This is known as blood pressure amplification (Nichols, Nichols, & McDonald, 2011). The ratio of the systolic ankle blood pressure to the brachial systolic blood pressure provides the ABI (Aboyans et al., 2012), which was initially described by Winsor in the last century (Winsor, 1950).

An ABI value in the range between 1.00 and 1.29 is considered normal, while ABI values above 1.30 imply non-compressible arteries. ABI levels of 0.90 and less indicate reduced arterial supply to the lower extremity. Values between 0.41 and 0.90 suggest mild to

moderate diminution of arterial supply, and ABI values equal to or less than 0.40 indicate severely diminished arterial supply (Hirsch et al., 2006; Rooke et al., 2011).

Factors affecting ABI measurement

ABI measurement can be affected by procedural factors and by individual physiological factors (Aboyans et al., 2012). Some of the technical factors that affect ABI measurement include incorrect cuff size, using a spiral versus a parallel cuff wrapping method, and measuring systolic ankle blood pressure in the sitting position (60, 63-65). Adherence to protocol is thus essential to limit procedural factors affecting ABI measurement.

Physiological factors related to the patient that can affect ABI measurement include height, gender, heart rate, ethnicity, and having smoked ten minutes prior to ABI measurement (Aboyans et al., 2007; Bird et al., 1999; London, Guerin, Pannier, Marchais, & Stimpel, 1995; F. B. Smith, Lee, Price, van Wijk, & Fowkes, 2003; Su et al., 2007; Zheng et al., 2005).

1.2.2. Epidemiology of lower extremity PAD

Prevalence and incidence

The prevalence of lower extremity PAD is high in older populations and among individuals exposed to risk factors. In 2000, the prevalence among American adults aged 40 years and older was 8.5 million, and PAD was estimated to affect 7.2% of the U.S. population at that time (Allison et al., 2007). The incidence of PAD in the same age range is estimated to be 2.35% per year (using a sample of insurance claims in the U.S.) (Nehler et al., 2014). A retrospective cohort analysis conducted between 2003 and 2008 utilizing insurance claims in the U.S. estimated the mean annualized prevalence and incidence of lower extremity PAD among adults to be approximately 10.7% and 2.35%, respectively (Nehler et al., 2014). Prevalence and incidence estimates vary among different studies and populations. In the Framingham study, a higher incidence of lower extremity PAD was related to

older age and the presence of atherosclerosis risk factors (Kannel & McGee, 1985; Murabito et al., 2002a).

Morbidity and mortality

Age-standardized death rates for peripheral vascular disease in 2010 were 0.7 per 100,000, which has increased by 53% since 1990 (Lozano et al., 2012). In 1990 DALY's for peripheral vascular disease was 14 per 100,000; it has increased by 51.7% since then (Murray et al., 2012). Years lived with disability from peripheral vascular disease in 2010 was 6 per 100,000, representing an increase of 26.0% since 1990 (Vos et al., 2012).

1.2.3. Risk factors for peripheral artery disease

PAD is caused by peripheral atherosclerosis. As a result, PAD is affected by the aforementioned risk factors of atherosclerosis, particularly cigarette smoking and diabetes mellitus, which are the strongest risk factors affecting lower-extremity PAD (Criqui, Denenberg, Langer, & Fronek, 1997; Go et al., 2014; Hirsch et al., 2006).

Cigarette smoking and lower-extremity PAD are strongly associated. In approximately twenty thousand men and women, it was found that 80% of individuals with lower extremity PAD were current or ex-smokers (Fowkes et al., 1992; G. D. Smith, Shipley, & Rose, 1990). The effect of smoking on the risk of lower extremity PAD is dose dependent (Cole et al., 1993; Powell et al., 1997; Price et al., 1999). Diabetes is another well-recognized risk factor for lower extremity PAD. Twelve to twenty percent of individuals with lower extremity PAD are diabetics (Hiatt, Hoag, & Hamman, 1995; Meijer et al., 1998), and the risk of developing lower extremity PAD in diabetics is two to four times the risk in non-diabetics (Beks et al., 1995; Criqui et al., 1997; Hiatt et al., 1995; Meijer et al., 1998; Newman et al., 1993).

Abnormal lipid levels are a somewhat weaker risk factor for lower-extremity PAD, and the strength and direction of the association varies according to different lipid subtypes. Increased levels of low-density lipoprotein and decreased levels of high-density lipoprotein are positively associated with lower extremity PAD (Fowkes et al., 1992; Hiatt et al., 1995;

Murabito et al., 2002b), while an inconsistent association between increased levels of tri-glyceride and lower-extremity PAD exists (Greenhalgh et al., 1971; Mowat et al., 1997; Novo et al., 1992). There is an almost parallel relationship between increasing levels of total cholesterol and an increase in the risk of developing lower-extremity PAD, where an increase in total cholesterol by 10 mg/dL increases the risk of developing lower extremity PAD by 5% to 10% (Ingolfsson, Sigurdsson, Sigvaldason, Thorgeirsson, & Sigfusson, 1994; Murabito, D'Agostino, Silbershatz, & Wilson, 1997; Newman et al., 1993).

Elevated blood pressure is a strong risk factor for many atherosclerotic changes causing CAD. However, it is a weaker risk factor for lower extremity PAD (Criqui et al., 1997; Murabito et al., 1997; Novo et al., 1992), and the directionality and strength of the association varies among studies (Fowkes et al., 1992; Murabito et al., 1997; G. D. Smith et al., 1990).

1.3. Abdominal aorta dilatation and aneurysm

Definition

Commonly, the AAD is defined as an AAA when the antero-posterior diameter measures 3 cm or more. Other plane diameters have been used, however the antero-posterior diameter yields reproducible results and therefore it is more commonly used (Hirsch et al., 2006).

1.3.1. Pathophysiology of AAD and AAA

The abdominal aorta is a site of predilection and of early onset of atherosclerosis, which may lead to abdominal aortic dilatation and loss of the tapered cylindrical shape of this segment of the aorta. The pathophysiological processes resulting in ADD and AAA are complex, and although atherosclerosis plays a role in AAD and AAA, other cellular and molecular changes have been identified (Hirsch et al., 2006). In AAAs the tunica media is mainly involved, unlike atherosclerosis, where the tunica intima is the main arterial layer involved (Davies, 1998). In both atherosclerosis and aneurysmal formation, inflammatory processes

have been identified as part of the pathophysiological pathway. Destruction of the elastic lamina of the tunica media is a main histopathological feature in AAAs (Davies, 1998; Hirsch et al., 2006). In aneurysmal formation, inflammatory infiltrates, specifically macrophages, have been identified in the medial layer (Agmon et al., 2003; Davies, 1998). The inflammatory process stimulates macrophages and smooth muscle cells to produce metalloproteinase (MMP) enzymes that degrade the elastic lamina connective tissue formed of elastin and collagen (Davies, 1998; Goodall, Porter, Bell, & Thompson, 2002; Reed, Reed, Stemmermann, & Hayashi, 1992). The destruction in the tunica media leads to loss of elastic recoil and weakening of the aortic wall and consequently the inability to withstand systolic pressure.

1.3.2. Methods to measure AAD and AAA

Diagnostic imaging used to evaluate AAD and diagnose AAA include ultrasonography (US), CT scanning, and magnetic resonance arteriogram (MRA) scanning. In clinical practice, ultrasonography is commonly used to screen and diagnose AAA. Methods such as CT and MRA are considered the “gold standard” radiological techniques and are used in pre- and postoperative evaluation (Hirsch et al., 2006; Rubin, Armerding, Dake, & Napel, 2000). Incidental abdominal aneurysm diagnoses are not uncommon in older adults, as they are subject to more radiological imaging. AAAs can be detected on plain radiographs, ultrasound images, and CT images that are targeting other organs (Hirsch et al., 2006).

Ultrasonography

Ultrasonography is the least invasive and least expensive diagnostic imaging method used to measure AAD and diagnose AAAs. B-mode US and duplex US are both used (Hirsch et al., 2006). The accuracy of US in diagnosing AAAs depends on their anatomical location. For infrarenal aneurysms, US specificity approaches 100%, and its sensitivity is between 92% and 99% (Hirsch et al., 2006). The specificity and sensitivity for US considerably drops, barely reaching 50%, for diagnosing suprarenal and iliac aneurysms (Hirsch et al., 2006; Lamah & Darke, 1999). Using duplex US can slightly improve the accuracy of de-

tecting AAAs in the suprarenal and iliac arteries (Fillinger, 2000; Hirsch et al., 2006; Lamah & Darke, 1999).

Computed tomography

Computed tomographic imaging using contrast is the diagnostic and evaluative technique preferred by many clinicians. Contrast-enhanced CT determines the widest transverse diameter of the AAA and how it relates to the renal arteries, the length and caliber of the normal abdominal aortic segment inferior to the renal arteries, arterial disease in the adjacent abdominal aortic branches, and the presence of other non-arterial anomalies in the para-aortic soft tissue (Coulam & Rubin, 2001; Papanicolaou et al., 1986).

Magnetic resonance arteriogram

MRA is the preferred diagnostic and evaluative technique for preoperative AAAs when the presence of mural calcification is suspected (Hirsch et al., 2006). MRA is more time consuming and expensive than CT and US.

1.3.3. Epidemiology of AAD and AAA

Population distribution of AAD and AAA

The prevalence of AAAs is affected by a number of factors, which include age, gender, sex, cigarette smoking, and family history. The prevalence of AAAs measuring 2.9-4.9 cm in diameter estimated in northern European cohorts for men between 45 and 54 years of age is approximately 1.3%, and it increases reaching 18.5% in men between 75-84 years of age (Boll, Verbeek, van de Lisdonk, & van der Vliet, 1998; Go et al., 2014; Singh, Bonaa, Jacobsen, Bjork, & Solberg, 2001; Wilmlink & Quick, 1998). The prevalence among women in the same age groups is almost half that seen in men. It rarely exists in women between 45 and 54 years of age and ranges between 1% and 4.8% in women between 75-84 years of age (Boll et al., 1998; Go et al., 2014; Hirsch et al., 2006; Singh et al., 2001).

Morbidity and mortality

From twenty one different regions of the world, DALY's for all ages and age-standardized DALY's for AAAs have increased by an average of 34.6% and 3.6%, respectively, from 1990 to 2010 (Murray et al., 2012). Globally, deaths attributed to aortic aneurysms across all ages calculated from 187 different countries increased by 45.3% during the same period, while the age-standardized death rate from aortic aneurysms decreased by 12.7% during the same period (Lozano et al., 2012). An 18-study meta-analysis was recently conducted, mostly comprised of prospective studies with a mean follow-up of 4 years based, on 15,475 individuals diagnosed with a small aneurysm and undergoing follow-up (Powell et al., 2011; Sweeting, Thompson, Brown, Powell, & collaborators, 2012). The pooled mean growth in the diameter of AAAs was approximately 2.21 mm/year, which did not vary by gender. The rate of AAA growth was significantly and consistently affected by smoking status and diabetes mellitus (after adjusting for medical history, drug history, and demographics) (Sweeting et al., 2012). Abdominal aortic aneurysms showed a faster rate of growth by 0.35 mm/year in current smokers compared to ex-smokers and never-smokers (Sweeting et al., 2012). The presence of diabetes mellitus slowed the rate of AAA growth by 0.51 mm in a continuous fashion (Sweeting et al., 2012).

The rupture rates widely varied among the studies included in the meta-analysis (0.71/1000 person-years to 11.03/1000 person-years). The heterogeneity of rupture rates was attributed mainly to varying baseline AAA diameters. Higher hazard ratios for AAA rupture were seen in current smokers and women—2.02 and 3.76, respectively (Sweeting et al., 2012). In addition, mean arterial blood pressure and pulse pressure elevation (per 10 mmHg) were associated with a higher hazard ratio for AAA rupture—1.32 and 1.11, respectively (Sweeting et al., 2012).

1.3.4. Risk factors

The atherosclerosis risk factors mentioned in section B.1.2. are commonly present in AAA patients, with a stronger association observed with smoking, age, gender, and body surface area (Agmon et al., 2003; Reed et al., 1992).

1.4. Arterial stiffness

1.4.1. Pathophysiology of arterial stiffness

Arterial stiffness begins early in life and is the result of progressive pathophysiological changes that occur in the large elastic arteries; it consists of structural and cellular transformations leading to reduced distensibility. Arterial stiffness is an incompletely understood process, and it is widely considered to be a contributor to cardiovascular morbidity and mortality (Boutouyrie et al., 2002; Covic, Haydar, Bhamra-Ariza, Gusbeth-Tatomir, & Goldsmith, 2005; Khadilkar, Chiplonkar, Pandit, Kinare, & Khadilkar, 2012; Kim et al., 2011; Laurent et al., 2001; Sutton-Tyrrell et al., 2005; Vlachopoulos, Aznaouridis, & Stefanadis, 2010). The process of arterial stiffening can be accelerated by cardiovascular risk factors, including arterial hypertension (Arnett et al., 2000; Kaess et al., 2012; Laurent et al., 2003; Liao et al., 1999), tobacco use (Doonan et al., 2010; Jatoi, Jerrard-Dunne, Feely, & Mahmud, 2007; Yu-Jie, Hui-Liang, Bing, Lu, & Zhi-Geng, 2013), elevated plasma glucose levels (Cruickshank et al., 2002; Henry et al., 2003; Martens, van der Graaf, Dijk, Olijhoek, & Visseren, 2008), and elevated lipid levels (Urbina et al., 2013; Wang et al., 2011).

Arterial stiffness affects large elastic arteries more than medium and small muscular arteries (Benetos, Laurent, Hoeks, Boutouyrie, & Safar, 1993; Gillessen, Gillessen, Sieberth, Hanrath, & Heintz, 1995; Lakatta & Levy, 2003; Zieman, Melenovsky, & Kass, 2005). The compliance of large elastic arteries is primarily maintained by secretion and degradation of elastin and collagen proteins (Zieman et al., 2005). Arterial stiffness develops due to disequilibrium in this process and compositional changes in the arterial wall resulting in diminished amounts of normal elastin coupled with increased amounts of abnormal collagen

(Johnson, Baugh, Wilson, & Burns, 2001; Zieman et al., 2005).

The structural and cellular changes in the arterial wall resulting in the development of arterial stiffness involve more than one layer, and some of these changes are shared in more than one layer. The innermost layer of the arterial wall (tunica intima) exhibits pathophysiological changes that contribute to arterial stiffening including disorganization and abnormal changes of endothelial cells, increased production of abnormal collagen, breakdown of elastin and development of frayed elastin structure, and increased permeability causing infiltration of smooth muscle cells and macrophages. The changes in the middle layer of the arterial wall (tunica media) demonstrate changes in collagen, elastin, and smooth muscle cells similar to those seen in the intimal layer (Lakatta, 2003; Lakatta & Levy, 2003; Zieman et al., 2005). Hemodynamic forces affect these changes, and they do not occur homogeneously throughout the arterial tree.

Central arterial stiffness

Differences in the degree of arterial stiffening occur in various segments of the aorta, due to inherent variability in the elasticity of the anatomical aortic segments (R. T. Lee & Kamm, 1994a, 1994b).

In this dissertation we chose to include heart-carotid PWV (hcPWV) as the measure for central arterial stiffness (although it is not as reliable as cfPWV) in to avoid measurement error introduced in cfPWV estimates, which include the abdominal aorta and its dilatation (the dependent variable of these analyses).

Peripheral arterial stiffness

The peripheral arterial system is primarily composed of medium-sized muscular arteries. As mentioned above, these arteries undergo slower stiffening changes than large elastic arteries. This can be explained in part by the inherent variability in the cellular components and structure of peripheral arteries compared to central arteries. In young adults, central arteries are more elastic than peripheral arteries, i.e., the “stiffness gradient” (Latham

et al., 1985; Laurent, Boutouyrie, & Lacolley, 2005; Laurent et al., 2006). Reversal of the stiffness gradient is influenced by aging and hypertension (Benetos et al., 1993; Boutouyrie et al., 1992).

1.4.2. Methods to measure arterial stiffness

Arterial stiffness can be assessed using various techniques and equations (Appendix 2) (Chirinos, 2012); many of these techniques assess regional stiffness, while systemic stiffness is assessed by “models of the circulation” (Laurent et al., 2006). PWV is a valid, reproducible non-invasive measure of arterial stiffness (Chirinos, 2012). It has been used more frequently in recent studies to evaluate regional stiffness, which speak to the changes in the arterial wall examined (Laurent et al., 2006). Arterial stiffness measured by PWV is dependent on the arterial wall properties and the wall thickness/lumen diameter ratio. This relationship is best described by the Moens–Korteweg equation, $PWV = \sqrt{\frac{h E_{inc}}{D \rho}}$, where h is wall thickness, E is Young’s modulus of the arterial wall, D is arterial diameter, and ρ is blood density (Chirinos, 2012).

The degree of arterial stiffness measured by PWV is currently used in clinical practice in some Asian and European countries to evaluate cardiovascular health and assess cardiovascular morbidity and mortality.

1.4.3. Epidemiology of arterial stiffness

Interest in evaluating central and peripheral arterial stiffness has grown in the past decade or so. Central arterial stiffness is more commonly evaluated in association with cardiovascular outcomes than peripheral arterial stiffness (Mattace-Raso et al., 2006; Meaume et al., 2001; Shokawa et al., 2005; Sutton-Tyrrell et al., 2005; Willum-Hansen et al., 2006). However, current AHA guidelines do not list arterial stiffness as a phenotype recommended to estimate cardiovascular disease risk, and no conventional cut points have been proposed for PWV in the U.S. (Greenland et al., 2010). Arterial stiffness measured by PWV has been

linked to cardiovascular outcomes in a number of population-based studies (Mattace-Raso et al., 2006; Mitchell et al., 2010; Sutton-Tyrrell et al., 2005; Willum-Hansen et al., 2006).

The relative risk of cardiovascular outcomes due to increased arterial stiffness is estimated by comparing tertiles (Mattace-Raso et al., 2006) or quartiles (Mitchell et al., 2010; Sutton-Tyrrell et al., 2005), and in both instances, higher levels of PWV are associated with a higher relative risk of cardiovascular outcomes ranging from 1.25 to 3.4 (Mattace-Raso et al., 2006; Mitchell et al., 2010; Sutton-Tyrrell et al., 2005; Willum-Hansen et al., 2006).

CHAPTER 2: STUDY AIMS AND HYPOTHESIS

The study aims that guided this doctoral research were stated as follows:

- I. Describe the distribution of AAD at proximal, mid-, and distal locations by levels of PAD measured by ABI at the cohort Visit 5 examination. Descriptive analyses will be limited to age, gender and race for the study population included in these analyses.
 - Examine the distribution of peripheral artery disease by age, gender, and race.
 - i. We anticipate that stratifying by age, gender, and race will elicit differences in the distribution of peripheral artery disease.
 - Examine the distribution of abdominal aorta diameters at proximal, mid-, and distal locations according to age, gender, and race
 - i. We anticipate that stratifying by age, race, and gender will elicit differences in the distribution of abdominal aorta diameters at proximal, mid-, and distal locations.
 - Characterize the strength and shape of the association between ABI and abdominal aorta diameters at proximal, mid-, and distal locations and across the range of ABI values.
 - i. We hypothesize that decreasing levels of ABI will be associated with wider abdominal aorta diameters.
 - ii. We hypothesize that the strength of association will increase from proximal to distal levels of the abdominal aorta.
 - Examine the role of demographic characteristics, as well as the history of cigarette smoking, elevated blood pressure, and type 2 diabetes as covariates and potential

effect modifiers of observed associations between ABI and abdominal aorta diameters.

- i. We anticipate that the strength of association between peripheral artery disease and abdominal aorta diameters will vary due to potential confounders and/or effect modifiers such as cigarette smoking, elevated blood pressure, and type 2 diabetes.

II. Describe the association of central and peripheral arterial stiffness measured by hcPWV and faPWV, respectively, and abdominal aorta diameters at proximal, mid-, and distal locations at the cohort Visit 5 examination

- Examine the distribution of central and peripheral arterial stiffness by age, gender, and race.

- i. We anticipate that stratifying by age, gender, and race will elicit differences in the distribution of central and peripheral arterial stiffness.

- Characterize the strength and shape of the association between (a) central arterial stiffness, measured by hcPWV, and abdominal aorta diameters at proximal, mid-, and distal locations; and (b) peripheral arterial stiffness, measured by faPWV, and abdominal aorta diameters at the three locations stated above.

- i. We hypothesize that increasing levels of hcPWV and faPWV will be associated with wider abdominal aorta diameters.

- ii. We hypothesize that the strength of association will increase from proximal to distal levels of the abdominal aorta.

- Examine the role of demographic characteristics and the history of cigarette smoking, elevated blood pressure, and type 2 diabetes as covariates and potential effect modifiers of observed associations between hcPWV and abdominal aorta diameters as well as between faPWV and abdominal aorta diameters.

- i. We anticipate that strength of association between arterial stiffness and abdominal aorta diameters will vary due to potential effect modifiers such as cigarette smoking, hypertension, and type 2 diabetes.
 - Examine the differences in the associations between central and peripheral arterial stiffness measured by hcPWV and faPWV, respectively, and both the anterior-posterior (AP) and transverse abdominal aorta diameters.
 - i. We hypothesize the association will be stronger using the anterior posterior abdominal aorta diameter.
- III. Examine the ability of ABI and PWV to statistically predict abdominal aorta diameters by deriving predictive risk equations to classify AAD at clinically meaningful levels.
 - i. We hypothesize that lower levels of ABI will statistically predict abnormally dilated abdominal aorta diameters at clinically relevant cut points.
 - ii. We hypothesize that higher levels of PWV will statistically predict abnormally dilated abdominal aorta diameters at clinically relevant cut points.

CHAPTER 3: PUBLIC HEALTH RELEVANCE AND POTENTIAL CLINICAL IMPACT

Abdominal aortic aneurysms are common in older adults; their prevalence can reach 12.5% in men between 75-84 years of age (Hirsch et al., 2006). AAAs are frequently asymptomatic, present late, and are often diagnosed as incidental findings resulting in high levels of complications, morbidity and mortality. The burden of morbidity and mortality of AAAs has increased globally in the last decade (Lozano et al., 2012), although there are indications that the prevalence of AAAs may be declining in the United States. It is plausible that earlier diagnoses of AAAs will help to reduce their impact on morbidity and fatality. Exploring options for cost-effective, non-invasive methods to identify persons with abdominal aortic dilatation and AAAs is seen as an important step toward decreasing the morbidity and mortality from AAAs.

The insidious progression of AAAs along with the potential for sudden rupture render early detection important. Consensus on the cost effectiveness of ultrasound screening for abdominal aortic dilatation has not been reached, and evaluation of AADs or screening for AAAs is not routinely performed in clinical practice. While b-mode ultrasound is the technique commonly used as the first line of investigation for abdominal aorta dilation, the method is operator-dependent, time consuming, and the equipment costs are considerable. The line of research submitted in this proposal is predicated on the testable expectation that simple, noninvasive measures of arterial atherosclerosis and sclerosis may help identify persons at increased risk of having AAD or AAAs, and that these measures could facilitate targeted screening for AAAs in practice settings.

3.1. ABI and abdominal aorta diameters

ABI is a cost-efficient, accurate, and well-established tool to identify impaired perfusion of a lower extremity, allowing for efficient diagnostic evaluation of PAD. As a marker of PAD, low ABI levels are indicative of increased likelihood of coronary artery disease, carotid artery stenosis, and cerebrovascular accident (Manzano et al., 2012; Papamichael et al., 2000; Zheng et al., 1997). PAD also has been shown to coexist in persons with AAA (Axelrod et al., 2002). AADs/AAAs and peripheral arterial disease are due to atherosclerotic changes to the arterial wall and share pathophysiological pathways. This study will expand on these commonalities and examine the association between measures of lower extremity occlusive disease and pathologic dilatation of the abdominal aorta. A limited number of studies have examined the relationship between AAA and peripheral arterial disease (Allardice, Allwright, Wafula, & Wyatt, 1988; MacSweeney et al., 1993). Insights into associations between ABI and ultrasound measures of abdominal aorta diameters will allow us to infer whether the well-established and simple measures of ABI have potential as indicators of the likelihood of abdominal aorta morphology associated with clinically defined AAA. To our knowledge, the ability to statistically predict AAD and AAA from ABI has not been examined. It is one of the aims of this dissertation to examine this predictive ability and to evaluate the potential for a predictive algorithm of relevance to clinical practice.

3.2. PWV and abdominal aorta diameters

Arterial stiffness has been proposed as a noninvasive measurement to quantify the risk of cardiovascular disease (Franklin, 2008). Arterial stiffening results from remodeling of the arterial wall resulting in diminished amounts of normal elastin coupled with increased amounts of abnormal collagen (Johnson et al., 2001; Zieman et al., 2005). Arterial stiffening occurs with aging in the abdominal aorta, to varying degrees at various segments, due to inherent differences in the elasticity of the anatomical aortic segments (R. T. Lee & Kamm, 1994a). To our knowledge, the cross-sectional association between arterial stiffness and

AAD/AAAs has not been characterized in a community-based population of older adults. The purpose of this study is to examine our ability, based upon central arterial stiffness (hcPWV) and peripheral arterial stiffness (faPWV), to predict the diameter of the abdominal aorta at three pre-specified sites and to assess whether the degree of central and/or peripheral arterial stiffness measured by hcPWV and faPWV, respectively, are related to morphologic changes in the abdominal aorta. We have chosen the aforementioned segments because they evaluate two arterial territories with different structural and physiological characteristics. The hcPWV will allow us to assess the association of central arterial stiffness with the atherosclerotic changes that occur in the abdominal aorta. The faPWV will allow us to examine the association of peripheral arterial stiffness (muscular arteries) with those changes.

Our conclusions may speak to the potential merit of using arterial stiffness measures such as hcPWV and/or faPWV as convenient, reliable, and non-invasive tools to infer the presence of atherosclerotic changes and dilatation of the abdominal aorta.

CHAPTER 4: RESEARCH DESIGN AND METHODS

4.1. Study design

We used data from the Atherosclerosis and Risk in Communities (ARIC) study, a longitudinal, multi-center, bi-ethnic, population-based cohort of 15,792 men and women aged 45 to 64 years of age at intake in 1987. There were five visits required: The base-line visit occurred between 1987 and 1989. Visits 2 through 4 occurred in 3-year intervals between 1990-1992, 1993-1995, and 1996-1998. The fifth visit occurred between 2011 and 2013. The study was designed to examine atherosclerosis and its clinical outcomes, changes in cardiovascular risk factors, and cognitive function. In addition, the ARIC study recorded anthropometric measurements, physical function, lung function, cardiovascular biomarkers and phenotypes, medical history, and other information relevant to the objectives of the study.

We used a cross-sectional design to examine the aims proposed for this dissertation. AADs, ABI, hcPWV, and faPWV were measured at visit 5. We used the data collected at this visit to characterize the distribution of AADs at specified levels of the abdominal aorta, as well as the pattern and strength of association of AADs with ABI, hcPWV, and faPWV. We took into account demographic data and potential confounders and effect modifiers. In addition, we used a cross-sectional design to build on the aforementioned analysis to examine the ability to statistically predict AADs from ABI, hcPWV, and/or faPWV.

4.2. Study population

The analytic sample was the ARIC study. The ARIC study used a prospective epidemiologic cohort and was conducted in four locations in the U.S.; Washington County, Maryland; Minneapolis, Minnesota; Jackson, Mississippi; and Forsyth County, North Caroli-

na. The four locations included rural, suburban, and urban settings ("The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators," 1989). The ARIC study was designed to examine the etiology, natural history, and clinical manifestations of atherosclerosis, taking into account cardiovascular risk factors, race, gender, location, and date. The study started in 1987 and was sponsored by the NHLBI. Around 4,000 participants between 45 and 64 years of age were randomly selected from each of the four communities listed above. Age-eligible persons were randomly sampled from listings in Washington County, Minneapolis, and Jackson, Mississippi, using driver's licenses, private county health censuses, persons eligible for jury duty, and persons with state identification cards ("The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators," 1989). However, in Forsyth county persons were identified by area sampling ("The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators," 1989).

The first visit was from 1987 to 1989. Medical, social, and demographic data were obtained from 15,792 persons. Three re-examination visits were conducted every three years, with 93%, 86%, and 80% response rates for the second, third, and fourth visits, respectively. The fifth visit was conducted between June 2011 and August 2013. The response rate for visit 5 was 65%, which represents the 6,538 participants that took part in visit 5 divided by the 10,036 cohort members alive through August 2013.

4.3. AAD: Measurements and data quality

Abdominal aorta diameters were measured by high resolution, real-time duplex ultrasound (Philips IE33). To ensure data quality, involved personnel, radiologists, and certified technologists were recruited and trained to follow standardized ARIC protocols.

Transverse images at five different segments of the abdominal aorta were taken to identify the antero-posterior and transverse diameters. The transverse images were taken at the following anatomical positions: proximal aorta below the superior mesenteric artery,

proximal infrarenal aorta 2 cm below the renal arteries, distal infrarenal aorta 1 cm superior to the aortic bifurcation, and the point of maximal abdominal aortic dilatation if it was not at the level of the proximal or distal infrarenal aortas. Additional transverse images were taken in the case of a possible AAA (maximum diameter ≥ 2.8 cm). In addition, a longitudinal view was taken of the infrarenal abdominal aorta from the renal arteries to the bifurcation of the abdominal aorta. Participants with a history of previous AAA repair or previous aortic bypass surgery for occlusive atherosclerotic disease were not scanned. All abnormal abdominal aortic scans and a 5% random sample of normal scans were sent to ARIC's aortic imaging core laboratory for diagnosis of AAAs and other possible pathologies (Table 1). To support the quality of the scans, 10 randomly selected studies were evaluated for each technologist, and recommendations for improvement were distributed to all technologists. Based on 900 quality control abdominal aorta scans (Table 2), 32% were excellent, 29% were good, 15% were fair, and 23% were poor.

Table 1. Completion Status of Quality Control Measures Based on ARIC Data Retrieved October 23, 2013

Procedure	Time interval (months)	Total tests received from reading center	Number of QC re-quired	Total QC records entered	Total QC in the previous time interval	% QC completed from selection for the previous time interval
Abdominal aorta scan	1	5913	All the abnormal plus 5% of the normal scan	900	1	NA
PWV/ABI	1	5672	40/month	487	37	97

Table 2. Abdominal Aorta Scan Quality Control Measures Based on ARIC Data Retrieved October 23, 2013

Procedures	Excellent		Good		Fair		Poor		NA		Total
	N	%	N	%	N	%	N	%	N	%	
Abdominal aorta scan	284	32	265	29	131	15	209	23	11	1	900

4.4. Arterial stiffness and PAD: Measurements and data quality

Femoral-ankle pulse wave velocity and ABI were used to evaluate peripheral arterial stiffness and PAD, respectively, and heart-carotid pulse wave velocity was used to evaluate central arterial stiffness. ABI, hcPWV, and faPWV were measured concurrently at ARIC visit 5 using an automated non-invasive waveform analyzer, the VP-1000 Plus device (Omron Co., Ltd., Kyoto, Japan). This analyzer had been selected on the basis of prior validation studies and because it would reduce observer-dependent variability as well as exam time. Trained and certified technicians performed the measurement process by following a standardized protocol. Four size-appropriate blood pressure cuffs were attached to both arms and ankles to record the systolic blood pressure and pressure pulse waves, respectively. A carotid sensor, a femoral sensor, and two ECG sensors were applied. Two measurements were taken to reduce process variability; the second measurement was obtained two to five minutes after the first measure. A third measurement was performed if the study technician experienced difficulties in obtaining an optimal pulse wave form on the display, in which case technologists waited 2-5 minutes to obtain a third measurement. The average of the last 2 non-zero measurements were used.

Table 3. PWV/ABI Quality Control Quality Measures Based on ARIC Data Retrieved October 23, 2013

Procedure Quality	Optimal		Good		Acceptable		Poor		Unacceptable		NA		Total
	N	%	N	%	N	%	N	%	N	%	N	%	
PWV/ABI	380	78	85	17	16	3	0	0	0	0	6	1	487

The right and left ABI values are the average of the ankle systolic blood pressure of the respective limb, divided by the corresponding average brachial systolic blood pressure. The higher-average brachial systolic pressure was used if there was a difference of 10 mm

Hg or more between the right and left averages and either the left or right pressure was higher for both measurements.

Currently, no clinical threshold levels for hcPWV and faPWV have been identified. Because of this, heart- carotid PWV and faPWV were recorded for research purposes, but the results were not reported to participants. A summary report of the ABI values was delivered to participants and their health care providers about 6 weeks after the ARIC exam visit. According to the AHA standards, ABI values between 1.00-1.30 are considered normal, the range 0.91-0.99 is considered borderline, 0.41-0.90 is indicative of mild to moderate diminished arterial supply, equal or less than 0.40 is indicative of severely diminished arterial supply, and more than 1.40 is attributed to incompressibility of the arteries and arterial calcification (Hirsch et al., 2006; Rooke et al., 2011).

Table 4. ICCs and 95% CIs for faPWV, hcPWV, and ABI

Index	ICC (95% CI)	SEM	MDC ₉₅
Right faPWV *	0.69 (0.59, 0.79)	108.7	301.4
Left faPWV *	0.57 (0.43, 0.71)	117.3	325.1
hcPWV *	0.44 (0.26, 0.61)	215.0	596
Right ABI §	0.48 (0.34, 0.64)	0.08	0.22
Left ABI §	0.61 (0.48, 0.73)	0.07	0.20

ICC: Intra-class Correlation Coefficient; SEM: Standard Error of Measurement;
MDC₉₅: Minimal Detectable Change
* First author: Snyder (Snyder et al., 2015)
§ First author: Al-Qunaibet (Al-Qunaibet et al., 2015)

Data quality assurance was maintained by following standardized protocols and procedures, recruiting qualified personnel, training certified ARIC technicians, quarterly equipment maintenance and calibration, providing feedback and troubleshooting, and quality control reviews. Throughout the study, random samples of records for PWV/ABI were reviewed for all centers; forty records per month were reviewed, reaching a total of 487 records (Table 3). Quality scores were calculated based on the 487 records reviewed per year, and 78% of

the records were considered of optimal quality, 17% were of good quality, 3% were acceptable, and none were graded as poor or of no quality (Table. 3). The repeatability of hcPWV, faPWV, and ABI was characterized in a subset of ARIC participants (N = 79) (Al-Qunaibet et al., 2015; Snyder et al., 2015). The participants in the subset underwent two examinations 4-8 weeks apart using the standardized protocols applied in the full cohort to measure ABI and PWV. The intra-class correlation (ICC), corresponding 95% confidence intervals (95% CI), minimal detectable change (MDC₉₅), and standard error of measurement were calculated indicating acceptable-to-substantial repeatability measures for ABI, faPWV, and hcPWV (Table 4).

Based on the PWV repeatability study performed on ARIC visit 5 data, we considered the repeatability of faPWV and hcPWC acceptable (Snyder et al., 2015). The ICCs and 95% CIs indicate substantial repeatability for right faPWV ICC 0.69 (0.59, 0.79), moderate repeatability for left faPWV ICC 0.57 (0.43, 0.71), and moderate repeatability for hcPWV ICC 0.44 (0.26, 0.61), according to the categorization of Landis et al. (Landis & Koch, 1977). To our knowledge, the repeatability and accuracy of faPWV using the Omron VP-1000 plus device used in the ARIC study at visit 5 has not been thoroughly examined. However, similar automated devices have demonstrated high repeatability and accuracy (Asmar et al., 1995; Cooper, Tepper, Barinas-Mitchell, Woodard, & Sutton-Tyrrell, 2012; Tanaka et al., 2006; Yamashina et al., 2002).

The faPWV ICC within technicians and between technicians using an automated noninvasive Omron VP-2000 has been reported to be 0.96 and 0.87, respectively (Cooper et al., 2012), indicating almost perfect agreement according to categorization proposed by Landis et al. The coefficient of variation for faPWV has been reported to be 3.3% in 17 healthy individuals based upon measurements using an automatic waveform analyzer (Tanaka et al., 2006), and this is almost identical to the coefficient of variation for the femoral artery intima-media thickness measured ultrasonographically (Kumeda et al., 2002).

However, we were not able to find contrasts made between left and right faPWV repeatability in the literature to compare to the left and right faPWV repeatability conducted in the ARIC study.

The AHA recognizes the ABI as a source of objective data that provides level B evidence in many clinical scenarios (Hirsch et al., 2006) and is a non-invasive measure with well-established accuracy (Feigelson, Criqui, Fronek, Langer, & Molgaard, 1994; Nassoura et al., 1996). The ICCs were calculated in ARIC visit 5 as a statistic for reliability; they indicate fair reliability for right ABI (ICC = 0.48, 95%CI 0.34, 0.64) and left ABI (ICC = 0.61, 95% CI 0.48, 0.73), according to the Landis et al. categorization (Landis & Koch, 1977). Prior to ARIC visit 5, ABI had been measured using DINAMAP™, another automated oscillometric device ("The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators," 1989), and the reliability coefficient was 0.61 (95% CI 0.51, 0.70) (Weatherley, Chambless, Heiss, Catellier, & Ellison, 2006). The validity and reliability of automated oscillometric ABI have been measured against manually measured ABI using Doppler, the gold standard for ankle blood pressure measurement in calculating ABI (Hirsch et al., 2006), and there is an overall agreement on the high reliability and acceptable validity of automated oscillometric ABI measurement (Kollias, Xilomenos, Protogerou, Dimakakos, & Stergiou, 2011; Richart, Kuznetsova, Wizner, Struijker-Boudier, & Staessen, 2009; Verberk, Kollias, & Stergiou, 2012).

4.5. Statistical analyses overview

As mentioned above, the population for this study was the ARIC cohort at visit 5, and we used a cross-sectional design to pursue the three aims stated for this dissertation. The primary outcome was abdominal aorta diameter at three standardized locations (in centimeters), measured ultrasonographically. We analyzed AADs on a continuous scale and a categorical scale. Abdominal aortic aneurysm was considered to be present when the anterior posterior diameter of the abdominal aorta was 3 cm or more (Hirsch et al., 2006). Therefore,

we dichotomized AADs according to the 3 cm threshold and also created distribution-based categories for AADs at proximal, mid-, and distal locations.

There were two traits of main interest for this analysis: central and peripheral arterial stiffness measured by hcPWV and faPWV respectively, and peripheral arterial disease measured by ABI. Established clinical cut points do not exist for hcPWV and faPWV; therefore, arterial stiffness was analyzed on a continuous scale. Peripheral arterial disease is suggested by an ABI of < 0.90 , and a normal ABI range is 1.00 to 1.40(Hirsch et al., 2006). We similarly analyzed ABI on a categorical and continuous scale. We included covariates that are established or suspected risk factors for dilated AADs and that could potentially confound the peripheral arterial disease by AAD relationship, central arterial stiffness by AAD relationship, and peripheral arterial stiffness by AAD relationship. These factors included age, gender, and race. Cigarette smoking, systolic blood pressure, blood pressure medication, and diabetes were introduced as covariates in sensitivity analyses.

Aim I: Describe the distribution of abdominal aorta diameters at proximal, mid-, and distal locations by levels of peripheral artery disease measured by ABI at the ARIC cohort Visit 5 examination.

Aim I analyses were performed with three goals: a) to examine the distribution of ABI in the ARIC cohort visit 5, b) to examine the distribution of AADs at proximal, mid-, and distal locations, c) to characterize the strength and shape of association between ABI and AADs at proximal, mid-, and distal locations, and across the range of ABI values. The outcome of interest for Aim I is AAD at the proximal, mid-, and distal locations. The exposure of interest for Aim I is PAD as measured by ABI. The outcome and exposure were both analyzed on continuous and categorical scales, as stated above.

4.5.1 Distribution of PAD

We performed univariate analyses of ABI on a continuous scale and calculated the mean, median, and standard deviation, assessing the shape of the distributions. In addition, we used the four ABI categories described previously in section B.2.1. that consist of ≤ 0.40 , 0.41-0.90, 0.91-0.99, 1.00-1.29, and > 1.30 (Hirsch et al., 2006; Rooke et al., 2011). To analyze ABI on a categorical scale, we tabulated frequencies for the four ABI categories. Following the analyses of ABI in the ARIC cohort at visit 5, we examined the anticipated heterogeneity in ABI values, stratifying by gender and race.

4.5.2 Distribution of AADs

We examined the distribution of AADs as a continuous, dichotomous, and categorical variable. Initially, we explored the distribution of AADs as a continuous variable and assessed any impact of missing data or extreme values. The mean, standard deviation, and the shape of the distribution were calculated. We proceeded by superimposing cut points, thus creating distribution-based categories. We also used a cut point of 3 cm anterior-posterior diameter to create a dichotomous variable. Appropriate descriptive statistics were used for categorical and dichotomous AADs. The aforementioned statistical analysis steps were repeated for AADs at proximal, mid-, and distal locations. Therefore, in this section of analyses we were able to compare the variation in the descriptive statistics for AADs at three different anatomical levels.

4.5.3 Strength of association between PAD and AADs

We examined the strength and shape of association between the exposure of interest (ABI) and the outcome of interest (AADs) at proximal, mid-, and distal locations. To thoroughly examine the association, we repeated the statistical analyses to include the exposure and outcome as both continuous and categorical variables. This mandated creating a set of bivariable analyses that included continuous exposure and outcome, continuous exposure and categorical outcome, continuous exposure and dichotomous outcome, categori-

cal exposure and outcome, categorical exposure and continuous outcome, and categorical exposure and dichotomous outcome. Each variation of outcome and exposure analyses was repeated for AADs at the above-mentioned anatomical locations. We used Pearson's Chi-Square and the test for trend to perform bivariable comparisons between ABI and AADs, both as categorical variables. We used one-way analysis of variance to examine the strength and shape of association between ABI on a categorical scale and AADs on a continuous scale. To assess the association between ABI and AADs as continuous variables, we used Pearson's correlation and quintile regression.

4.5.4 Assess covariates as confounders and effect modifiers for the associations between ABI and AADs

Covariates of interest include age, gender, cigarette smoking, elevated blood pressure, and type 2 diabetes. We performed descriptive analyses for continuous and categorical covariates, assessing the covariates as confounders or possible modifiers of the association between ABI and AADs.

Aging, cigarette smoking, elevated blood pressure, and diabetes are the most important covariates according to the literature to better characterize the concurrent association between ABI and AAD. Therefore, we considered it to be a priority to exercise analytic control of the concurrent/contemporaneous effect of cigarette smoking, elevated blood pressure, and diabetes in the estimation of cross-sectional associations with measurements of AAD. To do so, we adjusted for the above-mentioned covariates and characterized the degree and strength of the association and the change in estimates compared to the crude estimates. Thereafter, we performed stratification to examine and compare the degree and level of association to that calculated from adjustment models. We acknowledge that residual confounding between long-term exposures and chronic conditions cannot be removed in a cross-sectional analysis among older adults.

Based on the conclusions reached from the above analyses, we proceeded to perform multivariable analyses. The exposure of interest and outcome of interest were analyzed on continuous and categorical scales. We used analysis of covariance and percentile regression to estimate the mean difference in AAD on a continuous scale between normal and abnormal ABI levels, adjusted for covariates. We also estimated the mean difference in AAD for a unit change in ABI when analyzed on a continuous scale adjusted for covariates. We fit a multinomial regression model analyzing AAD on a nominal scale. We estimated the odds of dilated abdominal aorta diameters for each of the normal and abnormal ABI levels, adjusting for covariates. We also estimated the odds of dilated abdominal aorta diameters for selected ABI values. Throughout the process of multivariable analyses, we took into account the possibility of effect modifiers and dealt with them accordingly.

Aim II: Describe the distribution and association of central and peripheral arterial stiffness measured by hcPWV and faPWV, respectively, and anterior-posterior abdominal aorta diameters at proximal, mid-, and distal locations at the cohort Visit 5 examination.

Aim II analyses were performed with three goals: a) to examine the distribution of central PWV and peripheral PWV in the ARIC cohort at visit 5, b) to characterize the strength and shape of the association between central arterial stiffness measured by hcPWV and AADs at proximal, mid-, distal locations, and c) to characterize the strength and shape of association between peripheral arterial stiffness measured by faPWV and AADs at proximal, mid-, distal locations. The outcome of interest for aim II was AADs at proximal, mid-, and distal locations. The outcome was analyzed on continuous, dichotomous, and categorical scales, as previously explained in Aim I. Central and peripheral arterial stiffness were the exposure variables. They were measured by hcPWV and faPWV, respectively, and were analyzed as continuous variables. Each exposure variable was analyzed independently.

4.5.5 Distribution of central and peripheral arterial stiffness

This part of Aim II involves descriptive analyses of hcPWV and faPWV on a continuous scale. We performed univariate analyses calculating the mean, median, standard deviation, and interquartile ranges, assessing the shape of the distributions. We anticipated that the distribution of arterial stiffness would differ by age, race, and gender. To address this, we compared the mean for hcPWV and faPWV in the different categories of race and gender. Gender and race are dichotomous independent variables. A 2-sample t-test was performed to compare changes in PWV values for gender and race categories.

4.5.6 Strength of association between arterial stiffness and AADs

We examined the strength and shape of the association between the exposures of interest (central and peripheral arterial stiffness) and the outcome of interest (AADs at proximal, mid, and distal locations). The strength of the association between the two exposures of interest and outcome was examined separately. The exposures were analyzed only on a continuous scale and the outcome on continuous, dichotomous, and categorical scales. Therefore, we created a set of bivariable analyses that included: continuous exposure and outcome, continuous exposure and categorical outcome, and continuous exposure and dichotomous outcome. Each variation for outcome and exposure analyses was repeated for each exposure (hcPWV and faPWV) and for anterior-posterior AADs at the above-mentioned anatomical locations. We used Pearson's correlation and quantile regression to examine the strength and shape of the association between hcPWV and AADs and between faPWV and AADs on a continuous scale. We used logistic regression to assess the strength and direction of the association between the exposures of interest on a continuous scale and AADs on a categorical scale.

4.5.7 The role of identified covariates on the associations between PWV (central and peripheral) and AADs

Covariates of interest include age, gender, cigarette smoking, elevated blood pressure, and type 2 diabetes. Aging, cigarette smoking, and type 2 diabetes are shareholders in the pathophysiological process of developing arterial stiffness and abdominal aortic dilatation. Elevated blood pressure is a strong hemodynamic determinant of PWV and AAD. It was important to examine how these covariates affected the strength and degree of the association between PWV (exposure) and AAD (outcome). As explained in Aim I, we employed stratification and adjustment. We assessed the change in the degree and level of association between PWV and AAD, how the estimates of AAD changed, and how useful the estimates were depending on the method used.

We performed descriptive analyses for continuous and categorical covariates and assessed the covariates as confounders or possible modifiers of the association between PWV (central and peripheral) and AADs. Based on the conclusions reached from the above analyses, we proceeded to perform multivariable analyses to assess separately the association between central arterial stiffness and AADs and between peripheral arterial stiffness and AADs. Central and peripheral arterial stiffness were analyzed on a continuous scale, and AADs were analyzed on a continuous scale and distribution-based categories. We used analysis of covariance and percentile regression to estimate the mean difference in AADs on a continuous scale for a unit change in PWV adjusted for covariates. We fit a multinomial regression model analyzing AAD on a categorical scale and PWV on a continuous scale. We estimated the odds ratio for dilated abdominal aorta diameters for selected central and peripheral pulse wave velocity values. Throughout the process of multivariable analyses, we took into account the possibility of effect modifiers and deal with them accordingly.

Aim III: Examine the ability to statistically predict abdominal aorta diameters from ABI and PWV by deriving predictive portability equations to classify AAD at clinically meaningful levels.

Aim III analyses was planned to build on the knowledge gained from the analyses proposed for Aims I and II. The purpose of Aim III was to create and test predictive models to estimate the probability of abdominal aortic diameters based upon ABI and PWV levels and suspected risk factors. We were planning to develop a parametric bi-normal model that includes the best predictors (variables) of abdominal aortic diameters. In a base model, we would have considered age, gender, race, cigarette smoking, elevated blood pressure, and diabetes in the model prediction of AAD. We would have considered the aforementioned factors since they are involved in the pathophysiology of the process, but we would have also considered other variables such as body surface area and lipid levels that improve the statistical prediction. Once we have assessed the goodness-of-fit using the Hosmer-Lemeshow decile of probability test (161, 162), we would have optimized the most parsimonious predictive model using multiple degrees of freedom likelihood ratio tests for groups of variables and by using a stepwise method. We would have then quantified the classification properties of the model using the c statistic (increment in the area under the receiver-operator curve [ROC]) to establish the accuracy, sensitivity, and specificity of the base model to predict AADs (Zou, O'Malley, & Mauri, 2007).

ABI, hcPWV, and faPWV would have then be added to the baseline parametric bi-normal model to assess improvements in its predictive ability, as quantified by the AUC and the net reclassification index (NRI). The latter would have been used to assess the model's predictive ability to assign a higher probability to individuals with abdominal aortic diameter dilatation. NRI is commonly estimated as $NRI = (\text{probability of cases moving upward} - \text{probability of cases moving downward}) - (\text{probability of non-cases moving upward} - \text{probability of non-cases moving downward})$ (Pencina, D'Agostino, D'Agostino, & Vasan, 2008). NRI

would have estimated the percent of individuals reclassified from one category to another when ABI and/or PWV are added as compared to a predictive model without ABI and/or PWV. We had planned to examine the correct movement of individuals from one AAD probability category to another. (The movement from a lower probability of dilated AAD to a higher probability of dilated AAD is considered an upward movement) (Pencina et al., 2008).

Finally, we would have attempted to correct for optimism and internally “validate” the model. Although an external validation is more desirable, at this point we do not know of any other study population that has been characterized comparably and can serve as a replication set. Bootstrapping, split tests and cross-validation are known as “validation” methods (Steyerberg et al., 2001). For this study we would have performed bootstrapping because the study size is not large enough for split validation and because bootstrapping provides stable estimates and lower bias than split tests and cross-validation (Steyerberg et al., 2001). The number of iterations that would have been used to arrive at stable estimates would have been determined during study analysis. All analyses will be performed using Stata 13 (College Station, TX).

CHAPTER 5: MANUSCRIPT 1- PERIPHERAL ARTERIAL DISEASE AS AN INDICATOR OF ENLARGED ABDOMINAL AORTA DIAMETERS. THE ATHEROSCLEROSIS RISK IN COMMUNITIES (ARIC) STUDY.

5.1 Introduction

Ankle brachial index (ABI) is a non-invasive tool used to assess peripheral arterial occlusive disease. Large cohort studies have reported an association of lower levels of ABI and central atherosclerotic changes, including subclinical atherosclerosis, clinical coronary artery disease, incident ischemic strokes, and recurrent strokes (Feringa et al., 2007; A. J. Lee et al., 2004; McDermott et al., 2005; Otah et al., 2004; Papamichael et al., 2000; Resnick et al., 2004; Tsai et al., 2001; Zheng et al., 1997). Furthermore, ABI has been shown to aid in identifying persons with moderate to high cardiovascular risk and is a predictor of cardiovascular morbidity and mortality (A. J. Lee et al., 2004; Papamichael et al., 2000; Resnick et al., 2004). While ABI has been associated with atherosclerotic occlusive disease in the coronary, carotid, and peripheral arteries, the abdominal aorta is also a site of predilection and of early onset of atherosclerosis that may lead to abdominal aortic dilatation and loss of the tapered, cylindrical shape of this segment of the aorta. Abdominal aortic aneurysms (AAAs) are conventionally defined as an anterior-posterior diameter of the abdominal aorta of 3 cm or more (Hirsch et al., 2006). The pathophysiology of AAA is complex and involves atherosclerotic changes and remodeling of the arterial wall by increased production of collagen and degradation of smooth cells, which results in arterial stiffening (Ailawadi, Eliason, & Upchurch, 2003; Allison, Hiatt, Hirsch, Coll, & Criqui, 2008; Nordon, Hinchliffe, Loftus, & Thompson, 2011; Raaz et al., 2014; P. K. Shah, 1997). Low ABI values, which indicate a higher likelihood of coronary artery disease, carotid artery stenosis, and/or

peripheral artery disease (PAD), have been shown to coexist in persons with abdominal aortic aneurysms (Axelrod et al., 2002).

The ABI is an established marker of peripheral, atherosclerotic occlusive arterial disease. Its use in general clinical practice has been recommended by a consensus of professional associations (Hirsch et al., 2006). The American Heart Association (AHA) recommends measuring the ABI in individuals who are 70 years or older, suffering from leg symptoms on exertion, or with chronic wounds, for whom PAD is the suspected diagnosis (level of evidence: C) (Hirsch et al., 2006). The AHA also recommends measuring the ABI in diabetics or individuals with a history of smoking who are 50 years of age or older (level of evidence: C) (Hirsch et al., 2006). In contrast, imaging procedures to assess the morphologic characteristics and diameters of the abdominal aorta that may be indicative of underlying atherosclerosis are recommended only for high risk groups (Hirsch et al., 2006; "Summaries for patients. Screening for abdominal aortic aneurysm: U.S. Preventive Services Task Force recommendation statement," 2014). Measurement of the ABI with a Doppler probe or one of the several validated oscillometric devices that are available is inexpensive and easy to perform in a practice setting, in contrast to the measurement of abdominal aorta diameter (AAD) by one of several imaging techniques available. Therefore, the ability to glean information about abdominal aortic dilatation or AAA from an ABI measurement presents itself as a potentially cost effective and clinically attractive option.

There is limited information available on the association between PAD and AAD, most of it based on small populations of individuals selected on the basis of PAD manifestations (Allardice et al., 1988; MacSweeney et al., 1993). Reports indicate a high prevalence of AAA (6.4%-20%) in such individuals. These findings may not be generalizable beyond study populations enriched for atherosclerosis and thus at high risk for atherosclerotic manifestation elsewhere. Whether ABI is associated with abdominal aorta dilatation or AAA in the general population has not been reported, to our knowledge.

Insights into the strength of the association between ABI and abdominal aortic ultrasound measures will allow us to assess whether information about abdominal aortic diameter can be inferred from ABI levels in a population-based study. Accordingly, this study examined the association between ABI and the anterior-posterior diameters of the abdominal aorta at pre-specified anatomical sites in a population-based, biracial cohort of men and women ages 70-89 years.

5.2 Methods

5.2.1 Study population

We conducted a cross-sectional analysis of data from the 5th examination of the Atherosclerosis Risk in Communities (ARIC) study cohort (2011-2013) sponsored by the National Heart, Lung, and Blood Institute (NHLBI). The ARIC study is a prospective epidemiologic study of adults aged 45 and 64 years at intake in 1987-89, drawn as probability samples from four U.S. communities (Washington County, Maryland; suburban Minneapolis, Minnesota; Jackson, Mississippi; and Forsyth County, North Carolina) ("The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators," 1989). The response rate for visit 5 was 65%, which represents 6,538 participants. Of those, 5,683 completed the measurements needed for this study.

We excluded from these analyses 881 examinees due to characteristics that precluded the measurement of ABI or AAD or that affected data quality. We excluded participants with missing AAD values, a body mass index (BMI) $\geq 40\text{kg/m}^2$, aortic stenosis, moderate or greater aortic regurgitation, aortic revascularization, peripheral revascularization, evidence of a major arrhythmia (Minnesota code 8-3-1) on a 12-lead electrocardiogram, and missing ABI values. Only whites and African-American participants were included and racial groups that were represented in numbers insufficient for analysis were excluded. The study was approved by the Institutional Review Board at each participating institution. Written informed consent was provided to the participants for each examination.

All measurements were obtained by trained technicians following standardized protocols. Participants were asked to fast for 8 hours prior to their clinic visit and to avoid tobacco use and vigorous physical activity. They were also requested to bring all medications (prescription and non-prescription) with them. Participants provided medical history and lifestyle information by completing interviewer administered questionnaires. Blood and urine specimens were obtained and shipped for assay and long term storage at three core laboratories. Anthropometric measurements, a standard 12-lead electrocardiogram, standing height measurement, body weight measurement and three seated blood pressure measurements were obtained using an oscillometric automated sphygmomanometer (Omron Co., Ltd., Kyoto, Japan). Hypertension was defined as systolic blood pressure (mean of 2nd and 3rd measures) \geq 140 mmHg or diastolic blood pressure (mean of 2nd and 3rd measures) \geq 90 mmHg, or on medication for high blood pressure. Diabetes was defined as present if glucose value \geq 126 mg/dL or non-fasting glucose value \geq 200 mg/dL, or using medication for diabetes or a self-report of physician-diagnosed diabetes. Details are available in Manual 2 (Home and Field Center Procedures) at (<https://www2.csc.c.unc.edu/aric/cohort-manuals>).

Abdominal aorta diameters

Abdominal aorta diameters were measured by high resolution, real-time duplex ultrasound (Philips IE33). The participants were asked to fast for at least 8 hours prior to their 5th ARIC clinic visit as described above. To ensure data quality, the radiologists and certified technologists were trained to follow standardized ARIC protocols. Transverse and anterior-posterior diameters were measured at three standardized levels of the abdominal aorta. The images were taken at the following anatomical positions: proximal aorta below the superior mesenteric artery, mid aorta 2 cm below the renal arteries, distal infrarenal aorta 1 cm superior to the aortic bifurcation, and the point of maximal abdominal aortic dilatation if it was not at the level of the proximal or distal infrarenal aorta. Additional transverse images were taken in the case of a possible AAA (maximum diameter \geq 2.8 cm). Participants with a history

of previous AAA repair or previous aortic bypass surgery for occlusive atherosclerotic disease were not scanned. In this study we will focus on proximal anterior-posterior abdominal aorta diameters.

Ankle-brachial index

ABI was measured using the automated waveform analyzer VP-1000 Plus (Omron Co., Ltd., Kyoto, Japan) (Cortez-Cooper, Supak, & Tanaka, 2003) following a standardized protocol. This device employs a double cuff technology where one cuff inflates while the other detects oscillation. The participant was in the supine position with both arms resting along his/her side (Meyer et al., 2016). Two electrocardiogram clips were attached on the inner sides of both wrists, and size-appropriate blood pressure cuffs were placed on both arms and ankles. Blood pressure was measured simultaneously in the four limbs at least twice at an approximately 5-minute interval. The VP-1000 Plus estimates ABI for each lower extremity as $ABI = \text{ankle systolic blood pressure} / (\text{higher of left and right arm systolic blood pressure})$ and the lower ABI value for each individual was used in the analysis.

Statistical analysis

We examined the distribution, means, and standard deviations of ABI and AAD in the ARIC cohort at visit 5. We then characterized the strength and shape of the association between ABI and AAD across the range of ABI values. In examining the association, we selected the continuous forms of ABI and AAD to be included in the final statistical model, as they best captured the association. The final linear regression model included AAD as the outcome and ABI as the exposure, with the first- and second-order terms of ABI adjusted for age.

The mean, standard deviation, and the shape of the distribution were examined for each continuous variable, and frequencies were tabulated for categorical variables. We considered the following as potential covariates and effect modifiers of the association between ABI and AAD: age, gender, race, cigarette smoking, elevated blood pressure, and diabetes

mellitus. To achieve our study goal to assess the ability to predict AAD from ABI only, the only covariate adjusted for was age, since it is not our purpose to account for or partially explain the mechanisms behind an association of ABI and AAD. We also assessed the ability of ABI to predict AAD in the presence of other characteristics (gender, race, elevated blood pressure, diabetes, and smoking) that can plausibly aid in the prediction of AAD. The analytic steps were repeated to examine the association between ABI with mid-anterior-posterior AAD and distal anterior-posterior AAD. All statistical tests are 2-sided, with a nominal significance level of $P < 0.05$. All analyses were performed using Stata, version 14.0 (StataCorp LP, College Station, TX).

5.3 Results

In our study population, 4,802 of ARIC visit 5 participants met our criteria for inclusion in the analysis. As shown in Table 5, 1,059 (22.0%) were African-American, 2,841 (59.1%) were women, 2,565 (57.2%) were current or prior smokers, 1,440 (30.3%) were diabetics, and 3,450 (72.5%) were hypertensives. The mean age and BMI were 75.3 ± 5.1 years and 27.9 ± 4.5 kg/m², respectively.

The overall mean and standard deviation for proximal, mid-, and distal anterior-posterior AAD were 1.95 ± 0.32 cm, 1.81 ± 0.33 cm, and 1.70 ± 0.35 cm, respectively (Table 5). The variation in AAD by race and gender is shown in Figure 3. The median values for anterior-posterior AAD at proximal, mid-, and distal locations were 1.9 cm, 1.8 cm, and 1.7 cm, respectively (Table 6), and less than 1% (N = 39) of participants had an AAD larger than 2.9 cm (Table 6). The overall mean for ABI was 1.10 ± 0.14 (Table 5), the ABI was approximately normally distributed with a median value of 1.13; approximately 7% of the participants had an ABI value below 0.9 (N = 343). The variation in ABI by race and gender is shown in Figure 4.

There was statistically significant ($P \leq 0.05$) effect measure modification of the association between ABI and AAD by race and smoking status. The difference in the magnitude

of the association between strata in the presence or absence of the effect-modifying variable was less than 4 mm in anterior-posterior proximal AAD. We considered the small magnitude of this modification to be ignorable and did not include these covariates in the estimation of the results presented here.

The estimates of association (95% confidence intervals) between the ABI and proximal anteroposterior AAD adjusting for age were, -1.26 (-1.77, -0.74) for ABI and 0.74 (0.49, 0.99) for squared. Significant P values (< 0.0001) for both ABI and ABI squared indicate non-linear associations between ABI and AAD. The fitted scatter plot for the association between ABI and AAD approximates a shallow concave shape showing a gradual increase in the AAD at the lower (< 0.5) and higher (> 1.4) ABI values (Figure 5). The estimated mean and (95% confidence intervals) for proximal anteroposterior AAD in a 75 year old participant (median age for study cohort) at ABI values of 0.5, 1.1, and 1.4 is 1.98 cm (1.91, 2.05), 1.94 cm (1.93, 1.95), and 2.11 cm (2.08, 2.15), respectively. We examined how the association between ABI and the proximal anteroposterior AAD would change by adding gender to the model. The association was no longer statistically significant once gender was added, and the estimates and (95% confidence interval) for ABI and ABI squared were 0.1 (-0.4-0.6) and -0.01 (-0.3-0.2). The adjusted R-squared was ~ 0.017 for the model that only adjusted for age and for the model that adjusted for both age and gender.

In a fully adjusted model (Table 7), the estimates of association between ABI and AAD were visibly attenuated. The pattern of association between ABI and both mid and distal anteroposterior AADs was the same but weaker than that seen between ABI and proximal anteroposterior abdominal aorta diameter (results not shown).

5.4 Discussion

In a population-based, cross-sectional examination of older men and women, ABI is associated with the anterior-posterior diameters of the abdominal aorta. Abdominal aorta diameters are greater at low as well as at high ABI values. It is worth noting that the U-

shaped association is consistent with atherosclerotic pathophysiological changes underlying higher and lower ABI measurements (Allison et al., 2008; Heald, Fowkes, Murray, Price, & Ankle Brachial Index, 2006; McDermott et al., 2005; Resnick et al., 2004). Although the association met nominal levels of statistical significance, the magnitude of the association is small and is not considered to have practical implications for clinical practice, or of utility in predicting the presence of abdominal aortic dilatation.

Abdominal aortic aneurysms (anterior-posterior AAD of 3 cm or more) tend to coexist with peripheral atherosclerosis, and the prevalence of PAD in patients with abdominal aorta aneurysms varies between 9% and 40% (Axelrod et al., 2002; Hassen-Khodja et al., 1998; MacSweeney et al., 1993). The aforementioned large variation is due to the dissimilarities in the burden of atherosclerosis in the populations inducted into these studies. Not much is known about the association between ABI and AAD less than 3 cm. Our study was able to examine the association between ABI and AAD (across its ranges), and it documented a statistically significant association of small magnitude between ABI and AAD, which, however, has little clinical relevance in our assessment.

The reported prevalence of AAAs (aortic diameters 2.9-4.9 cm) in men between 75-84 years of age ranges between 1.3%-18.5% and between 1%-4.8% in women in the same age range (Boll et al., 1998; Go et al., 2013; Singh et al., 2001). For this report, participants were excluded if they had been diagnosed with AAA or undergone surgical repair for aortic dilatation prior to the examination. Consequently, AAD of 2.9 cm or more was rare and under-represented in our study population (N = 39), limiting our ability to characterize the association between ABI levels and larger abdominal aorta diameters.

Abdominal aortic aneurysms are a health concern in that they are a condition of low prevalence but have unforeseen and often fatal outcomes. On a global scale, age-standardized disability-adjusted life years (DALY's) for AAAs in twenty-one different regions of the world have increased by an average of 3.6% from 1990 to 2010 (Murray et al., 2012).

Similarly, the global age-standardized death rate attributed to aortic aneurysms calculated from 187 different countries increased by 12.7% during the same period (Lozano et al., 2012).

There is controversy concerning the screening for AAAs. On the one hand, the prevalence of AAAs is low and the costs outweigh the benefits of screening on a population-based level, while on the other hand the dire complications of AAAs warrant early detection to reduce morbidity and mortality. The U.S. Preventive Services Task Force (USPSTF) recommends that men between the ages of 65 and 75 who have a history of smoking undergo a one-time screening for AAA (strength of recommendation is grade B). The USPSTF also recommends offering selective screening to men between the ages of 65 and 75 who are non-smokers (strength of recommendation is grade C). The USPSTF further concluded that current evidence is insufficient to assess the benefits versus the harms of screening women between the ages of 65 and 75 who have a smoking history (strength of recommendation is grade I) (LeFevre & Force, 2014; "Summaries for patients. Screening for abdominal aortic aneurysm: U.S. Preventive Services Task Force recommendation statement," 2014).

The recommendations by the USPSTF are similar to those by the American Heart Association. The AHA recommends selective screening for high-risk populations, which includes individuals with a family history of AAA and men of the ages 65 to 75 with smoking history (Hirsch et al., 2006). The above recommendations aim to decrease the morbidity and mortality in high-risk populations, although current screening recommendations do not improve the survival rate for low-risk populations. Therefore, a search for a non-invasive and cost-effective tool that is able to indicate the presence of a dilated abdominal aorta remains a priority. This study found no evidence that ABI measurements are a promising approach to statistically predict increased abdominal aorta diameters in a population setting of low to average risk of AAA. Alternative or complementary strategies that consider biomarkers

(Folsom et al., 2015) or instrumentations that can index AAA or abdominal aorta dilatation may yet help to reduce the morbidity and mortality caused by AAAs.

Table 5. Characteristics of Study Participants at the 5th ARIC Cohort Examination (N = 4,802)

Characteristic	Mean ± SD N (%)	Stratified by gender		Stratified by race	
		Mean ± SD, N (%)		Mean ± SD, N (%)	
		Male (n = 1,962)	Female (n = 2,840)	Black (n = 1,058)	White (n = 3,744)
Age, mean (years) ± SD	75.3 ± 5.1	75.6 ± 5.1	75.2 ± 5.04	74.5 ± 4.9	75.6 ± 5.1
Body mass index, mean (kg/m ²) ± SD	27.9 ± 4.5	28.03 ± 4.04	27.8 ± 4.8	29.2 ± 4.8	27.6 ± 4.4
Female, N (%)	2,840 (59.1)				
African American, N (%)	1,058 (22.0)				
Current smoker, N (%)	275 (5.8)	117 (42.5%)	158 (57.5%)	72 (26.2%)	203 (73.8%)
Current/former smoker (vs. never), N (%) (missing = 317)	2,565 (53.4)	1,254 (48.9%)	1,311 (51.1%)	505 (19.7%)	2,060 (80.3%)
Pack-years	26.3 ± 22.5	30.6 ± 24.6	22.0 ± 19.1	18.6 ± 16.4	28.3 ± 23.3
Diabetes*, N (%) (missing = 41)	1,440 (30.3)	658 (45.7%)	782 (54.3%)	425 (29.5%)	1,015 (70.5%)
Hypertension†, N (%) (missing = 46)	3,450 (72.5)	1,372 (39.8%)	2,078 (60.2%)	909 (25.3%)	2,541 (73.7%)
HTN Medication Use in Last 4 weeks, N (%) (missing = 9)	3,686 (72.7)				
ABI	1.10 ± 0.14	1.13 ± 0.15	1.09 ± 0.12	1.04 ± 0.16	1.12 ± 0.13
Proximal AP aorta diameters (cm)	1.95 ± 0.32	2.10 ± 0.32	1.85 ± 0.28	1.90 ± 0.32	1.96 ± 0.32
Mid-AP aorta diameters (cm)	1.81 ± 0.33	1.98 ± 0.35	1.69 ± 0.26	1.77 ± 0.32	1.82 ± 0.33
Distal AP aorta diameters (cm)	1.70 ± 0.35	1.88 ± 0.38	1.58 ± 0.26	1.74 ± 0.32	1.70 ± 0.35

Abbreviations: ABI (ankle-brachial index); AP (anterior-posterior); SD (standard deviation); HTN (hypertension)

* Diabetes: defined as present if glucose value ≥ 126 mg/dL or non-fasting glucose value ≥ 200 mg/dL or using medication for diabetes or self-reported diagnosis of diabetes

† Hypertension: defined as present if systolic blood pressure (mean of 2nd and 3rd measures) ≥ 140 mmHg or diastolic blood pressure (mean of 2nd and 3rd measures) ≥ 90 mmHg or medication is being taken for high blood pressure

Table 6. Percentile Values of Anterior-posterior Abdominal Aorta Diameters, by Location (N = 4,802)

Abdominal aorta diameter (cm)	Percentiles							
	5%	10%	25%	50%	75%	90%	95%	99%
Proximal anterior-posterior	1.5	1.6	1.7	1.9	2.1	2.3	2.5	2.7
Mid-anterior-posterior	1.4	1.5	1.6	1.8	2.0	2.2	2.3	2.8
Distal anterior-posterior	1.3	1.4	1.5	1.7	1.9	2.1	2.2	2.8

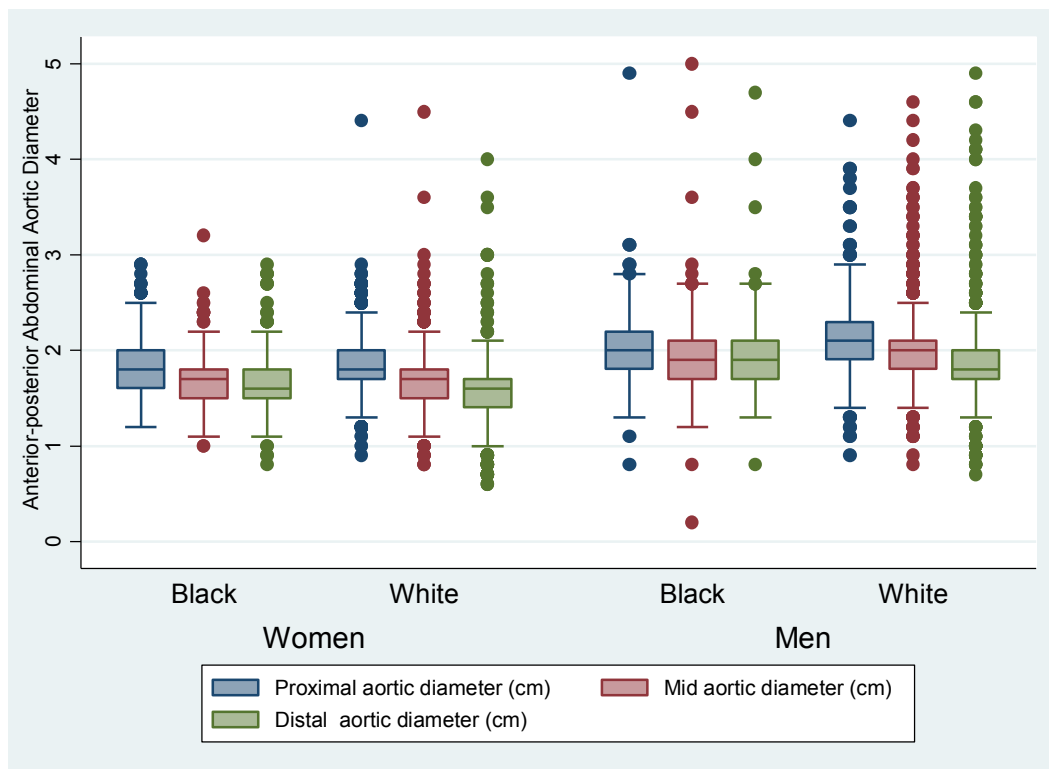


Figure 3. Anterior-posterior aortic diameter at proximal, mid- and distal anatomical locations, stratified by race and gender

Box plot description: horizontal line within box represents the median, upper horizontal line of box is the 75th percentile, lower horizontal line of box is the 25th percentile, upper horizontal line outside the box is the 90th percentile, lower horizontal line outside the box is the 10th percentile, and circles represent outliers.

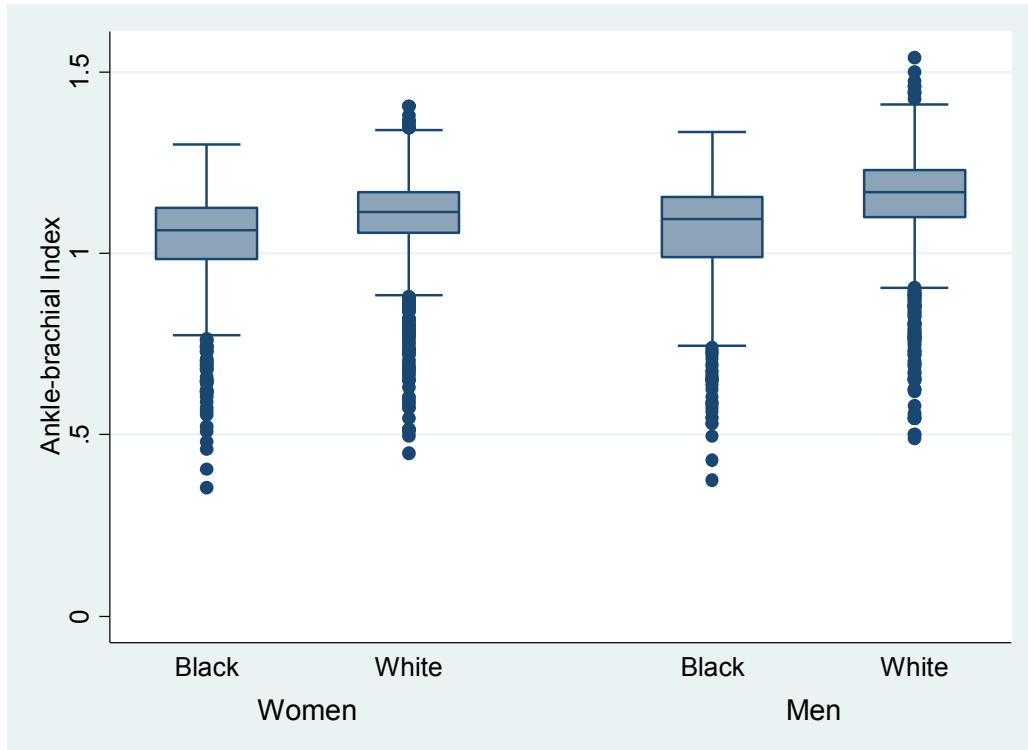


Figure 4. Ankle-brachial index stratified by race and gender

Box plot description: horizontal line within box represents the median, upper horizontal line of box is the 75th percentile, lower horizontal line of box is the 25th percentile, upper horizontal line outside the box is the 90th percentile, lower horizontal line outside the box is the 10th percentile, and circles represent outliers.

Table 7. β coefficients and 95% CIs for the Association of Anterior-posterior Proximal Abdominal Aortic Diameter with the Ankle-brachial Index

	ABI		ABI ²	
	β coefficients [95% CI]	<i>p</i> value	β coefficients [95% CI]	<i>p</i> value
Model 1*	0.11 [-1.77, -0.74]	< 0.0001	0.74 [0.49, 0.99]	< 0.0001
Model 2†	0.11 [-0.40, 0.61]	0.67	- 0.004 [-0.25, 0.25]	0.97

Abbreviations: CI (confidence interval); ABI (ankle-brachial index)

* Model 1 is adjusted for age.

† Model 2 is additionally adjusted for age, race, gender, hypertension, smoking status, and diabetes.

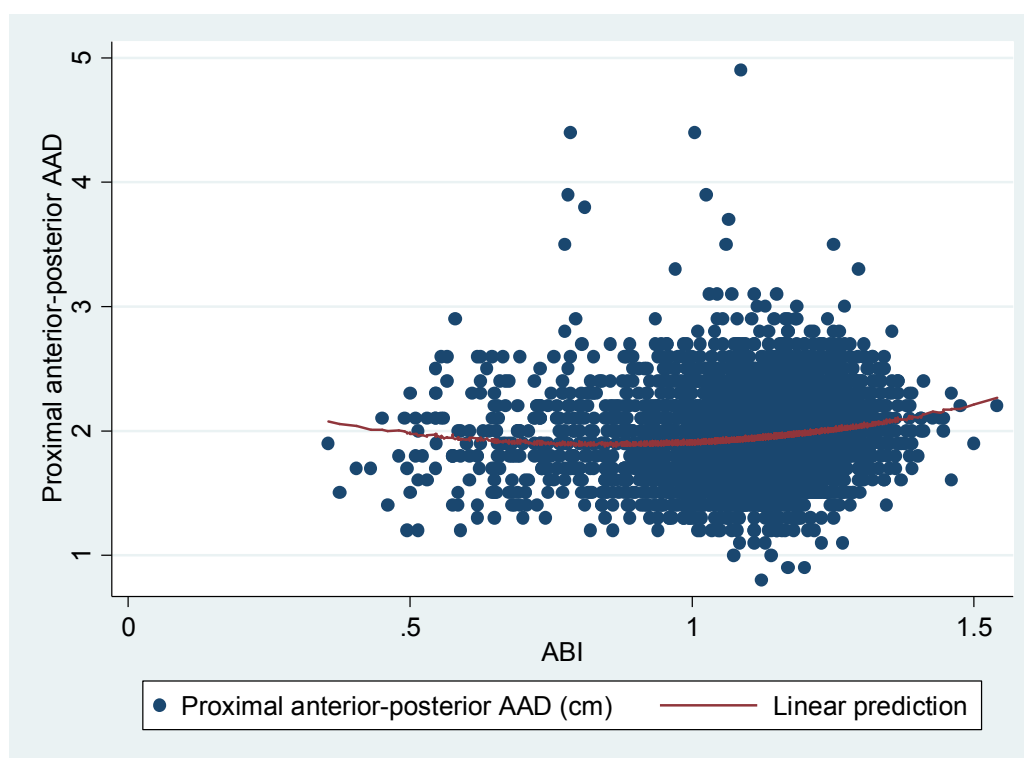


Figure 5. Scatter plot and best linear fit of anterior-posterior diameters of the proximal abdominal aorta vs. ankle-brachial index (ABI) of systolic blood pressure

Data points shown are age-adjusted predicted values from a regression model that includes ABI and its 2nd-order term.

CHAPTER 6: MANUSCRIPT 2- ARTERIAL STIFFNESS AS AN INDICATOR OF ENLARGED ABDOMINAL AORTA DIAMETERS. THE ATHEROSCLEROSIS RISK IN COMMUNITIES (ARIC) STUDY.

6.1 Introduction

Among the biomarkers considered in the prediction of cardiovascular morbidity and mortality, arterial stiffening has emerged as a non-invasive measure of risk (Franklin, 2008; Mattace-Raso et al., 2006; Mitchell et al., 2010; Sutton-Tyrrell et al., 2005; Willum-Hansen et al., 2006). Arterial stiffening results from remodeling of the arterial wall with loss of elastin, coupled with increases in abnormal collagen (Johnson et al., 2001; Zieman et al., 2005). Arterial stiffening occurs predominantly in the central arterial system with the aorta as a site of predilection, where arterial stiffening takes place to varying degrees at various segments due to inherent differences in the elasticity of the anatomic aortic segments (R. T. Lee & Kamm, 1994a).

The abdominal aorta is susceptible to aneurysmal dilatation, a diagnosed condition that is conventionally defined as an anterior-posterior diameter of the abdominal aorta of 3 cm or more (Hirsch et al., 2006). The pathophysiology of aortic abdominal aneurysm (AAA) is complex and involves atherosclerotic changes and remodeling of the arterial wall, with increased production of collagen, loss of elastic fibers, and degradation of smooth cells that result in arterial stiffening (Ailawadi et al., 2003; Allison et al., 2008; Nordon et al., 2011; Raaz et al., 2014; P. K. Shah, 1997).

The clinical and public relevance of AAA lies in the unforeseen and dire complications associated with aneurysmal rupture. The overall mortality of patients with acute AAA who seek medical care can reach 70% (Basnyat, Biffin, Moseley, Hedges, & Lewis, 1999; Bown, Sutton, Bell, & Sayers, 2002; Verhoeven et al., 2008). Current screening guidelines

for AAA by the American Heart Association are selective and focus on older men with a history of smoking (Hirsch et al., 2006).

Identification of a non-invasive biomarker that is sensitive and specific in identifying individuals likely to have abdominal dilatation has the potential of reducing the mortality and morbidity associated with AAA. Given the involvement of arterial stiffening in the pathophysiology of abdominal aorta dilatation and AAA development, we posited an association between arterial stiffness and abdominal aorta diameter. Based on the literature indicating that pulse wave velocity (PWV) is a valid and reproducible measure of arterial stiffness (Chirinos, 2012), we used PWV as a non-invasive surrogate for arterial stiffness in order to examine the association between PWV and the anterior-posterior diameters of the abdominal aorta at pre-specified anatomical sites in a population-based, biracial cohort of men and women ages 70-89 years.

6.2 Methods

6.2.1 Study population

We conducted a cross-sectional analysis of data from the 5th examination of the Atherosclerosis Risk in Communities (ARIC) study cohort (2011-2013) sponsored by the National Heart, Lung, and Blood Institute (NHLBI). ARIC is a prospective epidemiologic study of adults aged 45-64 years at intake in 1987-89, drawn as probability samples from four U.S. communities (Washington County, Maryland; suburban Minneapolis, Minnesota; Jackson, Mississippi; and Forsyth County, North Carolina) ("The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators," 1989). The response rate for visit 5 was 65%, which represents 6,538 participants. Of those, 5,683 completed the measurements include in these analyses.

Of the 5,683 participants with a complete 5th exam, 1,459 were excluded from these analyses due to characteristics that may interfere with PWV measurements or due to missing observations. We excluded participants with missing abdominal aorta diameter (AAD), a

body mass index (BMI) $\geq 40\text{kg/m}^2$, aortic stenosis, moderate or severe aortic regurgitation, aortic revascularization, peripheral revascularization, evidence of a major arrhythmia (Minnesota code 8-3-1) on a 12-lead electrocardiogram, and missing PWV values. Only white and African-American participants were included, since other race groups were not represented in numbers sufficient for analysis. The study was approved by the Institutional Review Boards at each participating institution. Written informed consent was provided to the participants for each examination. After exclusions, our final analytical sample included 4,224 participants.

All measurements for the ARIC visit 5 were obtained by trained technicians following standardized protocols. Participants were asked to fast for 8 hours prior to their clinic visit and to avoid tobacco use and vigorous physical activity. They were also asked to bring all medications (prescription and non-prescription) to the exam. Participants provided medical history and lifestyle information by completing interviewer administered questionnaires. Blood and urine specimens were obtained and shipped for assay and long term storage at three core laboratories. Anthropometric measurements, a standard 12-lead electrocardiogram, standing height measurement, body weight, and three seated blood pressure measurements were obtained using an oscillometric automated sphygmomanometer (Omron Co., Ltd., Kyoto, Japan). Hypertension was defined as present if systolic blood pressure (mean of 2nd and 3rd measures) ≥ 140 mmHg or diastolic blood pressure (mean of 2nd and 3rd measures) ≥ 90 mmHg or medication is being taken for high blood pressure. Diabetes was defined as present if glucose value ≥ 126 mg/dL or non-fasting glucose value ≥ 200 mg/dL or using medication for diabetes or a self report of physician-diagnosed diabetes. Details are available in Manual 2 (Home and Field Center Procedures) at <https://www2.csc.unc.edu/aric/cohort-manuals>.

Abdominal aorta diameters

Abdominal aorta diameter was measured by high resolution, real-time duplex ultrasound (Philips IE33). The participants were asked to fast for at least 8 hours prior to their 5th ARIC clinic visit as described above. To ensure data quality, the radiologists and certified technologists were trained to follow a standardized protocol. Transverse and anterior-posterior diameters were measured at three pre-specified levels of the abdominal aorta: at the proximal aorta below the superior mesenteric artery, the mid aorta 2 cm below the renal arteries, the distal infrarenal aorta 1 cm superior to the aortic bifurcation, as well as the point of maximal abdominal aortic dilatation if not at one of the locations mentioned. Additional transverse images were taken in the case of a possible AAA (maximum diameter ≥ 2.8 cm). In this study, we focus on proximal anterior-posterior abdominal aorta diameters. Participants with a history of previous AAA repair or previous aortic bypass surgery for occlusive atherosclerotic disease were not scanned. Outliers equal to three standard deviations from the mean were excluded.

Pulse wave velocity

PWV measurements were performed using the automated non-invasive waveform analyzer VP-1000 Plus (Omron Co., Ltd., Kyoto, Japan) (Cortez-Cooper et al., 2003) following a standardized procedure described previously (Meyer et al., 2016). Briefly, trained and certified technicians performed the measurement protocol while the participant was in the supine position with both arms resting along his/her side. Four size-appropriate blood pressure cuffs were attached to both arms and ankles to record the systolic blood pressure and pressure pulse waves, respectively. A carotid sensor, a femoral sensor, and two electrocardiogram sensors were applied. Two measurements were taken to reduce process variability; the second measurement was obtained two to five minutes after the first measure. A third measurement was performed if the study technician experienced difficulties in obtaining an optimal pulse wave form; technologists waited 2-5 minutes to obtain this measurement. The

average of the last 2 non-zero measurements was used. The distance between two arterial sites divided by the transit time was used to estimate PWV. The segments examined in this report are heart-carotid PWV (hcPWV), carotid-femoral PWV (cfPWV), and bilateral femoral-ankle PWV (faPWV).

6.2.2 Statistical analysis

We examined the distribution and calculated the means and standard deviations of PWV and AAD in the ARIC cohort at visit 5. We then characterized the strength and shape of the association between PWV segments and AAD across the range of PWV values. Associations were characterized based on the continuous forms of PWV and AAD for inclusion in the final statistical model, as they best captured the association.

Participant characteristics were estimated as means and standard deviations, medians and 25th and 75th percentiles, or frequencies and percentages, where appropriate. We examined the role of age, gender, race, cigarette smoking, elevated blood pressure, and diabetes mellitus as covariates and possible effect modifiers of the association between PWV segments and AAD. We performed bi-variable analyses between the aforementioned covariates and both AAD and PWV segments. The covariates statistically associated ($p < 0.05$) with both AAD and PWV segments were adjusted for in Models 2,4, 6, and 8. Model 1 was adjusted for age to assess the ability to statistically predict proximal AAD from hcPWV. Model 2 included adjustment for age, gender, race, elevated blood pressure, diabetes, and smoking to assess the ability of hcPWV to statistically predict proximal AAD. Model 3 was adjusted for age to assess the ability to statistically predict proximal AAD from cfPWV. Model 4 was adjusted for age, gender, race, diabetes, and hypertension to assess the ability to statistically predict proximal AAD from cfPWV. Model 5 was adjusted for age to assess the ability to statistically predict proximal AAD from right faPWV. Model 6 was adjusted for age, race, smoking status, and diabetes to assess the ability to statistically predict proximal AAD from right faPWV. Model 7 was adjusted for age to assess the ability to statistically

predict proximal AAD from left faPWV. Model 8 was adjusted for age, race, smoking status, and diabetes to statistically predict proximal AAD from left faPWV. Due to the very small magnitude of association between PWV segments and AAD we calibrated PWV segments to one standard deviation throughout our modeling steps.

The analytical steps were repeated to examine the association between PWV with mid-anterior-posterior AAD and distal anterior-posterior AAD. To optimize model fit, we examined the improvement in model diagnostics by adding quadratic and third-order terms for PWV. All statistical tests are 2-sided, with a nominal significance level of $P < 0.05$. All analyses were performed using Stata, version 14.0 (StataCorp LP, College Station, TX).

6.3 Results

Altogether, 4,224 ARIC visit 5 participants met our criteria for inclusion in the analysis. The mean age was 75.3 ± 5.1 years and the mean BMI was 27.9 ± 4.5 kg/m². The majority of the participants were women (60.4%), 22.7% were African-American, 52.6% were/are smokers, 29.4% were diabetics, and 71.3% were hypertensive (Table 8).

The overall mean values for the PWV segments were; $1,132.8 \pm 344.5$ cm/s for hcPWV, $1,159.5 \pm 302.7$ cm/s for cfPWV, $1,099.2 \pm 180.8$ cm/s for right faPWV, and $1,067.8 \pm 174.8$ cm/s for left faPWV. The distribution of PWV varied slightly (less than one standard deviation) across gender and race (Table 8). The overall mean and standard deviation for proximal, mid-, and distal anterior-posterior AAD were 1.94 ± 0.31 cm, 1.80 ± 0.33 cm, and 1.70 ± 0.33 cm, respectively (Table 8). AAD was smaller among women compared with men, and there were no apparent differences by race (Figure 6). The median values for anterior-posterior AAD at proximal, mid- and distal locations were 1.9 cm, 1.8 cm, and 1.7 cm, respectively (Table 9). The overall mean for PWV segments were $1,132.8 \pm 344.5$ cm/s for hcPWV, $1,159.5 \pm 302.7$ cm/s for cfPWV, $1,099.2 \pm 180.8$ cm/s for right faPWV, and $1,067.8 \pm 174.8$ cm/s for left faPWV. The distribution of PWV varied slightly (less than one standard

deviation) across gender and race (Table 8). The covariates retained in the regression models varied by each PWV segment and are shown in Table 3.

A linear fit best described the association between hcPWV and AAD. The estimates of association and (95% confidence intervals) between proximal anteroposterior AAD and hcPWV, adjusting for age and gender, were 0.02 cms/s (0.02, 0.03), $p < 0.0001$). The fitted scatter plot for the association between hcPWV and proximal anteroposterior AAD is linear, showing a gradual increase in the AAD as hcPWV increases (Figure 7). The estimated mean and (95% confidence intervals) for proximal anteroposterior AAD in a 75 year old participant (median age for study cohort) for hcPWV at the 25th (903 cm/s), 50th (1061.3 cm/s), and 75th (1282.5 cm/s) percentiles is; 1.91 cm (1.90, 1.92), 1.93 cm (1.92, 1.94), and 1.97 cm (1.96, 1.98) respectively.

In a fully adjusted model (Table 10), the estimates were about the same. The pattern of association was similar between hcPWV and distal anterior-posterior AAD.

Carotid-femoral PWV exhibited a weaker association with aortic diameter that was confined to the proximal AAD. The estimates of association and (95% confidence intervals) for cfPWV and cfPWV squared, adjusting for age and gender, were 0.06 (0.01, 0.1) and -0.01 (-0.02, -0.004), respectively. Significant P values (< 0.05) for both cfPWV and cfPWV squared indicate non-linear associations between cfPWV and AAD.

Right and left faPWV were weakly associated with AAD only at the proximal level. The estimates of association and (95% confidence intervals) were 0.01 (0.001, 0.02) for right faPWV and 0.01 (0.003, 0.02) left faPWV, adjusting for age and gender; both P values were (>0.05). None of the covariates specified a priori (see above) reached nominal statistical significance ($P \leq 0.05$) as effect measure modifiers on the association between PWV segments and AAD.

6.4 Discussion

To our knowledge, this is the first report on the association between central and peripheral arterial stiffness and AAD in a biracial, population-based cohort of older men and women. Our results indicate that only hcPWV is associated with anterior-posterior abdominal aorta diameter throughout its segments: the greater the value of hcPWV, the greater the AAD at the proximal, mid-, and distal locations. Although the association met nominal statistical significance, the magnitude of the association is small and not clinically meaningful or useful in clinical practice to indicate the presence of abdominal aortic dilatation.

Heart-carotid pulse wave velocity is not widely used to measure arterial stiffness but was of interest in this study because it estimates stiffness from the carotid artery to the ascending aorta and excludes the abdominal aorta, our exposure of interest. Exclusion of the abdominal aorta is crucial since arterial stiffness measured by PWV takes into account the arterial wall properties such as the wall thickness to lumen diameter ratio. This relationship is best described by the Moens–Korteweg equation, $PWV = \sqrt{\frac{h E_{inc}}{D \rho}}$, where h represents wall thickness, E_{inc} Young's modulus of the arterial wall (stress/strain ratio), D arterial diameter, and ρ blood density (Chirinos, 2012). Measurements of cfPWV are thus not independent of AAD and as a result are to some degree biased. This has been shown in a comparison of cfPWV before and after endovascular repair in patients diagnosed to have AAA. cfPWV was consistently higher before aneurysmal repair and lower 4 weeks after surgery (C. W. Lee et al., 2013a).

It has been reported that hcPWV can indicate the presence of central atherosclerotic changes in hypertensive individuals (C. Li et al., 2015), but we are not aware of prior studies of hcPWV as an indicator of abdominal aorta dilatation. We are thus unable to compare our results to other estimates of the association between central arterial stiffness measured by hcPWV and AAD. Nonetheless, the association between AAD and the elastic properties of

aortic segments has been addressed with other imaging modalities (Kadoglou et al., 2012; Kroner et al., 2013; C. W. Lee et al., 2013a; Nollen, Groenink, Tijssen, Van Der Wall, & Mulder, 2004; Vande Geest, Sacks, & Vorp, 2006), and the available evidence predominantly supports an association of AAD with central arterial stiffness (Kadoglou et al., 2012; Kroner et al., 2013; Luo, Fujikura, Tyrie, Tilson, & Konofagou, 2009; Nollen et al., 2004; Raaz et al., 2015; Vande Geest et al., 2006). Furthermore, human aneurysmal and non-aneurysmal abdominal aorta tissue specimens were compared with biaxial tensile testing to evaluate arterial stiffening and extensibility (Vande Geest et al., 2006). The aneurysmal tissue exhibited higher levels of circumferential stiffness and lower extensibility compared to the normal abdominal aorta tissue (Vande Geest et al., 2006).

The specificity of regional PWV measured by magnetic resonance imaging (MRI) in detecting the absence of aortic diameter growth has been estimated to be 78%, and its sensitivity did not exceed 33%, based on a two-year longitudinal study (N = 47) that examined the diagnostic accuracy of regional PWV measured by MRI in predicting luminal growth of the aorta (Kroner et al., 2013). The ability of regional PWV to predict the absence of aortic luminal growth differed by aortic segment: The specificity at the abdominal aorta segment was 90% for the suprarenal segment and 83% for the infrarenal segment (Kroner et al., 2013). In another longitudinal study (N = 78), participants were followed for approximately 6 years and aortic diameter, aortic distensibility, and aortic stiffness were evaluated by MRI (Nollen et al., 2004). Aortic stiffness assessed by flow wave velocity did not significantly change during follow-up, but local aortic distensibility predicted aortic dilatation. Aortic distensibility was a stronger predictor for the ascending thoracic aorta than it was for the abdominal aorta (Nollen et al., 2004).

Examination of the association between arterial stiffness and AAD in murine models led to the conclusion that the pattern and speed of pulse wave propagation varies between non-aneurysmal specimens and those with induced AAA (Luo et al., 2009; Raaz et al.,

2015). Induced aneurysmal specimens exhibited a non-uniform movement of pulse waves through the aneurysmal wall, while the pulse waves moved uniformly through normal abdominal aortic segments (Luo et al., 2009). The development of artificially induced abdominal aneurysms in mice also revealed that stiffening gradually increases in the segment targeted to artificially induce AAA (Raaz et al., 2015).

Peripheral arterial stiffness measured by faPWV was mostly not associated with AAD in our study. This may be explained by the arterial wall composition in the peripheral arterial system. Its greater density of smooth muscle tissue than that of the central arterial tree renders the peripheral arterial system less prone to arterial stiffening (Bezie et al., 1998; Fischer & Llaurodo, 1966; Laurent et al., 2006).

As a limitation of the results presented here, it should be noted that individuals were excluded from this study if they had been diagnosed with AAA or undergone surgical repair for aortic dilatation prior to the examination. Consequently, enlarged aortic diameters, such as AAD of 2.9 cm or more, were under-represented in our study population, limiting our ability to characterize the association between arterial stiffness and larger abdominal aorta diameters.

Abdominal aortic aneurysms are a condition of low prevalence but are often undetected and have unforeseen, life-threatening consequences. The reported prevalence of AAAs (aortic diameters 2.9-4.9 cm) ranges between 1.3%-18.5% among men 75-84 years of age and between 1%-4.8% among women in the same age range (Boll et al., 1998; Go et al., 2013; Singh et al., 2001). On a global scale, age-standardized, disability-adjusted life years (DALY's) for AAAs in twenty-one regions of the world increased by an average of 3.6% (from 44/100,000 to 46/100,000) from 1990 to 2010 (Murray et al., 2012). Although the age-standardized death rates from 1990 to 2010 decreased by 12.7% (from 3.3/100,000 to 2.9/100,000), the percentage of deaths attributed to aortic aneurysms in 187 countries in-

creased by 45.3% (from 3986.3 to 3776.3 deaths of all ages) during the same period (Lozano et al., 2012) as an indication of the case fatality of this condition.

The merits of screening for AAAs continue to be debated, given the low prevalence and high costs that ostensibly outweigh the benefits of screening at the population level. On the other hand, the dire complications of AAAs warrant early detection to reduce morbidity and mortality. The U.S. Preventive Services Task Force (USPSTF) recommends that men between the ages of 65 and 75 who have a history of smoking undergo screening for AAA (strength of recommendation is grade B). The USPSTF also recommends offering selective screening to men between the ages of 65 and 75 who are non-smokers (strength of recommendation is grade C). The USPSTF further concluded that the current evidence is insufficient to assess the benefits versus the harms of screening women between the ages of 65 and 75 who have a smoking history (strength of recommendation is grade I) (LeFevre & Force, 2014; "Summaries for patients. Screening for abdominal aortic aneurysm: U.S. Preventive Services Task Force recommendation statement," 2014).

The recommendations by the USPSTF are similar to those by the American Heart Association (AHA). The AHA recommends selective screening for high-risk populations, which includes individuals with a family history of AAA and men between the ages 65 to 75 who have a smoking history (Hirsch et al., 2006). The above recommendations aim to decrease the morbidity and mortality in high-risk populations; current screening recommendations would not improve the rate of AAA complications for low-risk populations. Therefore, a search for non-invasive and cost effective tools that indicate the presence of a dilated abdominal aorta remains a priority. This study found no evidence that measures of central arterial stiffening are a promising approach to index a greater likelihood of increased abdominal aorta diameters in a population setting of low-to-average risk of AAA.

Alternative or complementary strategies that consider biomarkers (Folsom et al., 2015) or non-invasive measurement modalities that can index AAA or abdominal aorta dilatation may yet help to reduce the morbidity and mortality caused by AAAs.

Table 8. Characteristics of Study Participants at the 5th ARIC Cohort Examination (N = 4,224)

Characteristic	Mean ± SD N (%)	Stratified by gender		Stratified by race	
		Mean ± SD, N (%)		Mean ± SD, N (%)	
		Male	Female	Black	White
Age, mean (years) ± SD	75.3 ± 5.1	75.4 ± 5.1	75.21 ± 5.03	74.5 ± 5.0	75.6 ± 5.0
Body mass index, mean (kg/m ²) ± SD	27.9 ± 4.5	27.9 ± 3.9	27.7 ± 4.8	29.1 ± 4.8	27.4 ± 4.3
Female, N (%)	2,553 (60.4)				
African American, N (%)	957 (22.7)				
Current smoker, N (%)	275 (5.8)	117 (42.5%)	158 (57.5%)	72 (26.2%)	203 (73.8%)
Ever-smoker, N (%) (missing = 275)	2,222 (56.3)	1,062 (47.8%)	1,160 (52.2%)	506 (19.7%)	2,060 (80.3)
Pack-years (missing = 2,204)	25.8 ± 22.0	30.2 ± 24.3	21.4 ± 18.4	18.0 ± 16.1	27.8 ± 22.9
Diabetes*, N (%) Lower cutpoint 126 mg/dL (missing = 37)	1,243 (29.4)	557 (44.8%)	686 (55.2%)	380 (30.6%)	863 (69.4%)
Hypertension†, N (%) ≥ 140 (missing = 39)	3,013 (71.3)	1,160 (38.5%)	1,853 (61.5%)	816 (27.1%)	2,197 (72.9%)
HTN medication use in last 4 weeks, N (%)	3,028 (71.7)				
hcPWV cm/s	1,132.8 ± 344.5	1,256.7 ± 382.9	1,051.8 ± 289.5	1,147.5 ± 350.7	1,128.6 ± 342.6
cfPWV cm/s	1,159.5 ± 302.7	1,182.0 ± 307.1	1,144.3 ± 298.8	1,228.8 ± 333.9	1,139.0 ± 289.7
Right faPWV cm/s	1,099.2 ± 180.8	1,098.2 ± 183.2	1,099.9 ± 179.2	1,052.9 ± 179.5	1,112.9 ± 178.9
Left faPWV cm/s	1,067.8 ± 174.8	1,066.9 ± 176.3	1,068.4 ± 173.8	1,030.4 ± 171.4	1,078.9 ± 174.3
Proximal aorta diameters (cm)	1.94 ± 0.31	2.10 ± 0.32	1.85 ± 0.27	1.90 ± 0.32	1.96 ± 0.32
Mid-aorta diameters (cm)	1.80 ± 0.33	1.98 ± 0.34	1.69 ± 0.26	1.78 ± 0.32	1.81 ± 0.33
Distal aorta diameters (cm)	1.70 ± 0.33	1.87 ± 0.36	1.58 ± 0.26	1.74 ± 0.32	1.70 ± 0.34

Abbreviations: AP (anterior-posterior); SD (standard deviation); HTN (hypertension); hcPWV (heart-carotid pulse wave velocity); cfPWV (carotid-femoral pulse wave velocity); faPWV (femoral-ankle pulse wave velocity)

* Diabetes: defined as present if glucose value ≥ 126 mg/dL or non-fasting glucose value ≥ 200 mg/dL or using medication for diabetes or self-reported diagnosis of diabetes

† Hypertension: defined as present if systolic blood pressure (mean of 2nd and 3rd measures) ≥ 140 mmHg or diastolic blood pressure (mean of 2nd and 3rd measures) ≥ 90 mmHg or medication is being taken for high blood pressure

Table 9. Percentile Values of Anterior-posterior Abdominal Aorta Diameters, by Location (N = 4,224)

Abdominal aorta diameter (cm)	Percentiles							
	5%	10%	25%	50%	75%	90%	95%	99%
Proximal anterior-posterior	1.5	1.6	1.7	1.9	2.1	2.3	2.5	2.7
Mid-anterior-posterior	1.4	1.5	1.6	1.8	2.0	2.2	2.3	2.8
Distal anterior-posterior	1.3	1.4	1.5	1.7	1.9	2.1	2.2	2.8

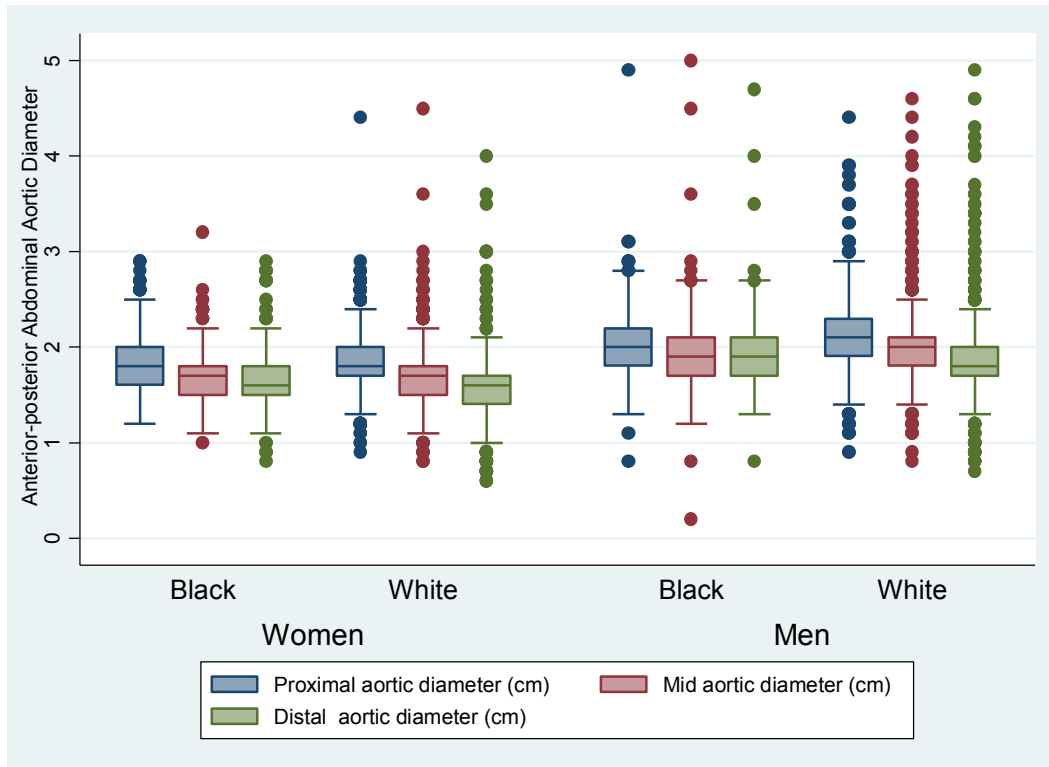


Figure 6. Anterior-posterior aortic diameter at proximal, mid- and distal anatomical locations, stratified by race and gender

Box plot description: horizontal line within box represents the median, upper horizontal line of box is the 75th percentile, lower horizontal line of box is the 25th percentile, upper horizontal line outside the box is the 90th percentile, lower horizontal line outside the box is the 10th percentile, and circles represent outliers.

Table 10. β Coefficients and 95% CIs for the Association of Anterior-posterior Proximal Abdominal Aortic Diameter with Heart-carotid, Carotid-Femoral, and Femoral-Ankle Segments of Pulse Wave Velocity

	β coefficients [95% CI]	<i>p</i> value
<i>hcPWV</i>		
Model 1*	0.02 [0.02, 0.03]	< 0.0001
Model 2**	0.03 [0.02, 0.04]	< 0.0001
<i>cfPWV</i>		
Model 3†	0.06 [0.01, 0.1]	0.02
Model 4††	0.07 [0.01, 0.1]	0.01
<i>Right faPWV</i>		
Model 5‡	0.01 [0.001, 0.02]	0.03
Model 6‡‡	0.01 [0.001, 0.02]	0.03
<i>Left faPWV</i>		
Model 7€	0.01 [0.003, 0.02]	0.01
Model 8€€	0.01 [0.005, 0.02]	0.003

Abbreviations: CI (confidence interval); PWV (pulse wave velocity); hcPWV (heart-carotid PWV); cf (carotid-femoral PWV); and faPWV (femoral-ankle PWV)

All β coefficients are calibrated to one standard deviation (SD), and the SD for hcPWV, cfPWV, right faPWV, and left faPWV are, respectively, 344.5, 302.7, 180.8, and 174.8.

* Model 1 is adjusted for age.

**Model 2 is adjusted for age, gender, and smoking status.

† Model 3 is adjusted for age.

†† Model 4 is adjusted for age, gender, race, diabetes, and hypertension.

‡ Model 5 is adjusted for age.

‡‡ Model 6 is adjusted for age, race, smoking status, and diabetes.

€ Model 7 is adjusted for age.

€€ Model 8 is adjusted for age, race, smoking status, and diabetes.



Figure 7. Scatter plot and best linear fit of anterior-posterior diameters of the proximal abdominal aorta vs. heart-carotid pulse wave velocity (hcPWV).

Data points shown are age-adjusted predicted values from a linear regression model that includes hcPWV and age.

CHAPTER 7: MANUSCRIPT 3-THE ANKLE-BRACHIAL INDEX AND PULSE WAVE VELOCITY AS STATISTICAL PREDICTORS OF AAD

This study set out to assess ABI and/or PWV as correlates of abdominal aorta diameter and to derive risk equations to predict the presence of AAD for potential use in clinical settings and population research. Our plan was to develop a parametric binomial model from the best predictors (variables) of abdominal aortic diameter. Based on the small magnitude of the associations between ABI and PWV and AAD, there is insufficient justification to proceed to develop risk prediction equations. Such predictive risk models would likely achieve a good fit but poor discrimination and suboptimal classification performance. Their usefulness and clinical applicability would therefore be questionable. Thus, Aim 3 was deemed not applicable for ABI and PWV.

CHAPTER 8: DISCUSSION

8.1 Recapitulation of overall specific aims

This dissertation examined peripheral arterial disease as an indicator of abdominal aorta diameter in a large bi-racial, population-based study of older adults. It also examined arterial stiffness as an indicator of abdominal aorta diameter in this population. Due to the small magnitude of the association between both peripheral arterial disease and arterial stiffness with abdominal arterial diameter, we concluded that deriving risk equations to predict the presence of enlarged AAD would be of little clinical relevance.

8.2 Discussion of results

This work documents the association between biomarkers of atherosclerosis and arteriosclerosis and abdominal aorta diameters. ABI and PWV were the biomarkers used to assess peripheral atherosclerosis and arteriosclerosis, respectively. We observed a statistically significant association between both ABI and PWV and AAD.

ABI, a biomarker of peripheral arterial disease, was used in this study to assess the strength of the association between ABI and AAD at proximal, mid-, and distal locations of the abdominal aorta. We observed a U-shaped relationship between ABI and AAD. This relationship was consistent at all three locations of the abdominal aorta. Although this association reached statistical significance, it was of small magnitude and thus not a good indicator of AAD. In the process of selecting the best fitting model, splines with nodal points at ABI values of 0.5 and 1.3 were examined; they did not improve model fit in comparison to the linear regression model with quadratic term for ABI. Based on the literature a number of covariates were predefined as possible confounders and effect measure modifiers, including smoking, hypertension, diabetes, body surface area, gender, race, and age. A fully adjusted

model was fit including age, race, gender, hypertension, smoking, diabetes, and body surface area, as well as one only adjusted for age, since it was not our purpose to account for, or partially explain the mechanisms behind the association between ABI and AAD.

The associations observed in this population-based cohort have not been examined in similar large cohorts. Prior reports based on atherosclerosis-rich cohorts have examined the association of peripheral arterial disease and abdominal aortic aneurysms and confirmed the coexistence of PAD and AAA to varying degrees (Allardice et al., 1988; Axelrod et al., 2002; MacSweeney et al., 1993). We believe that the generally healthy nature of the population in this study and the under-representation of dilated abdominal aortic diameters in these study participants contributed to the weak but statistically significant association of ABI and AAD that we observed.

As a manifestation of arteriosclerosis, arterial stiffness was examined in this study for its hypothesized association with AAD. We studied this association with AAD for both central and peripheral arterial stiffness, and we observed different associations. Heart-carotid PWV (hcPWV) and carotid-femoral PWV (cfPWV) are biomarkers of central arterial stiffness, and their association with AAD was examined separately. This work documented a monotonic and linear association between hcPWV and AAD throughout the three locations of the abdominal aorta. A fully adjusted model was fit that included age, gender, smoking, and body surface area. Since it was not our purpose to account for, or partially explain any mechanisms underlying an association between hcPWV and AAD we base our conclusions on a parsimonious model adjusted for age and gender.

To our knowledge, no prior studies have examined the association of hcPWV and AAD. A number of reports that examined the association using different biomarkers of central arterial stiffness are found in the literature, most of which support the association of central arterial stiffness and dilated abdominal aorta diameter (Kadoglou et al., 2012; Kroner et

al., 2013; C. W. Lee et al., 2013b; Luo et al., 2009; Nollen et al., 2004; Raaz et al., 2015; Vande Geest et al., 2006).

Carotid-femoral PWV is commonly used in studies to evaluate central arterial stiffness (Laurent et al., 2006). In our study, we observed a statistically significant association between cfPWV and AAD at the proximal abdominal aorta, and as we moved distally the association ceased to meet nominal levels of statistical significance. Notably, the measurement of PWV is in part dependent on the arterial diameter, as a result of which the estimated association between this segmental cfPWV measure and AAD is to some degree biased.

Peripheral arterial stiffness was mostly not associated with AAD. Arterial stiffening occurs to a lesser degree in the peripheral arterial systems than in the central arterial system (Laurent et al., 2006), reflecting inherent compositional differences between central and peripheral arteries (Bezie et al., 1998; Fischer & Llaurodo, 1966). We believe that the compositional differences between the central and peripheral arterial system may explain the inconsistencies in the associations observed.

Our aims were to characterize ABI and/or PWV as indicators of abdominal aorta diameter and to derive risk equations predictive of the presence of dilated AAD. Given the small magnitude of the observed associations between both ABI and PWV and AAD, there was insufficient justification to proceed to the derivation of risk equations.

In conclusion, this doctoral research demonstrated an association between both central arterial stiffness and peripheral atherosclerosis and the abdominal aorta diameter. The magnitude of the association was small and therefore did not warrant the creation of a predictive risk model. The search for other biomarkers or non-invasive measurement modalities that can index dilated AAD may help reduce the mortality and morbidity caused by abdominal aortic aneurysms.

8.3 Degree to which the goals of doctoral research have been met

Doctoral research is expected to demonstrate scientific depth, rigor, and to add to the current state of knowledge or clinical practice. The Epidemiology Academic Policies Manual identifies originality, depth, scholarship, and communication skills as the Department's standards for doctoral research. With the input of my advisor and committee members, I submit that the doctoral research embodied in this dissertation and the manuscripts generated from it sufficiently address the four standards required by the Department. Originality was met through the novelty of the study questions examined. To our knowledge, this study is the first to examine arterial stiffness and peripheral arterial disease as indicators of AAD in a population based, biracial cohort. Thus, this study adds new knowledge about the association of both arterial stiffness and peripheral arterial disease and abdominal aorta diameter.

The depth requirement was met through the investigation of two independent variables related to atherosclerosis and arteriosclerosis. In addition, a comprehensive and systematic analytical plan was followed to achieve the aims of this dissertation.

Scholarship was addressed through the comprehensive review of the state of the science and the rigorous process followed to complete this dissertation. The study questions were thoroughly examined and justified, and the available literature was studied in depth to gain adequate knowledge about the topic in hand.

Finally, the scientific writing skills requirement was met through the initial independent development of the two manuscripts, including the formulation of the rationale that puts the study question in context, describing the study design and methods used, summarizing the relevant results, and constructing a discussion section that describes the importance of the work done and relating it to the current state of knowledge. Once the initial manuscripts were formulated and distributed to committee members, I received substantive and editorial comments that were taken into account in finalizing them.

8.4 Strengths and limitations

The strengths of this study on the association between peripheral arterial disease and abdominal aorta diameter and between arterial stiffness and abdominal aorta diameter include the novelty of the associations examined, the population-based nature of the study population, and the biomarkers used to evaluate PAD and arterial stiffness, which were estimated using an automated, validated, and reliable device. A further strength of the study lies in the large number of participants included in our analysis. This study includes more than 4,000 participants, a significant improvement over previous studies that have examined these biomarkers. . Also, the study population of older adults adds to relevance to the results, since the outcome of interest is more prevalent in this age group. Not least, the ARIC study conducted the examination by implementing standardized protocols and trained personnel to ensure data quality.

Several limitations of this study should be noted. The cross-sectional design prevented us from assessing changes in AAD that may occur in concert with a change in ABI and/or PWV. The reliability of the ABI and hcPWV measures was estimated, and observed to be fair. Other limitations due to possible measurement error include estimating the distance for cfPWV by measuring the carotid-femoral length over the body, which may not be an accurate estimate of the corresponding arterial segment, and calculation of faPWV using height-based formulas validated only in Japanese populations. Lastly, dilated aorta diameters are infrequent in this study population and may have resulted in underestimation of the magnitude of association.

8.5 Future directions

Replication of this study in a population enriched with enlarged aorta diameters may serve to derive estimates of association more applicable to clinical settings. Also, longitudinal studies that monitor the change of AAD associated with the change in ABI and or PWV would be desirable to better assess the nature and strength of the association between pe-

Peripheral arterial disease and abdominal aorta dilatation and arterial stiffness and abdominal aorta dilatation. Further, other biomarkers may more accurately predict abdominal aorta diameter, thus creating an opportunity for risk prediction to discriminate between normal and dilated abdominal aorta diameter.

APPENDIX 1: IRB CERTIFICATION

IRB Notice

Page 1 of 2

IRB Notice

IRB [irb_no_reply@unc.edu]

Sent: Tuesday, April 28, 2015 8:45 AM

To: Al Qunaibet, Ada

Cc: Couper, David; Heiss, Gerardo; Hinderliter, Alan L; Loehr, Laura Ross; Miller, William C

To: Ada Al Qunaibet
Epidemiology Operations

From: Office of Human Research Ethics

Date: 4/28/2015

RE: Notice of IRB Exemption

Exemption Category: 4 Existing data, public or deidentified

Study #: 15-0751

Study Title: Arterial Stiffness and Peripheral Arterial Disease as Indicators of Abdominal Aorta Diameters

This submission has been reviewed by the Office of Human Research Ethics and was determined to be exempt from further review according to the regulatory category cited above under 45 CFR 46.101(b).

Study Description:

Purpose: To examine the association between the components of arteriosclerosis and atherosclerosis, namely atherosclerosis and sclerosis, in the central and lower extremity arteries with abdominal aorta diameters and aortic aneurysms.

Participants: The Atherosclerosis and Risk in Communities (ARIC) study visit 5 cohort and it includes 6,538 participants.

Procedures (methods): a cross-sectional study design will be employed

Investigator's Responsibilities:

If your study protocol changes in such a way that exempt status would no longer apply, you should contact the above IRB before making the changes. There is no need to inform the IRB about changes in study personnel. However, be aware that you are responsible for ensuring that all members of the research team who interact with subjects or their identifiable data complete the required human subjects training, typically completing the relevant CITI modules.

The IRB will maintain records for this study for 3 years, at which time you will be contacted about the status of the study.

The current data security level determination is Level I. Any changes in the data security level need to be discussed with the relevant IT official. If data security level II and III, consult with your IT official to develop a data security plan. Data security is ultimately the responsibility of the Principal Investigator.

Please be aware that approval may still be required from other relevant authorities or "gatekeepers" (e.g., school principals, facility directors, custodians of records), even though the project has determined to be exempt.

<https://outlook.unc.edu/owa/?ae=Item&tt=IPM.Note&id=RgAAAABFMabdIEpzQYjwKVg...> 2/2/2016

CC:

David Couper, Biostatistics Operations

Gerardo Heiss, Epidemiology Operations

Alan Hinderliter, Medicine - Cardiology

Laura Loehr, Epidemiology Operations

William Miller, Medicine-Infectious Diseases IRB Informational Message - please do not use email

REPLY to this address

APPENDIX 2: NONINVASIVE AND INVASIVE VASCULAR DIAGNOSTIC TOOLS (HIRSCH ET AL., 2006)

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Diagnostic Tool*	Benefits	Limitations
Ankle-brachial indices (ABIs)	A quick and cost-effective way to establish or refute the lower extremity PAD diagnosis (see text)	May not be accurate when systolic blood pressure cannot be abolished by inflation of an air-filled blood pressure cuff (non-compressible pedal arteries), as occurs in a small fraction of diabetic or very elderly individuals
Toe-brachial indices	A quick and cost-effective way to establish or refute the lower extremity PAD diagnosis (see text) Can measure digital perfusion when small-vessel arterial occlusive disease is present Useful in individuals with noncompressible posterior tibial or dorsalis pedis arteries	Requires small cuffs and careful technique to preserve accuracy
Segmental pressure examination	Useful to establish or refute the PAD diagnosis (see text) Useful to provide anatomic localization of lower extremity PAD when these data are required to create a therapeutic plan Can provide data to predict limb survival, wound healing, and patient survival Useful to monitor the efficacy of therapeutic interventions	May not be accurate when systolic blood pressure cannot be measured by inflation of an air-filled blood pressure cuff owing to noncompressible pedal arteries, as occurs in a small fraction of diabetic or very elderly individuals
Pulse volume recording	Useful to establish the diagnosis of PAD in vascular laboratories or office practice Helpful in predicting the outcome in CLI and risk of amputation Can be used to monitor limb perfusion after revascularization procedures	Usefulness maintained in patients with noncompressible vessels (ABI value greater than 1.3) Qualitative, not quantitative, measure of perfusion May not be accurate in more distal segments Less accurate than other noninvasive tests in providing arterial anatomic localization of PAD May be abnormal in patients with low cardiac stroke volume
Continuous-wave Doppler ultrasound	Useful to assess lower extremity PAD anatomy, severity, and progression Can provide localizing information in patients with poorly compressible arteries Can provide quantitative data after successful lower extremity revascularization	"Pulse normalization" downstream from stenoses can diminish test sensitivity Test specificity greater for patent superficial femoral arteries than for aortoiliac occlusive disease Does not provide visualization of arterial anatomy Limited accuracy in tortuous, overlapping, or densely calcified arterial segments, and insensitive for iliac arteries (in context of obesity, bowel gas, and vessel tortuosity)
Duplex ultrasound	Can establish the lower extremity PAD diagnosis, establish anatomic localization, and define severity of focal lower extremity arterial stenoses Can be useful to select candidates for endovascular or surgical revascularization	Useful tool to provide graft surveillance after femoral-popliteal or femoral tibial or pedal surgical bypass with venous (but not prosthetic) conduit Accuracy is diminished in proximal aortoiliac arterial segments in some individuals (e.g., due to obesity or the presence of bowel gas) Dense arterial calcification can limit diagnostic accuracy Sensitivity is diminished for detection of stenoses downstream from a proximal stenosis Diminished predictive value in surveillance of prosthetic bypass grafts

Continued on Next Page

Table 15. Continued

Diagnostic Tool*	Benefits	Limitations
Toe-tip exercise testing, with pre-exercise and postexercise ABIs	Useful to diagnose lower extremity PAD when resting ABI values are normal Can be performed in the absence of a treadmill, with increased convenience and low cost	Provides qualitative (rather than quantitative) exercise diagnostic results Lower workload may not elicit symptoms in all individuals with claudication
Treadmill exercise testing, with and without pre-exercise and postexercise ABIs	Helps differentiate claudication from pseudoclaudication in individuals with exertional leg symptoms Useful to diagnose lower extremity PAD when resting ABI values are normal Objectively documents the magnitude of symptom limitation in patients with claudication, especially when used with a standardized treadmill protocol Demonstrates the safety of exercise and provides data to individualize exercise prescriptions in individuals with claudication before initiation of a formal program of therapeutic exercise training Useful to measure the objective functional response to claudication therapeutic interventions	Requires use of a motorized treadmill, with or without continuous electrocardiogram monitoring, as well as staff familiar with exercise testing protocols
Magnetic resonance angiography (MRA)	Useful to assess PAD anatomy and presence of significant stenoses Useful to select patients who are candidates for endovascular or surgical revascularization	Tends to overestimate the degree of stenosis May be inaccurate in arteries treated with metal stents Cannot be used in patients with contraindications to the magnetic resonance technique (e.g., pacemakers, defibrillators, intracranial metallic stents, clips, coils, and other devices)
Computed tomographic angiography (CTA)	Useful to assess PAD anatomy and presence of significant stenoses Useful to select patients who are candidates for endovascular or surgical revascularization Helpful to provide associated soft tissue diagnostic information that may be associated with PAD presentation (e.g., aneurysms, popliteal entrapment, and cystic adventitial disease) Patients with contraindications to magnetic resonance angiography (e.g., pacemakers or defibrillators) may be safely imaged Metal clips, stents, and metallic prostheses do not cause significant CTA artifacts Scan times are significantly faster than for MRA	Single-detector computed tomography lacks accuracy for detection of stenosis Spatial resolution lower than digital subtraction angiography Venous opacification can obscure arterial filling Asymmetrical opacification of the legs may obscure arterial phase in some vessels Accuracy and effectiveness not as well determined as MRA Treatment plans based on CTA have not been compared with those of catheter angiography Requires iodinated contrast and ionizing radiation (although radiation exposure is less than with catheter angiography) Because CTA requires administration of iodinated contrast, use is limited in individuals with established renal dysfunction
Contrast angiography	Definitive method for anatomic evaluation of PAD when revascularization is planned	Invasive evaluation is associated with risk of bleeding, infection, vascular access complications (e.g., dissection or hematoma), atheroembolization, contrast allergy, and contrast nephropathy May provide limited visualization of tibial-pedal vessels in patients with CLI and poor inflow to the leg Below-knee vessels may be difficult to identify by digital subtraction angiography Multiple projections may be necessary to visualize eccentric lesions

*Tools are listed in order from least invasive to most invasive and from least to most costly.
CLI indicates critical limb ischemia; PAD, peripheral arterial disease.

APPENDIX 3: INDICES OF ARTERIAL STIFFNESS (CHIRINOS, 2012)

Table 2 Indices of arterial stiffness

Index	Definition	Formula	Comments
Incremental Elastic Modulus (E_{inc})	It is the “local” <i>slope</i> of the <i>incremental</i> change in circumferential stress and the <i>incremental</i> change in circumferential length of the wall material at the operating range of stress and strain.	$\frac{3 \times (1+A/WCSA)}{DC}$ where WCSA equals: $(De^2 + Di^2) \times \frac{\pi}{4}$	Indicator of the stiffness of the arterial wall material. Also called Young’s incremental elastic modulus.
Compliance	Change in arterial volume relative to the change in arterial pressure	$\frac{\Delta V}{\Delta P}$	Influenced by wall stiffness, arterial size and wall thickness.
Elastance	Change in arterial pressure relative to the change in arterial volume, or the inverse of compliance	$\frac{\Delta P}{\Delta V}$	Influenced by wall stiffness, arterial size and wall thickness.
Distensibility	Fractional change in arterial volume relative to the change in arterial pressure	$\frac{\Delta V}{V} \frac{1}{\Delta P}$	Influenced by wall stiffness and thickness. It is analogous to compliance, but normalized for arterial size.
Compliance Coefficient	Absolute change in cross-sectional area relative to the change in arterial pressure	$\frac{\Delta A}{\Delta P}$ $\frac{D_{max}^2 - \Delta D_{min}^2}{\Delta P} \times \frac{\pi}{4}$	Estimation of compliance based on cross-sectional (rather than volume) measurements. It relates linearly to compliance under the assumption of a perfectly homogeneous arterial segment and no changes in segmental arterial length.
Distensibility Coefficient	Fractional change in cross-sectional area relative to the change in arterial pressure	$\frac{\Delta A}{A} \frac{1}{\Delta P}$ $\frac{2D_{min} \times \Delta D + \Delta D^2}{D^2 \Delta P}$	Analogous to compliance coefficient, normalized for arterial caliber. It is identical to distensibility under the assumption of a perfectly homogeneous arterial segment and no changes in segmental arterial length. It is inversely proportional to the wall thickness/diameter ratio and the incremental elastic modulus of the wall material.
Peterson’s Elastic modulus	Arterial pressure change for a given fractional diameter change. Also called pressure-strain modulus. Since the $D/\Delta D$ becomes the unit if diameter is doubled, it is often defined as the “Pressure change required for a theoretical 100% increase in diameter”.	$\frac{\Delta P}{\frac{\Delta D}{D}}$	Not a measure of the elastic properties of the wall material. Somewhat analogous to the inverse of distensibility. It is influenced by the incremental elastic modulus of the wall material and wall thickness.
β Stiffness Index	Logarithm of the ratio of maximum/minimum pressure over fractional diameter change	$\ln \left(\frac{P_{max}}{P_{min}} \right) \frac{1}{\frac{\Delta D}{D}}$	Due to the mathematical correction of the logarithm of P_{max}/P_{min} , values within individuals are less sensitive to distending pressure.

WCSA wall cross-sectional area, *De* external vessel diameter (inter-adventitial diameter) measured in diastole, *Di* internal vessel diameter (interintimal diameter) measured in diastole

ΔP is the difference between maximum and minimum pressure. ΔV is the difference between the corresponding maximum and minimum volume. ΔA is the difference between maximum and minimum cross-sectional vessel area. D_{max} is the maximum vessel diameter. D_{min} is the minimum vessel diameter

APPENDIX 4: AAA OVER-READER DATA COLLECTION FORM

OMB#: 0925-0281
Exp. 3/31/2014



AAA OVER-READER DATA COLLECTION FORM

ID NUMBER:

FORM CODE: A A O

DATE: 03/01/2012
Version 1.0

ADMINISTRATIVE INFORMATION

0a. Completion Date: / /
Month Day Year

0b. Over Reader ID:

1. Are the diameters in Q3 of the AAT form correct as reported, or are there changes to make?

Diameters as reported are completely correct..... → **Go to Question 4a**

Diameters vary from those reported..... → **Fill in any diameter boxes below that are incorrect with the correct values. If an image quality is too poor to provide data, enter '9.9'.**

2. Enter diameters with correct values.

"Proximal Aorta" (just below SMA)

2a. cm x cm
AP Transverse

"Mid Aorta" (2 cm inferior to renal)

c. cm x d. cm
AP Transverse

"Distal Aorta" (1 cm above bifurcation)

e. cm x f. cm
AP Transverse

"Maximum Diameter" or "Fusiform Aneurysm Diameter" between renal arteries and bifurcation (needed only if not at mid aorta or distal aorta sites)

g. cm x h. cm
AP Transverse

3. Other Potential Abnormalities:
"Saccular Aneurysm"

3a. - cm x 3b. - cm
AP Transverse

4. Check all of the following that apply. If you have any comments, they can be written in.

Alert

4a. AAA \geq 5.0 cm

4a1. specify location and size of AAA:

4b. Other alert abnormality.....

4b1. the participant's scan showed:

Abnormal

4c. AAA of 3.0-4.9 cm.....

4c1. specify location and size of AAA:

4d. Saccular aneurysm.....

4d1. specify location:

4e. Other non-alert clinically relevant abnormality...

4e1. the participant's scan showed:

Normal

4f. Normal or no clinically relevant pathology (This includes tech-labeled aneurysms of 2.80 to 2.99 cm but MD verifies as < 3.0 cm).....

Prior Intervention

4g. Evidence of previous aortic aneurysmal surgery (endovascular repair or surgical graft)?...

4h. Evidence of previous aortic stent or angioplasty?.....

5. Quality was:

Excellent.....

Good.....

Fair.....

Poor.....

6. Over-reader comments to Technologist: _____

7. Check here if the field center handled an urgent alert (ER, AICL notification) incorrectly:.....

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