THE EFFECTS OF PSYCHOSOCIAL FACTORS ON CARDIOMETABOLIC RISK IN NON-HISPANIC BLACK ADULTS

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ABSTRACT

Patricia Pagan Lassalle: The Effects of Psychosocial Factors on Cardiometabolic Risk in Non-Hispanic Black Adults
(Under the direction of Michelle L. Meyer)

Introduction: Racism is a public health crisis. Ongoing events, including racial injustice and the global pandemic, highlighted the effects of systemic racism in all aspects of life. Racial discrimination is a chronic stressor that may lead to heightened cardiovascular disease (CVD) risk. Non-Hispanic Black American adults (NHB) experience greater burden of perceived discrimination (PD), perceived stress (PS), and CVD risk when compared with non-Hispanic Whites, but it is not fully understood. Although PD and PS have been identified as contributors to CVD, their associations with arterial stiffness (AS) are unknown. Objective: Thus, the objective of this dissertation is to determine the importance of psychosocial factors (PD and PS) as modifiable factors for AS in NHB. We hypothesize there will be an association between PD and AS, and that the association will be mediated by PS. Further, that there will be evidence of effect measure modification (EMM) by biological sex. Additionally, we will compare three commonly used non-invasive AS devices. We hypothesize all three devices will be comparable and reliable. Studies & Methods: In addition to a comprehensive scoping review (study 1), this dissertation will include a secondary data analysis of the Jackson Heart (JHS) and the Atherosclerosis in Community Risk (ARIC) (study 2) shared cohort evaluating participants with PD, PS, and AS data, and an experimental agreement and reliability study (study 3). For study 3, we enrolled 60 healthy adults (18-84 years) who attended two visits for arterial stiffness assessment by three arterial stiffness devices. Results: Findings from our scoping review

indicated there is a positive association between PD and AS, but varies by region, clinical status, and sex. Our secondary analysis found an inverse association between PD and AS, and no evidence of mediation by PS or EMM by sex. Finally, there was moderate to good agreement and reliability between all three non-invasive devices. Conclusions: There is an association between PD and AS, but it may vary in direction and magnitude based on the population studied. There is moderate to good agreement and reliability between devices. Future studies are needed to fully characterize the association between PD and AS.

To my wonderful husband, Taylor. I wouldn't have been able to complete it without all your support. Thank you for being my support and friend.

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LIST OF ABBREVIATIONS

AS	Arterial stiffness
aSEE	Absolute Standard Error of Estimate
BP	Blood Pressure
CAD	Clinically acceptable difference
cfPWV	Carotid-Femoral Pulse Wave Velocity
CI	Confidence Interval
cIMT	Carotid intima-media thickness
CV	Cardiovascular
CVD	Cardiovascular disease
D	Path length
DBP	Diastolic Blood Pressure
EMM	Effect measure modification
h	Hour
htPWV	Heart-thigh Pulse Wave Velocity
ICC	Intraclass correlation coefficient
m/s	Meter per second
mmHg	Millimeters of mercury
PD	Perceived discrimination
PS	Perceived stress
POS	Posture
PWV	Pulse Wave Velocity
r	Pearson’s Correlation Coefficient
RCT	Randomize Clinical Trial

RSE	Relative Standard Error of Estimate
SBP	Systolic Blood Pressure
SEM	Standard Error of Measurement
sSEE	Standardized Standard Error of Estimate
Tc	Transit time to carotid pulse
Tcf	Transit time to femoral pulse
TDI	Total deviation index
TT	Transit Time
Y	Year

CHAPTER 1: INTRODUCTION

Dissertation Structure

This chapter outlines the structure of this dissertation which comprises 6 chapters and is depicted in Table 1.

Table 1. Dissertation Structure		
CHAPTER	TITLE	PURPOSE
1	Introduction	Introduction to thesis
2	Literature Review	Review of key concepts
3	Study 1 Rationale	Rationale for each study
4	Study 2 Rationale	
5	Study 3 Rationale	
6	Study 1: Associations of perceived discrimination, stress and arterial stiffness in non-Hispanic Black adults: literature review	Thesis Studies
7	Study 2: Associations of perceived discrimination and stress with arterial stiffness in non-Hispanic Black adults	
8	Study 3: Agreement, repeatability, and reliability of the OMRON, VICORDER, and VaSera	
9	Conclusion	Summarize key findings
10	References	

Chapter 1 (this chapter) provides a rationale for this dissertation and each of the incorporated studies. Chapter 2 is a literature review, which briefly outlines the significance of the proposed research. Chapters 3-5 provide a more in-depth rationale for each study. Chapters 6-8 are the primary research studies each presented in manuscript format. Finally, Chapter 9 summarizes the key findings, discusses the implications of these findings, then makes recommendations for future research.

Table 2 lists and defines the key concept of relevance to this dissertation.

Table 2. Key Definitions	
Term	Definition
Arterial Stiffness (AS)	The biological process of reduced elasticity and increased rigidity within the artery, which is associated with aging and atherosclerosis.
Agreement	Quantifies how close measurements are and is measured on the same scale of the measurement, otherwise known as the accuracy of measure.
Perceived discrimination	When an individual or group of individuals perceive or experience discrimination which may include events that are not discriminatory according to the law or scientific definitions.
Perceived Stress	Perceived stress can be defined as the feelings and thoughts that an individual appraises the amount of stress they are under at a given time point or over time.
Psychosocial factors	Characteristics or facets that influence individual psychologically and/or socially.
Racial discrimination	The behavioral manifestation of negative attitudes and judgement towards an individual or group of individuals.
Social determinants of health	Conditions in the environments in which people are born, live learn, work, play, worship, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks.
Systemic racism	Assigning of value and opportunities based on skin color, often leading in racial discrimination.
Pulse wave velocity (PWV)	The speed of the forward pressure-wave in the arterial tree following ventricular ejection; the referent measurement of arterial stiffness.
Race and Ethnicity	Race and Ethnicity are dynamic social constructs shaped by geographic, cultural, and sociopolitical forces, without scientific or biological meaning.
Repeatability	Refers to the precision of a measure or how consistently it is measuring a value[1]
Reliability	Refers to variation in repeat measurements on the same individual under identical conditions

Dissertation Rationale

Racism is a public health crisis.[2] Past and ongoing events stemming from racial injustice and the global pandemic have continued to highlight the effects of systemic racism on all aspects of life. Systemic racism, which is the assigning of value and opportunities based on skin color, often leads to racial discrimination. Racial discrimination, the behavioral manifestation of negative attitudes and judgement,[3] is a chronic stressor that may contribute to advanced vascular

aging and heightened cardiovascular disease (CVD) risk.[4] The non-Hispanic Black (NHB) population, which comprises 13% of the population, experiences a greater burden of perceived discrimination (PD), greater stress,[5] and higher CVD risk when compared with non-Hispanic Whites.[6,7] Although perceived discrimination and stress have been identified as contributors to CVD, their association with arterial stiffness, a measure of vascular aging and subclinical CVD risk, is unknown. We hypothesize there will be a positive association between PD and arterial stiffness. Further, we hypothesize that chronic perceived stress (PS) will mediate the association between perceived racial discrimination and arterial stiffness and, therefore, may be a modifiable public health target to reduce CVD risk in NHB.

However, prior to understanding the association of PS and discrimination with arterial stiffness in NHB, it is imperative to adequately assess arterial stiffness. Therefore, we will also evaluate the agreement and reliability of three non-invasive devices that measure arterial stiffness. All three devices are commonly used (Jackson Heart Study [JHS], Atherosclerosis in Communities Study [ARIC], and the Multi-ethnic Study of Atherosclerosis [MESA]), yet differ in the technique (i.e., tonometer-based [Omron VP-1000 Plus, Japan] or cuff-based methods [VaSera VS-1500, Japan & VICORDER, Skidmore Medical, UK]) to assess arterial stiffness, and in the measure of arterial stiffness (VaSera VS-1500, Japan). Determining the agreement and reliability of these three devices will provide a strong foundation for this proposal, contribute to the harmonization of existing arterial stiffness data across multiple populations, and further characterize arterial stiffness and CVD risk in NHB and other minority populations in the US.

Overall Objectives and Approach

The goal of this dissertation will be to (a) determine the importance of psychosocial factors as modifiable factors for arterial stiffness and CVD risk in minority populations and (b) compare commonly used devices that assess arterial stiffness. To support these goals, a strong

foundational knowledge of the existing literature will be established via a literature review (Study 1) providing a rationale for the following 2 studies. We will focus on arterial stiffness, measured as carotid to femoral pulse wave velocity (cfPWV) (or heart to thigh pulse wave velocity [htPWV]) rather than overt CVD as it provides a representation of CVD risk accrual over the lifespan.[8] Study 2 will identify the extent to which perceived lifetime discrimination and PS are associated with arterial stiffness. Further, study 2 will address a critical gap and evaluate the relationship between arterial stiffness and perceived lifetime discrimination in a population-based study of both NHB men and women. In NHB, lifetime PD has been associated with hypertension[9] and coronary artery disease in men and women,[6] and with arterial stiffness in women but not men.[10] Therefore, we will also evaluate biological sex as an effect modifier for the relationship between PD and arterial stiffness. Lastly, PS has been associated with hypertension in NHB,[9,11] and related to development of CVD later in women at later life.[12] Due to previous associations with blood pressure and other CVD risk factors, it is recommended that studies assessing PD account for PS.[10,13] However, only one study has previously investigated whether PS mediates the association between PD and arterial stiffness.[10] Finally, Study 3 will determine the agreement and reliability of three non-invasive cardiovascular devices that assess arterial stiffness through cuff-based or tonometry-based methods.

Specific Aims

For Study 1, Aim: Consolidate and synthesize the literature pertaining to the relationship between PD and arterial stiffness, measured as pulse wave velocity, in NHB adults.

For Study 2, we will draw on the Jackson Heart Study (JHS) and Atherosclerosis Risk in Communities Study (ARIC) shared cohort, of which ~825 NHB participants have arterial stiffness measurements to address the aims below. Perceived discrimination and stress were

measured at JHS baseline (2000-2004) and arterial stiffness was measured at ARIC Visit 5 (2011-2013).

Study 2, Aim 1: (a) Determine the association between PD (i.e., lifetime, everyday, and burden of discrimination) and arterial stiffness in NHB adults; and (b) Determine if biological sex is an effect modifier of the relationship between PD and arterial stiffness. Strategy: (a) We will determine the association between PD and arterial stiffness using multivariable linear regression and adjust for age, sex, body mass index, hypertension medication, diabetes, and mean arterial pressure. (b) We will evaluate for effect measure modification by biological sex and stratify the results if statistically significant at $p<0.1$, as this is a common statistical threshold. Hypotheses: (a) Individuals with high PD will have higher arterial stiffness; and (b) Biological sex will act as an effect modifier for the relationship between PD and arterial stiffness, with a stronger association in women.

Study 2, Aim 2: Determine if the association between lifetime discrimination and arterial stiffness is mediated by perceived chronic stress in NHB. Strategy: We will use a simple mediation approach. Then, we will estimate confidence intervals using the bootstrap method, as it does not impose the normal distribution assumption.[14] Hypothesis. Perceived chronic stress will mediate the association between discrimination and arterial stiffness.

Study 3, Aim 1: Compare arterial stiffness measurements from three non-invasive devices. Strategy: We will target a sample of 100 volunteers 18-84 years old without cardiovascular or metabolic disease, without impaired cognitive ability, and are not pregnant from the University of North Carolina at Chapel Hill community and the Jackson, Mississippi site. Two devices will be on the participant given time and one of the devices will be substituted for a third device. Devices will be randomized to one side of the body, measurements taken in

triplicate, and the closest two averaged with a minute in between measurements. Hypothesis: Arterial stiffness values will be comparable between devices.

Study 3, Aim 2: (a) To estimate the reliability of all three devices. Strategy: Participants will be asked to attend a second visit, and all measures will be repeated as in their first visit. Hypothesis: The cuff-based method will have good reliability defined as an intra-class correlation coefficient (ICC) >0.75.

Innovation and Significance

This dissertation is significant in that it will be the first to assess the association of PD and PS with arterial stiffness in a population-based cohort among one of the largest US minority groups. Additionally, the comparison of these commonly used devices will allow for harmonization of existing arterial stiffness data and improve the characterization of CVD risk in multiple high-risk populations. This proposal presents an innovative paradigm shift as it could identify PD and PS as risk factors for arterial stiffness, a subclinical indicator of CVD risk and vascular aging. Understanding the importance of perceived chronic stress in NHB may lead to the development of new interventions to modify stress and PD. Key strengths of this dissertation include: (i) a well-characterized, diverse cohort, (ii) inclusion of sex as a biological risk factor, (iii) measure of subclinical CVD, (ii) extensive knowledge on how to operate the non-invasive devices, and (iv) a well-resourced multidisciplinary support team.

CHAPTER 2: LITERATURE REVIEW

Goals

The goals of this dissertation will be to (a) investigate the associations between perceived discrimination (PD), perceived stress (PS), and arterial stiffness in non-Hispanic Black (NHB) adults; and (b) determine the agreement, repeatability, and reliability of three non-invasive devices that assess arterial stiffness. Completion of the project may lead to novel CVD risk reduction targets and provide a foundation for subsequent mechanistic evaluation. Below is the conceptual model for this dissertation, which will focus on concepts within the red rectangle (Figure 1). As part of this literature review, the following sections will discuss important definitions, CVD risk in NHB adults, CVD risk progression and assessment, the importance of social determinants of health (in particular, PD and PS), and propose a mechanism by which PD increases CVD risk.

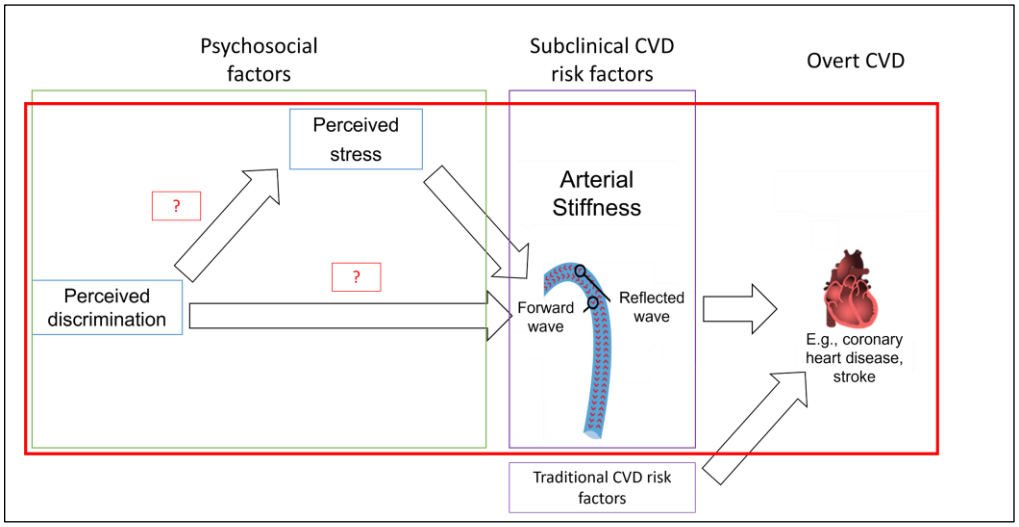

Figure 1. Conceptual framework

Definitions

This section will focus on operationally defining key terms that will be used throughout this dissertation.

Cardiovascular Disease

Cardiovascular disease is the umbrella term for all conditions affecting the heart and blood vessels. CVD is the leading cause of death in the US, accounting for 1 in every 4 deaths annually.[15] Although there is no one cause for the development of CVD, traditional and subclinical risk factors have been identified. The presence of these risk factors has been associated with development of CVD later in life. Traditional risk factors have been classified as modifiable or non-modifiable risk factors. Non-modifiable risk factors include age, sex, race, and family history. Modifiable risk factors include high blood pressure, high blood cholesterol, smoking, diabetes, overweight or obesity, lack of physical activity, and an unhealthy diet. Although initiatives to tackle modifiable CVD risk factors have been developed, these are limited to individuals who have developed the risk factors, otherwise known as primary prevention.[16] However, in order to curb CVD, it is important that we take a primordial prevention approach, where the focus is on preventing the development of these risk factors.[16] In order to enforce a primordial prevention approach, it is critical we are able to identify subclinical markers of CVD, among these arterial stiffness. This proposal will focus on arterial stiffness as an ideal marker of cardiovascular aging and predictor of future CVD events.

Arterial Stiffness

Arterial stiffness is the functional and structural stiffening of blood vessels. Increased aortic arterial stiffness negatively affects normal hemodynamics, and the increased pressure transmission can damage end-organs, particularly the heart, increasing myocardial load.[17–19] Under homeostatic conditions, the arterial system has a stiffness gradient characterized by

greater arterial distensibility in central arteries and decreasing distensibility towards the periphery in medium-sized arteries and smaller vessels (e.g., arterioles). Central arteries have a high concentration of elastin fibers within the arterial wall which lends to increased distensibility; whereas the smaller, peripheral arteries and vessels have lower elastin content and increased collagen and smooth cell concentration which is associated with reduced distensibility.[20] When the central arteries stiffen, their ability to expand and recoil is compromised. The arteries are less able to store elastic energy within the arterial wall to promote blood flow during diastole. This decrease in elastic energy results in higher energy demand on the heart, requiring more blood to be transported over longer distances in systole resulting in higher pulsatility and end-organ damage.[8] Our team has shown that arterial stiffness is a sensitive marker of vascular aging and CVD risk that increases across the lifespan[19,21–23] and can be used to track whether vascular aging is accelerated (e.g., due to risk factors) or attenuated (e.g., lifestyle) over time.

The most widely used and clinically relevant non-invasive measure of arterial stiffness is pulse wave velocity (PWV), otherwise known as the velocity of pressure waveforms as they propagate along an arterial segment. Carotid to femoral PWV (cfPWV) is considered the referent standard measure of PWV because it encompasses most of the aorta, the major elastic vessel in the human body susceptible to functional stiffening.[20]

Race and Ethnicity

According to the updated guidance on reporting of race and ethnicity in Medical and Science Journals, race and ethnicity are dynamic social constructs shaped by geographic, cultural, and sociopolitical forces, thus are without scientific or biological meaning.[24] Historically, race has referred to broad categories of people that are divided arbitrarily according to ancestral origin and/or phenotypic characteristics, whereas ethnicity has referred to a person's

cultural identity (i.e., language, customs, etc.). We will operationally define race as a social construct that classifies individuals or groups of individuals according to a phenotypic appearance governing the distribution of risks and opportunities in our race-conscious society.[25] Ethnicity will be defined as a social construct referring to individuals' cultural identity (i.e., language, customs, etc.). For the purposes of this proposal, we will report race and ethnicity as an aggregate.

Perceived Discrimination

Before we define PD, it is important to define racism. The CDC defines racism as a "system of structuring opportunity and assigning value based on the social interpretation of how one looks…("race"), that unfairly disadvantages some individuals and communities, unfairly advantages other individuals and communities, and undermines realization of the full potential of our whole society through the waste of human resources."[26] Often racism is defined at three separate levels: systemic, interpersonal, and internalized.[25–27]

- Systemic racism (often interchangeably used with institutional or structural): "Structures, policies, practices, and norms resulting in differential access to the goods, services, and opportunities of society by 'race' (e.g., how major systems—the economy, politics, education, criminal justice, health, etc.—perpetuate unfair advantage)."[26]
- Interpersonal (personally mediated) racism: "Prejudice and discrimination, where prejudice is differential assumptions about the abilities, motives, and intents of others by 'race,' and discrimination is differential actions towards others by 'race.' These can be either intentional or unintentional."[26]
- Internalized racism: "Acceptance by members of the stigmatized 'races' of negative messages about their own abilities and intrinsic worth."[26]

For this proposal, PD will be defined and measured as the behavioral manifestation of a negative attitude, judgment, or unfair treatment towards members of a group.[3] It is a multi-dimensional construct that is a chronic stressor that may contribute to advanced vascular aging and heightened cardiovascular disease (CVD) risk.[4]

Perceived Stress

PS can be defined as the feelings and thoughts that an individual appraises as the amount of stress they are under at a given time point or over time.[28] We focused on perception of stress as two individuals may perceive the same stress event differently. Further, the evaluation of PS allows for an indirect measure of an individual's relationship to their environment including the resources (i.e., coping resources, personality, and support) that will determine their appraisal of a threatening or overwhelming situation. The most common measure of PS is the PS scale developed by Cohen, Kamark, and Mermelstein.[29]

The Problem: NHB at Greater Risk of CVD but Not Fully Understood

Cardiovascular disease (CVD) is the leading cause of death for men and women, and many minority groups in the United States (US) account for 1 in every 4 deaths annually.[15] Among different groups, non-Hispanic Black adults (NHB) have the highest CVD mortality rate in the US, including the highest age-adjusted mortality rates for hypertension, stroke, coronary heart disease, heart failure, and peripheral artery disease.[15] In addition, there is evidence of biological sex differences in CVD risk, with NHB males having higher prevalence of total CVD than NHB females, and females having greater prevalence of obesity, metabolic syndrome risk factors and other co-morbidities associated with CVD.[15] In an attempt to comprehend the disproportionate burden of risk and a widening gap in racial disparities, social determinants of health, and in particular psychosocial factors, have become important indicators of health.[6,30] However, prior to determining CVD risk in NHB, it is important to adequately measure and

ascertain risk. The following sections will outline the different ways to assess CVD risk including traditional risk factors, subclinical risk factors, and overt CVD.

Development of CVD

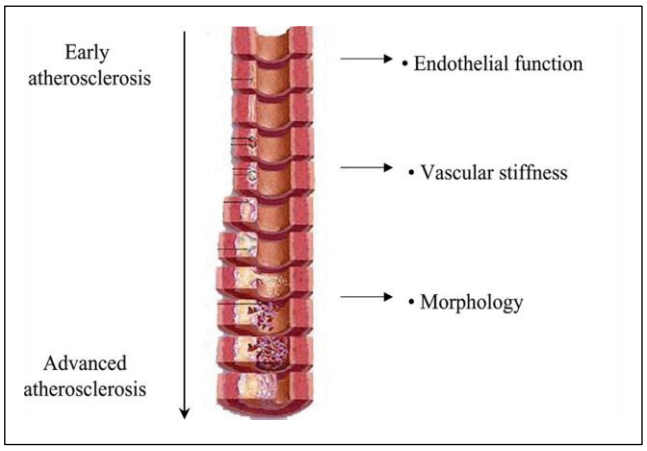

Figure 2. Subclinical CVD continuum. *Obtained from Avest, Stalehoef, and De Graaf 2007*

To understand the development of CVD, it is important to understand the processes of atherosclerosis and arteriosclerosis. Atherosclerosis and arteriosclerosis are complementary yet differing processes of vascular aging.

Atherosclerosis describes the process by which the artery ages from the inside out due to the deposition of plaque, cholesterol, and other substances along the arterial wall (Figure 2). The atherosclerotic process begins with injury to endothelium, or the inner lining of the arterial walls. Injury can be due to a number of factors including: preexisting conditions (e.g., obesity, diabetes, hypertension), infections, alcohol, smoking, high fat meals, and/or turbulent blood flow.[31] Injury to the endothelium causes an immune cascade that results with the transportation of low density lipoprotein ("bad cholesterol") and deposition between the endothelium and the arterial wall forming a fibrous cap that recruits smooth muscles and eventually takes the form of plaque.[31] Atherosclerosis is a chronic, inflammatory disease that exists along a continuum from subclinical to clinical atherosclerotic disease.[32]

Conversely, arteriosclerosis is the process by which the artery ages from the outside in and is related to the change of the composition arterial wall.[4] Most commonly, arteriosclerosis is due to degradation of elastin and greater deposition of collagen (which adds rigidity) within the

arterial wall. A common measure of the arteriosclerotic process is arterial stiffness. Similar to atherosclerosis, arteriosclerosis can be accelerated due to presence of traditional risk factors and/or chronic comorbid conditions (i.e., diabetes, hypertension).[33] Figure 2 provides a visual depiction of the progression from atherosclerosis to arteriosclerosis.

Traditional CVD Risk Factors

Although there is no one cause for the development of cardiovascular disease, traditional CVD risk factors have been associated with the development of CVD. Traditional CVD risk factors have been classified as modifiable or non-modifiable risk factors. Non-modifiable risk factors include age, biological sex, race, and family history. Modifiable risk factors include high blood pressure, high blood cholesterol, high blood glucose, smoking, diabetes, overweight or obesity, lack of physical activity, and an unhealthy diet.

In relation to the traditional risk factors of CVD, NHB adults have worse age-adjusted prevalence of body mass index, physical activity, healthy diet score, blood pressure and diabetes compared to non-Hispanic White adults (NHW).[15] NHB adults have a lower prevalence of meeting both aerobic and muscle-strengthening guidelines compared to NHW. NHB females have a higher prevalence of obesity, and both males and females have a higher prevalence of extreme obesity compared to other racial/ethnic groups.[15] NHB adults have the highest prevalence of hypertension.[15] However, the higher burden of CVD risk in NHB adults not fully understood.

Key Message
TRADITIONAL RISK FACTORS DO NOT FULLY EXPLAIN CVD RISK

Currently, primary prevention approaches commonly target traditional CVD risk factors; however, effects of these strategies are limited since traditional risk factors do not fully explain the burden of CVD risk. As a result, there has been a transition towards more proactive approaches to avoid the development of risk factors in the first place, known as primordial

prevention. This is important since there is evidence of vascular aging can occur as early as youth.[16] This primordial prevention approach focuses on subclinical CVD risk factors. An example of this approach is the American Heart Association's Life Essential 8 focused on modifiable CVD risk factors.

Key Message
PSYCHOSOCIAL FACTORS ARE LINKED TO CVD

Subclinical CVD Risk

Subclinical CVD vascular measures of structure and function are on the stepping stones to overt CVD and stroke, and are predictive of several outcomes including aging and all-cause mortality.[34] Measures of subclinical CVD risk factors include invasive and non-invasive atherosclerotic and arteriosclerotic markers. We will focus on arterial stiffness as a predictor of CVD risk because it is a sensitive marker of vascular aging and CVD risk that increases across the lifespan,[19,21–23] and can be used to track whether vascular aging is accelerated (e.g., due to risk factors) or attenuated (e.g., lifestyle) over time. Early detection conferred from use of arterial stiffness could allow us to determine risk earlier in a high-risk population of NHB adults.

Key Message
PWV IS AN IDEAL MEASURE

In NHB males, there is evidence of greater cfPWV compared to NHW counterparts when age matched.[35] Within a NHB sample, there was evidence of effect measure modification by biological sex, with males having greater odds of elevated cfPWV values compared to females after adjusting for heart rate, mean arterial pressure, ratio of total to high density lipoprotein cholesterol, fasting glucose, and hypertensive medications.[36] Evidence of arterial stiffness in this population suggests it would be a good indicator of CVD risk in our population of interest. However, there are a variety of techniques and devices available to arterial stiffness, which acts as a barrier to integration in clinical practice.[20]

Social Determinants of Health, the Missing Link?

Figure 3. Social determinants of health
Obtained from Healthy People 2030, U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion

Social determinants of health are defined as "conditions in the environments in which people are born, live learn, work, play, worship, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks."[26] These can be grouped into five domains: economic stability, education access and quality, health care access and quality, neighborhood and built environment, and social and community context (Figure 3). Among social determinants are psychosocial factors, defined as "characteristics or facets that influence individuals psychologically and/or socially."[37] There is evidence linking psychosocial factors with CVD. As shown in Figure 4, when combined with traditional risk factors and inflammation markers, the odds of myocardial infarction are significantly increased.[38] In an attempt to comprehend the disproportionate burden of risk and a widening gap in racial disparities, psychosocial factors have become important indicators of health.[6,30] Two psychosocial factors of interest include PD and PS.

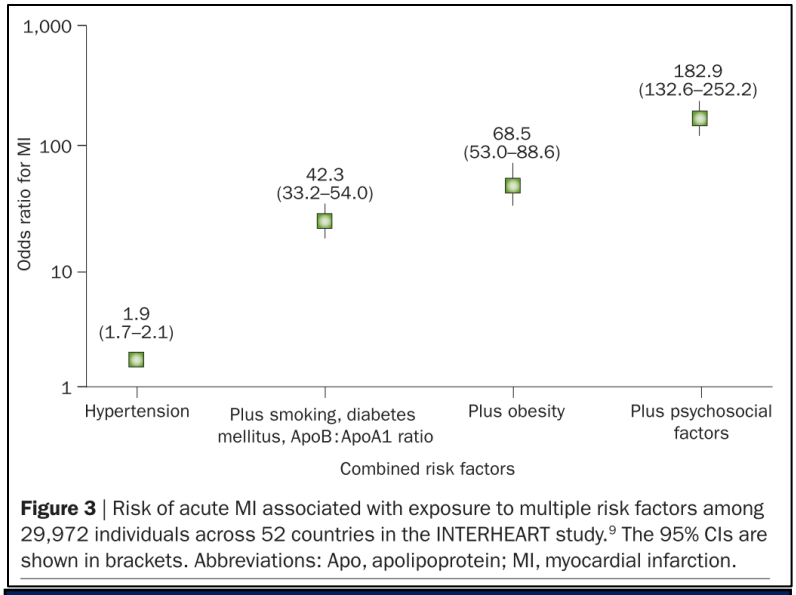

Figure 3 | Risk of acute MI associated with exposure to multiple risk factors among 29,972 individuals across 52 countries in the INTERHEART study.[9] The 95% CIs are shown in brackets. Abbreviations: Apo, apolipoprotein; MI, myocardial infarction.

Figure 4. Psychosocial factors associated with overt CVD.
Obtained from Yusuf et al. 2004

Perceived Discrimination May Heighten CVD Risk

Perceived discrimination is a multi-dimensional construct. It can be assessed through different scales of measurement including everyday discrimination, lifetime discrimination, and burden of lifetime discrimination. Everyday discrimination captures chronic and typical, but often minor, events of day-to-day interpersonal interactions, whereas lifetime discrimination attempts to capture the extent of lifetime exposure to discriminatory experiences in multiple domains of life. Lastly, burden of discrimination is the extent to which PD influences lifetime experiences and results in potential hardships.[9]

In NHB, PD has been associated with hypertension[9] and coronary artery disease in males and females,[6] and with arterial stiffness in females but not men in patients 6-months post-myocardial infarction.[10] Only one study has evaluated the relationship between PD and arterial stiffness in adults who are NHB compared to NHW, however it was in adults with coronary heart disease.[10] Although no association was found in the overall sample, there was an association

between arterial stiffness and everyday discrimination when restricted to NHB women.[10] Additionally, a meta-analysis evaluating the relationship between PD and health found evidence of a negative association between PD and healthy behaviors indicating less participation in healthy behaviors and more in unhealthy behaviors (i.e., smoking, alcohol/substance use and abuse).[3]

Further, it should be noted that PD is multi-dimensional and the association between PD and traditional CVD factors has been reported to vary based on the dimension measured.[9] For example, in a study evaluating the association between hypertension and PD, one standard deviation increase in lifetime and burden of discrimination, but not everyday discrimination, was associated with a 4% and 2% higher prevalence of hypertension, respectively.[9] Therefore, it is important to assess multi-dimensions of PD to understand if there is one or more dimension contributing to CVD risk.

Considering there is only one study evaluating PD and arterial stiffness in NHB, both the literature review and secondary data analysis studies will add to the body of evidence needed to determine if the association differs by biological sex. We hypothesize that the association between PD and arterial stiffness is at least partially mediated by PS (Figure 1).

Perceived Stress May Mediate the Association of Perceived Discrimination and Arterial Stiffness

We believe that PD affects CVD risk development via acute and chronic effects on multiple physiologic systems in particular eliciting a neuroendocrine stress response. To understand this process, it is important to discuss allostasis, the autonomic nervous system (ANS), and the hypothalamic-pituitary-adrenal (HPA) axis.

Allostasis is the natural process by which the body responds to stress.[39] This process involves perception of a potential threat (e.g., PD), which elicits the limbic system to stimulate the autonomic nervous system via the hypothalamus and pituitary gland (HPA axis) to signal the

adrenal medulla to secrete stress hormones (epinephrine and norepinephrine; immediate autonomic nervous response), and long-term cortisol through the sympathetic nervous system.[39,40] Changes to normal functioning of allostasis, allostatic load, as seen via chronic elevation can lead to harmful effects including hyper-reactivity or a blunted response to a stressful stimulus.[41] We believe that over time, the dysfunction of allostasis can lead to the progression of cardiovascular pathologies. In particular, it can lead to prolonged arterial inflammation, endothelial dysfunction, and thickening and stiffening of the vascular wall, leading to narrowing of vascular lumen.[42] This can ultimately lead to hypertension and thrombotic events.[42,43]

This mechanism is supported by the fact that PS has been associated with increased inflammation (e.g., elevated C-reactive Protein),[44–47] endothelial dysfunction, subclinical atherosclerosis (e.g., elevated carotid intima-media thickness),[48] and, in NHB, hypertension.[9,11,42,49] Further, although there is limited information on the chronic effects of PS on arterial stiffness, acute laboratory-based stressors increase arterial stiffness.[50] We believe that PD acts as a chronic stressor, and that both the acute and chronic effects of PS on arterial stiffness occur via prolonged arterial inflammation, endothelial dysfunction, and thickening and stiffening of the vascular wall, leading to narrowing of vascular lumen, and arterial stiffness.[42,50] Consequently, it is crucial to evaluate the association of PD, PS, and arterial stiffness.

Literature Review Summary

<u>Why is this Study Needed?</u>

- Determining the association between PD, PS, and arterial stiffness can lead to further characterization of CVD risk in NHB.

<u>What is Known?</u>

- PD and PS have been identified as contributors to overt CVD (i.e., hypertension).

What is Not Known

- The association between PD, PS, and arterial stiffness in a fully NHB sample is not known.

Critical Need

There is a critical need to study and further characterize CVD risk in NHB adults, and potentially identify two new public health targets to reduce CVD. Based on the review of literature, studies to enable the comparison of arterial stiffness devices across studies, and evaluate the association between PD, PS, and arterial stiffness in non-Hispanic Black adults are needed to further characterize CVD risk in NHB adults.

Key Considerations for Design and Implementation Research

- Internal validity
- Address key knowledge gaps that will guide future epidemiological and clinical research
- Researcher and participant burden
- Feasibility
- Training opportunities to foster independence

What this Study will Add

- This study is significant in that it will be the first to assess the association of PD and PS with arterial stiffness in a population-based cohort of one of the largest US minority groups.
- This proposal presents an innovative paradigm shift as it could identify PD and PS as risk factors for arterial stiffness, a subclinical indicator of CVD risk and vascular aging.

- Understanding the importance of PD and chronic stress in NHB may lead to the development of new interventions to modify PD and PS.
- This proposal will compare data from three non-invasive devices used to assess arterial stiffness, enabling the interpretation of arterial stiffness results across studies.

CHAPTER 3: RATIONALE FOR APPROACH FOR STUDY 1—ASSOCIATIONS OF PERCEIVED DISCRIMINATION ANDSTRESS WITH ARTERIAL STIFFNESS: A SCOPING REVIEW

Question to be Addressed

What are the associations between perceived discrimination (PD), stress (PS), and arterial stiffness in non-Hispanic Black (NHB) adults?

Aims

The primary aim of this literature review will be to consolidate and synthesize the literature pertaining to the relationship between PD and PS with arterial stiffness in NHB adults. Further, this secondary aim of this literature review will be to establish the foundation for study 2, focused on directly evaluating the associations between PD, PS, and arterial stiffness in NHB adults part of the Jackson Heart Study (JHS) and Atherosclerosis Risk In Communities (ARIC) Study shared cohort.

PICOS

The research question and search strategy were refined using PICOS: Problem, Intervention, Comparison Group, Outcomes, Study Design.

Participants

We will identify studies that evaluated NHB adults 18 years or older without cancer or cancer-related illness or cognitive impairment. Rationale: In order to lay a foundation for study 2, it is crucial to understand the current literature and identify trends in associations between PD, stress, and arterial stiffness.

Intervention

N/A

Comparison

We will identify any comparisons evaluating the association of PD and PS, with arterial stiffness measured as pulse wave velocity across race or ethnicity to determine the impact of lived experiences on development of CVD risk. We will evaluate if there is greater arterial stiffness according to race or ethnicity.

Outcome

We will examine studies with a measure of PD or PS and arterial stiffness.

Study Design

We will not specify a particular study design for the search to ensure we have an adequate sample of studies. We will evaluate systematic reviews and meta-analysis for additional articles, but these will not be included in the literature review.

Additional Limits

We will focus on English language studies from inception through December 2022.

Search Strategy

Concepts and Alternative Terms from Question

Below we list the main concepts and alternative terms for the literature search (Table 3):

Table 3. PICOS Keywords and Search Terms			
PICOS	KEYWORDS	SEARCH TERMS	SEARCH STRATEGIES
Patient	NHB adults (18 or older)	African American NHB Black	African American OR Non-Hispanic Black OR Black AND Adults
Intervention	N/A	N/A	N/A
Comparison	Not specified	Not specified	Not specified
Outcome	Perceived discrimination	Discrimination Perceived discrimination Racial discrimination	Discrimination OR Perceived discrimination OR Racial discrimination
Outcome	Perceived Stress	Stress Perceived stress Psychosocial stress Psychological stress	Stress OR Perceived stress OR Psychosocial stress OR Psychological stress
Outcome	Arterial stiffness	Arterial stiffness Pulse Wave Velocity cfPWV	Arterial stiffness OR Pulse Wave Velocity OR cfPWV
Study Type	RCT Systematic Review Meta-analysis Observational Cohort Case-Control Case Report/Case Series	Will not specify	Will not specify
Abbreviations: RCT, randomized clinical trial			

Terms Combined Using Boolean Operators

((((((discrimination) OR (perceived discrimination)) OR (perceived stress)) OR (stress) OR (psychosocial stress) OR (psychological stress)) AND ((arterial stiffness)) OR (cfPWV)) OR (PWV)). A more comprehensive list of search terms is provided in the supplement (Supplement 1).

Databases

Below we outline databases for the literature search. We focused on PubMed, Embase, SPORTDiscus, and Google Scholar due to ease of use and familiarity with the database (Table 4).

Table 4. Database Considerations

Consideration	Choices	Selection	Explanation
Database for search	• PubMed • Embase • SPORTDiscus • Google Scholar • Scopus • CINAHL Plus with Full Text	• PubMed • Embase • SPORTDiscus • CINAHL Plus with Full Text	These four databases are recommended, commonly used and are easy to use.

Inclusion/Exclusion Criteria

The following criteria will be used to select studies for inclusion in the review: i) Participants Inclusion: adults (aged 18 years and over), ii) measurement of arterial stiffness, iii) measurement of PD, iv) measurement of psychosocial stress, v) non-Hispanic Black adults included, vi) randomized control trial, and vii) observational studies (i.e., cross-sectional, and cohort). Exclusion criteria will be the following: i) under the age of 18 years old, ii) previous cancer or cancer-related illness, and iii) no non-Hispanic Black adults in the sample.

Methodological Quality

Methodological quality will be assessed using the most appropriate scale developed by the National Heart, Lung, Blood, Institute (NHLBI) for the study design. Two examples are provided below in table 5. These scales use a quality-weighing approach which is more inclusive and minimizes selection bias.[51] The quality-weighing approach assigns a weight according to a predetermined scale. For example, for the NHLBI Quality Assessment of Observational Cohort and Cross-sectional studies, a value on the ordinal scale 1-3 (good, fair, poor) is used as weight.

Table 5. Methodological Quality Considerations

Study Type	Consideration	Choices	Selection
RCT	Methodological Quality Assessment	• QA of Controlled Intervention Studies • QA of Systematic Reviews and Meta-Analysis • QA of Observational Cohort and Cross-sectional studies • QA case-control studies • QA case series studies	• QA of Controlled Intervention Studies
Cohort	Methodological Quality Assessment	• QA of Controlled Intervention Studies • QA of Systematic Reviews and Meta-Analysis • QA of Observational Cohort and Cross-sectional studies • QA case-control studies • QA case series studies	• QA of Observational Cohort and Cross-sectional studies

Abbreviations: QA, quality assessment

Data Extraction

Initially, article titles and abstracts will be screened for relevance. The full-text of potentially eligible articles will be obtained to review eligibility for inclusion. Then, this

extended literature review will be carried out in accordance with PRISMA ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines and registered with PROSPERO.

Level of Evidence

The evidence-based practice pyramid will be used to determine the level of evidence of each study.

Synthesis and Analysis Plan

For this review, each article will be considered the basic unit of analysis. If multiple publications are from one study, these will be evaluated separately.

CHAPTER 4: RATIONALE FOR APPROACH STUDY 2—ASSOCIATIONS OF PERCEIVED DISCRIMINATION AND STRESS WITH ARTERIAL STIFFNESS IN NON-HISPANIC BLACK ADULTS

Goal

The overarching goal is to determine the importance of perceived discrimination (PD) and stress as modifiable factors for arterial stiffness in NHB adults.

Aims

1. Determine the association between PD (i.e., lifetime, everyday, and burden of discrimination) and arterial stiffness in NHB adults. (b) Determine if biological sex is an effect modifier of the relationship between PD and arterial stiffness.

2. Determine if the association between lifetime discrimination and arterial stiffness is mediated by perceived chronic stress in NHB.

Approach Overview

We will examine the previously mentioned aims via a longitudinal secondary data analysis of the JHS and Atherosclerosis Risk in Communities (ARIC) shared cohort (~825 adults). Psychosocial measures will be obtained from JHS Visit 1 (2000-2004) and arterial stiffness data will be obtained from ARIC Visit 5 (2011-2013) (see population/sampling for additional explanations). We will conduct multivariable linear regression to determine the association of PD and arterial stiffness, and evaluate for effect measure modification of biological sex using the CAUSALmed procedure.[52] Additionally, we will use a bootstrap approach to calculate confidence intervals since it does not impose normality to determine if PS mediates the association between PD and arterial stiffness (Table 6)

Table 6. Study Overview					
Study	Population	Study Design	Primary Outcome	Secondary Outcome(s)	Experimental Timeline
3 (Secondary Data Analysis)	NHB adults (18-84 years old) with AS from JHS/ARIC shared cohort	Longitudinal Retrospective Secondary Data Analysis of JHS-ARIC shared cohort	AS PD PS	Mediation	• Psychosocial factors will be obtained from JHS Visit 1 (2001-2004) • Arterial stiffness data will be obtained ARIC Visit 5 (2011-2013) All data has already been collected and there will be no direct contact with participants.
Abbreviations: AS, arterial stiffness; PD, perceived discrimination; PS, perceived stress					

Measurement Considerations

This section will outline the primary constructs that will be evaluated as part of this thesis and the currently available and commonly used methods, the chosen method, and rationale for the methods chosen. More specifically, we will discuss arterial stiffness, perceived discrimination (PD), perceived stress (PS). Table 7 describes major measurement considerations for study 2.

Table 7. Major Measurement Considerations					
Aim (s)	Outcome	Construct	Choices	Selection	Explanation
	Primary	CVD risk	• Overt CVD (Hypertension, coronary heart disease, peripheral artery disease) • Non-invasive subclinical measures (AS, cIMT)	Non-invasive subclinical marker (AS)	AS provides a representation of CVD risk accrual over the lifespan.[8]
1	Primary	AS	• Applanation tonometry • Oscillometry • Ultrasound • MRI • Photoplethysmo-graphy	Applanation tonometry	PWV measures taken for JHS were made with the OMRON VP-1000 Plus which uses applanation tonometry.
1	Primary	Perceived Discrimi-nation	Questionnaires • Lifetime Discrimination • Everyday Discrimination • Burden of lifetime discrimination • Attribution of lifetime discrimination • Attribution of everyday discrimination • Attribution of burden discrimination	Questionnaires • Lifetime Discriminat ion • Everyday Discriminat ion • Burden of lifetime discriminati on	All these measures of perceived discrimination have been associated with traditional risk factors and have good psychometric testing.[9,53–55]
1	Primary	Perceived Stress	Questionnaires • Stress from discrimination • Weekly Stress Inventory • Global Perceived Stress Scale (GPSS)	Questionnaires • Stress from discriminati on • GPSS	The GPSS is commonly used, has the potential to generalize to the existing literature[5,46,49,56–58] and has good

					psychometric testing (α=0.78).[48] Stress from discrimination will be evaluated as evidence suggests that degree of stress from discrimination is a key determinant of effect on health.[9]
1	Secondary	Biological sex	• Only males • Only females • Both	All	Most research has focused on females, with limited data available for males. Will help determine if there are differences by biological sex.
Abbreviations: AS, arterial stiffness; cIMT, carotid intima-media thickness; MRI, magnetic resonance imaging; GPSS, Global perceived stress scale					

MEASURE 1: Arterial Stiffness (Primary Outcome)

Rationale for Measuring Arterial Stiffness

Arterial stiffness is widely used as an independent predictor of CVD in clinical and population-based studies, which is why we have focused on this measure for this study rather than overt CVD for this secondary data analysis. Increased arterial stiffness negatively affects normal hemodynamics, and the increased pressure transmission can damage end-organs, particularly the heart, increasing myocardial load.[17–19] Under normal conditions, the arterial system has a stiffness gradient characterized by greater arterial distensibility in central arteries

due to higher elastin fibers within the arterial wall and decreasing distensibility (due to lower elastin content) and increasing collagen and smooth cell content of the arterial matrix as it moves towards the periphery in medium-sized arteries and smaller vessels (e.g., arterioles).[20] When the central arteries stiffen, their ability to expand and recoil is compromised. The arteries are less able to store elastic energy within the arterial wall to promote blood flow during diastole. This decrease in elastic energy results in higher energy demand on the heart, requiring more blood to be transported over longer distances in systole resulting in higher pulsatility and end-organ damage.[8] Arterial stiffness is a sensitive marker of vascular aging and CVD risk that increases across the lifespan, [19,21–23] and can be used to track whether vascular aging is accelerated (e.g., due to risk factors) or attenuated (e.g., lifestyle) over time.

Methodological Options for Measuring Arterial Stiffness and Rationale for Chosen Approach

The most widely used and clinically relevant non-invasive measure of arterial stiffness is pulse wave velocity (PWV), otherwise known the velocity of pressure waveforms as they propagate along an arterial segment divided by the distance between the segments. Carotid to femoral PWV (cfPWV) is considered the referent standard measure of non-invasive PWV because it encompasses the majority of the aorta, the major elastic vessel in the human body susceptible to functional stiffening.[20] CfPWV can be obtained using non-invasive specialized devices. These devices include the OMRON VP-1000 Plus which uses applanation tonometry to determine PWV. Although there are other techniques and devices available, this study was limited to the measure chosen by the ARIC study. Below we discuss applanation tonometry and other techniques currently available.

Applanation tonometry uses pressure transducers placed directly over the skin at a pulse site (i.e., carotid artery, radial artery, and/or femoral artery) to obtain pressure waveforms in the trajectory from a proximal to a distal site. This technique accounts for the path length of the

pressure waveforms by measuring the distance from the proximal (carotid) to the distal (femoral) site. Although applanation tonometry is currently held as the standard, it highly dependent on operator proficiency, and requires extensive training. Oscillometry offers a user-friendly alternative, yet has not been as extensively used, although it has gained popularity. It is also important to note that other techniques exist to assess PWV including oscillometry, a combination of applanation tonometry and oscillometry, doppler ultrasound, and magnetic resonance imaging (MRI). Although doppler ultrasound and MRI are two important tools to assess PWV, these are expensive and often confined to radiology departments.[20] We focused on applanation tonometry since it was the technique used for the Jackson Heart Study and the Atherosclerosis Risk in Communities Study (ARIC) shared cohort. In the next section, we outline principles and key considerations for the OMRON device.

Principles and Key Considerations for PWV Measurements of Arterial Stiffness

OMRON® VP 1000 (Colin Co., Ltd., Tokyo, Japan)

The OMRON (VP 1000 Plus) (Colin Co., Ltd., Tokyo, Japan) device was used to measure cfPWV. PWV (m/s) was calculated by dividing arterial path length (D) by the pulse transit time (TT) between a proximal tonometer and a distal tonometer by taking the distance from the carotid pulse to the femoral pulse and subtracting the carotid to suprasternal notch distance. The proximal tonometer for cfPWV was at the carotid artery and the distal tonometer. The distal tonometer was at the femoral artery. Carotid and femoral tonometer placement are presented in Figure 5. Transit time is calculated by the OMRON software's proprietary algorithm that measures the time between the foot of the proximal pressure waveform to the foot of the distal pressure waveform. Pressure waveforms were simultaneously captured using applanation tonometry.

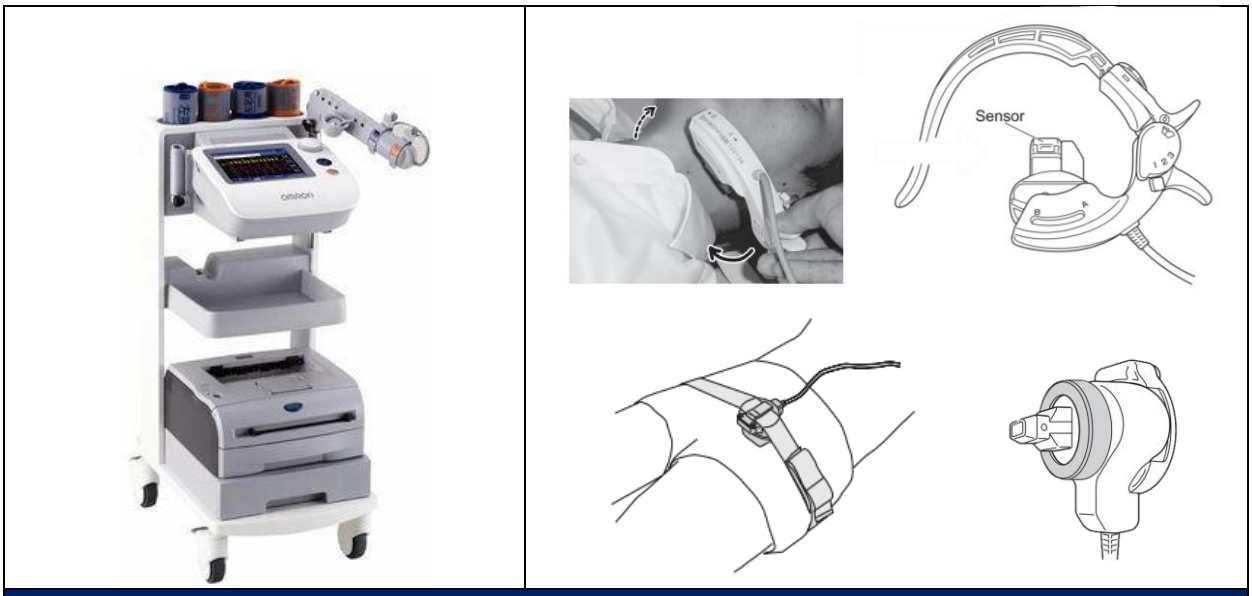

Figure 5. OMRON. Device (left) and example set-up (right)

Measurements were semi-automated. In relation to measurement frequency and quality control, measurements were made in duplicate and averaged. Additionally, JHS and ARIC had robust standard protocols and quality control procedures that ensured a rigorous study design and data collection.

MEASURE 2: Perceived Discrimination (Primary Exposure)

Rationale for Measuring Perceived Discrimination

Racism is a public health crisis.[2] Racial discrimination, the behavioral manifestation of negative attitudes and judgement towards an individual or group of individuals,[3] is a chronic stressor that may contribute to advanced vascular aging and heightened cardiovascular disease (CVD) risk.[4] The non-Hispanic Black (NHB) population, which comprises 13% of the population, has a greater burden of PD and higher CVD risk when compared with non-Hispanic White adults (NHW).[6,7] Although PD has been identified as contributor to CVD, the association with arterial stiffness, a measure of vascular aging and subclinical CVD risk, is unknown. Additionally, it should be noted that PD is multi-dimensional and the association between PD

and traditional CVD factors has been reported to vary based on the dimension measured.[9] Below, we outline the different methodological options for measuring PD as part of the JHS Visit 1 (2000-2004).

Methodological Options for Measuring Perceived Discrimination and Rationale for Chosen Approach

The JHS measured psychosocial factors at Visit 1 (2000-2004) using the JHS Discrimination Instrument (JHSDIS), which included several scales assessing PD. Among these were the lifetime discrimination scale, everyday discrimination scale adapted from the Williams' and Krieger scales', respectively. Additionally, attribution of lifetime/everyday/and burden of discrimination and responses to these experiences of discrimination were assessed obtaining a well-characterized assessment of PD within the sample. We chose to focus on lifetime discrimination, everyday discrimination, and burden from discrimination because they evaluate different dimensions of PD, as these measures of PD have been associated with traditional risk factors and have good psychometric testing (see Table 8 below).[9,53–55]

Table 8. Perceived Discrimination Measurement Scales Reliability			
Measurement Scale	Definition	α	Ref
Lifetime discrimination	Sum of the 9 items (range: 0-9), captures acute and observable experiences similar to life events	0.78	9,53–55
Everyday discrimination	Mean of 9 items, captures daily hassles associated with discrimination	0.88	9,55
Burden of lifetime discrimination	Sum of 3 items (reverse coded; range: 1-4), asks about the influence of perceived discrimination on lifetime experiences and potential hardships	0.63	9,53,55

Principles and Key Considerations for Perceived Discrimination Measurements

In relation to principles and key considerations for PD it is important to note that we are only evaluating PD at one time point. In an ideal scenario we would evaluate if PD changes

across the lifespan and determine the impact on arterial stiffness measures longitudinally. Additionally, evaluating the impact of resilience on PD could provide insight on the physiological impact of PD on arterial stiffness.

Other considerations for PD measurements include training. Although I have gained familiarity with the different scales of measurement, I still need additional guidance and formalized training to ensure proper use in the analysis. For this portion of my dissertation, we will enlist the help of Dr. Mario Sims, interim director of the JHS and co-lead of the JHS social determinants of health working group. In collaboration with Dr. Sims, I will receive the training to ensure adequate use of the scales and further considerations for the analysis.

MEASURE 3: Perceived Stress (Primary Exposure)

Rationale for Measuring Perceived Stress

Understanding whether PS mediates the association between PD is necessary to further characterize CVD risk in NHB adults and identify a public health target. Similar to PD, NHB adults experience greater PS compared to NHW. Although there is limited information on the chronic effects of PS on arterial stiffness, acute laboratory-based stressors have been reported to increase arterial stiffness.[50] We believe that both the acute and chronic effects of PS on arterial stiffness occur via prolonged arterial inflammation, endothelial dysfunction, and thickening and stiffening of the vascular wall, leading to narrowing of vascular lumen, and arterial stiffness.[42,50] This mechanism is supported by the fact that PS has been associated with increased inflammation markers (e.g., elevated C-reactive Protein),[44–47] endothelial dysfunction, and subclinical atherosclerosis (e.g., elevated carotid intima-media thickness),[48] and, in NHB, hypertension.[9,11,42,49]

Methodological Options for Measuring Perceived Stress and Rationale for Chosen Approach

Similar to PD, there are multiple measures to assess PS including the Global Perceived Stress Scale, weekly stress inventory, and the Reeder Stress Inventory, which all assess different dimensions of PS.[59] Within the JHS, available measures of PD included the weekly stress inventory, the Global Perceived Stress Scale, and stress from discrimination. For this proposal, we focused on the Global Perceived Stress Scale and stress from discrimination. We chose the Global Perceived Stress Scale for its common use, potential to generalize to the existing literature,[5,46,49,56–58] and its good psychometric testing.[48] Further, we chose to evaluate stress from discrimination as evidence suggests that the degree of stress from PD is a key determinant of health (see Table 9).[9]

Table 9. Perceived Stress Measurement Scales Reliability			
Measurement Scale	Definition	α	Ref
Stress from discrimination	"When you had experiences like these over your lifetime, have they been—very stressful (4), moderately stressful (2.5), or not stressful (1)?"	0.63	9,55
Global Perceived Stress Scale	Sum, 8 items (range: 0-24), asks about domain specific stressors experienced over the previous 12 months	0.78	5,46,49,56–58,60

Principles and Key Considerations for Perceived Stress Measurements

PS was also measured at one instance at JHS Visit 1. Under ideal conditions, we would evaluate PS across the lifespan and determine if changes in PS influence the longitudinal relationship between PD and PS. In terms of training with these scales of measurement, Dr. Sims will also be assisting with the use of PS in our analysis.

Covariates

In addition to the major measurement considerations, we will also adjust for covariates. The covariates for this analysis will include: biological sex (female/male), age (continuous and categorical), body mass index (continuous, kg/m^2), mean arterial pressure (calculated continuous variable, 1/3 Systolic Blood Pressure + 2/3Diastolic Blood Pressure), and/or medication use (antidiabetic and antihypertensive). The rationale for adjusting consists of minimizing confounding and bias since all these factors influence the development of arterial stiffness.

Methodological and Rigor Considerations

In this section we will discuss methodological and rigor considerations including: population sampling, biological sex, race and ethnicity, external validity, quality control and statistical considerations.

Population/Sampling

The JHS recruited 5,306 African American residents living in the Jackson, MS metropolitan area. The cohort includes non-institutionalized participants who were enrolled by the following four recruitment pools: 1) 17% random selection from Jackson, MS; 2) 30% volunteer; 3) 31% eligible residents from Jackson currently enrolled in the ARIC Study, and 4) 22% secondary family members (Figure 6). The final cohort of participants at baseline (Visit 1, 2001-2004) included 6.59% of all African American Jackson, MS residents aged 35-84 during the baseline exam (N=76,426, US Census 2000). The sample for this proposal is derived from the 31% of participants enrolled in both studies that have arterial stiffness measurements as part of ARIC Visit 5 and data for our psychosocial measures of interest at JHS Visit 1.

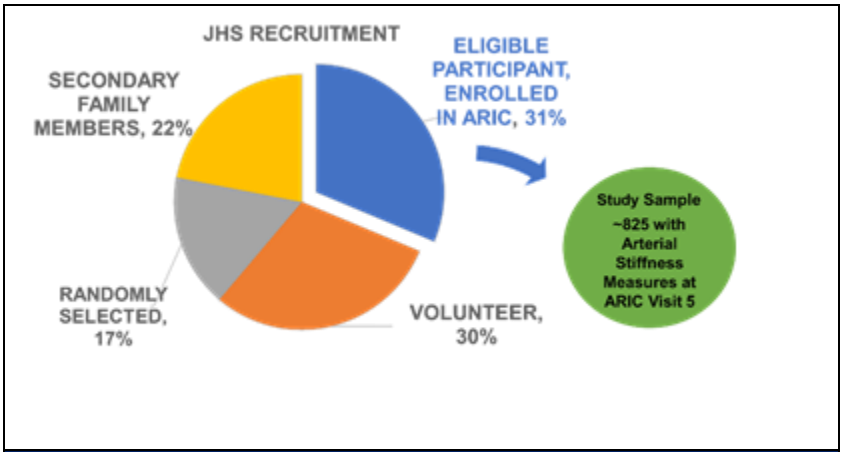

Figure 6. JHS recruitment

ARIC is a population-based, multi-site study that began in 1987. The study randomly selected and recruited a cohort sample of approximately 4,000 individuals (at each of the four sites) aged 45-64 from a defined population in their community. A total of 15,792 participants received an extensive examination, including medical, social, and demographic data. These participants were re-examined every three years. In 2011-2013, ~825 JHS cohort participants (264 men, 561 women) had arterial stiffness measurements from ARIC Visit 5. The JHS and ARIC contact the cohort yearly to assess changes in health status, document medical events and hospitalizations, and obtain additional sociocultural information. This study will evaluate ~825 cohort participants (264 men, 561 women) enrolled in both the JHS and the ARIC studies with arterial stiffness measurements. This is the optimal population to address this question as JHS and ARIC are two of the largest cohorts of their kind and are well-characterized. The findings from study 2 will be generalized to non-institutionalized adults 35-84 years old from Jackson, MS metropolitan area (Table 10).

Table 10. Eligibility Criteria			
Aims(s)	Criteria	Method	Rational
1-2	Age 35-84 years old with AS measurements	Eligible residents already enrolled in ARIC study	The JHS participants were middle to older aged.
Abbreviations: AS, arterial stiffness; ARIC, Atherosclerosis in Community Risk			

Exclusion Criteria

Missing information on cfPWV and exclusions recommended by the ARIC PWV Working group: participants with BMI ≥ 40 kg/m2 at Visit 5, major arrhythmias (Minnesota code 8-1-3, 8-3-1, and 8-3-2 from Visit 5 ECG), Minnesota code 8-1-2 from Visit 5 ECG with low quality PWV waveforms, aortic aneurysms/abdominal aorta diameter ≥5 cm by ultrasound at Visit 5, self-reported history of aortic or peripheral revascularization or aortic graft at Visit 5, echocardiographic evidence of aortic stenosis at Visit 5, moderate or greater aortic regurgitation at Visit 5, and missing covariates of interest at JHS Visit 1. We will exclude these factors to minimize bias of the cfPWV measurement.

Sex as a Biological Factor

Men and women have different trajectories for acquisition of cardiovascular risk factors and cardiovascular outcomes over the life course. Evidence evaluating PD and arterial stiffness is limited in men. Therefore, we believe that by using the JHS and ARIC shared cohort we will be able to further characterize this association between PD and arterial stiffness in both men and women and determine if biological sex is an effect measure modifier of the association. Aim 1 and Aim 2 have been powered to enable stratified mediation analysis by biological sex if there is evidence of effect measure modification.

Further, by design, the Jackson Heart Study (JHS) and Atherosclerosis Risk in Communities (ARIC) study are restricted to approximately 5,306 and 12,219 males and females

35+ years old at baseline, respectively. We will include more females than males, as ~68% of the overall sample population for this proposal will be female.

Ethnicity/Race

We will focus on NHB adults as our main goal is to further characterize CVD risk, as measured via arterial stiffness, in this population.

External Validity / Generalizability

The use of multiple common measurement scales of PD and PS will contribute to the generalization to other populations.

Quality Control

JHS and ARIC had robust standard protocols and quality control procedures that ensured a rigorous study design and data collection.

Statistical Considerations

Aim 1

We will determine the association between PD and arterial stiffness using multivariable linear regression. We will present results adjusted for age, sex, body mass index, hypertension medications, diabetes status, and mean arterial pressure. For Aim 1b, we will evaluate for effect measure modification by biological sex and stratify the results if statistically significant at $p<0.1$, as this is a commonly used threshold. Lastly, we will verify assumptions for multivariable linear regression, multi-collinearity, and evaluate for non-linearity of the associations.

According to the study design for aim 1, we could evaluate the association between PD with arterial stiffness using different statistical methods. Although arterial stiffness is a continuous variable, PD is an ordinal-level variable. Therefore, two statistical analyses that could be used for this analysis are the Spearman rank correlation or multivariable linear regression. We chose multivariable regression because it allows for evaluating the association between PD and

arterial stiffness after adjusting for covariates, whereas the correlation does not allow for that adjustment. For the analyses, we will dummy code PD by quartiles of PD. We will also convert PD scores into standard deviations to evaluate the association continuously.

Aim 2

For the mediation analysis, we will use a simple mediation for longitudinal data considering that the psychosocial factors were collected at JHS Visit 1 and arterial stiffness measures were obtained at ARIC Visit 5. Further, we will test the mediation effect using the bootstrap method that does not impose the normal distribution assumption.[14] Then, we will run the analysis including the following covariates from JHS Visit 1: age, smoking status, diabetes, body mass index, mean arterial pressure, hypertension, and/or medication use (antidiabetic and antihypertensive). If there is evidence of effect measure modification in Aim 1, mediation analyses will be stratified by biological sex. Covariates will be entered sequentially into the model and used for adjusting of results if statistically significant at a $p<0.05$. We will also evaluate for non-linearity of the associations.

According to the study design for aim 2, we could evaluate the mediation effect using either Sobel's method, the distribution of the product, or the bootstrap method. We focused on the bootstrap method as it does not impose normal distribution assumptions, it requires a smaller sample size, and is more powerful at detecting the mediation effect than Sobel's method.[14] When compared to the distribution of the product method, power for detecting mediation effect and sample size were similar for Sobel's and the bootstrap method. We decided on the bootstrap method due to the mentorship team's familiarity with the method. The proposed approach for aim 2 is outlined below (Table 11).

Table 11. Statistical Methods				
Aims(s)	Analysis	Choices	Selection	Explanation
2	Mediation	• Sobel's • Distribution of the product • Bootstrap	Bootstrap	• Does not impose normal distribution assumptions • Requires a smaller sample size than Sobel's for mediation analysis • More powerful at detecting mediation effect • Similar to distribution of the product but our team is more familiar with this approach
Abbreviations: AS, arterial stiffness; ARIC, Atherosclerosis in Community Risk				

Statistical Power

Aim 1/2

For a multiple linear regression model which already includes 6 covariates with a squared multiple correlation ρ^2 of 0.01 and an $\alpha = 0.05$, a sample size of 825 will have 80% power to detect a 0.009 increase in the correlation (ρ^2) due to including 1 additional covariate. Holding all other values constant, 90% power would result in detecting a 0.012 increase in ρ^2. If there is evidence of effect measure modification by biological sex, then aim 2 will be stratified by biological sex. For females, a multiple linear regression model with 6 covariates, a squared multiple correlation ρ^2 of 0.01, an $\alpha = 0.05$, and a sample size of 561 will have 80% power to detect a 0.014 increase in the correlation (ρ^2) due to including 1 additional covariate. Holding all other values constant, 90% power would result in detecting a 0.018 increase in ρ^2. For males, a multiple linear regression model with 6 covariates, a squared multiple correlation ρ^2 of 0.01, an $\alpha = 0.05$, and a sample size of 264 will have 80% power to detect a 0.029 increase in the correlation (ρ^2) due to including 1 additional covariate. Holding all other values constant, 90% power would result in detecting a 0.038 increase in ρ^2.

Potential Challenges & Alternative Strategies

Below we list potential challenges and alternative strategies for the proposed approach to study 3.

Accounting for Attrition and Selection Bias

Attrition and selection bias are of concern since health status and CVD are likely associated with ARIC Visit 5 participation. Data from annual follow up from both studies will be used to compare participant characteristics for the JHS-ARIC shared cohort at ARIC Visit 5 included in the analysis compared to those not included.

Accounting for Missing Data

Our strategy for handling missing data will depend on the amount missing. Exploratory data analysis will include plots of percent missing for each variable and the most common combinations of missing values. If the percent of missing data is low and missingness for the outcome is not easily explained with the available variables, complete case analyses will be used. However, if the percent missing is moderate (>5%), we will consider multiple imputation as an alternative strategy to account for missing data.

Alternative Measures of Perceived Discrimination and Stress

We propose to evaluate three scales of PD (i.e., lifetime, everyday, and burden of discrimination). An alternative would be to evaluate the attribution of discrimination and determine if the association with arterial stiffness is consistent. Attribution of discrimination (lifetime or everyday) would be assessed as: 1) no discrimination attributed to race, 2) low discrimination (<median) attributed to race, 3) high discrimination (≥median) attributed to race, 4) low discrimination attributed to nonracial factors, and 5) high discrimination attributed to nonracial factors, if participant responded yes to perceived lifetime and/or everyday discrimination, respectively. Further, for PS an alternative approach would be to create a

composite measure of PS that accounts for the dimensions measured by the global perceived stress scale and stress from discrimination.

Consideration for Variable Coding

We will evaluate all variables of interest as categorical and continuous and determine which coding scheme is more appropriate for the data. For analyses using threshold values, frequency distributions will be used.

CHAPTER 5: RATIONALE FOR APPROACH STUDY 3—AGREEMENT, REPEATABILITY, AND RELIABILITY OF THE OMRON, VICORDER, AND VASERA

Goal

The goal of this study is to determine the agreement and reliability data from three non-invasive devices used as part of large population-based cohorts.

Aims

1. (a) To compare arterial stiffness measurements from three commonly used non-invasive devices, and (b) evaluate the agreement of the devices across age.

- Determine the agreement of the OMRON VP-1000 Plus and VICORDER at a 25˚ angle.
- Determine the agreement of the OMRON VP-1000 Plus and VaSera VS-1500 at a supine posture.
- Determine the agreement of the VaSera VS-1500 and VICORDER at a 25˚ posture.
- Determine the agreement of the VaSera VS-1500 supine vs. 25˚ posture.

2. To determine the repeatability and reliability of PWV measures from three non-invasive devices.

- Determine the repeatability and reliability of the OMRON VP-1000 at a supine posture.
- Determine the repeatability and reliability of the VICORDER at a 25˚ angle.
- Determine the repeatability and reliability of the VaSera VS-1500 at a 25˚ angle.

Definitions

Table 12. Key Definitions	
Term	Definition
Agreement	quantifies how close measurements are, and is measured on the same scale of the measurement, otherwise known as the accuracy of measure[1]
Repeatability	refers to the precision of a measure or how consistently it is measuring a value[1]
Reliability	refers to variation in repeat measurements on the same individual under identical conditions[1]

Approach Overview

This study will be a 2-visit agreement, repeatability, and reliability study (Table 13). All measurements will be collected on two separate occasions in a quiet, dimly lit and environmentally controlled room. Participants will be familiarized with all experimental procedures and then given the opportunity to ask any questions prior to providing consent. Following 20 minutes of quiet rest, the participant will remain in a supine position, and arterial stiffness measurements on the OMRON (VP-1000 Plus) and VaSera (VS-1500) will be collected sequentially. Device placement will be randomized to the right or left side of the participant's body. After these values have been recorded, the OMRON will be substituted for the VICORDER. Then, the participant will be passively moved to the second posture (25˚ angle) and rest for 5 minutes. Arterial stiffness measurements with the VICORDER and VaSera (VS-1500) will be collected sequentially. Following the end of testing, second visit will be scheduled approximately 2 weeks from the first visit. Visit 2 will follow the same order as visit 1 (Figure 7).

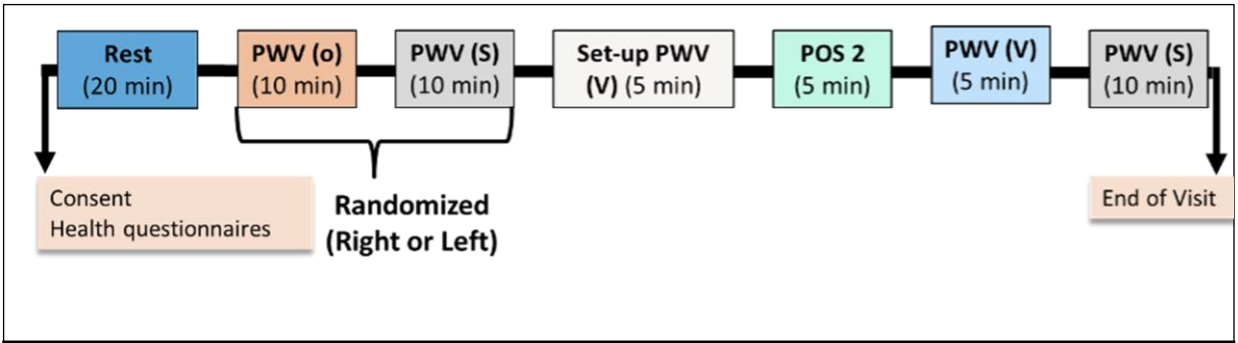

Figure 7. A visual representation of the experimental protocol.
Abbreviations: PWV (o), Pulse wave velocity with OMRON (VP-1000); PWV (o), Pulse wave velocity with VaSera (VS-1500); POS 2, posture 2; PWV (V), Pulse wave velocity with VICORDER. Pulse wave velocity measurements include blood pressure, ECG, phonocardiogram recordings and carotid-femoral measurements.

Table 13. Study Design Overview

Study	Population	Study Design	Primary Outcome	Secondary Outcome(s)	Experimental Timeline
3 (Experimental Study)	Healthy adults (18-84 years old)	Agreement/ Repeatability	AS	Within-day repeatability Between-day reliability	• 2 visits • 65 min/visit Primary outcome measured in triplicate for each device in a supine position for the OMRON and VaSera and at a 25˚ angle for the VaSera and VICORDER. Posture change will allow the determination of agreement under a physiologic perturbation.

Abbreviations: AS, arterial stiffness

Measurement Considerations

We chose these three devices (OMRON VP-1000 Plus, VICORDER, and the VaSera VS-1500) because they have been or will be used to assess PWV in large population-based cohort studies including the Jackson Heart Study (JHS) and the Atherosclerosis Risk in Communities Study (ARIC) shared cohort, the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), and for the Multi-Ethnic Study of Atherosclerosis (MESA). In the next section we provide specifics of arterial stiffness as a construct, methodological considerations, and outline principles and key considerations for each device.

Measure 1: Arterial Stiffness (Primary Outcome)

Rationale for Measuring Arterial Stiffness

Increased aortic arterial stiffness negatively affects normal hemodynamics, and the increased pressure transmission can damage end-organs, particularly the heart, increasing myocardial load.[17–19] Under normal conditions, the arterial system has a stiffness gradient characterized by greater arterial distensibility in central arteries due to higher elastin fibers within the arterial wall and decreasing distensibility (due to lower elastin content) and increasing collagen and smooth cell content as arteries move towards the periphery in medium-sized arteries and smaller vessels (e.g., arterioles).[20] When the central arteries stiffen, their ability to expand and recoil is compromised. The arteries are less able to store elastic energy within the arterial wall to promote blood flow during diastole. This decrease in elastic energy results in higher energy demand on the heart, requiring more blood to be transported over longer distances in systole resulting in higher pulsatility and end-organ damage.[8] Arterial stiffness is a sensitive marker of vascular aging and CVD risk that increases across the lifespan,[19,21–23] and can be used to track whether vascular aging is accelerated (e.g., due to risk factors) or attenuated (e.g., lifestyle) over time. Further, arterial stiffness is widely used as an independent predictor of CVD

in clinical and population-based studies, which is why we have focused on this measure for this study.

Methodological Options for Measuring Arterial Stiffness and Rationale for Chosen Approach

The most widely used and clinically relevant non-invasive measure of arterial stiffness is pulse wave velocity (PWV), otherwise known the velocity of pressure waveforms from one arterial segment to the next. Carotid to femoral PWV (cfPWV) is considered the gold standard measure of PWV because it encompasses the majority of the aorta, the major elastic vessel in the human body susceptible to functional stiffening.[20] CfPWV can be obtained using non-invasive specialized devices. These devices include the VICORDER, OMRON VP-1000 Plus, and the VaSera VS-1500) which use either applanation tonometry or oscillometry to determine PWV. The VICORDER and the VaSera devices use oscillometry to obtain PWV values, whereas the OMRON (VP-1000 Plus) uses applanation tonometry.

Applanation tonometry uses pressure transducers placed directly over the skin at a pulse site (i.e., carotid artery, radial artery, and/or femoral artery) to obtain pressure waveforms in the trajectory from a proximal to a distal site, whereas oscillometry uses cuff-based inflations to determine the trajectory of these pressure waveforms. Both these techniques account for the path length of the pressure waveforms by measuring the distance from the proximal to the distal site. Although applanation tonometry is currently held as the standard, it highly dependent on operator proficiency and requires extensive training. Oscillometry offers a user-friendly alternative, yet has not been as extensively used, although it has gained popularity. It is also important to note that other techniques do exist to assess PWV including a combination of applanation tonometry and oscillometry, doppler ultrasound, and magnetic resonance imaging (MRI). Although doppler ultrasound and MRI are two important tools to assess PWV, these are expensive and often confined to radiology departments.[20] We focused on applanation tonometry

and oscillometry since these are the more relevant techniques to the devices that will be used. Further, we chose these three devices because they have been or will be used to assess PWV in large population-based cohort studies including the JHS and ARIC shared cohort, the HCHS/SOL, and MESA. In the next section, we outline principles and key considerations for each device.

Principles and Key Considerations for PWV Measurements of Arterial Stiffness

Device 1: VICORDER (SMT Medical)

The VICORDER (SMT Medical) device will be used to measure cfPWV. PWV (m/s) is calculated by dividing arterial path length (D) by the pulse transit time (TT) between a proximal cuff and a distal arterial cuff. TT will be calculated by the VICORDER software proprietary algorithm that measures the time between the foot of the proximal pressure waveform to the foot of the distal pressure waveform. Measurements for D will be acquired by recording the straight-line distance between the edge of the proximal and distal cuffs, per manufacturer guidelines. For PWV measures including the carotid artery, the straight-line distance from the carotid artery to the sternal notch is included in calculations for D. Standard Hokason (Vellevue, WA) cuffs will be placed at the carotid pulse and at the femoral artery, and capture pressure waveforms simultaneously. The carotid cuff will inflate to a sub-diastolic blood pressure (~50 mmHg) to minimize discomfort (Figure 8).

Figure 8. VICORDER. Device (left) and example set-up (right)

Device 2: OMRON® VP 1000 (Colin Co., Ltd., Tokyo, Japan)

The OMRON (VP 1000 Plus) (Colin Co., Ltd., Tokyo, Japan) device will be used to measure cfPWV. PWV (m/s) is calculated by dividing D by the TT between a proximal tonometer and a distal tonometer. TT will be calculated by the OMRON software's proprietary algorithm that measures the time between the foot of the proximal pressure waveform to the foot of the distal pressure waveform. Measurements for D will be determined using the subtraction method, measuring the straight-line distance from the carotid pulse to the femoral pulse and subtracting the carotid to suprasternal notch distance, per manufacturer guidelines. Pressure waveforms will be simultaneously captured using applanation tonometry (Figure 9). The proximal tonometer for cfPWV will be at the carotid artery and the distal tonometer at the femoral artery.

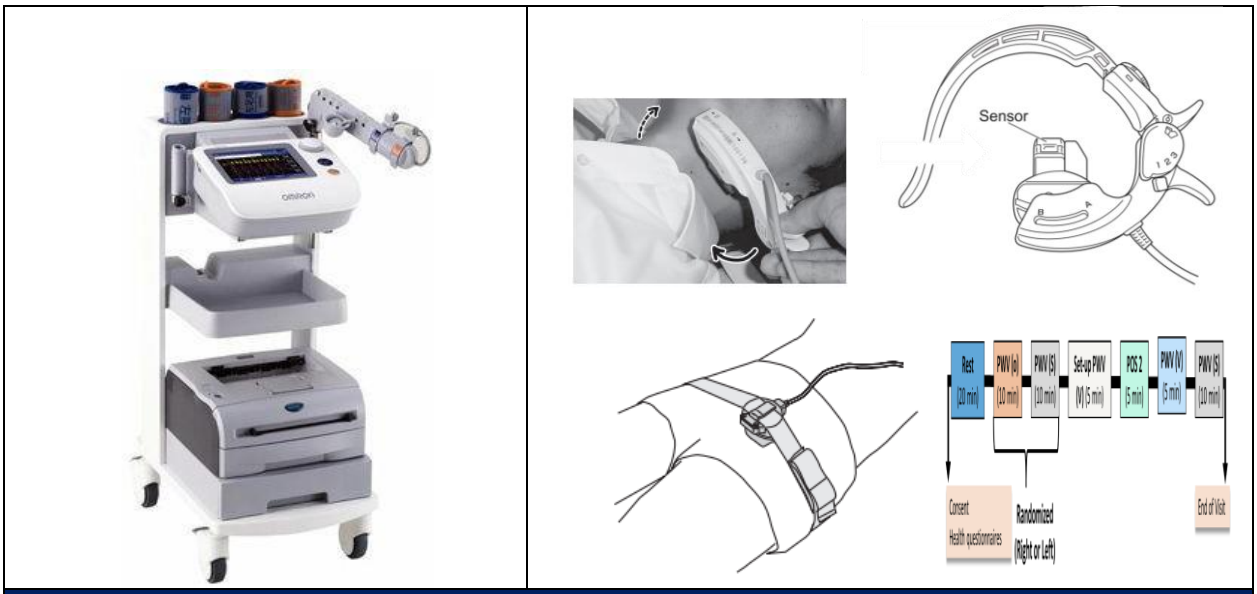

Figure 9. OMRON. Device (left) and example set-up (right)

Device 3: VaSera VS 1500 (Fukuda Denshi Co., Ltd., Tokyo, Japan)

The VaSera VS 1500 (Fukuda Denshi Co., Ltd., Tokyo, Japan) device will be used to measure PWV. cfPWV will be quantified as Heart-thigh PWV (htPWV), a validated and repeatable measure that does not require the placement of transducers. Heart-thigh PWV is calculated by the pulse wave velocity from the ascending aorta to femoral artery and the brachial artery blood pressure. The following equation is used to calculate htPWV: $2\rho \ln(Psys / Pdia) / (Psys – Pdia) (L1/T1)2$, where ρ is the blood density, Psys is the SBP of the upper arm, Pdia is the DBP of the upper arm, L1 is the length between the heart and the femoral artery cuff, and T1 is the time of the pressure wave to travel between the aorta and the femoral artery cuff. TT will be measured as the time delay between the proximal and distal 'foot' waveforms, i.e., the commencement of the sharp systolic upstroke. The device obtains time delays between the aortic and femoral arteries using a phonocardiogram and electrocardiogram signals (Figure 10).

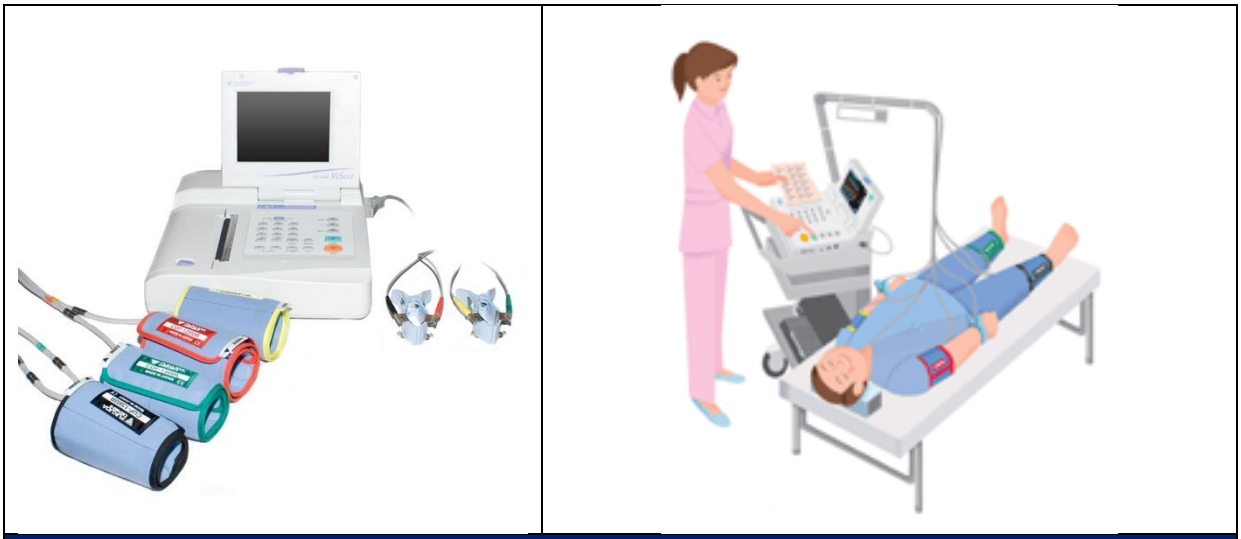

Figure 10. VaSera. Device (left) and example set-up (right)

For all three devices, measurements are semi-automated. In relation to measurement frequency and quality control, measurements will be made in triplicate for each device and the

closest 2 measurements averaged. Visual inspection of the waveforms will ensure adequate waveform quality. Additionally, device quality control measures will be noted as a secondary form of quality control.

Methodological and Rigor Considerations

In this section we will discuss methodological and rigor considerations including study design, considerations related to the experimental protocol, pre-visit control, internal validity, population sampling, biological sex, race and ethnicity, and statistical considerations.

Study Design Considerations

Since its inception, this study was delineated as an agreement and repeatability study. Taking that into consideration, the major considerations to minimize carry-over effects included posture, randomization of starting posture, device placement, and device order are explained below.

Table 14. Study Design Considerations				
Aim (s)	Consideration	Choices	Selection	Explanation

1, 2	Posture	• Supine
		• Seated
		• 25˚ angle
			• Supine
			  ○ OMRON VP-1000 Plus
			  ○ VaSera VS-1500
			• 25˚ angle
			  ○ VICORDER
			  ○ VaSera VS-1500
				• Seated posture was not feasible for the OMRON VP-1000 Plus. Femoral tonometer signal was too weak, almost non-existent.
				• Minimize participant and researcher burden.

1, 2	Starting Posture	• Randomized • Standardized	Standardized	• Randomizing order of posture (supine or 25˚) increased participant burden significantly. • OMRON VP-1000 Plus measurements were not feasible at a 25˚, nor were VICORDER measurements feasible at a supine posture. After extensive piloting, the protocol was revised. • Minimize participant and researcher burden.
1, 2	Device placement	• Randomized • Standardized	• Randomized to one-side (L or R)	• Randomized OMRON and VaSera devices. • Since the goal is to establish a more direct comparison between the OMRON and VICORDER, the OMRON will be substituted for the VICORDER for the second part of the visit.

1, 2	Device order	• Randomized • Standardized	• Standardized	• The OMRON device is challenging to use and using it first minimizes participant and researcher burden.

Considerations Related to Experimental Protocol

We chose an agreement and repeatability study since it is the most appropriate for our research question comparing three non-invasive devices. In this section, we describe the above considerations in more detail (Table 14). Firstly, we considered the posture at which we would compare the devices.

The initial protocol for this study included three points of randomization (starting posture, device placement, and device order). Following extensive piloting, we modified the protocol to minimize participant and researcher burden. Several methodological limitations contributed to this decision including the VICORDER measurements need to be taken at a 25˚ angle to limit jugular vein interference and the OMRON measurements were poor quality at a 25˚ angle (see figure 11a). At the 25˚ angle, the activation of postural muscles buried the femoral pulse making the pulse almost undetectable by the tonometer as shown in Figure 11b.

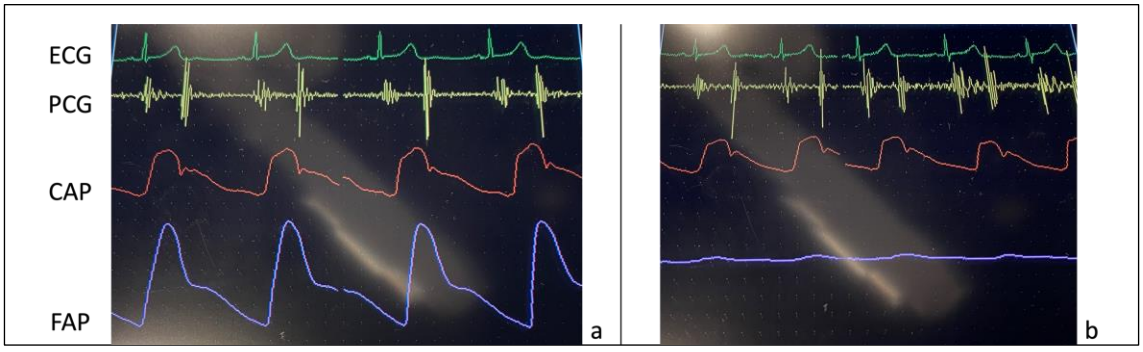

Figure 11. OMRON waveforms at a (a) supine and (b) 25˚ angle.

Additionally, randomization of device order posed challenges. Only 2 devices can be placed on a participant at a given time. To be able to switch devices and ascertain the path length distances, the participant would need to be in a supine position, and depending on the randomization, it would require a minimum of 5 minutes in the correct posture (supine or 25˚ angle) prior to taking measurements and potentially more to obtain a good signal. This process led to mismatch time commitment according to randomization. Those who were randomized to a 25˚ angle starting posture had 30-45 minute longer visits.

Pre-Visit Experimental Control

To ensure subjects report for each visit under standardized conditions, we will control the following factors. The factors are outlined in Table 15.

Table 15. Pre-Visit Considerations

Aims(s)	Consideration	Explanation	Control Procedure
1 (1,2)	Physical activity	Recent vigorous physical activity can alter AS.	No vigorous PA for 12 hours prior to the visit.
1 (1,2)	Food/Caffeine/Alcohol consumption	Influences AS and metabolism	Participants will be asked to fast for a minimum of 4 hours (excluding water). Visits will be in the morning to minimize participant burden.
1 (1,2)	Medications	Influences AS	Screened for medications that affect CV and metabolic systems. If taking medications or supplements not in the exclusion criteria, we will ask that the participant be consistent across visits. Questionnaires will be used to determine if taking any medication or supplements.
1 (1,2)	Mode of transport	Walking or cycling to their visit can influence AS	A parking pass will be provided to the participant and/or assistance to navigate public transportation.

Abbreviations: AS, arterial stiffness; PA, physical activity; CV, cardiovascular

Internal Validity

Considerations to maintain optimal internal validity for the participants, the laboratory environment, and data collection are listed in Table 16, 17, and 18, respectively.

Table 16. Internal Validity Considerations: Participants			
Study (Aim)	Consideration	Explanation	Control Procedure
1 (1,2)	Posture during measurement	Posture impacts AS	A wooden wedge or a 3-section table will be used to standardize 25˚ for OMRON VP-1000 Plus and VaSera measurements
1 (1,2)	Face mask use	All participants will be asked to remove their face mask.	If a participant is not comfortable removing mask a note will be made on the data collection sheet to determine if outlier during analysis
1 (1,2)	Movement	Participant movement can potentially alter results.	Ask participants not to move unnecessarily

To address the internal validity considerations for participants (Table 16), we focused on standardizing posture at which measurements were made, face mask (COVID-19 consideration), and movement. Due to multiple lab spaces and equipment limitations, we will have 2 ways to standardize posture. We will either use a wooden wedge or a 3-section table that allows to passively move participants to a 25˚ angle. In relation to face mask use, we are aware that participant comfort can contribute to the use or lack of use of a face mask during testing. Consequently, we will ensure that face mask use is consistent across visits for each individual participant. Finally, for movement we will ask participants at the beginning of each experimental to refrain from any unnecessary movement and repeat as needed during the visit.

Table 17. Internal Validity Considerations: Laboratory Environment			
Study (Aim)	Consideration	Explanation	Control Procedure
1 (1,2)	Temperature	Temperature can change the perceived comfort level of the participant and influence mental state.	A thermometer will be used to monitor laboratory temperature
1 (1,2)	Sound	Sudden sound can change arousal state of participant.	Will use laboratory curtains and/or noise cancelling headphones to reduce sound
1 (1,2)	Arousal	Surprises can increase arousal and create measurement error.	Prevent people walking up while testing
1 (1,2)	Instructions	Consistent procedure helps to eliminate sampling errors.	A standard script will be used to ensure consistency

Further, in relation to the lab environment, we have identified temperature, sound, arousal, and instructions (Table 17) as internal validity considerations. We will monitor for all these considerations and make note if there is any variation during testing sessions for post-analysis.

Table 18. Internal Validity Considerations: Data Collection			
Study (Aim)	Consideration	Explanation	Control Procedure
1 (1,2)	Data synchronization	Ensuring team is working on updated, full data set will allow for quicker analysis and less potential error.	Use lab data drive for all working data Use RedCap to organize and maintain survey and measurement data together
1 (1,2)	VICORDER Waveform Quality	Ensuring quality waveforms will allow for proper data analysis.	Operator assesses data prior to saving and confirms judgement with team
1 (1,2)	OMRON Waveform Quality	Ensuring quality waveforms will allow for proper data analysis.	Operator assesses data prior to saving and confirms judgement with team
1 (1,2)	VaSera Waveform Quality	Ensuring quality waveforms will allow for proper data analysis.	Operator assesses data prior to saving and confirms judgement with team

Finally, the last set of considerations focuses on data quality. We have made extensive standard operating procedures and training will be provided to the study team to ensure that the considerations outlined in Table 18 are met.

Population/Sampling

The findings from study will be generalized to healthy adults 18-84 years old free of cardiovascular and metabolic disease. This population will be representative and improve generalizability of the agreement and reliability of the three devices. Initially, the population was to be obtained from both the University of North Carolina – Chapel Hill and the JHS Jackson, Mississippi study site. However, due to the pandemic and pandemic-associated study delays this was no longer feasible. Therefore, this population will be recruited from the University of North Carolina - Chapel Hill (UNC-CH) campus and the broader community via social media, email, flyer, class presentation, and/or the Research for Me @ UNC online platform from the UNC-CH campus. The use of these various methods of recruitment will contribute to obtaining our wide age group. In addition, given that we are targeting a general population and only a limited number of participants are being recruited, we believe there is a high likelihood of having access to the projected number of individuals. Below we outline the inclusion (Table 19) and exclusion criteria (Table 20).

Table 19. Inclusion Criteria

Aims(s)	Criteria	Method	Rational
	Age 18-84 y	Screening interview	The JHS participants were middle to older aged, to generalize the results we will examine a wider age range and evaluate agreement across age to improve external validity

Abbreviations: y, years; JHS, Jackson Heart Study

Table 20. Exclusion Criteria			
Aims(s)	Criteria	Method	Rational
	Diagnosed CVD or CMD/Medication use	Screening email	May affect validity of results
	Drug or alcohol abuse	Screening email	Known to impact primary outcome
	Tobacco Use	Screening email	Known to impact primary outcome
	Pregnancy	Screening email	May affect within subject variability
Abbreviations: CVD, cardiovascular disease; CMD, cardiometabolic disease			

Sex as a Biological Factor

We will recruit both males and females. Further, we will evaluate the importance of biological sex in the agreement and reliability of all three devices. We will perform exploratory analyses to determine if there is evidence of any sex differences.

Ethnicity/Race

All ethnicities/race will have equal access to volunteer for the study. In addition, we will enlist the help of community partners including Initiative for Minority Excellence at UNC-CH to ensure we get a general sample including individuals of all ethnicities/race. Please refer to the "Unmet Recruitment" section for additional strategies to ensure adequate recruitment.

External Validity / Generalizability

Results will not be generalizable to all young-, middle-, and older-age adults. However, the findings from this study will serve to harmonize measurements from all three devices and allow for comparison to an established norm. Although not a perfect harmonization, this will allow for closer estimates and further characterization of CVD risk in many high-risk populations.

Statistical Considerations

Typical methods, the methods chosen for the analysis, and the explanation for the chosen methods used to analyze agreement and reliability are listed below (Table 21).

Table 21. Statistical Considerations				
Aim (s)	Consideration	Choices	Selection	Explanation
1, 2	Agreement Measures	• r • aSEE • sSEE • Bland-Altman • Mixed model LoA • RSE	• All	• r shows the overall agreement between measures • aSEE provides how far the data varies from the average • sSEE denotes the accuracy of the measurement • Bland-Altman provides the bias between the mean differences of the devices[62] • Mixed model LoA maximizes statistical power while accounting for correlated error variances[63] RSE provides the magnitude of the standard error relative to the size of the estimated value
1, 2	Repeatability Measures	• ICC • MDC • %MDC • SEM	• All	• ICC provides overall strength of relationship • MDC provides minimal change not due to error[64] • %MDC provide the relative minimal change not due to error • SEM evaluates the accuracy of the differences[65]
Abbreviations: r, Pearson product-moment correlation; aSEE, absolute standard error of estimate; sSEE, standardized standard error of estimate; RSE, relative standard error; LoA, limits of agreement; ICC, intra-class coefficient; MDC, minimal detectable change; SEM, standard error of measurement				

Agreement Measures

Five measures of agreement will be used between all three devices: i) an absolute standard error of estimate (aSEE), ii) a standardized standard error of estimate (sSEE), iii) Bland-Altman plots, iv) limits of agreement calculated from a mixed model, v) relative standard error (RSE), and iv) the total deviation index (TDI). The aSEE will be calculated as: aSEE = SD x $\sqrt{(1-r^2)}$[66], whereby SD is the standard deviation of the criterion measure and r is the Pearson product-moment correlation between the three devices. Although there is no universal criterion for r measures for assessing agreement, in general, r value estimates of <0.5, 0.5-0.75, 0.75-0.9, and >0.9 indicate poor, moderate, good, and excellent correlation. Therefore, we will accept the outcome as having good agreement if the lower limit of the 95% confidence interval (95% CI) for r exceeds 0.75 for measures of PWV. To calculate a 95% confidence interval for the aSEE, Pearson's correlation and associated 95% confidence intervals will be derived from regression analysis. sSEE will be calculated by dividing aSEE by the standard deviation of the criterion, whereby <0.20 is considered a trivial difference, 0.2-0.6 small, 0.6-1.2 moderate, 1.2-2.0 large and >2.0 very large difference.[66] Bland-Altman plots or regression plots will be generated to permit visual analysis of the uniformity of error over the range of participant measurement values. Finally, mixed model limits of agreement will be calculated according to approach outlined by Parker et al.[63] using the clinically acceptable difference (CAD) of 1 m/s. This clinically acceptable difference has been established in literature.[67] The paired PWV measures of each device with the OMRON device will be specified as the dependent variable nested within participant and activity (posture), and the device will be set as a fixed factor. The following random effects will be specified to calculate the variance ($\sigma 2$) components: subject ($\sigma 2\gamma$), day ($\sigma 2\alpha$), subject-day ($\sigma 2\alpha\beta$), subject-device ($\sigma 2\alpha\gamma$), device-day ($\sigma 2\beta\gamma$), and residual ($\sigma 2\varepsilon$). Subsequently, the absolute difference between devices will be estimated by calculating the

square root of the mean squared difference (√MSD). The relative standard error (RSE) will be calculated by expressing the relative to the mean of the test device √MSD. The coverage probability (CP) will determine the estimated proportion of values which fall with the CAD. Mixed effects limits of agreement plots will be generated to inspect and test the uniformity of error. Further, Q-Q plots of residuals and random effects will be visually inspected to verify model assumptions are met.

Repeatability and Reliability

To evaluate within-day repeatability and between-day reliability, we will estimate the intra-class correlation coefficient (ICC), standard error of measurement (SEM) and the minimal detectable change (MDC) along with corresponding 95% confidence intervals (95% CI). The ICC estimates and their 95% CI intervals will be estimated using a single-rating, absolute agreement, 2-way mixed-effects model in R. A mixed model was used as it is unaffected by sample size.[68] SEM will be calculated according to the formula: SD* √(1-ICC) and MDC according to the formula: 1.96*SEM*√2.[66] Although there is no universal criterion, in general, ICC estimates of < 0.5, 0.5-0.75, 0.75-0.9 and > 0.9 indicate poor, moderate, good and excellent reliability, respectively.[69] We will accept an outcome as reliable if the lower limit of the 95% CI for ICC exceeds 0.75.

Covariates

In addition to the major measurement considerations, we will also adjust for covariates. The covariates for this analysis will include: biological sex (female/male), age (continuous and categorical), body mass index (continuous, kg/m2), and mean arterial pressure (calculated continuous variable, 1/3 Systolic Blood Pressure + 2/3Diastolic Blood Pressure). The rationale for adjusting consists of minimizing confounding and bias since all these factors influence the development of arterial stiffness.

Potential Challenges & Alternative Strategies

In the sections below we outline potential challenges and alternative strategies including unmet recruitment targets and carry-over effects.

Unmet Recruitment Targets

A potential challenge for the completion of this study could be not achieving the recruitment goals for the overall sample or for biological sex. The principal investigator will work with North Carolina Translational and Clinical Sciences Institute (NCTraCS) and community partners to maximize recruitment efforts. Additionally, community partners will be used to ensure we have a representative sample of individuals of different racial and/or ethnic minority groups and ensure inclusive recruitment and study involvement.

Another consideration, in terms of alternate strategies to meet recruitment strategies for the older age group, would be to remove exclusion criteria pertinent to overt cardiovascular and cardiometabolic disease and/or medication use. More general inclusion criteria would allow us to recruit more older individuals and evaluate the influence of health status and medication use on the agreement and reliability of the devices.

Carry-Over Effects

The protocol outlined for study 3 may be susceptible to carry-over effects. Device order will not be randomized to minimize participant and researcher burden. Further, feasibility of a randomized cross-over is limited since the OMRON VP-1000 Plus is unable to be measured at a 25˚ and the VICORDER cannot be measured at a completely supine posture. Additionally, due to device complexity and to minimize burden of participant, we standardized the order of devices so that the OMRON VP-1000 Plus is used first to minimize a pressor effect induced by the carotid and/or femoral tonometers. We will analyze our data for carryover effects.

CHAPTER 6: ASSOCIATION BETWEEN PERCEIVED DISCRIMINATION AND ARTERIAL STIFFNESS-A SCOPING REVIEW

Overview

Introduction: Racial discrimination is a chronic stressor that may contribute to cardiovascular disease (CVD) disparities in non-Hispanic Black (NHB) adults. Compared to non-Hispanic White adults, NHB adults experience greater chronic perceived stress (PS), burden of perceived discrimination (PD), and CVD risk. However, the associations between PD and arterial stiffness (AS), a subclinical-CVD risk marker, have not been established, limiting our understanding of whether or how PD could influence CVD risk development. Purpose: This scoping review aimed to identify the extent of existing literature on the relationship between PD and AS. This review will focus on characterizing the existing evidence and not determining the effectiveness of the findings. Hypothesis: We hypothesized there would be a limited number of studies focused on the association. Methods: We searched PubMed, Embase, SPORTDiscuss with Full Text, and CINALH+ with Full text on June 28th, 2022. Inclusion criteria consisted of adults (aged 18 years and over), a measurement of pulse wave velocity (PWV; arterial stiffness), and randomized control trials or observational studies (i.e., cross-sectional and cohort studies). Results: We identified 419 articles, of which 58 were marked as duplicates and 355 did not meet our inclusion criteria. We reviewed the full text of six articles. Three articles evaluated the same cohort, so two were excluded to avoid violating assumptions of independence. Additionally, another study was excluded for not including a measure of discrimination. A total of three studies were included in our review. Two of the studies were cross-sectional and the third was a

longitudinal study. The studies were conducted in the United Kingdom (UK), the United States (US), and Brazil. The age of the study populations varied from young adults to older adults, and there was a study comprised of only post-MI patients. PWV was assessed using three different devices. Conclusion: Associations between PD and PWV varied by country. In the UK and Brazil studies, PD was associated with increased PWV. For the study conducted in the US, discrimination was only significantly associated with PD only in NHB women, but not NHB men or White women or men. In conclusion, associations varied by region and ethnic group analyzed. More studies are needed to characterize the influence of PD on CVD risk over the lifespan.

Keywords: discrimination, arterial stiffness, subclinical cardiovascular disease, cardiovascular disease risk

Introduction

Discrimination poses a public health risk. Perceived discrimination (PD) can be defined and measured as the behavioral manifestation of a negative attitude, judgment or unfair treatment towards members of a group.[3] It is a multi-dimensional construct and a chronic stressor that may contribute to advanced vascular aging and heightened cardiovascular disease (CVD) risk.[4] This is evidenced by associations of PD with diseases like hypertension and obesity[3] and with poor health behaviors— including poor sleep and smoking.[70,71] Although most research focused on PD and CVD risk has been primarily done in non-Hispanic Black (NHB) adults, more recent studies have evaluated the association in other racial/ethnic groups (i.e., whites) and indicated a potential association of discrimination with CVD risk.[72]

Currently, a challenge of assessing PD includes the existence of multiple instruments with different dimensions of PD, including domains (e.g., school, work, etc.) in which individuals are exposed and the consideration of chronic and acute exposures to discrimination.

For example, two common scales used to assess PD include the Major Lifetime Events scale (LES)[73] and the 10-item Everyday Discrimination Scale (EDS).[74] The LES focuses on capturing chronic exposures to PD in public spaces, work, police stations, educational institutions, and regarding housing. Whereas the EDS focuses on the impact of various forms of day-to-day unfair treatment over the previous 12 months.

Additionally, although the association between PD and CVD outcomes has been evaluated, most have focused on incident CVD[75] and all-cause mortality,[13] with some work done with subclinical measures of CVD. The work on subclinical CVD measures has been limited to studies of coronary artery calcification,[76] proteins (e.g., HS-CRP),[45,77] and carotid intima-media thickness.[78] However, the association between subclinical CVD risk factors and psychosocial factors has not been thoroughly elucidated. To be able to understand CVD risk over the lifespan, it is important to evaluate arterial stiffness.

Arterial stiffness is a marker of vascular aging and CVD risk,[19,21–23] and can be used to track whether vascular aging is accelerated (e.g., due to risk factors) or attenuated (e.g., lifestyle) over time. It is also widely used as an independent predictor of CVD in clinical and population-based studies.[8] Arterial stiffness offers prognostic value over and above traditional blood pressure measurements, making it an ideal measure to evaluate CVD progression and could provide insights especially in younger individuals. The most widely used and clinically relevant non-invasive measure of arterial stiffness is pulse wave velocity (PWV), otherwise known as the velocity of pressure waveforms as they propagate along an arterial segment. Carotid to femoral PWV (cfPWV) is considered the referent non-invasive measure of PWV because it encompasses the large, elastic aorta susceptible to both structural and functional stiffening.[20]

To understand the effect of discrimination on the development of cardiovascular disease outcomes, this scoping review will evaluate the existing literature to understand the relationship between PD and arterial stiffness (measured as PWV).

Objective

The primary aim of this scoping review is to consolidate and synthesize the literature pertaining to the relationship between PD and PWV in adults. We initially planned to focus on only NHB, but due a scarcity of data we expanded to all adults.

Methods

This scoping review was carried out in accordance with PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Review) guidelines, however, it was not pre-registered.[79] The research question and search strategy were refined using PICOS: Problem, Intervention, Comparison Group, Outcomes, and Study Design.

Data Sources and Searches

Electronic databases (PubMed, Embase, SPORTDiscus with Full Text, CINALH+ with Full text) were searched by one author (PPL). The keywords used for the search were derived from the following initial keywords: ((((((discrimination) OR (perceived discrimination)) OR (perceived stress)) OR (stress) OR (psychosocial stress) OR (psychological stress)) AND ((arterial stiffness)) OR (cfPWV)) OR (PWV)). These keywords were expanded and adapted for each of the search engines used. A comprehensive list of the search terms is available in the supplement. We excluded narrative reviews, letters, and unpublished data. We evaluated the reference lists of all identified studies and relevant reviews or editorials to ensure thorough identification of relevant studies. The search was limited to English language studies published between inception and June 28th, 2022. All studies identified through this process were then imported into an online systematic review software (Covidence).

Article Selection

For the purpose of this scoping review, the term ‘article’ is used synonymously with ‘study’, and ‘cohort’ will refer to the study population evaluated within a study included in this scoping review. Each article was considered the basic unit of analysis. If multiple publications were from one cohort, each was evaluated separately and the most relevant was maintained for analysis. Initially, article titles and abstracts were screened for relevance by two reviewers (PPL and CP) independently using the online systematic review software. The systematic review software tracked the progress of each reviewer and blinded the other reviewer to their peer's progress and their decision for the abstract. The full-text of potentially eligible articles was obtained to review eligibility for inclusion. The following criteria were used to select studies for inclusion in the review: i) participants were adults (aged 18 years and over), ii) measurement of PWV, iii) measurement of perceived discrimination, iv) randomized control trial, and vii) observational studies (i.e., cross-sectional and cohort). Additional exclusion criteria consisted of i) inclusion of individuals under the age of 18 years old and ii) previous cancer or cancer-related illness in the sample. We focused on young and older adults, as young adulthood is a time where habits are formed and can contribute to the development of disease later in life. Mid to older adulthood is when CVD pathology becomes evident. Additionally, we excluded cancer or cancer-related illnesses as these can lead to CVD and confound the association between PD and PWV.

Data Extraction and Quality Assessment

Data extracted for each eligible study included bibliographic information (author, publication year), baseline participant characteristics, details of study design, and results of reported outcomes. Study quality was assessed using the National Heart, Lung, Blood Institute’s Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (score: good,

fair, poor), which includes items related to randomization, blinding, and description of dropout/withdrawals.[80] Data extraction, quality assessment, and scrutiny of the available literature were completed by two researchers (PPL and CP).

Results

Literature Search and Trial Selection

A total of 419 potentially eligible articles were identified. Of these 419, 58 studies were duplicates. Following screening of abstracts and titles, 355 were excluded for not meeting the selection criteria. Of these, six studies were identified for a full-text review (Figure 12). One study was excluded because it did not measure PD.[81] Three studies evaluated the same cohort,[82–84] and two were excluded to avoid violating the assumption of independence and because of relevance. One study's main outcome was lung function, and the other focused on arterial wave augmentation.[82,83] A total of three studies were included in our analysis.[74,84,85]

Description of the Included Studies

Trial Setting and Participants

Included trial characteristics are summarized in Table 22. The trials were carried out in the United States (US) (n=1), the United Kingdom (UK) (n=1), and Brazil (n=1). The dates the studies were published ranged from 2016 to 2022 and the study conduct dates ranged from 2002 to 2014 for the DASH study, 2008-2010 for the ELSA-Brasil, and prior to 2020 for the Myocardial Infarction and Mental Stress 2 (MIMS2) study. The number of participants in each trial ranged from 313 to 13,284. All studies included male and female participants and multiple racial or ethnic groups. One study evaluated Black or White/Other race/ethnicity;[74] another 'Black', 'Brown', 'White', 'Asian descent', and 'Brazilian indigenous';[85] and another evaluated white British, Indian, Pakistani or Bangladeshi, black African (mainly Nigerian and Ghanaian), black Caribbean, and other ethnicities.[84] The mean age of the participants ranged from 22.0 years

to 51.6 years (SD: 8.9). Only one study evaluated a clinical population.[74] All studies used self-reported assessments of PD (EDS;[74] LES;[85] and standardized questions on unfair treatment on the grounds of race, skin color, country of birth, or religion[84]). One study used single-point oscillometry,[84] the other piezoelectric mechanotransducers,[85] and the other used applanation tonometry[74] to assess PWV. For the study using single-point oscillometry they used the Arteriograph 24-hour device (TensioMed, Budapest, Hungary),[84] the one using piezoelectric mechanotransducers used the Complior (Artech Medicale, Patin, France),[85] and the one using applanation tonometry used the SphygmoCor (AtCor Medical, Sydney, Australia).[74]

Methodological Quality Assessment

The methodological assessment of included trials is summarized in Table 22. The quality of the included studies ranged from fair to good, with a median quality score of fair. Two studies were cross-sectional and one longitudinal. Outcome and exposure measures were clearly defined for all studies. All studies clearly outlined how they identified their population of interest. Two of the studies evaluated the exposure continuously,[74,85] whereas the other dichotomized the exposure for the analysis.[84] All three studies adjusted for potential confounding variables on the relationship between PD and arterial stiffness. Two studies evaluated different levels of exposure as related to the outcome and specified participation rates of eligible persons.[84,85]

Synthesis of Results

In the Brazil and UK studies, PD was associated with greater (worse) PWV. In the US study, a similar association was evident only in NHB females, but not for NHB males or NHW males or females. For the Brazil studies, comparisons were made between ethnic groups with White as the referent group. The findings indicated that compared to White individuals, Black and Brown individuals with and without experiences of PD had greater PWV for the crude associations (Brown without PD: β=0.075 [0.003, 0.146] m/s; Brown with PD: β=0.455 [0.222,

0.687] m/s; Black without PD: β=0.418 [0.318, 0.518] m/s; Black with PD: β=0.297 [0.157, 0.436] m/s), and when adjusted for age, sex, research center, mean arterial pressure, heart rate (Brown without PD: β=0.085 [0.026, 0.144] m/s; Brown with PD: β=0.401 [0.218, 0.583] m/s; Black without PD: β=0. 183 [0.101, 0.264] m/s; Black with PD: β=0.251 [0.141, 0.361] m/s). When additionally adjusted for education, the association between PD and PWV in Brown individuals without PD was no longer statistically significant, but remained statistically significant for Brown individuals with PD (Brown with PD: β=0.365 [0.181, 0.548]), Black individuals without PD: β=0.124 [0.112, 0.039, 0.209]; and Black individuals with PD: β=0.223 [0.112, 0.333] m/s) (Table 22). These findings were consistent when evaluating the odds of having PWV>10 m/s for the crude association, and for the model adjusted for age, sex, research center, mean arterial pressure, and heart rate. However, for the model additionally adjusted for education, the odds of having PWV>10 m/s was significant for Brown individuals with or without PD (Brown w/o PD: OR=1.14 [1.01, 1.29] and Brown with PD: OR=2.01 [1.43, 2.81]), and for Black individuals with or without PD (Black w/o PD: OR=1.24 [1.05, 1.45] and Black with PD: OR=1.39 [1.12, 1.72]). Overall, Brown individuals with PD compared to White individuals had the highest β's and OR's of having PWV>10 m/s (Table 22).

For the UK study, after adjusting for age, brachial blood pressure at 21-23 years old, sex, ethnicity, waist to height ratio, and socioeconomic circumstances at 21-23 years old, PD was associated with a 0.25 m/s increase in PWV. Further, when they included adjustment for adolescent family affluence and circumstance, PD was associated with a 0.30 m/s increase in PWV (Table 22).

For the US study, the crude association between everyday PD and PWV was significant. However, the association was attenuated when adjusted for age, race, and gender. They observed

a similar attenuation of the results when adjusting for other demographic characteristics (e.g., poverty status, education, and marital status) and behavioral and disease risk factors (e.g., diabetes, coronary heart disease, depression, and PS). Further, when they evaluated the relationship by race and gender, there was a significant association between everyday PD and PWV in NHB females for the unadjusted and adjusted models for sociodemographic, behavioral and disease risk factors, respectively.

Discussion

In summary, PD seems to be positively associated with higher (worse) PWV. However, these results vary by geographic region, biological sex, clinical status, and study design. For this scoping review we identified three primary studies focused on assessing the relationship between PD and arterial stiffness across the world published between 2016 and 2022. According to our findings, there is a paucity of research specifically focusing on the association between PD and PWV, an indicator of CVD risk. We also noticed that findings were often adjusted for age, sex, racial/ethnic group, blood pressure, and socioeconomic status or position. Additionally, there was heterogeneity in the methods used to assess PD and PWV, which aligns with established limitations of both PD and PWV research. Lastly, the use of three different PD measurement scales may have an impact on the association between PD and PWV. Each PD scale used addresses different aspects of discrimination. The LES, which captures unfair treatment in public spaces, work, police stations, educational institutions, and regarding housing assesses PD chronically.[73] Whereas, the EDS focuses on the impact of various forms of day-to-day unfair treatment over the previous 12-months.[74] Both address chronic aspects of discrimination, yet the EDS is more focused on smaller events on day-to-day basis. Finally, the scale used for the UK study, focused on assessing unfair treatment as a result of gender and race discrimination or other types of gender or race-biased treatment, and does not specify a period of time.[86,87] Further, these

studies do support the need for further research in this area to fully characterize the relationship between PD and arterial stiffness.

Limitations

As this was a scoping review, it is important that we acknowledge some of the existing limitations. First, there is notable scarcity of literature on the association between PD and PWV. Second, not all studies evaluated differences by sex. Only one study evaluated the association within a clinical population. Although the findings come from several world regions, the findings may not be generalizable to all populations.

Conclusions

The goal of this scoping review was to consolidate and synthesize the literature pertaining to the relationship between PD and PWV in adults. There is a lack of research evaluating PD and PWV. This advocates for more high-quality research focused on assessing the association between PD and PWV, as experiences of PD could be contributing to the accrual of CVD risk, especially in minority populations. As noted previously, heterogeneity in the use of different scales of PD is a current limitation, so considering the use of multiple scales to assess PD simultaneously could improve generalization. Additionally, the use of consistent devices to assess PWV could improve generalizability and CVD risk assessment in the general population. Similarly, evaluating and reporting results by sex and clinical status could contribute to the generalizability of results. Further, expanding on our understanding of intersectionality in specific sectors of the population could contribute to the full characterization of PD and its effect on CVD risk. Finally, it is important to evaluate the effect of coping mechanisms (good and bad) and how these impact the association between PD and PWV.

Tables and Figures

Figures

Tables

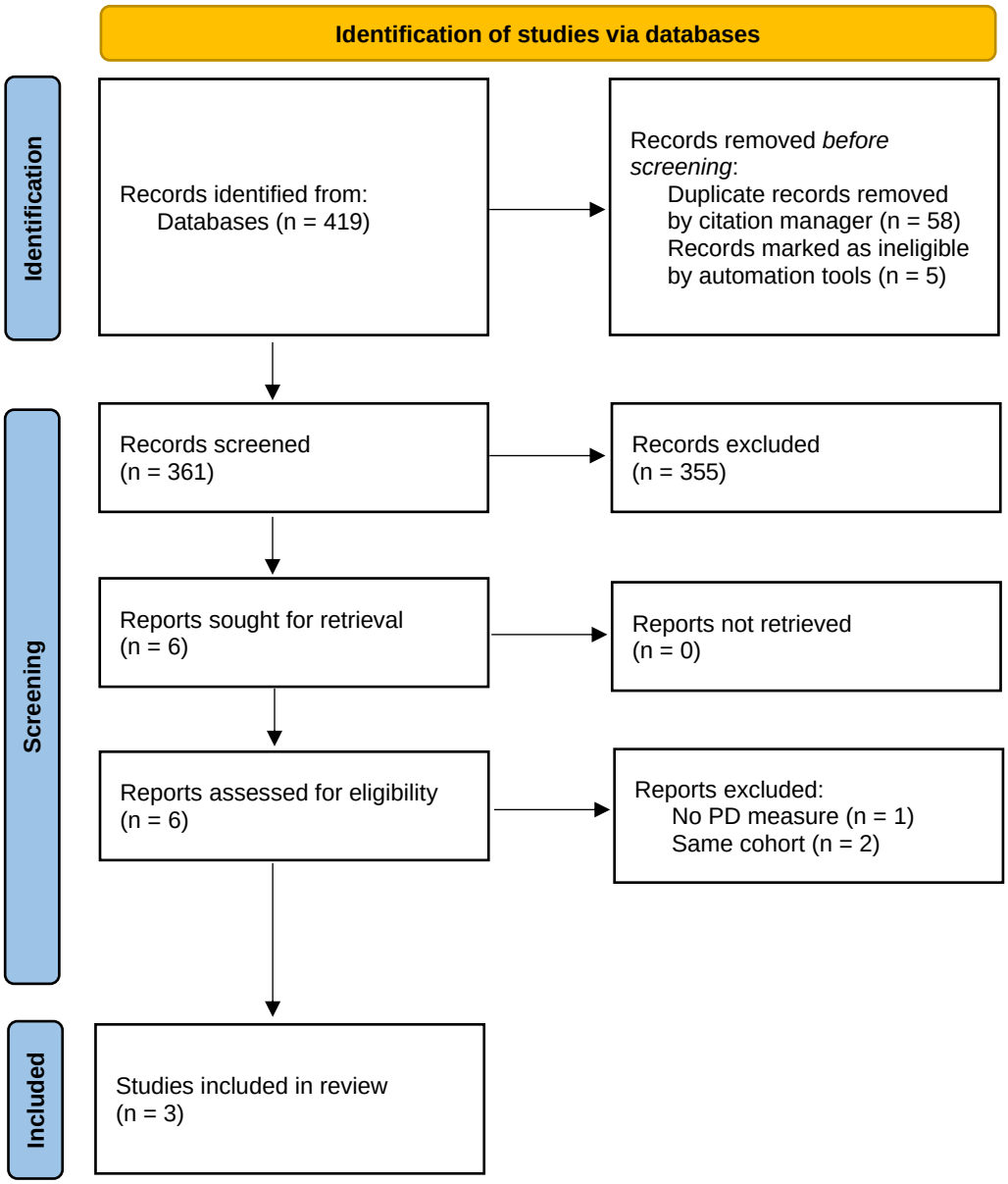

Figure 12. PRISMA diagram for study selection.

Table 22. Study Characteristics

Authors	**Country**	**Study Design**	**Sample size**	**Age (y)**	**Female (%)**	**Clinical population**	**Race/ ethnicity**	**PD Assessment**	**PWV Method**	**Outcomes**	**Quality**
Bromfield et al. 2020	US	Cross-sectional	313	50.8	49.2	Yes (Post-MI)	White Black	10-tem Everyday Discrimi-nation Scale (Self-reported)	Applana-tion tonometry	**PD on PWV as β (95% CI)* White/Other males: β=0.53 (-0.33-1.39) Black males: β=0.03 (-0.84-0.89) White/Other Females: β=-0.45 (-2.39-1.48) **Black females: β=0.85 (0.19-1.52)**	*Fair*
Camelo et al. 2022	Brazil	Cross-sectional	13,284	34-75	54.7	No	White Black Brown	Lifetime Major Events Scale (Self-reported)	Piezo-electric Mechano-transducers	***PD on PWV as β (95% CI)* Brown w/o PD: β=0.046 (-0.015-0.108) **Brown w/ PD: β= 0.365 (0.181-0.548)** **Black w/o PD: β=0.124 (0.039-0.209)** **Black w/ PD: β=0.223 (0.112-0.333)** ***High PWV (>10m/s) OR*	*Fair*

										Brown w/o PD: **OR= 1.14 (1.01-1.29)** **Brown w/ PD: OR= 2.01 (1.43-2.81)** **Black w/o PD: OR=1.24 (1.05-1.45)** **Black w/ PD: OR=1.39 (1.12-1.72)**	
Cruick-shank et al. 2016	UK	Longi-tudinal	665	21-23	~equal	No	White British Indian Pakistani/ Bangladeshi Black African Black Caribbean Other	Standardized questions on unfair treatment on the grounds of race, skin color, country of birth, or religion in various locations (Self-reported)	Single-point oscillometry	****PD on PWV as β (95% CI) (White=ref)* **β=0.30 (0.02-0.58)**	*Good*

*Adjusted for age, income, education, marital status, depressive symptoms, and perceived stress.
All β and ORs are compared to **White adults, adjusted for age, sex, research center, MAP, HR, and education.
***Adjusted for age, brachial blood pressure at 21-23 years, sex, ethnicity, waist to height ratio, socioeconomic circumstances at 21-23, adolescent family affluence and circumstance.

Supplement: Search Strategy Report

Date: 06/28/2022
Database: PubMed

Set #		Results
1	"Vascular Stiffness"[Mesh] OR "Pulse Wave Analysis"[Mesh] OR "Carotid-Femoral Pulse Wave Velocity"[Mesh] OR “vascular stiffness”[tiab] OR “vascular stiffnesses”[tiab] OR “vascular stiffening”[tiab] OR “arterial stiffness”[tiab] OR “arterial stiffnesses”[tiab] OR “arterial stiffening”[tiab] OR “arterial wall stiffness”[tiab] OR “arterial wall stiffnesses”[tiab] OR “arterial wall stiffening”[tiab] OR “artery stiffness”[tiab] OR “artery stiffnesses”[tiab] OR “artery stiffening”[tiab] OR “artery wall stiffness”[tiab] OR “artery wall stiffnesses”[tiab] OR “artery wall stiffening”[tiab] OR “aortic stiffness”[tiab] OR “aortic stiffnesses”[tiab] OR “aortic stiffening”[tiab] OR “aorta stiffness”[tiab] OR “aorta stiffnesses”[tiab] OR “aorta stiffening”[tiab] OR “aortic wall stiffness”[tiab] OR “aortic wall stiffnesses”[tiab] OR “aortic wall stiffening”[tiab] OR “arterial aging”[tiab] OR “pulse wave”[tiab] OR “pulse transit time”[tiab] OR “pulse transit times”[tiab] OR PWV[tiab]	23,139
2	“race factors”[mesh] OR ethnicity[mesh] OR “social discrimination”[mesh] OR “racial discrimination”[tiab] OR Prejudice[tiab] OR racism[tiab] OR ((race[tiab] OR ethnicity[tiab] OR ethnicities[tiab]) AND (stress[tiab] OR discriminat*[tiab]))	131,072
3	#1 AND #2	124

Database: Embase (Elsevier)

Set #		Results
1	'arterial stiffness'/exp OR 'pulse wave velocity'/exp OR ‘vascular stiffness’:ti,ab OR ‘vascular stiffnesses’:ti,ab OR ‘vascular stiffening’:ti,ab OR ‘arterial stiffness’:ti,ab OR ‘arterial stiffnesses’:ti,ab OR ‘arterial stiffening’:ti,ab OR ‘arterial wall stiffness’:ti,ab OR ‘arterial wall stiffnesses’:ti,ab OR ‘arterial wall stiffening’:ti,ab OR ‘artery stiffness’:ti,ab OR ‘artery stiffnesses’:ti,ab OR ‘artery stiffening’:ti,ab OR ‘artery wall stiffness’:ti,ab OR ‘artery wall stiffnesses’:ti,ab OR ‘artery wall stiffening’:ti,ab OR ‘aortic stiffness’:ti,ab OR ‘aortic stiffnesses’:ti,ab OR ‘aortic stiffening’:ti,ab OR ‘aorta stiffness’:ti,ab OR ‘aorta stiffnesses’:ti,ab OR ‘aorta stiffening’:ti,ab OR ‘aortic wall stiffness’:ti,ab OR ‘aortic wall stiffnesses’:ti,ab OR ‘aortic wall stiffening’:ti,ab OR ‘arterial aging’:ti,ab OR ‘pulse wave’:ti,ab OR ‘pulse transit time’:ti,ab OR ‘pulse transit times’:ti,ab OR PWV:ti,ab	41,838

2	'ethnic or racial aspects'/exp OR 'social discrimination'/exp OR ‘racial discrimination’:ti,ab OR Prejudice:ti,ab OR racism:ti,ab OR ((race:ti,ab OR ethnicity:ti,ab OR ethnicities:ti,ab) AND (stress:ti,ab OR discriminat*:ti,ab))	349,687
3	#1 AND #2	692
4	#3 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	317
5	#4 AND ('article'/it OR 'article in press'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)	51

Database: SPORTDiscus with Full Text (EBSCO*host*)

Set #		Results
1	“vascular stiffness” OR “vascular stiffnesses” OR “vascular stiffening” OR “arterial stiffness” OR “arterial stiffnesses” OR “arterial stiffening” OR “arterial wall stiffness” OR “arterial wall stiffnesses” OR “arterial wall stiffening” OR “artery stiffness” OR “artery stiffnesses” OR “artery stiffening” OR “artery wall stiffness” OR “artery wall stiffnesses” OR “artery wall stiffening” OR “aortic stiffness” OR “aortic stiffnesses” OR “aortic stiffening” OR “aorta stiffness” OR “aorta stiffnesses” OR “aorta stiffening” OR “aortic wall stiffness” OR “aortic wall stiffnesses” OR “aortic wall stiffening” OR “arterial aging” OR “pulse wave” OR “pulse transit time” OR “pulse transit times” OR “PWV”	1,703
2	DE "RACE discrimination" OR DE "RACE discrimination in sports" OR DE "RACISM" OR DE "RACISM in sports" OR DE "SCIENTIFIC racism" OR “racial discrimination” OR Prejudice OR racism OR ((race OR ethnicity OR ethnicities) AND (stress OR discriminat*))	6,965
3	#1 AND #2	12

Database: CINAHL+ with Full text

Set #		Results
1	MH "Arterial Stiffness" OR MH "Pulse Wave Velocity" OR “vascular stiffness” OR “vascular stiffnesses” OR “vascular stiffening” OR “arterial stiffness” OR “arterial stiffnesses” OR “arterial stiffening” OR “arterial wall stiffness” OR “arterial wall stiffnesses” OR “arterial wall stiffening” OR “artery stiffness” OR “artery stiffnesses” OR “artery stiffening” OR “artery wall stiffness” OR “artery wall stiffnesses” OR “artery wall stiffening” OR “aortic stiffness” OR “aortic stiffnesses” OR “aortic stiffening” OR “aorta stiffness” OR “aorta stiffnesses” OR “aorta stiffening” OR “aortic wall stiffness” OR “aortic wall stiffnesses” OR “aortic wall stiffening” OR “arterial aging” OR “pulse wave” OR “pulse transit time” OR “pulse transit times” OR “PWV”	6,748
2	MH "Race Factors" OR MH "Ethnic Groups+" OR MH "Discrimination+" OR MH "Racism+" OR “racial discrimination” OR Prejudice OR racism OR ((race OR ethnicity OR ethnicities) AND (stress OR discriminat*))	208,757
3	#1 AND #2	232

CHAPTER 7: ASSOCIATION BETWEEN PERCEIVED DISCRIMINATION AND ARTERIAL STIFFNESS IN NHB ADULTS

Overview

Introduction: Racial discrimination is a chronic stressor that may contribute to cardiovascular disease (CVD) disparities in non-Hispanic Black (NHB) adults. Compared to non-Hispanic White adults, NHB adults experience greater burden of perceived discrimination (PD), chronic perceived stress (PS), and CVD risk. However, the associations between PD, PS, and CVD risk, measured as arterial stiffness (AS), have not been tested in a population-based study of NHB adults in the US, limiting our understanding as to whether or how PD and PS should be public health targets. Purpose: The goal of this study was to determine 1) the association between PD and AS, 2) whether biological sex is an effect measure modifier of this association, and 3) if PS mediates the association between PD and AS. Methods: We evaluated 594 NHB males and females who participated in the Jackson Heart Study (JHS) and Atherosclerosis Risk in Communities Study (ARIC) shared cohort with complete data. PD (lifetime-, everyday-, and burden –of discrimination, and attributions of lifetime- and everyday-discrimination) and PS were measured at JHS baseline (2000-2004) and AS at ARIC Visit 5 (2011-2013). AS (carotid-femoral pulse wave velocity) permits the measurement of CVD risk as a continuous construct over the lifespan. Effect modification was evaluated by including an interaction term for sex and PD in the fully adjusted models, and mediation was evaluated using the CAUSALmed procedure. Models were adjusted for age, sex, body mass index, blood pressure medication, diabetes status, mean arterial pressure (MAP), and PS. Results: There was

an inverse association between higher levels of lifetime PD and cfPWV that was attenuated when accounting for age, sex, body mass index, blood pressure medication, diabetes status. When additionally adjusted for MAP and PS, the association was no longer statistically significant. Attribution analyses for lifetime PD indicated evidence of an inverse association with high racial PD, which attenuated when adjusted for covariates and lost significance when adjusted for PS and MAP. There was an inverse association between lower levels everyday PD and cfPWV, which was attenuated but remained statistically significant when adjusted for covariates. For attribution analyses, there was an inverse association for low nonracial PD, which attenuated when adjusted for covariates and was no longer significant when adjusted for PS and MAP. There was no association with burden of discrimination. There was no evidence of effect modification by sex or mediation by PS. Conclusion: There is evidence of a positive association between PD and cfPWV, but further studies would be beneficial to understanding PD's role in CVD risk development.

Keywords: discrimination, arterial stiffness, subclinical cardiovascular disease, cardiovascular disease risk

Introduction

Racism is a public health crisis.[2] Ongoing events stemming from racial injustice and the global pandemic highlighted the effects of racism on all aspects of life, including cardiovascular outcomes. Systemic racism, the assigning of value and opportunities based only on skin color, often leads to the behavioral manifestation of negative attitudes and judgment,[3] including racial discrimination. In turn, racial discrimination is a chronic stressor that may contribute to advanced vascular aging and heightened cardiovascular disease (CVD) risk.[4] Compared to non-Hispanic White adults, non-Hispanic Black (NHB) adults experience greater perceived discrimination

(PD),[6,7] chronic perceived stress (PS),[5] and CVD risk.[6,7] Yet, the associations between PD, PS, and CVD risk, assessed via arterial stiffness, have not been thoroughly examined.

Currently, most of the literature on PD in NHB has predominantly focused on incident CVD[75] and all-cause mortality,[13] with some studies focusing on subclinical measures of CVD. PD has been associated with hypertension[9] and coronary artery disease.[6] The work on subclinical CVD measures is limited to studies of coronary artery calcification,[76] proteins (e.g., HS-CRP),[45,77] and carotid intima-media thickness.[78] To date, only three studies have evaluated the association between PD and arterial stiffness.[10,84,85] However, these studies were all in different regions of the world, used different PD scales (evaluating different domains, chronic and acute exposures to discrimination), and focused on either a clinical or healthy population. Additionally, the associations between PD and subclinical CVD risk, assessed via arterial stiffness, have not been tested in a population-based study, and the considerable heterogeneity in existing studies evaluating PD and arterial stiffness highlights an existing challenge of assessing PD and identifies the need to understand the association between PD and arterial stiffness using multiple PD measures to further characterize PD and CVD risk accrual.

Despite the importance of considering PS when evaluating experiences of discrimination and health,[10] there is limited information on how PS could influence the relationship between PD and arterial stiffness. Acute laboratory-based stressors can increase arterial stiffness,[50] but no study to date has evaluated whether PS modifies the association between PD and arterial stiffness. This study tests this hypothesis by evaluating two measures of PS, Perceived Stress Scale and stress from discrimination,[9] as mediators of the association between PD and arterial stiffness.

In summary, the purpose of this study was to a) determine the association between PD (i.e., lifetime, everyday, and burden of discrimination) and arterial stiffness in NHB adults; (b) determine if biological sex is an effect modifier of the relationship between PD and arterial stiffness; and c) determine if the association between PD and arterial stiffness is mediated by PS in NHB.

Methodology

Ethical approval exemption for this project was obtained from the University of North Carolina at Chapel Hill on February 23, 2023**.**

Study Population

This study evaluated members of the Atherosclerosis Risk in Communities (ARIC) and the Jackson Heart Study (JHS) shared cohort. The JHS recruited 5,306 non-institutionalized NHB adults living in the Jackson, MS metropolitan area aged 35-84 years. The cohort includes individuals enrolled via the following recruitment pools: 1) 17% random selection from Jackson, MS; 2) 30% volunteer; 3) 31% eligible residents from Jackson currently enrolled in the ARIC Study, and 4) 22% secondary family members. ARIC is a population-based, multi-site study that began in 1987 that randomly selected and recruited a cohort sample of approximately 4,000 individuals (at each of the four sites) aged 45-64 from a defined population in their community. A total of 15,792 participants received an extensive examination, including medical, social, and demographic data. These participants were re-examined every three years. Details regarding the sampling, design, and recruitment for ARIC and JHS are extensively described elsewhere.[88–90] Briefly, we included the 30% of individuals recruited for the JHS that were already enrolled in the ARIC study with psychosocial measures from JHS Visit 1 (2000-2004) and arterial stiffness data from ARIC Visit 5 (2011-2013) (Figure 13). Participants provided written informed consent for both studies. JHS was approved by the University of Mississippi Medical Center, Jackson

State University, and Tougaloo College institutional review boards. Similarly, for ARIC, the study was approved by the institutional review boards at all field centers, coordinating centers, central labs, and reading centers.

Exclusions

Participants were excluded if they had missing information for cfPWV, and met exclusions recommended by the ARIC Pulse Wave Velocity Working group. This exclusions included participants with BMI ≥ 40 kg/m^2 at ARIC Visit 5, major arrhythmias (Minnesota code 8-1-3, 8-3-1, and 8-3-2 from Visit 5 ECG), Minnesota code 8-1-2 from Visit 5 ECG with low-quality cfPWV waveforms, aortic aneurysms/abdominal aorta diameter ≥5 cm by ultrasound at Visit 5, self-reported history of aortic or peripheral revascularization or aortic graft at Visit 5, echocardiographic evidence of aortic stenosis at Visit 5, moderate or greater aortic regurgitation at Visit 5, and missing any of the PD measures or covariates of interest at JHS Visit 1. We initially started with a sample of 5306 NHB individuals from JHS Visit 1 and 5683 individuals from the ARIC Visit 5. Of those in JHS, 5284 and 5220 had completed the stress and discrimination questionnaires, respectively. When we merged the datasets, only 808 of these individuals had data in all three datasets. When we then excluded according to the previous guidelines provided above, our final sample consisted of 594 individuals.

Arterial Stiffness Measure

Arterial stiffness was determined as carotid to femoral pulse wave velocity (cfPWV). We focus on arterial stiffness because it is widely used as an independent predictor of CVD in clinical and population-based studies.[8] Additionally, arterial stiffness is a sensitive marker of biological vascular aging and CVD risk, which can be accelerated (e.g., due to risk factors) or attenuated (e.g., lifestyle).[19,21–23] Among NHB, arterial stiffness is higher compared to NHW as early as childhood.[15]

CfPWV was measured by trained technicians using a standardized protocol with an automated waveform analyzer VP-1000 (OMRON, Kyoto, Japan).[91] CfPWV was calculated as distance divided by transit time. Distance for cfPWV was measured with a segmometer (Rosscraft, Surray, Canada) and calculated as the carotid to femoral distance minus the distance between the suprasternal notch to carotid. The protocol consisted of having the participant rest for 5-10 minutes. Then, carotid and femoral arterial waveforms were acquired for 30 seconds using applanation tonometry sensors on the left common carotid and femoral artery fastened by a neck collar and an elastic waistband around the hip, respectively. Bilateral brachial and ankle pressure waveforms were detected over 10 seconds via plethysmography and oscillometry using pressure sensors wrapped around brachial artery (above the middle antecubital fossa) and ankles. Measures were taken at least 2 times and averaged for the analysis.

Discrimination Measures

PD was assessed using three different scales of measurement: everyday discrimination, lifetime discrimination, and burden of discrimination as part of the JHS discrimination instrument (JHSDIS). The JHSDIS was administered by trained NHB interviewers during JHS Visit 1 clinical examination following the blood draws and blood pressure measurements. All PD scales had good internal consistency (Cronbach's alpha>0.63; Table 23). For our analyses, we divided each of the scales into quartiles to identify potential threshold effects. We evaluated everyday, lifetime, and burden of discrimination as continuous variables by transforming them into standard deviations. Additionally, we also used information regarding the reason for the discrimination (age, gender, race, height, or weight, or other) for both everyday and lifetime discrimination scales, as previously done by Sims and colleagues.[9] We combined these responses to create 5 discrete categories for both everyday and lifetime discrimination, respectively, as follows: 1. no discrimination, 2. low discrimination (below the median) attributed to race, 3. high

discrimination (at or above the median) attributed to race, 4. low discrimination (below the median) attributed to nonracial factors, and 5. high discrimination (at or above the median) attributed to nonracial factors.

Covariates

The covariates for this analysis included: biological sex (female/male), age (continuous), body mass index (continuous, kg/m^2), and MAP (calculated continuous variable, 1/3Systolic Blood Pressure + 2/3Diastolic Blood Pressure). Blood pressures used to calculate MAP were taken from ARIC Visit 5 so that values would be consistent with cfPWV values. The other covariates were taken from JHS Visit 1. The rationale for adjusting consists of minimizing confounding and bias since all these factors influence the development of cfPWV.[92]

Power

Power was determined using nQuery Advanced 8.2 (nQuery, San Diego). For a multiple linear regression model which already includes 6 covariates, a squared multiple correlation ρ^2 of 0.01, an $\alpha = 0.05$, and a sample size of 561 will have 80% power to detect a 0.01 increase in the correlation (ρ^2) due to including 1 additional covariate.

Statistical Analysis

We determined our analytical sample based on the criteria listed above and compared the analytical sample to the excluded sample. Then, we evaluated the association between everyday, lifetime, and burden of discrimination using a multivariable linear regression model. We adjusted for a priori covariates listed below. Covariates were entered sequentially into the model as follows. Model 1 evaluated the unadjusted association between PD and cfPWV. Model 2 adjusted for biological sex and age; Model 3 adjusted for sex, age, and BMI; Model 4 adjusted for sex, age, BMI, blood pressure medication (BPmeds), and diabetes status (no diabetes, pre-diabetic, or diabetic); Model 5 adjusted for sex, age, BMI, blood pressure medication (BPmeds),

and diabetes status (no diabetes, pre-diabetic, or diabetic) and mean arterial pressure (MAP); and Model 6 adjusted for all the previous covariates plus PS. Potential effect modification was evaluated by including a term of interaction between each PD measure and sex into the adjusted models. If there is evidence of effect measure modification by biological sex, then the results will be stratified by biological sex. Mediation by PS was assessed using the CAUSALMED procedure.[52] All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Participants

The mean age for the sample was 64.67 (4.97) years and 68% were female (Table 24). There was an equivalent distribution of upper- and lower-middle class individuals, 41.75% of the sample had management or professional occupations, and 56.73% who completed vocational school, trade school or college.

Table 25 shows important participant characteristics by quartiles of everyday and lifetime PD. The average age was similar across quartiles for both everyday and lifetime PD. There were differences between income, occupation, and education across quartiles of everyday and lifetime PD. For everyday PD, there was a greater percentage of individuals with vocational school, trade school, or college by higher PD quartiles; income and occupation varied by quartile. For lifetime PD, the percentage of higher education, affluence, and management/professional occupation increased per quartile, whereas construction, and production occupations decreased per higher lifetime PD quartile.

Participant Characteristics in Included Sample vs. Not Included JHS Sample

When we compared our analytical sample to the individuals in the JHS cohort not included in this analysis (n=4626), there were differences with regards to age, BMI, income, occupation, education, physical activity, hypertension, and diabetes status. Overall, the analytical

sample was older (excluded sample mean age 53.6 (13.0) years) and had a lower BMI. With regards to occupation, the analytical sample consisted of a greater percentage of individuals in management and service jobs, and a lower percentage of individuals in construction, farming, production, retirement, sick, and unemployed occupations. With regards to education, fewer individuals in the analytical sample had completed vocational, trade school or college, and more had less than a high school diploma in comparison to those excluded from the sample. Finally, a greater portion of the analytical sample had poor health regarding physical activity, hypertension, and pre-diabetes compared with those excluded from the analytic sample.

PD as Quartiles

There was a crude inverse association between experiences of everyday PD and cfPWV for quartile 2 compared with quartile 1. The association remained statistically significant even though marginally attenuated when adjusted for sex, age, BMI, BPmeds, diabetes status, MAP, and PS, respectively (Models 2-6, Table 26). Adjustment with additional covariates progressively improved model fit and explained up to 18% of the variance in cfPWV.

When evaluating experiences of lifetime PD, there was a crude inverse association between quartiles 3 and 4 with reference to the lowest quartile, although the overall model was not significant. When adjusted for sex and age (Model 2, Table 26), there was a statistically significant inverse association between lifetime quartiles 3 and 4 compared to quartile 1 and cfPWV. This association persisted although marginally changed when adjusted for BMI, BPmeds, and diabetes status (Models 3 and 4, Table 26). When adjusted for MAP and PS (Models 5-6, Table 26), the association was no longer significant. The inclusion of additional covariates improved model fit and explained up to 18% of the variance in cfPWV.

There was no crude association between burden of PD and cfPWV, and this lack of an association persisted even when adjusting for other covariates (Models 1-6, Table 26). However,

the inclusion of other covariates improved model fit and explained up to 17% of the variance in cfPWV.

Attribution of PD

With regards to experiences of everyday PD, attribution analyses indicated that compared to no discrimination, those with low everyday PD due to nonracial factors had lower cfPWV, but the overall association was not significant. When adjusted for sex and age (Model 2, Table 26), compared to no discrimination, there was a statistically significant inverse association between low everyday PD attributed to nonracial factors compared to no discrimination and cfPWV. The association remained, although marginally attenuated, when additionally adjusted for BMI, BPmeds, and diabetes status (Models 3 and 4, Table 26). When adjusted for MAP and PS (Models 5 and 6, Table 26), the association was no longer statistically significant. Inclusion of specified covariates improved model fit, explaining up to 18% of the variance in cfPWV.

When evaluating experiences of lifetime PD, attribution analyses indicated a similar association with cfPWV than when evaluated as quartiles. There was no crude association. When adjusted for sex and age, there was a statistically significant inverse association between high lifetime PD attributed to racial factors compared to no discrimination and cfPWV. This association persisted even if it marginally weakened as additionally adjusted for BMI, BPmeds, and diabetes status (Models 3 and 4, Table 26). When adjusted for MAP and PS (Models 5 and 6, Table 26), the association was no longer significant. The inclusion of additional covariates improved model fit and explained up to 18% of the variance in cfPWV.

Stress from Burden of PD

Concerning the stress from burden of discrimination, analyses did not indicate a crude association. When adjusted for sex and age (Model 2, Table 27), there was a statistically significant inverse association between experiences that were moderately stressful, but not for

very stressful experiences compared to experiences that were not stressful. The previous association remained statistically significant when adjusted for BMI, BPmeds, and diabetes status (Models 3 and 4, Table 27). However, when adjusted for MAP and PS (Models 5 and 6, Table 27), both moderate and very stressful experiences were inversely associated with cfPWV. The inclusion of additional covariates improved model fit and explained up to 18% of the variance in cfPWV.

Continuous PD

Lastly, we evaluated everyday, lifetime, and burden of PD as continuous variables (Table 27). For experiences of everyday discrimination, there was no evidence of a statistically significant association with cfPWV. Similar to our previous findings with the quartiles and attribution, experiences of lifetime PD had an inverse association with cfPWV, which persisted even though marginally attenuated when adjusted for BMI, BPmeds, and diabetes status (Models 3 and 4, Table 27). When adjusted for MAP and PS (Models 5 and 6, Table 27), the association was not significant. Finally, there was no crude or adjusted association between burden of PD and cfPWV.

Effect Modification by Sex

There was no evidence of effect modification by sex for either everyday, lifetime, or burden of PD.

Mediation Analyses

For the mediation analyses, we evaluated the unadjusted and fully adjusted models for continuous PD measures. There was no evidence of mediation of PS on the association between PD and cfPWV for experiences of everyday discrimination lifetime or burden of discrimination. The **β**'s were less than 0.01 for all mediation analyses and p-values not smaller than 0.5. Overall, there was no evidence of mediation by PS on the association of PD on cfPWV.

Discussion

The purpose of this study was to a) determine the association between PD (i.e., everyday, lifetime, and burden of discrimination) and cfPWV in NHB adults; b) determine if biological sex was an effect modifier of the relationship between PD and cfPWV; and c) determine if the association between PD and cfPWV was mediated by PS in NHB. Our findings suggest that compared to Q1, Q2 of everyday PD had lower cfPWV. This association persisted for Q2 after adjustment for additional covariates. Further, for lifetime PD, Q3 and Q4 had lower cfPWV, compared to Q1, which persisted until adjusted for MAP and PS. This suggests that MAP and PS may be accounting for some of the variance in cfPWV. With regards to burden of PD, there was no association with cfPWV independent of variable coding. Concerning the attribution of PD for everyday and lifetime experiences, our findings were similar to the quartile and continuous analyses. For attributions of everyday PD, cfPWV was lower among those with low everyday PD attributed to nonracial factors compared to with no discrimination. The association persisted until adjusted for MAP and PS. For attribution of lifetime PD, cfPWV was lower among those with experiences of high lifetime PD attributed to racial factors compared to no discrimination. Finally, there was no evidence of effect modification by sex or mediation by PS for everyday, lifetime, and burden PD. In our sample, there is evidence of an inverse association between lower levels of everyday PD and higher levels of PD and cfPWV, respectively.

This study was of particular importance as previous studies evaluating PD and cfPWV have only focused on one measure of PD and compared it across racial/ethnic groups. This study evaluated the association between PD and cfPWV with three dimensions of PD (everyday, lifetime, and burden) within a large population-based cohort of NHB adults in the US. Additionally, our focus on cfPWV, an independent predictor of CVD in clinical and population-based studies,[8] could contribute to our understanding of PD as a CVD risk factor. We focused on

cfPWV as it is a sensitive marker of biological vascular aging and CVD risk, which can be accelerated (e.g., due to risk factors) or attenuated (e.g., lifestyle).[19,21–23] In the below sections, we will discuss the strengths and limitations of this study, compare our findings to the existing literature, implications, and conclusions.

Limitations and Strengths

This study had several strengths. First, it leveraged data from a well-characterized cohort of NHB adults. Both the ARIC and JHS studies had robust study protocols and quality control measures. We assessed multiple commonly used dimensions of PD and PS, which contribute to the generalization of these findings to other populations. There was a wide range of PD experiences in our sample. Although these are notable strengths, limitations of the study should be taken into consideration when interpreting the findings. Below, we will outline some of the limitations of the current study. Since we only had cfPWV data for a subset of the JHS sample, this could have biased our results. However, to examine the potential bias we evaluated differences between the analytical sample and excluded JHS sample. Overall, the analytical sample was older, had lower BMI, was less educated, and had poor health with regards to physical activity, hypertension, and pre-diabetes than those excluded from the analyses. We did not have baseline cfPWV values, which limited our ability to examine causality and temporality. However, since the data were obtained at two different time points (visit 1 JHS and visit 5 ARIC) the exposure (PD) preceded our outcome (cfPWV). Additionally, we did not adjust for sociodemographic variables, including socioeconomic status, income, education, or physical activity. These factors and other unmeasured confounders we did not account for could be influencing the association between PD and cfPWV. Although the JHS-ARIC shared cohort is well-characterized, participants were from the Jackson, Mississippi, metropolitan area which has a high concentration of NHB individuals. It has been previously reported that NHB individuals

living in areas with a high percentage of NHB report less PD.[93] Further, although our models accounted for up to 18% of the variance between PD measures on cfPWV, there is still considerable variance unaccounted for that could be driving the existing associations. In part, the unaccounted variance could be due to the ~11-year follow-up between the exposure and the outcome. Finally, there could be survivor bias in our sample as we evaluated the psychosocial measures at JHS visit 1 (2000-2004) and the cfPWV measures at ARIC visit 5 (2011-2013).

Comparison to the Literature

Overall, we saw an inverse association between everyday and lifetime PD and cfPWV, which attenuated when we adjusted for cardiometabolic factors and PS. This contrasts with the existing literature evaluating PD and cfPWV. Previously, Bromfield et al. found that there was a positive association between everyday PD and cfPWV in Black women, but not for White women, White men, or Black men in a sample of patients who were 6-months post-myocardial infarction.[10] Some notable differences between their sample and our sample include differences in sample characteristics. The mean age of their sample was 50.8 years, whereas our sample was almost 15 years older, with a mean age of 64.7 years. The mean cfPWV values for their NHB adults in their sample was 7.70 (2.00) m/s, less than the mean for our sample which was 12.40 (3.40) m/s. Compared to the European referent norms,[92] the Bromfield sample was below the mean for their age group, whereas our sample was above the mean for their age group. Similarly, both Cruickshank et al. and Camelo et al. evaluated younger individuals.[84,85] Cruickshank et al.'s sample was 21-23 years old with a cfPWV of 7.40 m/s. Camelo et al.'s sample had a mean age of 51.60 (8.90) years with an average cfPWV of 9 m/s. It is possible there could be an age-dependent association between everyday and lifetime PD and cfPWV, with a stronger association evident earlier in life, before the cumulative effects of CVD risk factors impact PWV. The directionality of this potential age-dependent association of should be evaluated

further to fully characterize the role of PD for CVD risk accrual, since it is possible there could be a positive association earlier in life and an inverse association later in life.

Further, another potential explanation could be that older adults in our sample reported lower levels of discrimination, as has been previously evaluated.[13] Previously in the JHS, it has been shown that more educated younger individuals tend to report higher levels of PD and also have lower risk of all-cause mortality due to demographic and behavioral factors, even after adjustment for demographics, comorbidities socioeconomic factors, and social support.[13] Our analytic sample was approximately 15 years older than the excluded JHS participants. The combined effect of lower reported discrimination and higher cfPWV could have contributed to an inverse association between PD and cfPWV.

In addition, it could be that the association between PD and cfPWV is affected by other behavioral factors we didn't adjust for. PD has been linked with negative behaviors, including greater smoking and alcohol consumption in NHB, as well as beneficial behaviors like physical activity. Borrell and colleagues found that there was a positive association between alcohol consumption and smoking with PD, but also that NHB individuals who reported moderate to high discrimination were more likely to engage in physical activity compared with those reporting no discrimination within the Coronary Artery Risk Development in Young Adults study (CARDIA) cohort.[93] Smoking and alcohol have both been linked with worsened cfPWV, whereas physical activity is seen as protective for cfPWV. If the participants in our sample were more physically active as a result of their experiences of PD, rather than smoking or consuming alcohol, then that could cause the association to be inverse. Future analyses of this sample should consider evaluating the impact of these factors. It could also be a product of the potential for

survivor bias in our sample, with the more resilient individuals comprising a greater portion of our sample.

Further, the three studies that have previously assessed the association between PD and cfPWV saw a positive association when evaluated multiple racial/ethnic groups. Contrastingly, when we evaluated a sample of NHB individuals only, the association was inverse. This could suggest that positive association could be a product of higher levels of PD within racial/ethnic groups in comparison to a referent group, as has been clearly documented.[6,7] These differential levels of PD within racial/ethnic groups could be contributing to the detection of the association. This aligns with previous findings evaluating other CVD outcomes within the JHS study.[13] Dunlay and colleagues found that there was no independent association between everyday or lifetime PD with risk of incident coronary heart disease, stroke, or heart failure hospitalizations within a fully NHB sample, in contrast to the previous literature evaluating multi-ethnic cohorts.[75] As previously stated, it could be that the effect seen when evaluating multiple-racial ethnic groups is a byproduct of heterogeneity of PD levels when comparing multiple racial/ethnic groups. The greater variation between racial/ethnic groups could contribute to the detection of an association.

Implications

Next steps for these analyses will be to adjust by socioeconomic status, smoking, alcohol, and physical activity. Further, future studies should evaluate the impact of coping mechanisms. It has been previously shown that although NHB may be at higher risk, they may engage in higher physical activity to cope with experiences of discrimination,[93] leading to lower cfPWV. It is also important to consider that PD can change over time and that we only had cfPWV data for a subset of the population measured ~11 years after the PD assessments. Future studies should

evaluate how the association changes within this sample, specifically since cfPWV has been added to the next JHS exam.

Conclusions

In summary, in our sample of NHB adults within the JHS-ARIC shared cohort with all measures for PD (everyday, lifetime, and burden), there is an unexpected inverse association between lower levels of everyday PD and cfPWV, and higher levels of lifetime PD and cfPWV. However, this association is attenuated to non-significance when adjusted for MAP and PS. There is no evidence of effect modification by sex or mediation by PS. These findings suggest that in a NHB adult population, higher levels of PD are associated with lower cfPWV. Consequently, more work focused on how other behavioral and sociodemographic confounding factors, including coping, could impact this association.

Tables and Figures

Figures

Tables

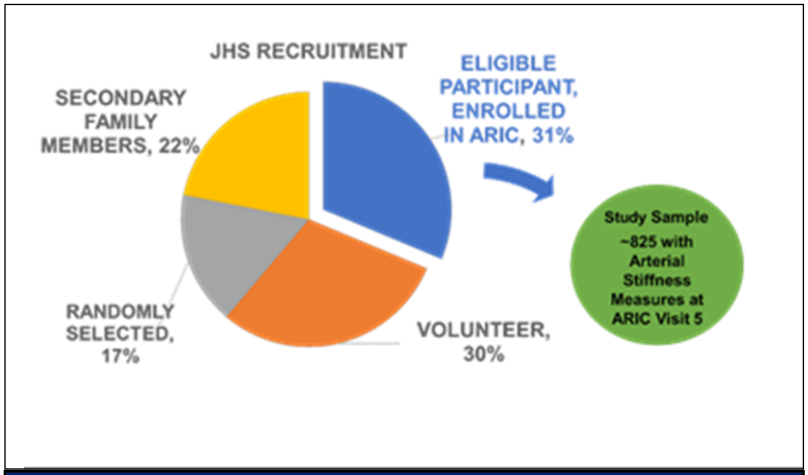

Figure 13. JHS recruitment

Table 23. Jackson Heart Study Psychosocial Factors

Measurement Scale	Definition	α	Ref
Lifetime discrimination	Sum of the 9 items (range: 0-9), captures acute and observable experiences similar to life events	0.78	[9,53–55]
Everyday discrimination	Mean of 9 items, captures daily hassles associated with discrimination	0.88	[9,55]
Burden of lifetime discrimination	Sum of 3 items (reverse coded; range: 1-4), asks about the influence of PD on lifetime experiences and potential hardships	0.63	[9,53,55]

Table 24. Participant Characteristics

Variables	Frequency (%) or Mean (SD)
Age (years)	64.67 (4.97)
Female	407 (69%)
Income	
Affluent	173 (29.12)
Upper-middle	169 (28.45)
Lower-middle	148 (24.92)
Poor	45 (7.58)
Missing	59 (9.93)
Occupation	
Construction	25 (4.21)
Management/Professional	248 (41.75)
Military	1 (0.17)
Production	75 (12.63)
Sales	79 (13.30)
Service	166 (27.95)
Education	
Less than high school education	136 (22.90)
High school grad (or equivalent)	120 (20.20)
Vocational school, trade school or college	337 (56.73)

Missing	1 (0.17)
Diabetes	141 (23.74)
Hypertension	413 (69.53)
Physical activity	
Poor	313 (52.69)
Intermediate	192 (32.32)
Ideal	89 (14.98)
BMI (kg/m^2)	30.14 (5.21)
Perceived Stress total score	4 (3.80)
Everyday discrimination total score	1.96 (0.90)
Lifetime discrimination total score	2.97 (2.04)
Burden of discrimination total score	2.28 (0.79)
Stress from discrimination	
Not stressful	163 (27.44)
Moderately stressful	308 (51.85)
Very stressful	123 (20.71)
Attribution of everyday discrimination	
Nonracial/high	150 (25.25)
Nonracial/low	104 (17.51)
Race/high	169 (28.45)

Race/low	74 (12.46)
No discrimination	97 (16.33)
Attribution of lifetime discrimination	
Nonracial/high	94 (15.82)
Nonracial/low	82 (13.80)
Race/high	228 (38.38)
Race/low	119 (20.03)
No discrimination	71 (11.95)
cfPWV (m/s)	12.42 (3.40)

Note: BMI, body mass index; *cf*PWV, carotid to femoral pulse wave velocity

Table 25. Participant Characteristics by Quartiles of Everyday and Lifetime PD

	Everyday				Lifetime			
Variables	Q1 (ref)	Q2	Q3	Q4	Q1 (ref)	Q2	Q3	Q4
Age (years)	65.70 (5.33)	64.70 (4.91)	64.76 (5.11)	63.56 (4.31)	64.78 (5.14)	64.89 (5.04)	64.61 (4.81)	64.46 (4.95)
Income								
Affluent	26 (18.18)	59 (34.30)	44 (33.08)	44 (30.14)	32 (20.78)	29 (24.58)	57 (31.67)	55 (38.73)
Upper-middle	38 (26.57)	53 (30.81)	42 (31.58)	36 (24.66)	36 (23.38)	42 (35.59)	52 (28.89)	39 (27.46)
Lower-middle	48 (33.57)	35 (20.35)	23 (17.29)	42 (28.77)	52 (33.77)	27 (22.88)	43 (23.89)	26 (18.31)
Poor	14 (9.79)	11 (6.40)	11 (6.27)	9 (6.16)	15 (9.74)	12 (10.17)	10 (5.56)	8 (5.63)
Missing	17 (11.89)	14 (8.14)	13 (9.77)	15 (10.27)	19 (12.34)	8 (6.78)	18 (10.00)	14 (9.86)
Occupation								
Construction	7 (4.90)	5 (2.91)	4 (3.01)	9 (6.16)	8 (5.19)	6 (5.08)	6 (3.33)	5 (3.52)
Management/Professional	43 (30.07)	75 (43.60)	71 (53.38)	59 (40.41)	41 (26.62)	45 (38.14)	81 (45.00)	81 (57.04)
Military	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.68)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.70)

Production	30 (20.98)	18 (10.47)	11 (8.27)	16 (10.96)	31 (20.13)	14 (11.86)	20 (11.11)	10 (7.04)
Sales	19 (13.29)	23 (13.37)	17 (12.78)	20 (13.70)	18 (11.69)	21 (17.80)	23 (12.78)	17 (11.97)
Service	44 (30.77)	51 (29.65)	30 (22.56)	41 (28.08)	56 (36.36)	32 (27.12)	50 (27.78)	28 (19.72)
Education								
Less than high school education	46 (32.17)	37 (21.51)	24 (18.05)	29 (19.86)	49 (31.82)	25 (21.19)	43 (23.89)	19 (13.38)
High school grad (or equivalent)	34 (23.78)	38 (22.09)	24 (18.05)	24 (16.44)	41 (26.62)	35 (29.66)	31 (17.22)	13 (9.15)
Vocational school, trade school or college	63 (44.06)	97 (56.40)	85 (63.91)	92 (63.01)	64 (41.56)	58 (49.15)	105 (58.33)	110 (77.46)
Missing	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.68)	0 (0.00)	0 (0.00)	1 (0.56)	0 (0.00)
Diabetes	39 (27.27)	36 (20.93)	26 (19.55)	40 (27.40)	18 (25.35)	30 (25.42)	40 (22.22)	37 (26.06)
Hypertension	108 (75.52)	122 (70.93)	92 (69.17)	91 (62.33)	117 (75.97)	85 (72.03)	122 (67.78)	89 (62.68)
Physical activity								
Poor	89 (62.24)	84 (48.84)	64 (48.12)	76 (52.06)	95 (61.69)	62 (52.54)	90 (50.00)	66 (46.48)

Intermediate	39 (27.27)	54 (31.40)	49 (36.84)	50 (34.25)	42 (27.27)	40 (33.90)	59 (32.78)	51 (35.92)
Ideal	15 (10.49)	34 (19.77)	20 (15.04)	20 (13.70)	17 (11.04)	16 (13.56)	31 (17.22)	25 (17.61)
BMI (kg/m^2)	30.49 (5.19)	30.36 (5.16)	29.42 (4.15)	30.19 (6.08)	30.75 (6.09)			

Note: BMI, body mass index; *cf*PWV, carotid to femoral pulse wave velocity

Table 26. Adjusted Estimates for PD on cfPWV (N=594)

	Dependent Variable: cfPWV											
	MODEL 1	p-value	MODEL 2	p-value	MODEL 3	p-value	MODEL 4	p-value	MODEL 5	p-value	MODEL 6	p-value
	β		β		β		β		β		β	
Everyday[a]												
Q2	-1.01	0.009	-0.833	0.026	-0.843	0.024	-0.739	0.045	-0.726	0.040	-0.717	0.043
Q3	-0.762	0.062	-0.614	0.121	-0.660	0.096	-0.532	0.177	-0.418	0.268	-0.394	0.298
Q4	-0.19	0.633	0.146	0.708	0.139	0.723	0.188	0.627	0.287	0.439	0.340	0.369
R^2	0.015	0.029	0.076	<0.001	0.081	<0.001	0.105	<0.001	0.183	<0.001	0.184	<0.001
Lifetime[a]												
Q2	-0.451	0.277	-0.457	0.256	-0.527	0.193	-0.507	0.206	-0.423	0.271	-0.423	0.274
Q3	-0.754	0.043	-0.725	0.045	-0.754	0.037	-0.726	0.043	-0.552	0.109	-0.551	0.112
Q4	-0.847	0.032	-0.843	0.029	-0.854	0.027	-0.819	0.031	-0.611	0.095	-0.611	0.100
R^2	0.010	0.120	0.071	<0.001	0.075	<0.001	0.1	<0.001	0.175	<0.001	0.175	<0.001
Burden[a]												
Q2	-0.342	0.388	-0.400	0.299	-0.409	0.287	-0.383	0.313	-0.233	0.522	-0.233	0.523

Q3	-0.136	0.726	-0.170	0.651	-0.197	0.600	-0.085	0.819	-0.029	0.935	-0.023	0.950
Q4	-0.305	0.476	-0.619	0.140	-0.614	0.143	-0.675	0.103	-0.509	0.200	-0.500	0.217
R^2	0.002	0.819	0.065	<0.001	0.069	<0.001	0.097	<0.001	0.173	<0.001	0.173	<0.001
Stress from burden of discrimination[b]												
Moderately stressful	-0.630	0.055	-0.667	0.037	-0.659	0.039	-0.701	0.027	-0.731	0.016	-0.737	0.016
Very stressful	-0.600	0.139	-0.689	0.081	-0.670	0.089	-0.759	0.052	-0.780	0.037	-0.792	0.037
R^2	0.007	0.1374	0.069	<0.001	0.073	<0.001	0.101	<0.001	0.179	<0.001	0.179	<0.001
Attribution of everyday discrimination[c]												
Race/low	-0.828	0.114	-0.703	0.167	-0.779	0.127	-0.838	0.098	-0.719	0.138	-0.721	0.137
Race/high	-0.540	0.211	-0.300	0.477	-0.348	0.411	-0.320	0.579	-0.168	0.657	-0.151	0.710
Nonracial/low	-1.138	0.018	-1.045	0.025	-1.08	0.021	-0.936	0.044	-0.792	0.075	-0.784	0.078
Nonracial/high	-0.847	0.056	-0.603	0.431	-0.664	0.125	-0.628	0.142	-0.421	0.305	-0.407	0.325
R^2	0.011	0.1605	0.071	<0.001	0.076	<0.001	0.101	<0.001	0.176	<0.001	0.177	<0.001

Attribution of lifetime discrimination[c]												
Race/low	-0.608	0.232	-0.758	0.125	-0.762	0.123	-0.731	0.135	-0.547	0.244	-0.543	0.248
Race/high	-0.862	0.062	-0.978	0.029	-0.949	0.034	-0.924	0.037	-0.595	0.164	-0.589	0.171
Nonracial/low	-0.036	0.948	-0.06	0.911	-0.015	0.978	-0.074	0.888	0.175	0.731	0.179	0.725
Nonracial/high	-0.911	0.088	-0.806	0.119	-0.807	0.119	-0.804	0.116	-0.546	0.266	-0.538	0.280
R^2	0.011	0.157	0.074	<0.001	0.078	<0.001	0.103	<0.001	0.177	<0.001	0.177	<0.001

Model 1 is unadjusted. Model 2 is adjusted for biological sex and age. Model 3 is adjusted for Model 2 + BMI. Model 4 is adjusted for Model 3 + BPmeds & Diabetes. Model 5 is adjusted for Model 4 + MAP. Model 6 is adjusted for Model 5 + perceived stress.
Note: BMI, body mass index; cfPWV, carotid to femoral pulse wave velocity; BPmeds, blood pressure medications.
[a]Reference category: Q1; [b]Reference category: Not stressful; [c]Reference category: No discrimination

Table 27. Adjusted Estimates for Continuous PD on cfPWV (N=594)

	Dependent Variable: cfPWV											
	MODEL 1	p-value	MODEL 2	p-value	MODEL 3	p-value	MODEL 4	p-value	MODEL 5	p-value	MODEL 6	p-value
	β		β		β		β		β		β	
Everyday	0.011	0.938	0.132	0.340	0.142	0.303	0.163	0.235	0.176	0.18	0.192	0.152
R^2	0.000	0.938	0.063	<0.001	0.067	<0.001	0.094	<0.001	0.172	<0.001	0.173	<0.001
Lifetime	-0.298	0.033	-0.292	0.0322	-0.290	0.033	-0.288	0.033	-0.206	0.112	-0.205	0.119
R^2	0.008	0.033	0.068	<0.001	0.072	<0.001	0.099	<0.001	0.173	<0.001	0.173	<0.001
Burden	-0.106	0.448	-0.199	0.145	-0.200	0.143	-0.206	0.127	-0.179	0.166	-0.18	0.176
R^2	0.001	0.448	0.065	<0.001	0.069	<0.001	0.096	<0.001	0.172	<0.001	0.172	<0.001

Model 1 is unadjusted. Model 2 is adjusted for biological sex and age. Model 3 is adjusted for Model 2 + BMI. Model 4 is adjusted for Model 3 + BPmeds & Diabetes. Model 5 is adjusted for Model 4 + MAP. Model 6 is adjusted for Model 5 + perceived stress.
Note: BMI, body mass index; *cf*PWV, carotid to femoral pulse wave velocity; BPmeds, blood pressure medications.

CHAPTER 8: AGREEMENT, REPEATABILITY, AND RELIABILITY OF VICORDER, OMRON, VASERA ON MEASURES OF ARTERIAL STIFFNESS

Overview

Background: Adequately assessing cardiovascular disease risk is imperative as it is the one of the leading causes of mortality in the US. In particular, it is important to assess subclinical CVD risk. Arterial stiffness, measured as pulse wave velocity (PWV), is an ideal measure of subclinical CVD risk, as it has additional prognostic value compared to blood pressure. However, there are a variety of non-invasive devices available that seek to estimate PWV but use different techniques and algorithms. Therefore, it is essential that we determine how comparable these devices are, in particular, the OMRON, VaSera, and the VICORDER devices which have been or will be used to collect PWV as part of large population-based cohorts. Objectives: we evaluated the agreement and reliability of PWV taken by the VICORDER, the OMRON, and VaSera in generally healthy adults (18-84 years). Methods: 60 participants were recruited, of which 57 were included in the final sample. Participants reported to the lab on two occasions. We took measurements with the OMRON and VaSera devices sequentially at supine posture. Then, we took measures with the VICORDER and VaSera at a 25˚. Comparisons were made using intra-class correlation coefficient (ICC), limits of agreement (LoA), and root mean squared error (RMSE). Results: There was moderate to good agreement between the OMRON vs. VICORDER (ICC=0.82 [0.73, 0.91]), OMRON vs. VaSera (ICC=0.75 [0.63, 0.87]), VaSera vs. VICORDER (ICC=0.87 [0.82, 0.92]). However, there was evidence of small to significant bias based on the LoA for all comparisons. The RMSE was large for all comparisons. Conclusion:

There was moderate to good agreement for all devices. However, the evidence of bias suggests that measurements from the devices should not be directly compared.

Keywords: Agreement, PWV, JHS, HCHS/SOL, ARIC, arterial stiffness

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in the United States comprising 1 in every 4 deaths annually. CVD can be categorized as overt (e.g., having high blood pressure or coronary artery disease) or as subclinical CVD. Subclinical measures of CVD are the precursors of overt CVD and are often asymptomatic.[34] Arterial stiffness, marked by reduced elasticity in the arteries, has been shown to be predictive of overt CVD and have negative implications on central hemodynamics as well as myocardial afterload.[94] The most widely used and clinically relevant non-invasive measure of arterial stiffness is pulse wave velocity (PWV), otherwise known as the velocity of pressure waveforms as they propagate along an arterial segment. Carotid to femoral PWV is most commonly utilized measure and is an estimate of central arterial stiffness. CfPWV can be measured using specialized, non-invasive devices, and carries a prognostic value beyond that of blood pressure alone. These devices include but are not limited to the VICORDER, OMRON (VP-1000+), and the VaSera (VS-1500). The VICORDER and the VaSera devices use oscillometry (blood pressure cuffs) to obtain cfPWV values, whereas the OMRON uses applanation tonometry (pressure transducers placed over the skin).

All these devices seek to estimate cfPWV non-invasively but use different techniques and algorithms. Therefore, it is essential that we determine how comparable these devices are. In particular, the OMRON and the VICORDER devices have been or will be used to collect PWV as part of the Jackson Heart Study (JHS), the Atherosclerosis Risk in Communities Study (ARIC) cohort, and the Hispanic Community Health Study/Study of Latinos (HCHS/SOL).

Furthermore, even though the VICORDER has been compared to other commonly used devices,[95–100] the repeatability of the VICORDER has not been sufficiently examined. Additionally, it is unknown how the VaSera device, a more recent oscillometric PWV device, compares to these two devices. The VaSera device uses a similar PWV measurement to cfPWV, heart-thigh PWV (htPWV), a validated and repeatable measure that does not require the placement of transducers and works by calculating the pulse wave velocity from the ascending aorta to femoral artery. If this method is comparable to the other devices, it could indicate a more user-friendly alternative to obtain PWV.

Therefore, to address these gaps in knowledge, we will evaluate the agreement of PWV taken by the VICORDER, the OMRON, and VaSera. We will also evaluate the reliability of the VICORDER and VaSera devices. Moreover, we seek to assess whether these three devices similarly comparable results in generally healthy adults (18-84 years). To our understanding, this will be the first study to evaluate agreement of PWV measures in all three devices.

Methodology

This study is reported in accordance with CONSORT guidelines. Ethical approval was obtained from the University of North Carolina at Chapel Hill on December 22, 2020**.**

Participants

Sixty generally healthy males and females (18-84 years) were recruited to participate in a 2-visit agreement, repeatability, and reliability study. We had initially targeted 100 healthy individuals (half in NC and half in MS). However, due to the pandemic, we had to adjust our sample size as we were unable to recruit participants in Jackson, MS. A wide age range was used to obtain a representative sample of individuals that may benefit from an arterial stiffness assessment to determine their cardiovascular disease risk. Participants were recruited from the research triangle in Raleigh-Durham, NC mostly from the University of North Carolina at

Chapel Hill campus community. To ensure we had adequate participant recruitment, we used various modes of recruitment including class recruitment, flyers, social media, and listservs. In addition to various methods of recruitment, we also continually refined our recruitment materials to ensure that they were representative of the population of interest. Exclusion criteria consisted of pregnancy, current tobacco use, a history of arrhythmias (non-medically induced), and cancer or cancer-related illnesses.

Experimental Design

This study was a 2-visit agreement, repeatability, and reliability study evaluating three devices (the OMRON, VICORDER, and VaSera) at two different postures: supine and at a 25˚ with device placement randomized to either the left or right side of the body. We decided on this protocol following extensive piloting and feasibility of measurements. Based on extensive piloting, we determined that measurements taken at 25˚ with the OMRON were not feasible due to compression of the femoral artery. The VICORDER device measures were conducted only at a 25˚ to limit jugular vein interference of the carotid cuff. Concerning device order, the OMRON device was the most user and participant-dependent measure compared to other devices. As a result, device order was standardized to begin with the OMRON to minimize participant and researcher burden. Concerning device placement, we randomized the OMRON and VaSera to either the right or left side of the body. Since the OMRON and VICORDER were only feasible at one posture, the OMRON and VICORDER were assigned the same randomization side. A summary of the protocol is provided below (Figure 14). Since the starting posture and device order were not randomized, there is a potential for carry-over effects.

Pre-Experimental Control

Participants were instructed to arrive for testing visit between 6:00 and 10:00 am having refrained from consuming any alcohol, caffeine, or vigorous exercise for 12 hours prior to their

visit and fasted for at least 4 hours. To ensure visit to visit consistency, participants taking any medication were instructed to take them prior to both visits.

Same-Day Familiarization

Participants reported to the lab to review study documentation and complete their informed consent. Participants were then familiarized with the study equipment setup. After study documentation and familiarization were completed, height and weight were obtained, and participants were instructed to void their bladder prior to beginning the experimental visit.

Experimental Visit

The experimental visit consisted of at least 20 minutes of supine rest on a three-section table followed by PWV measurements. Measurements were taken with one device at a time, starting in a supine posture and beginning with the OMRON. After measures were taken with both the OMRON and VaSera at a supine posture, the OMRON was replaced with the VICORDER, distances taken, and the participants were passively moved to a 25˚ using a three-section table or a wooden wedge. If a wedge or three-section table was used for a participant's first visit, it was also used for their second visit to ensure adequate consistency. Then, measurements were taken with the VICORDER and VaSera. All measures were taken in triplicate with a minute in between. The researchers used a standardized script to indicate when measurements would be taken and to provide instructions for maintaining still and breathing normally prior to all measurements.

Experimental Measures

Primary Outcome: Pulse Wave Velocity Measurement

PWV was assessed using three different devices.

Device 1: VICORDER (SMT Medical)

The VICORDER (SMT Medical) device was used to measure cfPWV. PWV (m/s) is calculated by dividing arterial path length (D) by the pulse transit time (TT) between a proximal cuff and a distal arterial cuff. Measurements for D were acquired by recording the straight-line distance between the edge of the proximal and distal cuffs, and the distance from the suprasternal notch to carotid cuff was subtracted. Standard Hokanson (Vellevue, WA) cuffs were placed at the carotid and femoral artery and inflated simultaneously using volume displacement. The carotid cuff consisted of a small balloon, which was inflated to a sub-diastolic pressure (~50 mmHg). TT was calculated by the VICORDER software's proprietary algorithm that measures the time between the foot of the proximal pressure waveform to the foot of the distal pressure waveform, using a maximum derivative approach.[101]

Device 2: OMRON® VP 1000 (Colin Co., Ltd., Tokyo, Japan)

The OMRON (VP 1000+) (Colin Co., Ltd., Tokyo, Japan) device was used to measure cfPWV. CfPWV (m/s) was calculated by dividing arterial path length (D) by the TT between a proximal tonometer and a distal tonometer. Measurements for D were acquired by taking the distance from the carotid pulse to the femoral pulse and subtracting the carotid to suprasternal notch distance. The proximal and distal tonometers were placed at the carotid pulse and femoral pulse, respectively. Transit time was calculated by the OMRON software's proprietary algorithm that measures the time between the foot of the proximal pressure waveform to the foot of the distal pressure waveforms captured simultaneously using applanation tonometry.

Device 3: VaSera VS 1500 (Fukuda Denshi Co., Ltd., Tokyo, Japan)

The VaSera (Fukuda Denshi Co., Ltd., Tokyo, Japan) device was used to measure PWV. PWV was quantified as Heart-thigh PWV (htPWV), a validated and repeatable measure that does

not require the placement of transducers. HtPWV is calculated by the pulse wave velocity from the ascending aorta to femoral artery and the brachial artery blood pressure. The following equation is used by the device to calculate htPWV: $2\rho \ln(Psys / Pdia) / (Psys – Pdia) (L1/T1)2$, where ρ is the blood density, Psys is the SBP of the upper arm, Pdia is the DBP of the upper arm, L1 is the length between the heart and the femoral artery cuff, and T1 is the time of the pressure wave to travel between the aorta and the femoral artery cuff. Since measurements using the VaSera were made unilaterally, L1 distance, used for the calculation of transit time, was standardized by measuring from the 2nd rib where a phonocardiogram was placed and the femoral pulse. Transit time was measured as the time delay between the proximal and distal 'foot' waveforms, i.e., the commencement of the sharp systolic upstroke, using a diastolic minimum method.[101] The device obtains time delays between the aortic and femoral arteries using heart sounds obtained from the phonocardiogram and ECG sensors identifying the R-wave during the cardiac cycle.

Randomization

There was no allocation to treatment groups as this was an observational study. However, devices were randomized to either the right or left side of the body. Random allocation sequence was obtained using a random number generator and 61 sets of 2 unique numbers generated from a number range of 1-2 (www.randomizer.org). Random allocation sequence was assigned prior to the visit based on scheduling order.

Quality Control

For our outcome of interest, PWV, all measurement and analysis were conducted by a single observer. Waveforms were inspected during data collection, and within device quality control measures noted to ensure good quality.

Sample Size

Sample size was determined using nQuery Advanced 8.2 (nQuery, San Diego). Obtaining two observations per person (i.e., two visits), a sample size of 50 participants, we had 80% power to detect an ICC of 0.9 vs. ICC of 0.95 for an a of 0.05.

Data Management and Statistical Analyses

Agreement Measures

Five measures of agreement were used between all three devices: (i) intra-class correlation coefficient (ICC) from a mixed model, (ii) Bland-Altman and line of identity plots, (iii) limits of agreement calculated from a mixed model, (iv) relative mean standard error from a mixed model (RMSE), and v) the percentage of the RMSE (%RMSE). Although there is no universal criterion for ICC and assessing agreement, in general, estimates of <0.5, 0.5-0.75, 0.75-0.9, and >0.9 indicate poor, moderate, good, and excellent agreement, respectively.[69] Therefore, we will accept the outcome as having good agreement if the lower limit of the 95% confidence interval (95% CI) for the measure exceeds 0.75 for measures of PWV. The linear mixed models were generated according to the protocol outlined by Parker et al.[63] using the clinically acceptable difference (CAD) of 1 m/s for PWV. For the mixed model, the PWV values were specified as the dependent variable nested within participant and activity (visit and posture) and the device was set as fixed factor. The following random effects were specified to calculate the following variance components: intercept-participant, intercept-visit, intercept-posture, device-participant, device-visit, device-posture, and residual ($\sigma 2\mathcal{E}$). For the paired comparisons (OMRON vs. VICORDER, OMRON vs. VaSera, VaSera vs. VICORDER, and VaSera-supine vs. VaSera-25˚), PWV measures from the referent device for each comparison were specified as the dependent variable nested within participant and visit, and the device was set as a fixed factor with random effect of intercept-participant. Q-Q plots of residuals and random effects were

visually inspected to verify model assumptions were met. The RMSE was calculated using residuals generated from the above-mentioned linear mixed model. The residuals from the model were squared and summed (MSE). Then, the MSE was square rooted to generate the RMSE. The RMSE was then divided by the mean of the criterion device and multiplied by 100 to obtain a percentage (%RMSE). A <0.20 will be considered a trivial difference, 0.2-0.6 small, 0.6-1.2 moderate, 1.2-2.0 large and >2.0 very large difference.[66] Bland-Altman plots and regression plots were generated to permit visual analysis of the uniformity of error over the range of participant measurement values.

Harmonizing Data from Devices

To ensure an adequate comparison, between device PWV values for the non-referent device were adjusted using a standard regression calibration approach.[102,103] The adjusted values were entered into the model replacing the uncorrected values of the test device and analysis re-run.

Repeatability and Reliability

To evaluate between-day reliability, we estimated the intra-class correlation coefficient (ICC) and the minimal detectable change (MDC) along with corresponding 95% confidence intervals (95% CI). The ICC estimates and their 95% CI intervals were estimated using a single-rating, absolute agreement, 2-way mixed-effects model in R. A mixed model was used as it is unaffected by sample size.[68] MDC was calculated using the formula: 1.96*(Standard Error of Measurement)*$\sqrt{2}$.[66] Although there is no universal criterion, in general, ICC estimates of < 0.5, 0.5-0.75, 0.75-0.9 and > 0.9 indicate poor, moderate, good and excellent reliability, respectively.[69] We will accept an outcome as reliable if the lower limit of the 95% CI for ICC exceeds 0.75.

Covariates

In addition to the major measurement considerations, we also adjusted for covariates. We adjusted for biological sex (female/male), age (continuous), body mass index (continuous, kg/m2), and mean arterial pressure (MAP, calculated continuous variable, 1/3Systolic Blood Pressure + 2/3Diastolic Blood Pressure). The rationale for adjusting consists of minimizing confounding and bias since all these factors influence PWV.[92]

Data Management

All data were entered into a secure web platform for developing and managing databases (REDCap). Data for each visit was entered manually by one researcher and verified independently by a second researcher to ensure data quality. Range validation was enabled for entered fields to ensure that values entered were feasible. Values from previous visit were piped into the data collection form for the second visit to ensure that measurements were consistent. The primary researcher made annotations and diagrams using anatomical landmarks to ensure consistency between visits. Missing data were excluded from the analyses.

Subgroups

Due to the small sample size, analyses by racial/ethnic category were not feasible. However, analyses by participant age and sex will be presented below.

Results

Participants

Participant characteristics are described in Table 28. Sixty participants were recruited. Of the sixty participants, two were withdrawn due to measurement feasibility concerns, and one completed only one visit due to scheduling problems, to comprise a sample of fifty-seven participants with completed visit 1 and visit 2. Participants self-identified as non-Hispanic White (n=38), African American (n=2), White-Hispanic (n=4), Asian (n=3), Mixed (black, white, &

brown) (n=1), and 12 did not provide this information. For the agreement analyses, we used all participants with data from visit 1. For the reliability analyses, we included only those with data for both visit 1 and visit 2. Sample size for the analyses varied by paired comparison due to the available data from the OMRON. From the sample, 27 individuals were randomized to left-sided measurements and 30 to right-sided measurements with the VaSera, indicating successful randomization. Participants were actively recruited from January 2021 to February 2023. Mean follow-up between visits was at least 2 weeks.

Among our sample, 9 individuals self-reported having high blood pressure (Table 28). Of these, 5 reported taking anti-hypertensive medications (i.e., lisonopril/hctz). Three reported either pre-hypertension or borderline hypertension. One of them indicated that the hypertensive event was during pregnancy 25 years prior and also suffered from Gitelman syndrome.

Primary Outcome: Agreement of PWV

Overall, our findings show 79.5% (OMRON=38.2%, VaSera=22.2%, VICORDER=19.1%) of the total variance in PWV is due to between-participant variation, 16.3% due to posture differences (OMRON=7.77%, VaSera=4.78%, VICORDER=3.71%), 1.6% due to visit differences (OMRON=0.52%, VaSera=0.02%, VICORDER=1.04%) , and 2.6% due to random error (Table 29). To understand this variance, the paired device comparisons will be described below.

OMRON vs. VICORDER

When comparing the OMRON to the VICORDER, mean PWV values were similar between devices (8.34 [7.83, 8.85] and 8.43 [8.09, 8.78] m/s, respectively). There was moderate to good agreement as determined by the ICC (0.82 [0.73, 0.91]). When evaluating the limits of agreement, there was a small mean bias (-0.14 [-2.68, 2.41] m/s) as compared to our CAD of 1 m/s. However, the confidence intervals were wide, which is consistent with results from the line

of identity plot. Visual inspection of the line of identity plot indicated there was bias from the VICORDER to overestimate PWV at the low values (<8 m/s) and underestimate at the high PWV (>10 m/s) values (Figure 15). The RMSE (2.13 [1.77, 2.48] m/s) and %RMSE were very large compared to our CAD of 1 m/s. On average, observed values deviated 25.53% from the regression line. Additionally, we also adjusted for MAP. Agreement as described by the ICC decreased (0.75 [0.63,0.87]) and the %RMSE increased slightly (26.99 [22.53, 31.45] %). Overall, there seems to be moderate agreement between the OMRON and VICORDER for the uncorrected measurements.

OMRON vs. VaSera

When comparing the OMRON to the VaSera, mean PWV values were different between devices (8.36 [7.84, 8.87] and 6.06 [5.71, 6.41] m/s, respectively). There was moderate to good agreement as determined by the ICC (0.75 [0.63, 0.87]). When evaluating the limits of agreement, there was significant mean bias (2.24 [-0.02, 4.50] m/s) as compared to our CAD of 1m/s and the confidence intervals were wide. Visual inspection of the line of identity plot indicated the VaSera consistently underestimated PWV values (Figure 16). Further, the RMSE (2.84 [2.37, 3.30] m/s) and %RMSE are very large compared to our CAD of 1 m/s. On average, observed values deviated 33.93% from the regression line. When we adjusted for MAP, the ICC decreased slightly (0.74 [0.61,0.86]) and the %RMSE (34.60 [28.71, 40.48] %) increased slightly. Overall, there seems to be moderate agreement between the OMRON and VaSera for the uncorrected measurements.

VaSera vs. VICORDER

When comparing the VaSera to the VICORDER, mean PWV values were different between devices (8.03 [7.77, 8.29] and 6.27 [6.02, 6.53] m/s, respectively). There was good agreement as determined by the ICC (0.87 [0.82, 0.92]). When evaluating the limits of

agreement there was significant mean bias (-1.75 [-3.62, 0.13]) as compared to our CAD of 1 m/s, and the confidence intervals were wide which is consistent with results from the line of identity plot. Visual inspection of the line of identity plot indicated the VICORDER measurements overestimate PWV consistently (Figure 17). The RMSE (2.59 [2.38, 2.81] m/s) and %RMSE were large compared to the CAD, with observed values deviating 41.29% from the regression line, on average. When adjusted for MAP, the ICC (0.85 [0.79, 0.91]) and the %RMSE (39.49 [36.53, 42.46] %) decreased slightly. Overall, there seems to be moderate agreement between the VaSera and VICORDER for the uncorrected measurements.

VaSera-supine vs. VaSera -25˚

When comparing the VaSera at a supine and 25˚ posture, mean PWV values were different between devices (5.76 [5.50, 6.03] and 6.27 [6.02, 6.53] m/s, respectively). There was poor to moderate agreement as determined by the ICC (0.49 [0.34, 0.66]). When evaluating the limits of agreement there was moderate mean bias (-0.51 [-1.43, 0.41] m/s) as compared to our CAD of 1 m/s and the confidence intervals were wide, which is consistent with results from the line of identity plot. Visual inspection of the line of identity plot indicates the VaSera at a 25˚ consistently overestimates PWV (Figure 18). The RMSE (2.95 [2.73, 3.18] m/s) and %RMSE large in comparison to the CAD, with observed values were 51.26% lower than the regression line, on average. When we adjusted for MAP, the ICC increased slightly (0.49 [0.33, 0.66]) and the %RMSE (50.58 [46.70, 54.46] %) decreased slightly. Overall, there seems to be poor agreement between the VaSera at both postures for the uncorrected measurements.

Secondary Outcome: Harmonizing the data

OMRON vs. VICORDER

To account for some variation across devices, we adjusted the VICORDER PWV values using a regression calibration approach. Most of the agreement values stayed the same (Table 30), except mean bias, which decreased slightly (-0.01 [-2.60, 2.59] m/s).

OMRON vs. VaSera

Likewise, when we adjusted the VaSera values using a regression calibration approach, most of the agreement values stayed the same (Table 31), except the mean bias decreased (-0.01 [-2.15, 2.13] m/s) and the %RMSE (35.19 [29.39, 41.00] %) increased slightly.

VaSera vs. VICORDER

For the adjusted models, most of the agreement values stayed the same (Table 32), except mean bias which decreased (0.02 [-1.86, 1.91] m/s) and the %RMSE increased slightly (41.40 [37.98, 44.82] %).

VaSera-supine vs. VaSera -25˚

When the VaSera 25˚ was adjusted using a regression calibration approach, most of the agreement values were unchanged (Table 33), except the mean bias decreased slightly (0.00 [-0.92, 0.92] m/s) and the ICC increased slightly (0.48 [0.33, 0.66]).

Secondary Outcome: Reliability of Devices

All devices were reliable between visits (Table 34).

OMRON

Mean values for visit 1 and visit 2 were 8.59 (± 2.34) and 8.46 (± 2.08) m/s. Visual inspection the line of identity plot and Bland-Altman plot did not indicate any systemic bias. The ICC (0.95 [0.91, 0.97]) indicated excellent between-day reliability. The MDC was a 0.25 [0.18,

0.33] m/s difference, less than our CAD of 1 m/s. Most of the variance was due to between-participant differences (95%) with remaining variance due to random error (5%).

VICORDER

Mean values for visit 1 and visit 2 were 8.03 (± 1.40) and 8.06 (± 1.40) m/s. Visual inspection the line of identity plot and Bland-Altman plot did not indicate any systemic bias. The ICC (0.90 [0.85, 0.94]) indicated excellent between-day reliability. The MDC was a 0.16 [0.13, 0.20] m/s difference, less than our CAD of 1 m/s. Most of the variance was due to between-participant differences (90%) with remaining variance due to random error (10%).

VaSera

Mean values for visit 1 and visit 2 were 6.07 (± 1.41) and 6.00 (± 1.45). Visual inspection the line of identity plot and Bland-Altman did not indicate any systematic bias. The ICC indicated excellent between-day reliability (0.95 [0.94, 0.97]). The MDC was a 0.08 [0.07, 0.09] m/s difference, less than our CAD of 1 m/s. Most of the variance was due to individual differences (95%) and minor due to random error (5%).

Ancillary Analyses

In addition to the analyses above, it was important to determine the impact of sex and age on our agreement results. The results, including sex and age in the mixed models adjusted for MAP, are presented below. We evaluated the effect of BMI, but it did have any impact on the values reported below.

OMRON vs. VICORDER

Compared to the model adjusted for MAP, adding sex had no effect on the ICC (0.75 [0.63, 0.87]), but increased both the RMSE (2.29 [1.90, 2.69] m/s) and %RMSE (27.51 [22.81, 32.21] %) slightly; both still large compared to the CAD. Similarly, including both age and sex had no effect on the ICC, but both the RMSE (2.07 [1.73, 2.41] m/s) and RSME% (24.87 [20.80,

28.94] %) decreased and were lower than the uncorrected model values, indicating that sex and age may be accounting for some error.

OMRON vs. VaSera

Compared to the model adjusted for MAP, adding sex had no effect on the ICC (0.74 [0.61, 0.86]), but decreased both the RMSE (2.82 [2.34, 3.30] m/s) and %RMSE (35.00 [29.05, 40.96] %); both still large compared to the CAD. Similarly, including both age and sex the ICC (0.77 [0.66, 0.88]) increased and both the RMSE (2.47 [2.34, 3.30] m/s) and RSME% (30.69 [29.05, 40.96] %) decreased and were lower than the uncorrected model values.

VaSera vs. VICORDER

Compared to the model adjusted for MAP, adding sex had no effect on the ICC (0.85 [0.79, 0.91]), but slightly decreased both the RMSE (2.46 [2.02, 2.89] m/s) and %RMSE (39.15 [32.16, 46.13] %); both are still large compared to the CAD. Including both age and sex decreased the ICC (0.76 [0.67, 0.85]), the RMSE (2.22 [2.34, 3.30] m/s), and the RSME% (35.40 [29.15, 41.64] %).

VaSera-supine vs. VaSera-25˚

Compared to the model adjusted for MAP, adding sex slightly decreased the ICC (0.47 [0.31, 0.64]), but slightly increased both the RMSE (2.95 [2.76, 3.15] m/s) and %RMSE (51.23 [47.83, 54.63] %); both are still large compared to the CAD. Including both age and sex had no effect on the ICC, but decreased the RMSE (2.62 [2.43, 2.82] m/s) and RSME% (45.51 [42.11, 48.91] %).

Discussion

The purpose of this study was to evaluate the agreement of PWV measures taken by the VICORDER, the OMRON (VP-1000), and the VaSera (VS-1500) and determine the reliability of the devices. Moreover, we wanted to assess whether these three devices produced comparable

results in generally healthy adults (18-84 years). Our findings indicate that overall, most of the variance in our results was due to between-participant differences (79.5% [OMRON=38.2%, VaSera= 19.1%, and VICORDER=22.2%]) and less variation due to posture (16.3% [OMRON=7.77%, VaSera= 4.78%, and VICORDER=3.71%]), visit (1.6% [OMRON=0.52%, VaSera= 0.02%, and VICORDER=1.04%]), and random error (2.6%). To understand this variance, we evaluated the different paired device comparisons. There was moderate to good agreement for the OMRON vs. VICORDER, OMRON vs. VaSera, VaSera vs. VICORDER, but poor to moderate agreement for the VaSera-supine vs. VaSera-25˚ according to the ICC values. There was evidence of small mean bias for the OMRON vs. VICORDER, and for the VaSera-supine vs. VaSera-25˚, and significant mean bias for the OMRON vs. VaSera and VaSera vs. VICORDER comparisons. All comparisons had large RMSE values with reference to our CAD of 1 m/s. Generally, adjustment for MAP marginally reduced the ICC and changed the RMSE and %RMSE for all comparisons, except for the VaSera-supine vs. VaSera-25˚ where it marginally improved. With regards to paired comparisons, correction with the regression calibration approach did not change or marginally reduced the ICC. The calibration approach decreased bias as measured by limits of agreement, but either had no effect on or marginally increased the %RMSE. Finally, adjustment for sex and age, for the uncorrected data had no impact on the ICC but did reduce the RMSE and %RMSE. With regards to the reliability and repeatability of the VaSera and VICORDER, both showed excellent between-day reliability and repeatability. We also analyzed the OMRON repeatability to ensure consistency with previously established literature on the device, and it had excellent between-day reliability as well.

Limitations and Strengths

Although we tried to develop a rigorous protocol, there are some limitations of this study to consider. Sample size varied by paired comparisons in part due to the reliance on user

proficiency and individual dependent challenges with the OMRON device. Only individuals with a strong pulse that met the pressure threshold for the OMRON would have a PWV value. To account for the potential influence of higher blood pressure-dependent changes in PWV, and minimize the potential bias for individuals with high blood pressures, we adjusted for MAP to try to account for potential confounding factors. However, the device's ease of use could still have some residual bias. Since the device order and posture were unable to be randomized due to lack of feasibility, there is a potential for carry-over effects. Yet, we rigorously set-up our study design to minimize any additional sources of bias including randomizing side of the body at which we placed the devices accounting for potential left or right sided differences in measurements. Additionally, device measurement distance specifications differed slightly, with the VaSera distance differing the most from the OMRON and VICORDER, with measurements taken from the 2nd rib to the femoral pulse, and from the femoral pulse to the middle of femoral cuff. The regression calibration approach we used accounted for some of the differences due to the path length and use of different algorithms (derivative maximum or diastolic difference method).[101] Further, we actively recruited using a variety of methods, however, our sample is not representative of the diversity in the wider US population, which may affect the generalizability of our results to certain racial/ethnic groups. Yet, the sample was diverse with regard to participants' age and had a similar percentage of both sexes. Further, we were sufficiently powered to evaluate the changes in our outcome.

Comparison to the Literature

Overall, there was moderate to good agreement for all the paired comparisons except when comparing the VaSera-supine to VaSera-25˚. These results are consistent with the existing literature on these devices. Below we will describe how our findings relate to the existing literature.

When evaluating the uncorrected comparisons between the OMRON and VICORDER, the means were similar. These findings contrast with existing literature comparing oscillometric methods to applanation tonometry.[97,99,104] When comparing the VICORDER to the SphygmoCor device, Hickson and colleagues found that using the subtraction method for the distance calculation, the VICORDER underestimated PWV values by 1.6 ± 1.6 m/s. Interestingly, our results are similar in our SphygmoCor to the VICORDER comparison using the manufacturer distances both devices, where the means were similar between devices, but the VICORDER underestimating PWV>10 m/s. Similarly, both Butlin et al.[104] and Ellins and colleagues[99] found the VICORDER underestimated PWV values compared to the SphygmoCor when using the manufacturer-recommended distances. A potential explanation for the discrepancy between our results and those previously examined could be due to the differences in sample size for the paired comparisons in this study. As previously mentioned, of the three devices, the OMRON measurements were only obtained in a subset of the sample (n=33). OMRON measures were only obtained in participants whose pulse met the pressure threshold for the OMRON, which could have unintentionally excluded individuals with weaker pulses and may be influencing our results.

Concerning the uncorrected comparison between the OMRON and VaSera, the OMRON had higher mean values, which is consistent with previous literature.[97,104,105] It has been previously found that oscillometric measurements including a femoral cuff tend to underestimate PWV results, potentially due to the longer femoral segment included when using a femoral cuff below the femoral pulse.[97,106] Our values are also consistent with the findings from Fico et al. that indicated a mean difference between values of 0.14±1.25, with the OMRON having higher mean values compared with the VaSera.[105] Additionally, Fico and colleagues found there was a

significant linear association between measures from the two devices (r=0.68) supported by their Bland-Altman analyses. For this study, we found there was an even stronger significant correlation between devices at (0.86 [0.71, 0.91]). Similarly, yet more pronounced than Fico et al.'s findings, we saw a consistent systematic deviation from the line of identity with the VaSera consistently underestimating PWV values, which increased towards the more extreme PWV values.

Further, when considering the comparisons between the VaSera and VICORDER, there was moderate to good agreement between the devices, however, the VICORDER consistently overestimated PWV values. To our knowledge, the VaSera has only been compared against tonometric devices (OMRON and SphygmoCor),[105,107] this is the first study comparing it against an oscillometric device. Our findings are consistent with the previous comparisons, indicating that the VaSera yielded lower PWV values in comparison. However, we would have expected the values between the VaSera and VICORDER to be similar since both devices use oscillometry. A potential explanation could be that the path length and wave detection algorithm used for determining PWV values are contributing to the seen differences between devices, as has been previously shown.[108] The path length used by the VaSera includes part of the ascending aorta, which is more elastic leading faster transit times, and, consequently, lower PWV values. It could also be due to the measurement site, considering the VaSera uses a transfer function to estimate the PWV value at the level of the heart using a brachial cuff, and anatomical differences between the neck and arm could also be contributing. The VICORDER uses the maximum derivative approach, whereas the VaSera uses the diastolic minimum approach, which could contribute to comparison bias. Additionally, another factor to consider is the importance of posture. Per device recommendations and physiologic implications, the VICORDER cannot be

taken at a completely supine posture. For this study, we standardized the measures at a 25˚. However, the VaSera was validated at a supine posture.[109] Since the VaSera was not intended to be taken at a 25˚, we expected there to be a discrepancy in values. Yet, our findings suggest that there is still moderate to good agreement between devices, even though there is considerable bias with limits of agreement greater than our CAD, even after adjustment.

When evaluating the effect of posture by comparing the VaSera-supine vs. VaSera-25˚, our findings were consistent with the existing literature.[110–112] Previously, Maliha and Townsend[110] found the VaSera device ankle pressures and cardio-ankle vascular index measures were significantly higher when individuals were placed in a reverse Trendelenburg position (7˚) with their head elevated relative to the horizontal and ankles are lower compared to a supine posture. Similarly, Zwain and colleagues[112] saw a systemic increase at 30˚ and 60˚ compared to supine. Schroeder and colleagues saw an increase cardio-ankle vascular index at a 45˚ and 72˚ compared to supine. Posture had a significant impact as evidenced by a moderate agreement (ICC 0.49 [0.34, 0.66]).

Further, even though there was moderate to good agreement between devices, there was a bias present of more than the CAD of 1 m/s, associated with the risk of CVD. The limits of agreement within our sample for the paired comparisons (excluding the postural comparison for the VaSera) all had confidence limits greater than the CAD of 1 m/s. This means that based on these comparisons, we wouldn't be able to detect a clinically significant difference between devices. This remained true even after adjusting using the regression calibration approach. Therefore, with regard to harmonizing data, careful consideration of the differences between devices should be taken, and alternatives to account for this bias.

With regards to reliability, all devices had excellent between-day reliability. Compared to previous studies, our findings indicate better reliability for the OMRON (0.95 [0.91, 0.97] than those previously reported.[113] Meyer et al. found that there was moderate reliability for the OMRON single cfPWV measures with an ICC of 0.70 [0.59, 0.81].[113] This discrepancy between our study and Meyer et al.[113] could be due to the fact they had multiple sites and raters, introducing additional variation into the measurements. They also only evaluated single cfPWV measures not the average of the closest two cfPWV measures for each device. VaSera and VICORDER between-day reliability was consistent with previously reported values.[96,107]

Implications

This study estimates the level of agreement between three validated and commonly used PWV devices. From this study, we learned that there is moderate to good agreement between the different devices, in particular the OMRON and VICORDER. However, although there is moderate to good agreement, there is still considerable bias when comparing devices. This suggests although these devices are commonly used, they may not be directly interchangeable. Additionally, understanding the level of agreement could be a useful first step to harmonizing the existing data PWV from multiple populations, including population-based studies like the JHS, ARIC, HCHS/SOL, and Multi-Ethnic Study of Atherosclerosis. The harmonization of PWV data would contribute to our understanding of cardiovascular risk accrual across the lifespan in diverse populations and allow us to properly ascertain CVD risk across the lifespan.

Conclusions

In summary, there was moderate to good agreement between PWV values from the VICORDER, the OMRON (VP-1000), and the VaSera (VS-1500) and all devices had excellent between-day reliability. Next steps will be to harmonize PWV data from studies that use different devices.

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Tables and Figures

Figures

Tables

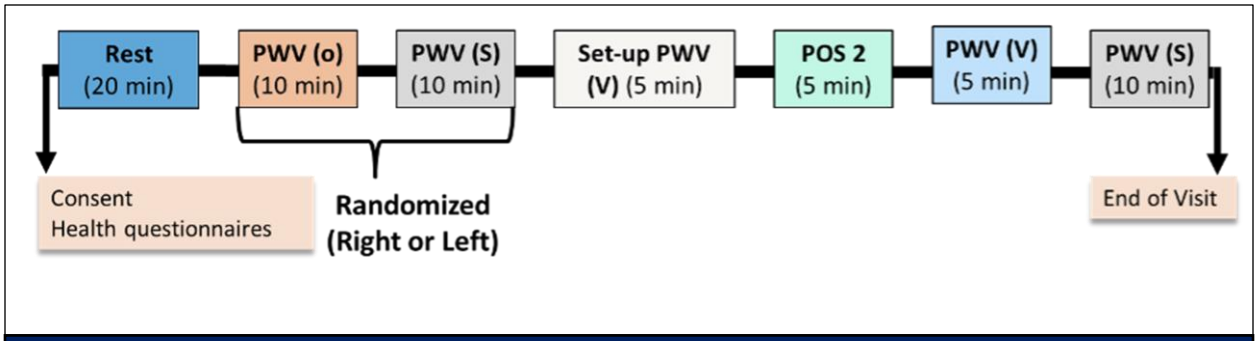

Figure 14. A visual representation of the experimental protocol.
Abbreviations: PWV (o), Pulse wave velocity with OMRON (VP-1000); PWV (S), Pulse wave velocity with VaSera (VS-1500); POS 2, posture 2; PWV (V), Pulse wave velocity with Vicorder. Pulse wave velocity measurements include blood pressure, ECG, phonocardiogram recordings and carotid-femoral measurements.

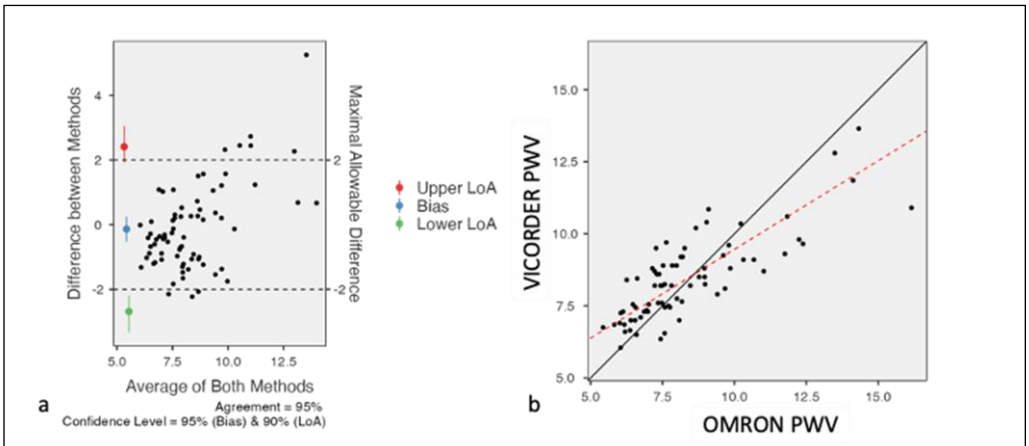

Figure 15. OMRON vs. VICORDER agreement. (a) Bland-Altman plot (b) Line of identity

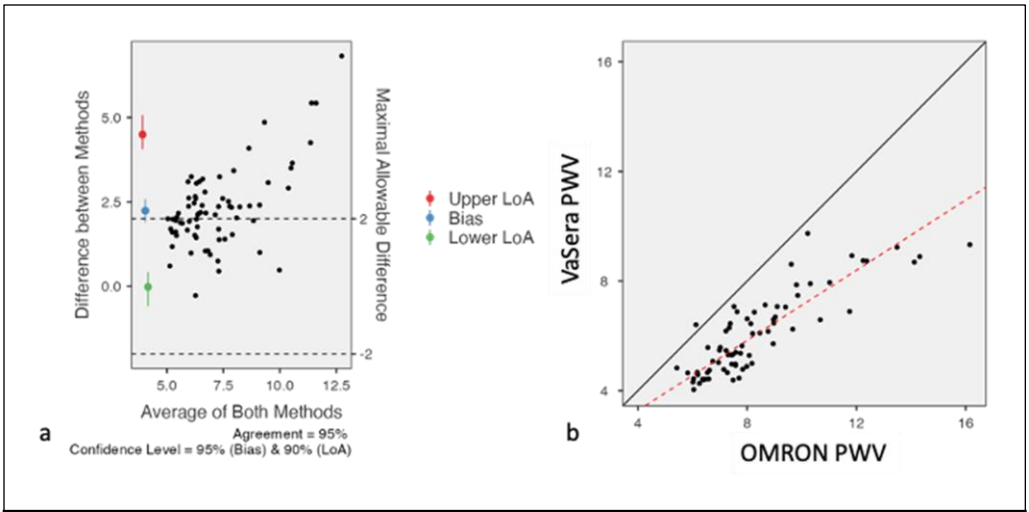

Figure 16. OMRON vs. VaSera agreement. (a) Bland-Altman plot (b) Line of identity

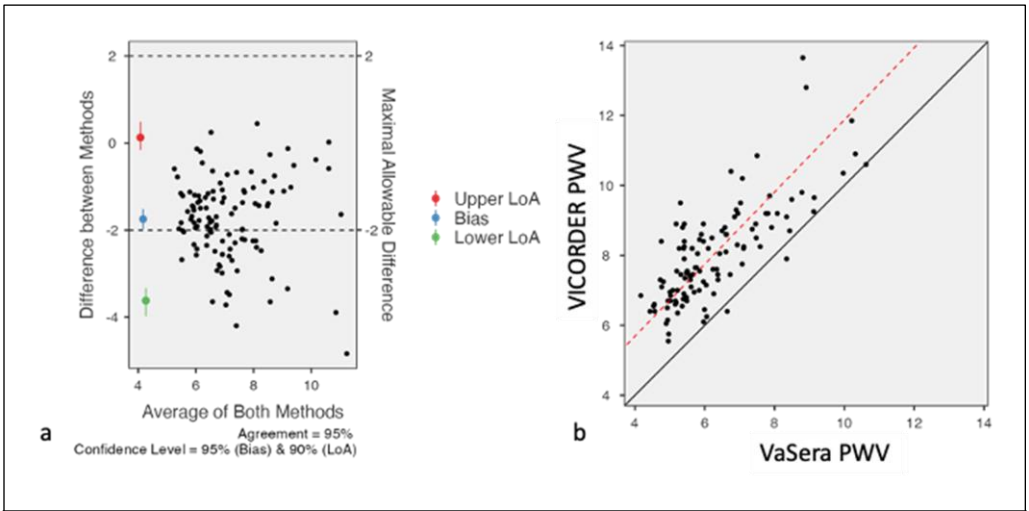

Figure 17. VaSera vs. VICORDER agreement. (a) Bland-Altman plot (b) Line of identity

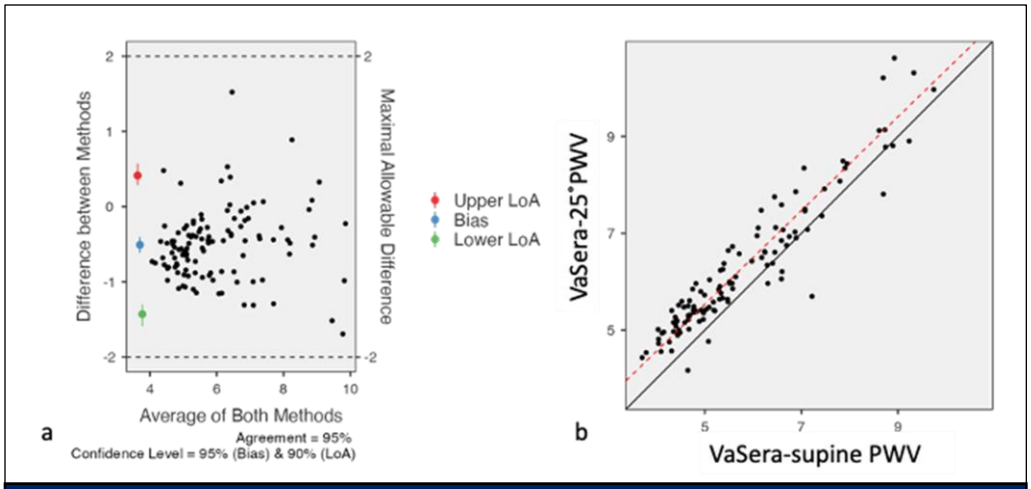

Figure 18. VaSera-supine vs. VaSera-25˚ agreement. (a) Bland-Altman plot (b) Line of identity

Table 28. Participant Characteristics

Variable	N	Mean or %	SD
Age (years)	58	40.6	19.0
BMI (kg/m^2)	58	24.5	3.8
Weight (kg)	58	70.2	13.2
Height (cm)	58	169.0	8.1
Female	58	55%	
Hispanic ethnicity	58	7.0%	
Race	58		
White	58	65.0%	
Black or African American	58	3.3%	
Asian	58	5.0%	
Mixed race	1	1.7%	
Missing	15	25.0%	
Clinical Status	58	19.0%	
Hypertension Status	58	15.5%	
Other	58	3.5%	

Note: Hypertension status, self-reported by participants.

Table 29. Overall Variance from Mixed Model Approach

Groups		Var	%	%Total
Participant	OMRON	2.22	38.2	79.5
	VICORDER	1.28	22.2	
	VaSera	1.11	19.1	
Posture	OMRON	0.45	7.77	16.3
	VICORDER	0.22	3.71	
	VaSera	0.28	4.78	
Visit	OMRON	0.03	0.52	1.6
	VICORDER	0.06	1.04	
	VaSera	0.00	0.02	
Residual		0.15	2.63	2.6
		5.80	100	100.00

Table 30. OMRON vs. VICORDER Agreement

	Uncorrected			Adjusted MAP			Regression Calibrated		
	X	SD	n	X	SD	n	X	SD	n
OMRON	8.34	2.18	73	8.34	2.18	73	8.34	2.18	73
VICORDER	8.43	1.47	73	8.43	1.47	73	8.30	1.38	73
	X	LCI	UCI	X	SD	n	X	LCI	UCI
Association									
ICC	0.82	0.73	0.91	0.75	0.63	0.87	0.82	0.73	0.91
Agreement									
LOA (m/s)	-0.14	-2.68	2.41				-0.01	-2.60	2.59
RMSE (m/s)	2.13	1.77	2.48	2.25	1.88	2.62	2.13	1.77	2.48
RMSE (%)	25.53	21.26	29.80	26.99	22.53	31.45	25.53	21.28	29.77

Abbreviations: SD, standard deviation; UCI, upper confidence limit; LCI, lower confidence limit; ICC, intra-class correlation coefficient; LOA, limits of agreement; RMSE, root mean squared error

Table 31. OMRON vs. VaSera Agreement

	Uncorrected			Adjusted MAP			Regression Calibrated		
	X	SD	n	X	SD	n	X	SD	n
OMRON	8.36	2.19	72	8.36	2.19	72	8.06	2.19	72
VaSera	6.06	1.49	72	6.06	1.49	72	8.33	1.73	72
	X	LCI	UCI	X	LCI	UCI	X	LCI	UCI
Association									
ICC	0.75	0.63	0.87	0.74	0.61	0.86	0.75	0.63	0.87
Agreement									
LOA (m/s)	2.24	-0.02	4.50				-0.01	-2.15	2.13
RMSE (m/s)	2.84	2.37	3.30	2.89	2.40	3.38	2.84	2.37	3.30
RMSE (%)	33.93	28.33	39.53	34.60	28.71	40.48	35.19	29.39	41.00

Abbreviations: SD, standard deviation; UCI, upper confidence limit; LCI, lower confidence limit; ICC, intra-class correlation coefficient; LOA, limits of agreement; RMSE, root mean squared error

Table 32. VaSera vs. VICORDER Agreement

	Uncorrected			Adjusted MAP			Regression Calibrated		
	X	SD	n	X	SD	n	X	SD	n
VaSera	6.27	1.38	114	6.27	1.38	114	6.27	1.38	114
VICORDER	8.03	1.41	114	8.03	1.41	114	6.24	0.68	114
	X	LCI	UCI				X	LCI	UCI
Association									
ICC	0.87	0.82	0.92	0.85	0.79	0.91	0.87	0.82	0.92
Agreement									
LOA (m/s)	-1.75	-3.62	0.13				0.02	-1.86	1.91
RMSE (m/s)	2.59	2.38	2.81	2.48	2.29	2.66	2.60	2.38	2.81
RMSE (%)	41.29	37.87	44.72	39.49	36.53	42.46	41.40	37.98	44.82

Abbreviations: SD, standard deviation; UCI, upper confidence limit; LCI, lower confidence limit; ICC, intra-class correlation coefficient; LOA, limits of agreement; RMSE, root mean squared error

Table 33. VaSera-supine vs. VaSera-25˚

	Uncorrected			Adjusted MAP			Regression Calibrated		
	X	SD	n	X	SD	n	X	SD	n
VaSera-supine	5.76	1.42	114	5.76	1.42	114	5.76	1.42	114
VaSera-25˚	6.27	1.38	114	6.27	1.38	114	5.76	1.31	114
	X	LCI	UCI	X	LCI	UCI	X	LCI	UCI
Association									
ICC	0.47	0.31	0.64	0.49	0.33	0.66	0.48	0.33	0.65
Agreement									
LOA (units)	-0.51	-1.43	0.41				0.00	-0.92	0.92
RMSE (m/s)	2.95	2.73	3.18	2.92	2.69	3.14	2.95	2.73	3.18
RMSE (%)	51.26	47.39	55.14	50.58	46.70	54.46	51.26	47.39	55.14

Abbreviations: SD, standard deviation; UCI, upper confidence limit; LCI, lower confidence limit; ICC, intra-class correlation coefficient; LOA, limits of agreement; RMSE, root mean squared error

Table 34. Reliability Analyses

	OMRON			VICORDER			VaSera		
Visit	X	SD	n	X	SD	n	X	SD	n
1	8.59	2.34	33	8.03	1.40	57	6.07	1.41	112
2	8.46	2.08	33	8.06	1.40	57	6.00	1.45	112
Statistic	X	LCI	UCI	X	LCI	UCI	X	LCI	UCI
ICC	0.95	0.91	0.97	0.90	0.85	0.94	0.95	0.94	0.97
MDC	0.25	0.18	0.33	0.16	0.13	0.20	0.08	0.07	0.09
MDC%	2.86	2.15	3.79	2.01	1.62	2.47	1.31	1.13	1.52

Abbreviations: ICC, intra-class correlation coefficient; MDC, minimal detectable change

CHAPTER 9: DISSERTATION SUMMARY

Recap

The goal of this dissertation was to (a) determine the importance of psychosocial factors as modifiable factors for arterial stiffness and CVD risk in minority populations and (b) compare commonly used devices that assess arterial stiffness. To achieve these goals, a strong foundational knowledge of the existing literature was established via a scoping review (Study 1) providing a rationale for the following 2 studies. We focused on arterial stiffness, measured as pulse wave velocity (PWV) rather than overt CVD, as it provides a representation of CVD risk accrual over the lifespan.[67] Study 2 identified the extent to which perceived discrimination (PD) was associated with arterial stiffness. Further, Study 2 addressed a critical gap and evaluated the relationship between arterial stiffness and PD in a population-based study of both NHB men and women. Finally, Study 3 determined the agreement and reliability of three non-invasive cardiovascular devices that assess arterial stiffness through cuff-based or tonometry-based methods. A summary of the key findings is provided below and in Table 35.

Key Findings

According to our scoping review, there was evidence of a positive association of PD with higher (worse) PWV. According to our findings, there is a paucity of research specifically focusing on the association between PD and PWV, an indicator of CVD risk. We identified three primary studies focused on assessing the relationship between PD and AS across the world published between 2016 and 2022. However, these results vary by geographic region, biological sex, clinical status, and study design. We also noticed that findings were often adjusted for age,

sex, racial/ethnic group, blood pressure, and socioeconomic status or position. The studies often compared experiences of PD between racial/ethnic groups against a referent group (often White individuals). Additionally, there was heterogeneity in the methods used to assess PD and PWV, which aligns with established limitations of both PD and PWV research. Lastly, the use of three different PD measurement scales may have an impact on the association between PD and PWV as they evaluate distinct aspects of PD experiences.

Contrastingly, when we evaluated the association using multiple dimensions of PD (lifetime, everyday, and burden of PD) within a fully NHB sample of individuals from the ARIC-JHS shared cohort, our findings differed. Overall, there was evidence of an inverse association for PD and PWV. Our findings suggested that compared to Q1, Q2 of everyday PD had lower PWV. This association persisted for Q2 after adjustment for additional covariates. Further, for lifetime PD, Q3 and Q4 had lower PWV, compared to Q1, which persisted until adjustment for MAP and PS. This suggests that MAP and PS may be accounting for some of the variance in PWV. With regards to burden of PD, there was no association with PWV independent of variable coding. Concerning the attribution of PD for everyday and lifetime experiences, our findings were similar to the quartile and continuous analyses. For attributions of everyday PD, PWV was lower among those with low everyday PD attributed to nonracial factors compared with no discrimination. The association persisted until adjustment for MAP and PS. For attribution of lifetime PD, PWV was lower among those with experiences of high lifetime PD attributed to racial factors compared to no discrimination. Finally, there was no evidence of effect modification by sex or mediation by PS for everyday, lifetime, and burden PD.

We believe this unexpected inverse association was due to our sample's age, high mean PWV, and the fact we did not compare against other racial/ethnic groups. In particular, these

findings may suggest there is an age-dependent association between PD and PWV, with stronger associations between PD and PWV evident earlier in life, before the cumulative effects of CVD risk factors impact PWV. Previously, it has been shown that younger, more educated individuals tend to report higher levels of PD, whereas older adults are more likely to report lower levels of PD.[13] Additionally, there is a possibility that the association we identified could be influenced by confounding factors we did not adjust for. For example, smoking, alcohol consumption, and physical activity have all been associated with experiences of PD. Smoking and alcohol consumption are considered negative behaviors, whereas physical activity is considered beneficial. Borrell and colleagues found that there was a positive association between alcohol consumption and smoking with PD, but also that NHB individuals who reported moderate to high discrimination were more likely to engage in physical activity compared with those reporting no discrimination within the Coronary Artery Risk Development in Young Adults study (CARDIA) cohort.[93] Smoking and alcohol have both been linked with worsened PWV, whereas physical activity is seen as protective for PWV. If the participants in our sample were more physically active, as a result of their experiences of PD, rather than smoking or consuming alcohol, then that could cause the association to be negative. Additionally, our results may be influenced by survivor bias, with the more resilient individuals comprising a greater portion of our sample. It could also potentially be that previously identified positive associations are by-products of differences in experiences of PD between racial/ethnic groups and could contribute to the detection of the association.

Finally, concerning the agreement and reliability of three non-invasive devices that assess PWV, there was moderate to good agreement for all comparisons, except for comparisons across posture for the VaSera, and excellent reliability for all devices. However, there was evidence of

considerable bias, even after adjustment using a regression calibration approach, and other covariates. Understanding the level of agreement could be a useful first step to harmonizing the existing data PWV from multiple populations, including population-based studies like the JHS, ARIC, HCHS/SOL, and Multi-Ethnic Study of Atherosclerosis.

Implications

The goal of this dissertation was to (a) determine the importance of psychosocial factors as modifiable factors for arterial stiffness and CVD risk in minority populations and (b) compare commonly used arterial stiffness devices. Our findings support our hypothesis that PD is important to CVD risk accrual, as measured by PWV. However, the directionality of the association may vary due to heterogeneity in methods for assessing PD and PWV. It could also be that the association is age-dependent and impacted by factors (e.g., smoking, alcohol consumption, and physical activity, among others) that we did not adjust for. Further, since the association could change over time, evaluating the longitudinal association of PD and PWV could provide insight into how the association can vary with age. We also learned that there is moderate to good agreement between the different devices, in particular the OMRON and VICORDER. However, although there is moderate to good agreement, there is still considerable bias when comparing devices. This suggests although these devices are commonly used, they may not be directly interchangeable.

Table 35. Summary of Findings
What did we know?
• Perceived discrimination and stress have been identified as contributors to overt CVD (i.e., hypertension). • PWV is a sensitive marker of vascular aging.
What did we not know?
• The association between perceived discrimination, stress, and arterial stiffness in a fully NHB sample is not known. • The agreement and reliability of three commonly used and validated, non-invasive cardiovascular devices that assess PWV is not known.
What have we learned?
• There is an association between PD and PWV, however the directionality and magnitude may vary. • The association varies by geographic region, biological sex, clinical status, and study design. • The association may be age-dependent or impacted by behavioral factors.
Why is this new information useful?
• This information aligns with our initial hypothesis that psychosocial factors are contributing to CVD risk accrual, as measured by PWV.
What do we need to know next?
• Evaluate the longitudinal association of PD and PWV. • Determine the impact of behavioral factors and coping mechanisms on the association of PD and PWV. • Harmonize existing PWV data from multiple cohorts.

Future Considerations for these Studies

Next steps for these analyses will be to adjust by socioeconomic status, smoking, alcohol, and physical activity. We will also evaluate the impact of the path length calculations within our agreement analyses.

Recommendation for Future Research

Future studies should evaluate the longitudinal association of PD and PWV and the impact of coping mechanisms. It has been previously shown that although NHB may be at higher risk, they may engage in higher physical activity that could be influencing this association.[93] It is also important to consider that PD can change over time. We only had PWV data for a subset of the population measured ~11 years after the PD assessments. Future studies should evaluate how the association changes within this sample, specifically since PWV has been added to the next

JHS exam. Finally, future studies should attempt to harmonize PD and PWV data from multiple cohorts. The harmonization of PWV data would contribute to our understanding of cardiovascular risk accrual in diverse populations and allow us to properly ascertain CVD risk across the lifespan.

REFERENCES

1. Bartlett, J. W. & Frost, C. Reliability, repeatability and reproducibility: analysis of measurement errors in continuous variables. *Ultrasound Obstet. Gynecol.* **31**, 466–475 (2008).

2. Devakumar, D. *et al.* Racism, the public health crisis we can no longer ignore. *The Lancet* **395**, e112–e113 (2020).

3. Pascoe, E. A. & Richman, L. S. Perceived Discrimination and Health: A Meta-Analytic Review. *Psychol. Bull.* **135**, 531–554 (2009).

4. Palombo, C. & Kozakova, M. Arterial stiffness, atherosclerosis and cardiovascular risk: Pathophysiologic mechanisms and emerging clinical indications. *Vascul. Pharmacol.* **77**, 1–7 (2016).

5. Spruill, T. M. *et al.* Association Between High Perceived Stress Over Time and Incident Hypertension in Black Adults: Findings From the Jackson Heart Study. *J. Am. Heart Assoc.* **8**, (2019).

6. Williams, D. R. & Leavell, J. The social context of cardiovascular disease: Challenges and opportunities for the Jackson Heart Study. in *Ethnicity and Disease* vol. 22 S1 (NIH Public Access, 2012).

7. Williams, D. R., Mohammed, S. A., Leavell, J. & Collins, C. Race, socioeconomic status, and health: Complexities, ongoing challenges, and research opportunities. *Ann. N. Y. Acad. Sci.* **1186**, 69–101 (2010).

8. Vlachopoulos, C. *et al.* Prediction of cardiovascular events and all-cause mortality with central haemodynamics: A systematic review and meta-analysis. *Eur. Heart J.* (2010) doi:10.1093/eurheartj/ehq024.

9. Sims, M. *et al.* Perceived discrimination and hypertension among African Americans in the Jackson Heart Study. *Am. J. Public Health* **102**, S258 (2012).

10. Bromfield, S. G. *et al.* Race and Gender Differences in the Association Between Experiences of Everyday Discrimination and Arterial Stiffness Among Patients With Coronary Heart Disease. *Ann. Behav. Med.* **54**, 761–770 (2020).

11. Taylor, J. Y. *et al.* The combined effects of genetic risk and perceived discrimination on blood pressure among African Americans in the Jackson Heart Study. *Med. U. S.* **96**, 43 (2017).

12. Felix, A. S. *et al.* Stress, resilience, and cardiovascular disease risk among black women: Results from the women's health initiative. *Circ. Cardiovasc. Qual. Outcomes* **12**, e005284 (2019).

13. Dunlay, S. M. *et al.* Perceived Discrimination and Cardiovascular Outcomes in Older African Americans: Insights From the Jackson Heart Study. *Mayo Clin. Proc.* **92**, 699–709 (2017).

14. Pan, H., Liu, S., Miao, D. & Yuan, Y. Sample size determination for mediation analysis of longitudinal data. *BMC Med. Res. Methodol.* **18**, 1–11 (2018).

15. Virani, S. S. *et al.* Heart Disease and Stroke Statistics-2021 Update A Report from the American Heart Association. *Circulation* **143**, E254–E743 (2021).

16. Gillman, M. W. Primordial prevention of cardiovascular disease. *Circulation* **131**, 599–601 (2015).

17. Credeur, D. P. *et al.* Impact of Prolonged Sitting on Peripheral and Central Vascular Health. *Am. J. Cardiol.* **123**, 260–266 (2019).

18. Barone Gibbs, B. *et al.* Effect of alternating standing and sitting on blood pressure and pulse wave velocity during a simulated workday in adults with overweight/obesity. *J. Hypertens.* **35**, 2411–2418 (2017).

19. Kucharska-Newton, A. M., Stoner, L. & Meyer, M. L. Determinants of vascular age: An epidemiological perspective. *Clin. Chem.* **65**, 108–118 (2019).

20. Segers, P., Rietzschel, E. R. & Chirinos, J. A. How to Measure Arterial Stiffness in Humans. *Arterioscler. Thromb. Vasc. Biol.* 1034–1043 (2020) doi:10.1161/ATVBAHA.119.313132.

21. Stoner, L., Kucharska-Newton, A. & Meyer, M. L. Cardiometabolic Health and Carotid-Femoral Pulse Wave Velocity in Children: A Systematic Review and Meta-Regression. *J. Pediatr.* **218**, 98–105 (2019).

22. Stone, K. *et al.* The aortic-femoral arterial stiffness gradient: an atherosclerosis risk in communities (ARIC) study. *J. Hypertens.* **39**, 1370–1377 (2021).

23. Stoner, L. *et al.* Associations between carotid-femoral and heart-femoral pulse wave velocity in older adults: the Atherosclerosis Risk In Communities study. *J. Hypertens.* **38**, 1786–1793 (2020).

24. Flanagin, A., Frey, T., Christiansen, S. L. & Committee, A. M. of S. Updated Guidance on the Reporting of Race and Ethnicity in Medical and Science Journals. *JAMA* **326**, 621–627 (2021).

25. Jones, C. P. Invited Commentary: "Race," Racism, and the Practice of Epidemiology. *Am. J. Epidemiol.* **154**, 299–304 (2001).

26. Prevention, C. for D. C. and. Health Equity Considerations and Racial and Ethnic Minority Groups | CDC. https://www.cdc.gov/coronavirus/2019-ncov/community/health-equity/race-ethnicity.html (2020).

27. Flanagin, A., Frey, T., Christiansen, S. L. & Committee, A. M. of S. Updated Guidance on the Reporting of Race and Ethnicity in Medical and Science Journals. *JAMA* **326**, 621–627 (2021).

28. Phillips, A. C. Perceived Stress. in *Encyclopedia of Behavioral Medicine* (eds. Gellman, M. D. & Turner, J. R.) 1453–1454 (Springer New York, 2013). doi:10.1007/978-1-4419-1005-9_479.

29. Cohen, S., Kamarck, T. & Mermelstein, R. A global measure of perceived stress. *J. Health Soc. Behav.* **24**, 385–396 (1983).

30. Rodriguez, C. J. *et al.* Status of cardiovascular disease and stroke in hispanics/latinos in the united states: A science advisory from the american heart association. *Circulation* **130**, 593–625 (2014).

31. Libby, P. Inflammation in atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* **32**, 2045–2051 (2012).

32. Singh, S. S., Pilkerton, C. S., Shrader, C. D. & Frisbee, S. J. Subclinical atherosclerosis, cardiovascular health, and disease risk: Is there a case for the Cardiovascular Health Index in the primary prevention population? *BMC Public Health* **18**, 1–11 (2018).

33. Payne, R. A., Wilkinson, I. B. & Webb, D. J. Arterial stiffness and hypertension: Emerging concepts. *Hypertension* **55**, 9–14 (2010).

34. Wendell, C. R., Waldstein, S. R., Evans, M. K. & Zonderman, A. B. Distributions of Subclinical Cardiovascular Disease in a Socioeconomically and Racially Diverse Sample. *Stroke* **48**, 850–856 (2017).

35. Heffernan, K. S., Jae, S. Y., Wilund, K. R., Woods, J. A. & Fernhall, B. Racial differences in central blood pressure and vascular function in young men. *Am. J. Physiol. Heart Circ. Physiol.* **295**, (2008).

36. Tsao, C. W. *et al.* Clinical Correlates of Aortic Stiffness and Wave Amplitude in Black Men and Women in the Community. *J. Am. Heart Assoc.* **7**, (2018).

37. Thomas, K. *et al.* Associations of Psychosocial Factors with Multiple Health Behaviors: A Population-Based Study of Middle-Aged Men and Women. *Int. J. Environ. Res. Public. Health* **17**, 1239 (2020).

38. Yusuf, P. S. *et al.* Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet Lond. Engl.* **364**, 937–952 (2004).

39. Logan, J. G. & Barksdale, D. J. Allostasis and allostatic load: Expanding the discourse on stress and cardiovascular disease. *J. Clin. Nurs.* **17**, 201–208 (2008).

40. Beckie, T. M. A Systematic Review of Allostatic Load, Health, and Health Disparities. *Biol. Res. Nurs.* **14**, 311–346 (2012).

41. Lockwood, K. G., Marsland, A. L., Matthews, K. A. & Gianaros, P. J. Perceived discrimination and cardiovascular health disparities: a multisystem review and health neuroscience perspective. *Ann. N. Y. Acad. Sci.* **1428**, 170–207 (2018).

42. Havranek, E. P. *et al.* Social Determinants of Risk and Outcomes for Cardiovascular Disease. *Circulation* **132**, 873–898 (2015).

43. Marón, F. J. M., Ferder, L., Saraví, F. D. & Manucha, W. Hypertension linked to allostatic load: From psychosocial stress to inflammation and mitochondrial dysfunction. *Stress* **22**, 169–181 (2019).

44. Albert, M. A. *et al.* Cumulative psychological stress and cardiovascular disease risk in middle aged and older women: Rationale, design, and baseline characteristics. *Am. Heart J.* **192**, 1–12 (2017).

45. Beatty Moody, D. L., Brown, C., Matthews, K. A. & Bromberger, J. T. Everyday discrimination prospectively predicts inflammation across 7-years in racially diverse midlife women: Study of women's health across the nation. *J. Soc. Issues* **70**, 298–314 (2014).

46. Mwendwa, D. T. *et al.* The influence of coping with perceived racism and stress on lipid levels in African Americans. *J. Natl. Med. Assoc.* **103**, 594–601 (2011).

47. Albert, M. A. *et al.* Perceptions of race/ethnic discrimination in relation to mortality among black women: Results from the black women's health study. *Arch. Intern. Med.* **170**, 896–904 (2010).

48. Medina-Inojosa, J. R. *et al.* Role of Stress and Psychosocial Determinants on Women's Cardiovascular Risk and Disease Development. *J. Womens Health* **28**, 483–489 (2019).

49. Gebreab, S. Y. *et al.* The contribution of stress to the social patterning of clinical and subclinical CVD risk factors in African Americans: The Jackson Heart Study. *Soc. Sci. Med.* **75**, 1697–1707 (2012).

50. Vlachopoulos, C. *et al.* Acute mental stress has a prolonged unfavorable effect on arterial stiffness and wave reflections. *Psychosom. Med.* **68**, 231–237 (2006).

51. Meline, T. Selecting Studies for Systematic Review: Inclusion and Exclusion Criteria. *Contemp. ISSUES Commun. Sci. Disord.* • **33**, 21–27 (2006).

52. Yung, Y.-F., Lamm, M. & Zhang, W. Paper SAS1991:2018 Causal Mediation Analysis with the CAUSALMED Procedure.

53. Wyatt, S. B. *et al.* Racism and cardiovascular disease in African Americans. in *American Journal of the Medical Sciences* vol. 325 315–331 (Lippincott Williams and Wilkins, 2003).

54. Krieger, N., Smith, K., Naishadham, D., Hartman, C. & Barbeau, E. Experiences of discrimination: validity and reliability of a self-report measure for population health research on racism and health. *Soc. Sci. Med. 1982* **61**, 1576–1596 (2005).

55. Sims, M., Wyatt, S. B., Gutierrez, M. L., Taylor, H. A. & Williams, D. R. Development and psychometric testing of a multidimensional instrument of perceived discrimination among African Americans in the Jackson Heart Study. *Ethn. Dis.* **19**, 56–64 (2009).

56. Logan, J. G., Barksdale, D. J., Carlson, J., Carlson, B. W. & Rowsey, P. J. Psychological stress and arterial stiffness in Korean Americans. *J. Psychosom. Res.* **73**, 53–58 (2012).

57. Huang, Y. *et al.* Poor sleep quality, stress status, and sympathetic nervous system activation in nondipping hypertension. *Blood Press. Monit.* **16**, 117–123 (2011).

58. Lehrer, H. M., Steinhardt, M. A., Dubois, S. K. & Laudenslager, M. L. Perceived stress, psychological resilience, hair cortisol concentration, and metabolic syndrome severity: A moderated mediation model. *Psychoneuroendocrinology* **113**, (2020).

59. Richardson, S. *et al.* Meta-analysis of perceived stress and its association with incident coronary heart disease. *Am. J. Cardiol.* **110**, 1711–1716 (2012).

60. Baik, S. H. *et al.* Reliability and validity of the Perceived Stress Scale-10 in Hispanic Americans with English or Spanish language preference. *J. Health Psychol.* **24**, 628 (2019).

61. Henry, S. K., Grant, M. M. & Cropsey, K. L. Determining the optimal clinical cutoff on the CES-D for depression in a community corrections sample. *J. Affect. Disord.* **234**, 270–275 (2018).

62. Giavarina, D. Lessons in biostatistics. *Past Present Future Stat. Sci.* **25**, 359–372 (2014).

63. Parker, R. A. *et al.* Application of Mixed Effects Limits of Agreement in the Presence of Multiple Sources of Variability: Exemplar from the Comparison of Several Devices to Measure Respiratory Rate in COPD Patients. *PLOS ONE* **11**, e0168321 (2016).

64. Kovacs, F. M. *et al.* Minimum detectable and minimal clinically important changes for pain in patients with nonspecific neck pain. *BMC Musculoskelet. Disord.* **9**, 43 (2008).

65. Lane, D. M. Standard Error of the Estimate. https://onlinestatbook.com/2/regression/accuracy.html.

66. Hopkins, W. G. Measures of reliability in sports medicine and science. *Sports Med.* **30**, 1–15 (2000).

67. Vlachopoulos, C., Aznaouridis, K. & Stefanadis, C. Prediction of Cardiovascular Events and All-Cause Mortality With Arterial Stiffness. A Systematic Review and Meta-Analysis. *J. Am. Coll. Cardiol.* **55**, 1318–1327 (2010).

68. Shrout, P. E. & Fleiss, J. L. Intraclass correlations: Uses in assessing rater reliability. *Psychol. Bull.* **86**, 420–428 (1979).

69. Koo, T. K. & Li, M. Y. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *J. Chiropr. Med.* **15**, 155–163 (2016).

70. Sims, M. *et al.* Psychosocial Factors and Behaviors in African Americans: The Jackson Heart Study. *Am. J. Prev. Med.* **52**, S48–S55 (2017).

71. Lewis, T. T., Williams, D. R., Tamene, M. & Clark, C. R. Self-Reported Experiences of Discrimination and Cardiovascular Disease. *Curr. Cardiovasc. Risk Rep.* **8**, 1–15 (2014).

72. Beatty Moody, D. L. *et al.* Everyday discrimination prospectively predicts blood pressure across 10 years in racially/ethnically diverse midlife women: Study of women's health across the nation. *Ann. Behav. Med.* **53**, 608–620 (2019).

73. Williams, D. R. *et al.* Perceived discrimination, race and health in South Africa. *Soc. Sci. Med.* **67**, 441–452 (2008).

74. Bromfield, S. G. *et al.* Race and Gender Differences in the Association Between Experiences of Everyday Discrimination and Arterial Stiffness Among Patients With Coronary Heart Disease. *Ann. Behav. Med.* **54**, 761–770 (2020).

75. Everson-Rose, S. A. *et al.* Perceived Discrimination and Incident Cardiovascular Events: The Multi-Ethnic Study of Atherosclerosis. *Am. J. Epidemiol.* **182**, 225 (2015).

76. Lewis, T. T. *et al.* Chronic exposure to everyday discrimination and coronary artery calcification in African-American women: The SWAN heart study. *Psychosom. Med.* **68**, 362–368 (2006).

77. Lewis, T. T., Aiello, A. E., Leurgans, S., Kelly, J. & Barnes, L. L. Self-reported experiences of everyday discrimination are associated with elevated C-reactive protein levels in older African-American adults. *Brain. Behav. Immun.* **24**, 438–443 (2010).

78. Troxel, W. M., Matthews, K. A., Bromberger, J. T. & Sutton-Tyrrell, K. Chronic stress burden, discrimination, and subclinical carotid artery disease in African American and Caucasian women. *Health Psychol.* **22**, 300–309 (2003).

79. Tricco, A. C. *et al.* PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. *Ann. Intern. Med.* **169**, 467–473 (2018).

80. NHLBI. Study Quality Assessment Tools | NHLBI, NIH. *NHLBI* https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools (2021).

81. TT, L. *et al.* Race, psychosocial factors, and aortic pulse wave velocity: the Health, Aging, and Body Composition Study. *J. Gerontol. A. Biol. Sci. Med. Sci.* **65A**, 1079–1085 (2010).

82. Lu, Y. *et al.* Longitudinal study of the influence of lung function on vascular health from adolescence to early adulthood in a British multiethnic cohort. *J. Hypertens.* **35**, 2185–2191 (2017).

83. Faconti, L. *et al.* Can arterial wave augmentation in young adults help account for variability of cardiovascular risk in different British ethnic groups? *J. Hypertens.* **34**, 2220–2226 (2016).

84. Cruickshank, J. K. *et al.* Ethnic differences in and childhood influences on early adult pulse wave velocity: The determinants of adolescent, now young adult, social wellbeing, and health longitudinal study. *Hypertension* **67**, 1133–1141 (2016).

85. Camelo, L. V. *et al.* Racial discrimination is associated with greater arterial stiffness and carotid intima-media thickness: the ELSA-Brasil study. *Ann. Epidemiol.* **72**, 40–47 (2022).

86. Krieger, N. Racial and gender discrimination: Risk factors for high blood pressure? *Soc. Sci. Med.* **30**, 1273–1281 (1990).

87. Krieger, N. & Sidney, S. Racial discrimination and blood pressure: the CARDIA Study of young black and white adults. *Httpsdoi-Orglibproxylibuncedu102105AJPH86101370* **86**, 1370–1378 (1996).

88. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am. J. Epidemiol.* **129**, 687–702 (1989).

89. Payne, T. J. *et al.* Sociocultural methods in the Jackson Heart Study: conceptual and descriptive overview. *Ethn. Dis.* **15**, S6-38–48 (2005).

90. Fuqua, S. R. *et al.* Recruiting African-American research participation in the Jackson Heart Study: methods, response rates, and sample description. *Ethn. Dis.* **15**, S6-18–29 (2005).

91. Cortez-Cooper, M. Y., Supak, J. A. & Tanaka, H. A new device for automatic measurements of arterial stiffness and ankle-brachial index. *Am. J. Cardiol.* **91**, 1519–1522, A9 (2003).

92. Collaboration, T. R. V. for A. S. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur. Heart J.* **31**, 2338–2350 (2010).

93. Borrell, L. N., Kiefe, C. I., Diez-Roux, A. V., Williams, D. R. & Gordon-Larsen, P. Racial discrimination, racial/ethnic segregation, and health behaviors in the CARDIA study. *Ethn. Health* **18**, 227–243 (2013).

94. Salvi, P. *Pulse waves: How vascular hemodynamics affects blood pressure*. *Pulse Waves: How Vascular Hemodynamics Affects Blood Pressure* (Springer International Publishing, 2016). doi:10.1007/978-3-319-40501-8.

95. Parikh, J. D., Hollingsworth, K. G., Kunadian, V., Blamire, A. & MacGowan, G. A. Measurement of pulse wave velocity in normal ageing: Comparison of Vicorder and magnetic resonance phase contrast imaging. *BMC Cardiovasc. Disord.* **16**, 1–7 (2016).

96. Shahin, Y., Barakat, H., Barnes, R. & Chetter, I. The Vicorder device compared with SphygmoCor in the assessment of carotid-femoral pulse wave velocity in patients with peripheral arterial disease. *Hypertens. Res.* **36**, 208–212 (2013).

97. Hickson, S. S. *et al.* Validity and repeatability of the Vicorder apparatus: A comparison with the SphygmoCor device. *Hypertens. Res.* **32**, 1079–1085 (2009).

98. Kis, E. *et al.* Measurement of pulse wave velocity in children and young adults: A comparative study using three different devices. *Hypertens. Res.* **34**, 1197–1202 (2011).

99. Ellins, E. A. *et al.* Arterial pathophysiology and comparison of two devices for pulse wave velocity assessment in elderly men: the British regional heart study. *Open Heart* **4**, e000645 (2017).

100. Van Leeuwen-Segarceanu, E. M. *et al.* Comparison of two instruments measuring carotid-femoral pulse wave velocity: Vicorder versus SphygmoCor. *J. Hypertens.* **28**, 1687–1691 (2010).

101. Xu, L. *et al.* Improving the accuracy and robustness of carotid-femoral pulse wave velocity measurement using a simplified tube-load model. *Sci. Rep. 2022 121* **12**, 1–15 (2022).

102. Spiegelman, D., Logan, R. & Grove, D. Regression Calibration with Heteroscedastic Error Variance. *Int. J. Biostat.* **7**, (2011).

103. Rosner, B., Spiegelman, D. & Willett, W. C. CORRECTION OF LOGISTIC REGRESSION RELATIVE RISK ESTIMATES AND CONFIDENCE INTERVALS FOR MEASUREMENT ERROR: THE CASE OF MULTIPLE COVARIATES MEASURED WITH ERROR. *Am. J. Epidemiol.* **132**, 734–745 (1990).

104. Butlin, M. *et al.* Carotid-femoral pulse wave velocity assessment using novel cuff-based techniques: comparison with tonometric measurement. *J. Hypertens.* **31**, 2237–2243; discussion 2243 (2013).

105. Fico, B. G., Gourley, D. D., Wooten, S. V. & Tanaka, H. Heart-Thigh Cuff Pulse Wave Velocity: A Novel Nontechnical Measure of Arterial Stiffness. *Am. J. Hypertens.* **32**, 1051–1053 (2019).

106. Butlin, M., Qasem, A. & Avolio, A. P. Estimation of central aortic pressure waveform features derived from the brachial cuff volume displacement waveform. *Conf Proc IEEE Eng Med Biol Soc* **2012**, 2591–2594 (2012).

107. Li, Y., Cordes, M., Hanssen, H. & Schmidt-Trucksäss, A. P2.31 COMPARISON OF TWO NONINVASIVE MEASUREMENTS FOR AORTIC PULSE WAVE VELOCITY: VASERA VERSUS SPHYGMOCOR. *Artery Res.* **6**, 172–172 (2012).

108. Millasseau, S. C., Stewart, A. D., Patel, S. J., Redwood, S. R. & Chowienczyk, P. J. Evaluation of carotid-femoral pulse wave velocity: influence of timing algorithm and heart rate. *Hypertens. Dallas Tex 1979* **45**, 222–226 (2005).

109. Yamashina, A. *et al.* Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens. Res. Off. J. Jpn. Soc. Hypertens.* **25**, 359–364 (2002).

110. Maliha, G. & Townsend, R. R. A study of the VaSera arterial stiffness device in US patients. *J. Clin. Hypertens.* **19**, 661–668 (2017).

111. Schroeder, E. C. *et al.* Effect of upper body position on arterial stiffness: influence of hydrostatic pressure and autonomic function. *J. Hypertens.* **35**, 2454–2461 (2017).

112. Zwain, A. A. M. H., Esawi, R. W. A. & Al-Dejeli, A. A. B. Cardiac index (CI) versus cardio ankle vascular index (CAVI) at different degrees of head-up tilt (HUT) in healthy subjects. *Open J. Mol. Integr. Physiol.* **2013**, 71–79 (2013).

113. Meyer, M. L. *et al.* Repeatability of Central and Peripheral Pulse Wave Velocity Measures: The Atherosclerosis Risk in Communities (ARIC) Study. *Am. J. Hypertens.* **29**, 470–475 (2016).