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LIFESTYLE CONTRIBUTORS TO CARDIOVASCULAR DISEASE RISK

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Adam J. Berrones, Student

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Dr. Heather E. Erwin, Director of Graduate Studies

LIFESTYLE CONTRIBUTORS TO CARDIOVASCULAR DISEASE RISK

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Education
at the University of Kentucky

By

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Lexington, Kentucky

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ABSTRACT OF DISSERTATION

LIFESTYLE CONTRIBUTORS TO CARDIOVASCULAR DISEASE RISK

Aortic stiffness is an independent risk factor that has prognostic value regarding future cardiovascular disease (CVD) events such as myocardial infarction, strokes, and heart failure. Although death rates due to coronary heart disease have declined in recent years, the leading global killer remains CVD and prevalence is still high. Understanding lifestyle contributors associated with aortic stiffness would provide the public with insight into targeting key health-related behaviors.

The purpose of this observational study was to examine the association of physical activity, physical function, and dietary quality as independent factors contributing to aortic stiffness in apparently healthy middle aged men. Fifty-two men between the ages of 30 and 59 years were recruited to participate in this study, which required two visits to the Exercise Physiology Laboratory. Aortic stiffness was measured by aortic pulse wave velocity (aPWV) and was not associated with total daily step counts ($r=-0.06$; $P=0.70$). However, aortic stiffness was inversely associated with physical function, determined with the sitting-rising test score ($r=-0.44$; $P<0.01$) and inversely associated with relative muscular strength, determined with peak handgrip strength in both hands normalized to body mass ($r=-0.41$; $P<0.01$). Additionally, aortic stiffness was inversely associated with dietary quality, determined with the Healthy Eating Index score ($r=0.51$; $P<0.01$).

In conclusion, key health-related behaviors in this study that explained a large percentage of the variation in aortic stiffness were physical function and dietary quality (Adj $r^2=0.47$; SEE=0.634). Hence, optimizing overall musculoskeletal fitness by focusing on strength, balance, coordination, and flexibility in addition to greater adherence to the U.S. Dietary Guidelines are key lifestyle contributors associated with reduced CVD risk in otherwise healthy middle aged men.

KEYWORDS: Aorta, Fitness, Strength, Muscle, Nutrition, Longevity

Adam Joseph Berrones

April 22, 2016

LIFESTYLE CONTRIBUTORS TO CARDIOVASCULAR DISEASE RISK

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April 22, 2016

Dedicated to my two sons, Franco and Felix.

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CHAPTER ONE: INTRODUCTION

Cardiovascular disease (CVD) related mortalities have declined in recent years yet still remain the leading cause of mortality in modern societies (43). CVD-related deaths are associated with arterial dysfunction that, in part, is attributable to stiffening of large elastic arteries such as the aorta (92). The underlying mechanism linking aortic stiffening to greater CVD risk is primarily due to increases in central pulse pressure, which elevates the myocardial oxygen demand and drives left ventricular hypertrophy (65). In addition, an elevated central pulse pressure increases the time spent in systole and decreases the time spent in diastole. Because coronary perfusion occurs during diastole, elevated central pulse pressure leads to reduced coronary perfusion (diastolic dysfunction) and ischemia (143). Ultimately, arterial dysfunction accelerates heart failure by placing a greater strain on the heart, thus increasing CVD risk.

Aging is the primary risk factor for CVD and is a critical component of arterial (aortic) stiffness etiology (92). Additionally, aging negatively affects arterial function due to progressive increases in central blood pressure which over time cause repetitive and cumulative damage to vital structural proteins such as elastin (81). When elastin for example begins to fragment and lose functionality, large elastic arteries (such as the carotids and femorals) cushion the ejecting blood from the left ventricle in a diminished capacity. In order to accommodate the pathological arterial protein elastin, enhanced depositions of collagen can be seen throughout all layers of the artery, which is the body's futile attempt to

preserve the cushioning effect that was lost with functional elastin (48, 130). This pathophysiological process of ineffective stroke volume buffering, and structural remodeling is the consequence of vascular stiffening, determined by the “gold standard” measure of aortic pulse wave velocity (aPWV) (124). Importantly, aPWV is a novel and powerful risk factor for CVD that predicts a first CV event after adjustment of traditional risk factors such as age, sex, diabetes, total and HDL cholesterol, smoking, and use of antihypertensive therapy (11).

Understanding lifestyle correlates to arterial stiffness in an aging population would provide valuable insight into the types of behaviors that are associated with CVD risk. For example, daily physical activity, fitness, body composition, and dietary quality. The Center for Disease Control and Prevention recommendation to optimize CV health is relatively simple in its approach. That is, engagement in physical activity and structured exercise through daily inclusion of aerobic and strength training modalities leads to maintenance and optimization of physical health. While, in conjunction with physical activity and structured exercise, maximizing dietary quality by reducing empty calorie foods and increasing nutrient-dense whole foods, is of paramount importance for preserving overall physical health. These two front-line, lifestyle approaches are usually recommended as a pair, and are vital for staving off the negative and pernicious effects of CVD such as arterial stiffness. However, in the context of an aging population, it has not been established if physical activity, defined as total daily step counts, is directly related to aPWV. Nor has it been established what

precise components of dietary quality are key for optimization of arterial health, structure, and function.

Several studies have examined step counts as a measure of physical activity and identified correlations with arterial stiffness (3, 6, 9, 23, 38). Although there are an array of validated methods to examine arterial stiffness, only aPWV is recognized as the gold-standard, and experts in the field have reached consensus on the predictive power and reproducibility of its measure (65). As such, previously demonstrated correlations in the literature between step counts and arterial stiffness were either derived from measurements *other than* the aPWV, and from questionnaires that attempted to estimate – not directly measure – physical activity (61, 99).

The relationship between physical activity and physical function is usually direct: *If an individual increases daily physical activity, then he can increase the capacity to perform mechanical work.* A variety of strength and conditioning assessments of physical function attempt to quantify the work performed, usually in a movement-specific or time-dependent manner. In short, being more physically active leads to an improved functional status for walking speed, leg strength, dynamic balance, modified push-ups, static back extension, and cardiorespiratory fitness in myriad adult populations (71, 107, 131, 133). Yet, one physical function assessment, handgrip strength, has been shown to be equivocal in its relation to arterial stiffness.

Adherence to the U.S. Dietary Guidelines is associated with reduced CVD risk generally, due to maintenance of physical health through nutrient-dense foods, and reduction of empty calorie, refined, and sodium-rich foods. However, there has been no study to date that has quantified and expressed overall dietary quality as one single metric, to determine whether adherence to the U.S. Dietary Guidelines is prophylactic. The Healthy Eating Index (HEI) score is comprised of a multi-component model of human nutritional needs, and is a validated and reliable measure encapsulating overall dietary quality according to the U.S. Dietary Guidelines (46). Expressing dietary quality as the HEI score is a strong predictor of CVD, all-cause mortality, and type-2 diabetes (121). It would be worthwhile to represent the quality of an aging American population's diet, and to associate with CVD risk such as large elastic artery stiffness.

Furthermore, age-standardized risk of CVD is accelerated in men compared with women (80), indicating that there is a sex-specific relationship to the overall incidence and disease course of CVD risk. The presentation of CVD in this relatively vulnerable population – a middle-aged male cohort – includes a stronger likelihood of abdominal aortic aneurysm, myocardial infarction, and unheralded coronary death (40).

The purpose of this study was to examine lifestyle contributors to CVD risk in middle-aged men aged 30 to 60 years. The hypotheses were that greater

physical activity and physical function are associated with reduced aortic stiffness, and 2) Higher dietary quality is associated with reduced aortic stiffness.

CHAPTER TWO: LITERATURE REVIEW

The aging process accelerates vessel wall stiffening more than any one factor (142). Age-driven stiffness of the arteries is arteriosclerosis, and is more pronounced in severity in the large elastic arteries (aorta, carotid) compared with the peripheral arteries (brachial, tibial). As a consequence of biological aging for example, from early adolescence to middle adulthood (10 – 50 years of age) one can expect approximately a 70% increase in central arterial (aortic) stiffness; whereas, peripheral artery stiffness may only increase by ~20% (90). Therefore, arterial stiffness is disproportionate in its development, and large elastic arteries such as the aorta, carotid, and femoral appear to harden more significantly than peripheral arteries such as the brachial, tibial, and radial arteries. As such, the impact to cardiovascular health will vary throughout systemic circulation in a site-specific manner.

The detrimental effects of increased arterial stiffness are multifaceted, and complicated. Although the discussion of these major three mechanisms will follow, arterial stiffness pathophysiology includes: 1) Increase in central systolic blood pressure; 2) Increase in left ventricular afterload; and 3) Decrease in diastolic perfusion pressure. Primarily due to these physiological mechanisms, arterial stiffness is an independent risk factor for cardiovascular disease (CVD) that is associated with greater morbidity and premature mortality (11). The gold-standard measure of arterial stiffness is the carotid-femoral pulse wave velocity (cfPWV) (65). In summary, arterial stiffness is a novel cardiovascular risk factor

that predicts incident CVD, and prospective data supporting the proposed pathophysiological mechanisms and their injurious consequences to cardiovascular health, are both mounting and convincing (11, 83, 84). Additionally, arterial stiffness accelerates target organ damage to the brain, heart, and kidneys (86). Hence, understanding lifestyle factors that relate to arterial stiffness could provide a front-line protection strategy against an aging (and failing) cardiovascular system.

To understand the pathophysiology of arterial stiffness, it would be important to briefly review the functional role of the arterial system. The primary function of the arterial system is to provide oxygen and nutrient rich blood to the various tissues and organs of the body. In addition, the arterial system, specifically the thoracic aorta, buffers the blood ejected from the heart by extending and recoiling to promote continuous blood flow in the capillaries (94). This anatomical arrangement has been compared to windkessels of antique fire engines (69). Moreover, the ability to buffer the ejected blood from the heart is purposeful for cushioning the pulsatility during systole, and for steady downstream propagation of blood flow through the arterial tree during diastole.

GENERAL PATHOPHYSIOLOGY OF ARTERIAL STIFFNESS

When the left ventricle for example contracts, it creates what is referred to as an incident pulse pressure wave. The pressure wave is the pulse. This initial pressure wave is clinically relevant to study because aging augments the peak

systolic pressure wave and amplifies blood pressure. Under normal, healthy physiological conditions the pulse pressure wave travels down the aorta and is partially reflected back to the heart while the remaining wave is transmitted to the microcirculation to promote low pulsatile capillary blood flow in tissues. The return, or reflective wave arrives at the heart during diastole, which provides the driving pressure for coronary artery perfusion during relaxation. When the aorta is stiffened, however, the pulse pressure wave moves more quickly through the vessel and a significant proportion of this wave will be transmitted to the microcirculation. The increased pulsatility of the transmitted wave results in greater pulsatile blood flow in tissue capillaries and causes damage to small blood vessels.

Moreover, the reflected wave as seen during aging will return to the heart sooner, during late systole when the heart is ejecting blood. This leads to an increase in afterload (blood pressure at the aortic root), which the left ventricle must overcome to pump eject blood through the aortic valve. This exact process is a contributing factor to hypertension, a traditional and established CVD risk factor. Additionally, the early arrival of the pulse pressure wave to the heart decreases the perfusion pressure in the coronary arteries, which reduces coronary blood flow at rest and during physiological stress such as exercise. Thus, increased arterial stiffness – specifically aortic stiffness – is implicated in heart-related pathologies including myocardial ischemia, heart failure, and infarcts.

Increases in SBP, Pulse Pressure, and Afterload

Arterial stiffness accelerates the return waves back to the left ventricle of heart, and elevates SBP and pulse pressure (systolic minus diastolic blood pressure). There is controversy regarding the causative factors of arterial stiffness. In short, this relationship of arterial stiffness and elevated SBP (hypertension) has been compared to the informal chicken-and-egg dilemma (81). The current general viewpoint is that hypertension in young adults accelerates arterial stiffness that is similar in severity to that of aging, due to the premature return and magnitude of the reflected waves occurring in late systole (65). Notwithstanding, there is evidence indicating arterial stiffness precedes the rise in blood pressure seen in hypertensive adults (81). In any regard, an increase in SBP gives rise to a stressed and over-worked myocardium, which has to increase oxygen consumption to overcome the afterload. In summary, increases in SBP, pulse pressure, and afterload signify arterial stiffening that is associated with left ventricular hypertrophy (LVH) (15, 73). LVH is an established risk factor for CVD prospectively linked to premature mortality and increased morbidity (15, 42, 90, 112).

Decrease in Coronary Perfusion Pressure

Isolated systolic hypertension is characterized by a normal diastolic blood pressure (DBP), but with a systolic pressure greater than 140 mmHg. Because the vast majority of the myocardial blood flow occurs during diastole, sufficient and robust coronary perfusion pressure is required to oxygenate the heart.

Interestingly, DBP increases with age up until approximately 60 years, and then decreases (114). Because arterial stiffness increases dramatically after 60 years of age, the fall in DBP with increasing arterial stiffness is explained by a diminished hydraulic buffering system. Recall that the principal function of large elastic arteries is to cushion the blood as it is ejected from the heart. Yet, with arterial stiffness, the capacity to "hydraulically" buffer is severely diminished, leading to greater peripheral "run-off" of stroke volume during systole (114). Results from the Framingham study, for instance, indicate elevated DBP is also associated with increased SBP, which allows arterial stiffness to perpetuate in an accelerated and vicious cycle (37). Collectively, these findings indicate that greater arterial stiffness in older age reduces coronary perfusion pressure, which is prospectively linked to myocardial ischemia, infarcts, unstable angina, and premature mortality.

MEASURING ARTERIAL STIFFNESS IN ADULT POPULATIONS

The changes within arteries leading to age-related arterial stiffening are largely due to functional and structural changes within the artery (90). These arterial changes result in volume and pressure changes, which can be assessed as indicators of arterial stiffness. For example, to determine the compliance, or elasticity of an artery one can quantify the changes in volume and pressure (compliance = $\Delta V/\Delta P$) during a cardiac cycle. Pulse pressure can also be easily assessed clinically and used as a surrogate measure of arterial stiffness. To gain even greater insight, however, Young's modulus, a ratio of force per unit

area (stress, units = Pa) per unit length (strain, ratio of the deformation to its original form, units = dimensionless), has also been used to characterize arterial wall stiffness using the incremental elastic modulus (E_{inc}). The E_{inc} can then be used to calculate pulse wave velocity (PWV) as described in the Moens-Kortweg equation: $PWV = \sqrt{(E_{inc} \bullet h / 2 r \rho)}$, where h is the vessel wall thickness, r is the vessel radius, and ρ is the density of blood. In brief, aging increases arterial stiffness (measured as PWV), which can be assessed throughout the arterial tree in a site-specific manner (90).

Pulse Wave Velocity

The viscoelastic properties of arteries vary widely across the arterial tree. Because of this, extrapolating segmental arterial properties and making conclusions about the entire arterial tree is not prudent (65). However, local and/or regional measures, of arterial stiffness of large elastic arteries can be assessed non-invasively, using ultrasonic echotracking systems, magnetic resonance imaging (MRI), or by using the pulse pressure wave that is generated with each contraction of the heart (65). The velocity of the pressure wave also varies across the arterial tree, such that, the velocity of this pressure wave is lower in the proximal aorta than in the periphery indicating the aorta is less stiff than peripheral arteries (69). Consequently, when arterial stiffness is high, as in aging, so is the PWV. The pressure wave can be conveniently palpated at the radial, femoral, or carotid arteries for routine and repeatable measurements.

To determine regional arterial stiffness of the aorta, which includes the entire aorta except the ascending segment, non-invasive carotid-femoral pulse wave velocity (cfPWV, also called aortic pulse wave velocity = aPWV, used interchangeably) can be utilized as it is considered the 'gold-standard' measurement (65). To obtain this measure the pulse waveforms are acquired non-invasively, either sequentially or simultaneously, at the carotid and femoral arteries using tonometry or Doppler flow probes relative to the R wave of the same left ventricular depolarization event. The superficial distance (**D**, meters) between the right common carotid and right femoral arteries, and the time delay (Δ**t** or transit time, seconds) between the feet of the two respective waveforms are acquired. By measuring the distance between the carotid and femoral arteries relative to the suprasternal notch, a reference point, height is accounted for in this measurement. cfPWV/aPWV is therefore calculated as D (meters) / Δt (seconds), which provides a regional measure of aortic stiffness. Logically, the greater the velocity of the pulse wave traveling down the aorta the greater the extent of arterial stiffening. Importantly, this 'gold-standard' measure of arterial stiffness is associated with cardiovascular events, independently of conventional risk factors (94).

PULSE WAVE ANALYSIS

Applanation tonometry is a technique used to assess central hemodynamic parameters that can influence arterial stiffness. There are many commercially available devices, but the SphygmoCor system (AtCor Medical, West Ryde,

Australia) is one of the most widely used and validated devices. The SphygmoCor cardiovascular measurement system uses a generalized mathematical transfer function to create an aortic pressure waveform that is computed both from the pressure waveform at the radial artery and brachial blood pressure. The Food and Drug Administration has accepted the central blood pressure values derived from peripheral waveforms via applanation tonometry as a "substantially equivalent" assessment of aortic pressure when compared with invasive catheterization measures (94). Hence, applanation tonometry is a validated, non-invasive alternative to catheterization and is commonly used in research and clinical settings.

CENTRAL HEMODYNAMICS

Central hemodynamics, which is blood pressure measured at the central (aortic) level, is a stronger predictor of incident CV events than peripheral (brachial) blood pressure (153). Therefore, determining central hemodynamic variables such as SBP, DBP, PP, and MAP, the researcher is able to take a biomedically worthwhile screen for CVD risk in aging adults. Clinically, blood pressure is typically measured in the arm at the brachial artery, thus constituting a "peripheral" measure of hemodynamics. Blood pressure measured at the aortic level, however, is a vital component of "central" hemodynamics and this central (aortic) location is increasingly being used for cardiovascular risk assessment due to its predictive value over and above brachial derived (peripheral) blood pressure (153). Again, current research indicates that central, not brachial,

hemodynamics is a stronger predictor of a first CV event, thus making central blood pressure values biomedically and societally relevant (153). One example of the discrepancy between the central and peripheral vasculature is the amplification phenomenon, which follows that pulse pressure is lower in the aorta compared with brachial artery. Yet, in conditions of aging, pulse pressure amplification is decreased due to increases in aortic stiffness and blood pressure. Central (aortic) hemodynamic parameters such as pulse pressure can be accurately and easily obtained with tonometry; furthermore, quartiles of central pulse pressure are stronger predictors of future CV events in contrast to quartiles of peripheral pulse pressure (111). Clinicians have historically relied on and continue to use peripheral blood pressure measures to determine treatment options. But, there are numerous data suggesting treatments based on central blood pressures may be more effective at identifying elevated CVD risk in adult populations (14, 33, 127).

Central Pulse Pressure

Pulse pressure, or the difference between systolic and diastolic blood pressure within arteries is an important surrogate marker for arterial stiffness. Based on the pressure-strain elastic modulus, E_p to define arterial stiffness, which is calculated by the equation $E_p = \Delta P / (\Delta D/D)$, where ΔP is the aortic pulse pressure; ΔD is the maximal change in aortic diameter during the cardiac cycle; and D is the mean aortic diameter during the cardiac cycle. This described characterization of arterial stiffness points to elevated central pulse pressure as a

major participant in the disease's etiology. Ultimately, the pressure-strain elastic modulus will be elevated in individuals whose aorta is unable to increase luminal diameter for a given pressure. Hence, pulse pressure is the pulsatile component of blood pressure that drives repetitive strain and contributes to fragmentation of aortic elastin, which can be used as a surrogate marker of arterial stiffness (81). It is important to consider within the context of enhancing cardiovascular risk prediction, that the routine use of central pulse pressure measurements in clinical practice has not been substantiated (82).

Pulse Pressure Amplification

The pulse pressure wave increases in amplitude as it travels away from the heart. To ascertain the pulse pressure amplification percentage, divide the central (aortic) pulse pressure *into* the peripheral (brachial) pulse pressure, and multiply by 100. This value is of clinical interest because the widening gap in pulse pressure between central vs. peripheral arterial locations indicates the presence of aortic stiffness (8). Great debate exists as to whether central or brachial blood pressure, or both, should be derived and reported clinically. Because aging is the principal determinant of the reduction in pulse pressure amplification (101), the interaction between central and peripheral blood pressure is an important clinical and biomedical target for measurement.

Augmentation Index (AIx)

AIx is the difference between the first and second systolic peaks relative to pulse pressure (65). The AIx measure is based on the return, or reflected, wave that is transmitted with each heartbeat. In arteries that confer greater stiffness the reflected wave returns to the left ventricle of the heart sooner causing amplification of the systolic blood pressure. The early arrival of the reflected wave increases the myocardial oxygen demand and requires greater mechanical work to overcome the augmented aortic root pressure (afterload), which is one deleterious consequence of arterial stiffness. AIx has also been used as a surrogate measure of arterial stiffness (81).

While the interpretation of AIx is straightforward, one limitation of using this measure as a substitute of cfPWV is AIx has a nonlinear relation with arterial stiffness with increasing age (149). After approximately 60 years of age AIx drops, but arterial stiffness when measured by the cfPWV, increases (76, 85). Therefore AIx is considered to be a more global, or whole-body, measure of stiffness, rather than a specific aortic stiffening endpoint as it assesses the cumulative reflected waves at the heart. AIx may be used to describe the magnitude of peripheral wave reflections, but care should be taken when using AIx as a measure of arterial stiffness, particularly in older populations. Moreover, due to the dependence on heart rate, it is important to standardize or normalize the augmentation index to pulse pressure at a specified heart rate. Many

common medical devices have an in-built feature that adjusts the augmentation index to a heart rate of 75 beats per minute.

Subendocardial Viability Ratio (SEVR%)

During a normal cardiac cycle, the percentage of time spent in diastole is approximately 67% (two-thirds). Recall that coronary blood supply occurs during diastole, when the demand for oxygen is high. However, during overt CVD the myocardium spends progressively more time in systole, in an effort to overcome the exaggerated afterload within the aortic root, and so the time spent in diastole is markedly decreased. Logically, this manifestation of CVD will lead to enlargement of the left ventricle, and ultimately heart failure. Hence, a marker of diastolic function has been established to represent the time spent in diastole *divided by* the time spent in systole. Aging, low cardiorespiratory fitness, and central obesity are strong (negative) predictors of the Buckberg ratio, or the SEVR% (16).

GLOBAL CONTRIBUTORS TO ARTERIAL STIFFNESS

Aging

In the United States, the proportion of patients greater than 65 years of age is increasing at a greater rate than the total population (144). Importantly, the primary determinant of cardiovascular health is age (92). Therefore understanding the impact of early, accelerated and/or heightened vascular aging are important initial steps for identifying vulnerable older populations. For

instance, during ‘normal’ arterial aging there are functional, structural, and cellular and molecular events, which collectively results in arterial stiffness. However, individuals where the arterial aging process is accelerated beyond what would be expected in a normal or reference population, additional increases in aPWV will be observed indicating greater CVD risk (63). Identifying the physiological mechanisms promoting age-related arterial stiffness and the accelerating factors contributing to greater CVD risk are thus clinically significant.

The Baltimore Longitudinal Study on Aging (BLSA) is a large prospective cohort study that assessed aPWV over a period of 7 years in a subset of 943 participants (2). Both older age and increased systolic blood pressure (SBP), or hypertension in this population, were the main longitudinal determinants of age-related increases in aPWV. Furthermore, the effect of SBP on the rate of increase in aPWV was evident even in prehypertensive subjects, and was associated with an accelerated rate of aPWV in a dose dependent manner. The isolated impact, however, of elevated SBP on arterial stiffness is difficult to partition and remains a current challenge. Notwithstanding, it has been shown that after controlling for traditional cardiovascular risk factors, including blood pressure, an increase in 5 m/s of aPWV is equivalent to aging 10 years, in terms of increased likelihood of CVD mortality (64). In very old populations (ie 70 to 100 years), aPWV is a strong independent predictor of cardiovascular mortality with an adjusted odds ratio of 4.60 (95% CI, 1.4 to 15.7) when aPWV was >17.7 m/s

(77). Thus, it is evident that both aging and even modest increases of SBP in older adults are primary factors in greater CVD risk in older populations.

To further highlight the influence of age on aortic stiffness in a large healthy normotensive population (age range = 18 to 90 yrs), it was shown that aPWV beyond 50 years increases at an accelerated rate (76). Therefore, the data suggest arterial stiffness is a more sensitive marker of vascular aging in older compared with younger adults. Hence, in this study, the relationship between arterial stiffness showed an exponential increase after the 5th decade of life, and the inclusion of age as a predictor of aPWV accounted for 60% of the total variance. Similarly in another study, after controlling for gender, body size, and heart rate, aPWV increased by 1.56 m/s per 10 years from age 20 to 80 years in which a marked trend occurred after 50 years of age (109).

Notably, in the presence of obesity and diabetes, arterial stiffness increases more rapidly with advancing age, which would be equivalent to a 70 year old adult (41, 83). These findings provide additional insight for age as the primary factor influencing arterial stiffness, which is accelerated at ~50 years of age, and for both obesity and diabetes as contributors to accelerated age-induced aortic stiffness. Further, the National Institute on Aging SardiNIA study, a population-based, follow-up study involving more than 4,000 community-living men and women (age range = 20 to 100 yrs) showed that aPWV increased by ~60% from age 30 to 70 years (123). An additional cross-sectional study using 102 Korean

adults (age range = 21 to 60s yrs) demonstrated that aging accounted for 37% of the total variance of arterial stiffness, which increased by 0.07 m/s per year (72). In summary, arterial stiffness increases linearly until approximately 50 years of age, after which time there is an acceleration of the stiffening process.

Cardiorespiratory Fitness

Aging is the strongest predictor of arterial stiffness for both women and men. Chronic, regular physical activity can blunt the age-related arterial stiffening, as indicated in physically active older adults with similar aPWV compared to middle aged adults (136). However, a significant difference in aPWV was still observed between groups indicating regular activity cannot fully reverse the age-related increase in arterial stiffness to those of younger adults. The strongest predictors of aPWV in this cohort were cardiorespiratory fitness (ie VO_{2peak}) and total and LDL cholesterol, which collectively explained up to 50% of the variance in central arterial stiffness (136). Similarly, VO_{2peak} has been shown to be associated with reduced PWV and body fatness, and greater amounts of regular physical activity in an apparently healthy middle aged adults (155). In addition, an important mechanistic relationship was shown in older but not younger adults between VO_{2peak} and relative left ventricular wall thickness ($R = -0.32$, $P < 0.05$), indicating that more favorable cardiac remodeling is predicated on greater cardiorespiratory fitness. In brief, greater physical activity and improved cardiorespiratory fitness is associated with reduced arterial stiffness and more favorable cardiac remodeling in middle-aged and older women.

Men with higher cardiorespiratory fitness also demonstrate reduced arterial stiffness, in part, through reductions in resting heart rate (104). In addition, it has been shown that men who engage in regular endurance exercise had lower aPWV than both resistance trained and sedentary (non-exercising) participants (96). This relationship of reduced arterial stiffness was dependent on greater cardiorespiratory fitness, reduced SBP, and reduced endothelin-1, a vasoconstrictor, in the endurance trained men (96). Importantly, it has also been demonstrated, for both men and women, greater cardiorespiratory fitness and reduced arterial stiffness is associated with improved occipitoparietal perfusion and better cognitive composite scores (memory and attention-executive function) than those with lower cardiorespiratory fitness and greater arterial stiffness (138). Thus, suggesting cardiorespiratory fitness and reduced arterial stiffness may influence important cognition centers in the brain. Collectively, these data indicate chronic exercise and/or increased cardiorespiratory fitness in men and women are important for attenuating the aging associated effects of arterial stiffness.

Strength Training

Regular, progressive strength training is an important exercise modality for preserving the aging associated decrements in lean muscle mass, strength, and physical function. However, reports have suggested strength training may increase measures of arterial stiffness. For example, Bertovic et al. (13)

compared apparently healthy young males who had regularly strength trained for 12 months to sedentary controls, and discovered that strength trained athletes had higher aortic characteristic impedance (defined as the pressure change generated by a given flow wave change in the absence of reflections) and β stiffness. Additionally, strength trained athletes had greater carotid and brachial pulse pressures compared with the sedentary controls (13). Similarly, young men (age range = 20 – 38 yrs) who engaged in resistance training for 4 months increased β stiffness and decreased carotid arterial compliance. These positive, structural changes were inversely related to alterations in left ventricular mass and hypertrophy indices (87). Interestingly, detraining from resistance-based exercise reversed the negative impact of strength training on arterial compliance, as arterial stiffness values returned to baseline after 4 months of detraining (87).

Last, it has been shown that young men (age = 21 yrs) who had been strength training for 2 years had greater aPWV, and increased plasma endothelin-1 levels, compared with endurance trained athletes and sedentary controls (96). Additionally, in middle aged men, strength trained vs. sedentary controls had greater β stiffness, SBP and MAP, indicating that resistance-based exercise promotes arterial stiffening. Whereas, vasoreactivity to a sympathetic stimulus was similar between the strength trained vs. sedentary controls, indicating endothelial function remains intact despite changes to other measures of large elastic artery function (60). In short, there is convincing evidence that strength training increases arterial stiffness in both young and middle aged men. However,

it is important to note that strength training is a recommended form of exercise to prevent age-related decreases in muscle mass, and that concomitant aerobic exercise offsets the influence of strength training on arterial stiffness (24, 79). Undeniably, strength training per current guidelines in conjunction with aerobic exercise is recommended.

Physical Activity

The association of increased step counts and reduced arterial stiffness has been shown in children (115) and diseased adult populations with hypertension (93) and type-2 diabetes (57). Moreover, the identical association persists in older adults (6, 38, 66). However, in a middle-aged population one significant confounding variable is gender. Given that several investigations have shown an inverse relationship between physical activity and arterial stiffness in both male and female subjects (3, 44), it would be worthwhile to isolate gender, and determine if more total physical activity is associated with arterial stiffness.

There are several validated and reliable methods to measure local, regional, and global arterial stiffness. Yet, the gold-standard method is the pulse wave velocity. In order to accurately characterize the influence of physical activity on arterial stiffness, directly measuring step counts and correlating with the aortic pulse wave velocity in a middle-aged group would be novel.

Physical Function

In young men, an inverse relationship between muscular strength and arterial stiffness was demonstrated independent of aerobic fitness (34). Physical function is essentially "what the human body can do" and is important for activities of daily living and maintenance of physical independence that is crucial during older years. The use of hand-grip strength as a measure of function (strength) is associated with lean muscle mass both in young populations as well as older ones (116), and is associated with old age disability (105). However, to date, no study has examined an otherwise apparently healthy middle-aged population to determine if the relationship between handgrip strength and arterial stiffness remains. To speculate, the association of reduced physical function and greater arterial stiffness may be due to a phenotypic shift in skeletal muscle. For example, when muscle contracts regularly as it does during regular aerobic and anaerobic exercise, the secretome changes in a favorable way. However, when sedentary time is increased and an individual does not move or exercise regularly, the secretome is unfavorably changed in a way that may negatively interact with the vasculature. One example is an increased in pro-inflammatory cytokines that communicate in a paracrine manner with the large arteries, thus leading to greater CVD risk as a result of insufficient skeletal muscle contractions.

In general terms, accumulation of regular physical activity leads to improved cardiorespiratory fitness, which is a health-related component of physical function (107). More specifically, regular physical activity is associated with

improvements in musculoskeletal tests such as modified push-ups, static back extension, and the one-leg standing balance test in an apparently healthy middle-aged adult population (133). Regarding older adults, improved 400 meter walking speed and time is associated with reduced arterial stiffness (45). And, greater physical activity is associated with delayed disability retirement due to maintenance of musculoskeletal health (62) such as lower body strength (71) which plays a crucial role in the prevention of functional decline with advancing years and decreasing physical activity (39). Thus, achieving greater amounts of physical activity directly and positively impacts the functional state of musculoskeletal health, and is inversely related to premature mortality in aging adults (131).

Body Composition

Assessment of body composition, particularly body fatness, and relating to measures of arterial stiffness is critical. However, there are many facets, and limitations for the different measures of body composition that need to be considered prior to discussing body composition and arterial stiffness. For example, fat and fat-free mass can be assessed by dual energy x-ray absorptiometry (DXA) and computed tomography (CT) scans that provide valid measures. Both DXA and CT scans are preferable measures; however, they are costly and are not always feasible for larger population studies. For larger studies, body mass index (BMI) is a common measure of total body fatness, which is determined with the ratio of weight (kg) to height (m^2). As such, BMI quantifies

total mass, and does not selectively quantify fat or fat-free mass. Hence, individuals who have a high BMI may not necessarily have a high body fat percentage, but instead could have a large amount of fat-free mass that could increase BMI but not reflect greater fat mass. In large part, however, BMI is a standard and valid method for assessing body fatness in sedentary and recreational active individuals, or those without large amounts of muscle mass.

Greater fat mass resulting in obesity has been implicated in arterial stiffness across the lifespan. As such, overweight and obese adolescents (n = 86; BMI ≥ 85th percentile) demonstrate a higher aortic and brachial SBP and PP, and mean arterial pressure (MAP), than adolescents of normal weight (n = 141; BMI < 85th percentile) (102). Moreover, overweight/obese adolescents have a 7% higher aPWV and 3.5% lower PP amplification than the adolescents of the normal weight group (102). It is particularly worrisome and likely that, given the negative implications of childhood obesity on arterial function, overweight and obese adolescents will carry unhealthy juvenile behaviors into adulthood that will give rise to early CVD risk. For instance, it has been shown in a large follow-up study that childhood body size or adiposity was associated with increased intima-media thickness and large artery stiffness as an adult (55). Thus, it is imperative to develop interventions to attenuate adolescent arterial stiffening that is due to obesity.

Overeating, or excessive caloric intake, and/or a sedentary lifestyle contribute to weight gain and obesity. When normal weight, non-obese adults were overfed for 6 to 8 weeks by ~1000 kilocalories/day (5 kg of weight gain), total abdominal fat, abdominal visceral fat, and waist circumference increased in parallel with arterial stiffness by 13% (95). These findings were similar in Amsterdam Growth and Health Longitudinal Study, in which they found that an increase of trunk mass by 10 kg was positively associated with carotid Young's elastic modulus (120). In short, the magnitude of abdominal visceral fat accumulation appears to be an important contributor of large artery stiffening in adults (95, 132).

In addition to short-term weight gain, chronic obesity in adults results in significant metabolic burden due to excessive fat storage, and ultimately, a clinical manifestation of arterial dysfunction. In large part, overweightness and obesity are considered to be important in arterial stiffening (4, 91, 95).

Contrary to this notion, it has been asserted that BMI is not very useful in predicting changes in arterial stiffness due to generalized obesity (152), and that the cardiovascular system of older adults may display an adverse association of body fat and arterial stiffness in contrast to young adults who may be more adaptable to the state of obesity (26). Waist circumference, in fact, was the only measurement positively associated with early atherosclerosis and arterial stiffness in the Supplementation en Vitamines et Mineraux Antioxydants

(SU.VI.MAX) study, in which over 1,000 middle-aged adults were assessed for body composition and carotid structure and function (28).

In support of this finding, older adults from the Health ABC study demonstrated an association of aPWV and abdominal visceral fat (the strongest predictor of arterial stiffness) that was consistent across tertiles of body weight (134). Additionally, older men with high amounts of total lean mass and low total fat mass exhibited the most favorable arterial profile, including reduced aPWV (12). For older women, greater trunk fat mass was the strongest predictor of arterial stiffness (35). Although general obesity does contribute to arterial stiffness for the population at large, some studies indicate abdominal obesity is a better predictor of arterial stiffness.

Dietary Quality

A recent population-based investigation, the Maine-Syracuse Longitudinal Study, examined older men and women for lifestyle habits that relate to arterial stiffness, including diet quality (27). The significant relationship demonstrated with the "recommended food score" and arterial stiffness indicates that the overall quality of one diet is directly related to CVD risk. These results may not be applicable to individuals beyond the study population. In other words, because the composite cardiovascular health scores were grouped in tertiles, the central limitation of this study is that the results of the nutritional questionnaire were not correlated with aPWV. Using a more robust, validated and reliable measure of overall dietary

quality would allow for insight into the specific components of human nutrition that are associated with arterial stiffness.

The Healthy Eating Index (HEI) is a valid and reliable measure of diet quality and determines adherence to the 2010 U.S. Dietary Guidelines for Americans (46). Compliance with the U.S. Dietary Guidelines is favorably associated with vascular health, including reduced arterial stiffness (119). Further, diets that score high on the HEI are associated with reductions in all-cause and CV-related mortality (121). Thus, the HEI score, a summated twelve component index of long-term (1 year) diet quality and food frequencies and preferences, provides more direct and specific insight into the exact dietary components associated with reduced arterial stiffness.

For instance, previous research has shown that the ratio of unsaturated to saturated fatty acid consumption is an important determinant of preserved cardiovascular health including arterial function and stiffness (49). Additionally, consumption of low-fat compared with whole-fat dairy was negatively correlated to the aPWV in 20 to 80 year old men and women (108). Further, greater fruit and vegetable consumption are inversely associated with arterial stiffness, even in young adulthood (1). It remains to be seen whether overall dietary quality is associated with aortic stiffness in any population.

KEY NUTRIENTS AND FUNCTIONAL FOODS

The role of dietary factors in both the acceleration and slowing of CVD is undeniable. Skewing the energy balance equation towards greater intake vs. expenditure is the principal cause of obesity, which in turn accelerates arterial stiffening and the risk of CVD events. Understanding the impact of food intake, in terms of quality and quantity, and how it relates to CVD is a 21st century puzzle that remains to be solved. Many so-called "heart healthy" diets that have been conventionally recommended such as reduced saturated fat intake have shown poor associations with overall CV health status, thus complicating matters (29). It now appears as though the relation of saturated fat intake to CVD risk is dependent upon the *source*, be it plant or animal based (10, 29). To date there is no consensus as to what exactly a "heart healthy" diet should consist of, and if in fact saturated fat intake is as pernicious as once thought.

Omega-3 Fatty Acids

Over the last 50 years studies have shown an array of health benefits among those following Mediterranean diets, including reduced CVD risk (122). Several advantages of following a Mediterranean diet is improved vasodilation, decreased blood pressure, and reductions in oxidative stress and inflammatory biomarkers (146). The purported mechanism of reduced CVD risk by the Mediterranean diet is due to the greater intake of long chain polyunsaturated omega-3 fatty acids. The plant based food sources of omega-3 fatty acids (alpha linolenic acid [ALA]) include flaxseed, hempseed, soybeans, and walnuts (117,

146). The marine sources of omega-3 fatty acids (eicosapentaenoic acid [EPA] and docosapentaenoic acid [DHA]) include algae, salmon, mackerel, and trout. Importantly, the metabolic conversion of the 18 carbon fatty acid ALA to the 20 carbon fatty acid EPA and 22 carbon fatty acid DHA is approximately 5% in humans, thus making it “essential” to consume EPA and DHA in copious amounts (17). In short, specific consideration should be given to the type of long chain polyunsaturated omega-3 fatty acid consumed, in particular EPA and DHA, due to their association with decreased CVD risk factors and improved vascular outcomes (18).

Unfortunately, the metabolic syndrome is a common disease, characterized by at least three of the following risk factors: abdominal obesity, low HDL cholesterol, high triglycerides, hypertension, and impaired fasting glucose. The metabolic syndrome accounts for up to 1/3rd of CVD in men (151), therefore assessing the influence of omega-3 fatty acids in a metabolic syndrome population is a promising therapy. As such, 12 weeks of oral supplementation with 2 g/day of omega-3 polyunsaturated fatty acids (46% EPA; 38% DHA) in middle-aged adults with metabolic syndrome reduced aPWV from 7.62 ± 1.59 at baseline to 7.22 ± 1.54 m/s ($P < 0.001$) at the end of the trial. Additionally, total cholesterol, triglycerides, LDL cholesterol, and IL-6 were significantly reduced, while plasminogen activator inhibitor 1 and flow mediated dilation increased, over the course of the 12-week intervention compared to baseline values ($P < 0.001$). The favorable effects of omega-3 supplementation on endothelial function and

arterial stiffness in adults with metabolic syndrome appear to be partially mediated through modification of the metabolic profile and inflammatory processes (140).

As mentioned previously, endothelial dysfunction is an early event in the pathogenesis of arteriosclerosis that increases CVD risk. Cigarette smoking is associated with dose related and (potentially) reversible impairment of endothelium dependent arterial dilation in asymptomatic young adults (22). The smoking related impairment in endothelium dependent arterial dilation promotes increases in the pro-inflammatory phenotype, leading to changes in the thrombosis/fibrinolysis system, which are important pathways for coagulation and the enzymatic breakdown of blood clots (5). In a randomized, placebo-controlled, double-blind, and crossover study, the effects of 12-week omega-3 polyunsaturated fatty acids supplementation (46% EPA; 38% DHA) in 20 healthy smokers (13 males; 7 females; mean age = 28 ± 3 yrs) who had been smoking greater than 20 cigarettes per day for greater than 5 years were determined (128). Treatment with omega-3 polyunsaturated fatty acids reduced aPWV from 5.87 ± 0.63 at baseline to 5.54 ± 0.76 m/s ($P = 0.007$) following the intervention. Additionally, TNF alpha and IL-6 were significantly reduced, while plasminogen activator inhibitor 1 and flow mediated dilation increased, over the course of the 12-week intervention compared with baseline values ($P < 0.05$). Supplementation with omega-3 fatty acids did not, however, influence the lipid profile. In short, the detrimental effects of regular cigarette smoking on endothelial function and

elastic properties of the arterial tree can be ameliorated by long chain omega-3 fatty acids such as EPA and DHA in asymptomatic adults, in part, through reductions in inflammation (128).

Sodium Restriction

The consumption of highly salted food is increasing worldwide, and these changes in salt intake present a major challenge on the physiological systems of the body (50). Much evidence exists regarding our high salt intake and its role in creating the large rise in blood pressure that occurs with age (50). Therefore, minimizing sodium intake has been an important strategy for addressing the age-associated increase in blood pressure, which is directly linked to the pathophysiological processes that underpin arterial stiffness. For example, Dietary Approaches to Stop Hypertension (DASH) have been successful in reducing systolic and diastolic blood pressures in a variety of adult populations, and so DASH-like diets that invoke these beneficial effects of reducing blood pressure and the concomitant decrease in arterial stiffness are highlighted in this subsection (118).

In a randomized, placebo-controlled study with a crossover design, eight men and three women (mean age = 60.2 yrs) with moderately elevated systolic blood pressure (139 ± 2 / 83 ± 2 mmHg) followed a low sodium (77 ± 99 mmol/day) or normal sodium (144 ± 7 mmol/day) diet for five weeks (56). aPWV for the low sodium condition was significantly reduced compared to that of the normal

sodium condition (7.0 ± 0.4 vs. 8.43 ± 0.36 m/s, P = 0.001). Furthermore, systolic blood pressure was significantly reduced as a result of the low sodium condition compared with baseline and the normal sodium condition (low sodium: 127 ± 3, baseline: 139 ± 2, normal sodium: 138 ± 5, P < 0.001).

It is important to consider that systolic blood pressure is a key determinant of large elastic artery (aortic) stiffness (59), which may explain the impact of low sodium consumption on reductions of aPWV in this middle-aged and older cohort of adults with moderately elevated systolic blood pressure.

Similarly, a study in a postmenopausal cohort of women of middle and older age (n = 17; mean age = 65 ± 10 yrs) used a three-month sodium restriction protocol (pre-intervention to post-intervention: 2685 ± 559 vs. 1421 ± 512 mg/day) to assess changes in arterial function (125). In addition to reductions in systolic blood pressure (~16 mmHg, P < 0.05), aPWV was also significantly reduced as a result of three months of sodium restriction (8.7 ± 2.0 vs. ~7.3 ± 1.1 m/s, P < 0.05). Again, this study highlights the influence of blood pressure reduction with sodium restriction to decrease central arterial stiffness in women whose systolic blood pressure ranged from 130 – 159 mmHg.

Additional studies have also demonstrated reductions in blood pressure and arterial stiffness in mildly hypertensive patients (n = 169; mean age = 50 ± 11 yrs; 147 ± 13 / 91 ± 8 mmHg) as a result of modest sodium restriction (51). In this study, the reduction in salt intake from 9.7 to 6.5 grams/day was successful in

reducing systolic blood pressure by 5 ± 12 mmHg ($P < 0.001$). Importantly, aPWV also dropped from 11.5 ± 2.3 to 11.1 ± 1.9 m/s, which was statistically significant ($P < 0.01$). These results demonstrate that a modest reduction in salt intake can improve CVD risk by attenuating systolic blood pressure and increasing compliance of the aorta. Because the reduction in salt intake was in accordance with current public health recommendations, the improvements (albeit slight) seen in arterial stiffness are promising not only for mildly hypertensive adults, but also normotensive adults. The research regarding sodium restriction in well-controlled clinical trials is undoubtedly scarce. However, the studies presented herein point to a meaningful connection between sodium consumption, systolic blood pressure, and arterial stiffness that deserves further clarification.

Antioxidant Vitamins (C and E)

It has been hypothesized that vascular function and structure will be improved if oxidative stress can be ameliorated by reducing free radicals and protecting nitric oxide (NO) from inactivation (68). Supplementation with antioxidant vitamins C and E, in particular, are recognized to protect against lipid peroxidation, a contributor to arterial stiffness. And many observational studies have shown that a high dietary intake or high blood concentrations of antioxidant vitamins are associated with reduced risk of CVD in general (126). Yet few studies have examined the potential effects of antioxidant supplementation on vascular stiffness and function in humans.

Using an emulsified preparation of a tocotrienol-rich vitamin E supplement, 36 healthy young men (mean age = 23.9 ± 0.39 yrs) were assigned to either 50, 100, or 200 mg daily supplementation of this compound for eight weeks (106). All treatment groups had higher plasma concentrations of vitamin E following the eight-week study duration ($P < 0.05$). Vitamin E supplementation had no effect on systolic blood pressure. However, aPWV was significantly reduced in both the 100 mg and 200 mg supplementation groups by 0.77 m/s and 0.65 m/s, respectively. This reduction in aortic stiffness was approximately 10% less than the values observed at baseline. Mechanistically, it has been shown that free radicals inactivate endothelium derived relaxing factor (EDRF), an important vasodilator (113). Therefore, it is plausible that the reductions in aPWV seen in this study were due to neutralization of free radicals, and preserved EDRF activity.

Vitamin C supplementation has been shown to restore NO activity by improving endothelium dependent vasodilation in adult patients with essential hypertension (135). The synergistic effects of vitamin C and E supplementation may exert a greater antioxidant effect beyond those effects in isolation. In a randomized, double-blind, placebo-controlled study with a crossover design a combined vitamin C (1 gram) and vitamin E (400 IU) treatment was given for eight weeks to 30 males (mean age = 50 yrs; range 42 to 60) with (never treated) essential hypertension (103). While combined treatment of vitamin C and vitamin E did not

affect blood pressure, a significant reduction in aPWV was observed (pre to post, ~9.1 to ~8.4 m/s, $P < 0.01$).

The combined effect of antioxidant vitamins C together with E may provide optimal conditions for endothelial NO formation (54). Therefore, independent of changes in blood pressure, improvements in aortic stiffness were demonstrated in this male population of untreated hypertensives that is possibly due to decreases in vascular oxidative stress, and enhanced NO bioavailability. Yet it remains to be determined whether apparently healthy middle aged adults would benefit from greater intake of vitamin C and/or E supplementation.

LIFESTYLE MODIFICATIONS

The first-line approach for prevention and treatment of most CVD risk factors is lifestyle & behavior modifications (137). Regular aerobic exercise is a beneficial way to lose weight, and promotes arterial compliance. The impact of excessive reduced aerobic fitness and excessive body mass on arterial stiffness is clear: The less fit and larger you are, the stiffer your arteries, independent of age (124). Thus, the physiological basis of weight gain (or weight loss) ultimately points back to the law of conservation of energy, which states that energy cannot be created or destroyed but rather changes forms.

Because food provides the human body with energy, and is accumulated then subsequently stored in adipose tissue, obesity can best be explained as a

condition of excessive caloric intake relative to caloric expenditure. The health benefits of a lifestyle modification such as weight loss can therefore be achieved either by 1) eating less, or 2) increasing levels of physical activity.

Calorie Restriction

Among normotensive overweight/obese young adults, weight loss is associated with a reduction in aortic stiffness (25). After a 1-year lifestyle intervention (diet/physical activity/reduced sodium), aPWV significantly decreased by 0.581 m/s after 6 months ($P < 0.0001$), by 0.32 m/s ($P = 0.02$) and after 12 months (25). This 1-year intervention resulted in an average weight loss of 6.4% ($P < 0.05$). Additionally, systolic blood pressure, triglycerides, CRP, insulin, and leptin decreased ($P < 0.05$); whereas, HDL cholesterol increased ($P < 0.05$).

Additional studies have also demonstrated the effectiveness of lifestyle intervention on arterial stiffness in populations with greater CVD risk. Obese men (mean age = 45 ± 2 yrs; BMI = 30 ± 1 kg/m^2) were placed on a low-calorie lifestyle intervention (1,380 kcal/day) for 12 weeks. aPWV significantly decreased from 9.79 ± 0.45 to 9.18 ± 0.29 m/s ($P < 0.05$). Additionally, plasma endothelin-1 (a vasoconstrictor) significantly decreased from 1.9 ± 0.1 to 1.3 ± 0.3 pg/mL ($P < 0.01$), and plasma nitrite/nitrate significantly increased from 24 ± 3 to 39 ± 4 μmol/L ($P < 0.01$), suggesting that enhanced endothelial function is responsible for the reduction (9%, $P < 0.01$) in aortic stiffness following weight loss due to a low-calorie diet. Other physiological variables that changed over the course of

the 12-week weight loss intervention were total cholesterol, triglycerides, and blood glucose ($P < 0.05$) (88).

Furthermore, a 12-week hypocaloric diet (1,200 to 1,500 kcal/day) administered to 25 overweight/obese, middle-aged and older adults (16 females; 9 males; mean age = 61.2 ± 0.8 yrs; BMI = 30.0 ± 0.6) demonstrated a significant reduction in aPWV by 1.87 ± 0.29 m/s ($P < 0.05$) (31). The magnitude of this improvement in arterial stiffness was positively related to the percent weight loss ($r = 0.59$; $P < 0.05$). Additionally, brachial and aortic systolic blood pressures, triglycerides, total cholesterol, and glucose were significantly reduced ($P < 0.05$). Notably, the observed reductions in arterial stiffness in this study (~ 1.5 to 2.0 m/s) would translate into a reversal of age-related arterial stiffening by ~15 to 20 years (31).

SUMMARY OF LITERATURE REVIEW

Large elastic artery dysfunction is a major cause of premature mortality and incident cardiovascular events such as myocardial infarction, stroke, and heart failure. The primary cause of cardiovascular disease as a result of aortic stiffness is increased wave reflections, afterload, and reduced coronary perfusion pressure. These two factors combined elevates the left ventricular oxygen consumption values which is associated with enlargement of the myocardium. And, the increased wave reflection and afterload significantly affects left ventricular filling and emptying patterns. In addition, prospective trials indicate,

after adjustment of traditional CVD risk factors, that increased aortic stiffness is injurious to target organs such as the brain, heart, and kidneys. Indeed, the increased pulsatility that results with greater aortic stiffness is essentially tantamount to increased kinetic energy, which is destructive to the microcirculation, specifically the endothelium. With the global rates of obesity increasing steadily, it is becoming increasingly important to understand lifestyle contributors to aortic stiffness, which would benefit public and community health.

CHAPTER THREE: METHODS

OVERVIEW OF EXPERIMENTAL APPROACH

This study employed a cross-sectional, observational design to examine the relationship between global, lifestyle contributors to CVD risk in apparently healthy middle-aged males. In total, 54 men were recruited for participation from around the University of Kentucky community by means of advertisement. Two men were excluded due to hypertension. Thus, 52 men completed this study. Each subject was required to visit the Exercise Physiology Laboratory in Seaton Building two times, with each visit lasting approximately one hour. Although complete details regarding each testing component will be provided later in this section, an overview of the study approach is as follows. The initial day of testing examined body composition with bioelectrical impedance analysis, and assessed CVD risk with aortic stiffness and pulse wave analysis. Then, a motion sensor (Fitbit Zip; tri-axial accelerometer) was programmed for each participant that was to be worn for the subsequent seven days. Participants were instructed to not change their normal recreation habits during this tracking period. During the second day of testing, each subject was tested for maximum grip strength and overall musculoskeletal fitness. In addition, each subject completed an exhaustive web-based nutritional food frequency questionnaire designed to measure dietary quality over the previous one-year.

SUBJECT RECRUITMENT METHODS, PRIVACY, AND PAYMENT

Subjects were actively recruited from Lexington and the surrounding communities, including from the University of Kentucky, through advertisement with the IRB-approved recruitment study flyer. All data were stored in a locked filing cabinet located within a locked room. Only study personnel had access to the private information of the study population. The data does not contain any traceable information and was stored on a password-protected computer. Data were used in a restricted manner and were summarized as group data. Subjects did not receive cash reward for their participation. Immediately after participation, each subject was offered an abbreviated report of his body composition, arterial stiffness, brachial blood pressure, and physical activity output. All information was provided to the subject under the understanding that the data collected during the study period was for research purposes only. Participants who were concerned with their cardiovascular health were advised to consult his primary care physician.

SCREENING

Informed consent was voluntarily obtained from each subject before they were allowed to participate in the study. The consent form was explained thoroughly and each subject had adequate time to read the form and ask questions. The original signed consent form was secured and appropriately filed for review to ensure confidentiality of data collected. If requested, all participants received a copy of the signed consent form.

Inclusion Criteria

Subjects were enrolled into the study if they had a resting brachial blood pressure of less than 140 over 90 mmHg. Additionally, each subject had to be a middle-aged man between the ages of 30 and 60 years of age. We anticipated a racially diverse study population and therefore enrolled all races.

Exclusion Criteria

Subjects were ineligible to participate in the study if resting brachial blood pressure was greater than 140 over 90 mmHg, indicating stage 1 hypertension according to the current guidelines of the American College of Sports Medicine (100). Additionally, habitual smoking, orthopedic limitations, and adherence to CV medications such as anti-hypertensives, lipid lowering drugs, vasodilators, or others, and resting peripheral (brachial) blood pressure greater than or equal to 140 over 90 mmHg indicating stage 1 hypertension. Women were not able to participate in this study in an effort to eliminate gender as a confounding variable. For example, middle aged men have significantly higher rates of CVD including angina, heart attack, stroke, and aneurysms compared with middle aged women (80). While women appear to have an accelerated rate of CVD following menopause, this research project aims to study a relatively susceptible, vulnerable male population that is more likely to fall victim to premature mortality and CVD. Thus, quantifying the relation of lifestyle factors and cardiovascular disease in middle-aged men, in isolation, would remove the known confounding influence of gender, and would be of great public benefit.

RESEARCH PROCEDURES

Physical Activity

Each subject was affixed with a tri-axial accelerometer, colloquially referred to as a fitness-tracking device (Fitbit Zip, Fitbit Inc., San Francisco, CA), which was worn on the right hip over the course of seven full days. A compliance form was issued to each subject to ensure adherence to the study protocol. Following this seven-day tracking period, physical activity data such as step counts, total distance, calories burned, and active minutes, were downloaded to a portable electronic tablet (iPad) for analysis. Research has validated the motion sensor used in this study compared against criterion methods (141).

Physical Function

Each subject was required to complete a maximum handgrip strength test on a calibrated hydraulic hand dynamometer (Baseline, Fabrication Enterprises Inc., White Plains, NY) according to the manufacturer's protocol. Specifically, each subject squeezed the hand dynamometer and maintained 90 degrees of elbow flexion, an adducted shoulder, and a neutral wrist position while standing. Three attempts were permitted with each hand in an alternating manner, and the peak value was recorded from each hand and data were summed. To normalize absolute handgrip strength and allow for inter-subject comparison, the data were subsequently divided by the subject's body weight and expressed as a ratio.

Following the maximum handgrip strength test, each subject was required to complete a sitting-rising test 5 times according to the standardized protocol (20). The test was performed with the subject barefoot, standing on a non-slippery yoga mat, and required the subject to lower himself from a standing position to a seated, erect posture on the floor. After one trial was performed (serving as the familiarization trial), each subject was given verbal cues and coaching as to how to improve the SRT score. The maximum score was ten possible points (5 points maximum for the sitting portion, and 5 points maximum for the rising portion). A 1-point deduction for using assistance such as a hand, knee, or side of the leg was taken from either sitting or rising portion. Loss of control or balance resulted in a 0.5-point deduction. In order to preserve validity and reliability, all five trials were video recorded with an electronic portable tablet (iPad) and were reviewed by a single investigator. The video files were locked in a storage locker under a key, and only the study personnel had access to the device and data. The highest sitting and rising score from any of the five trials was chosen as the component scores, which were summed to yield the composite SRT score, which is both valid and reliable at determining overall musculoskeletal fitness (20).

Body Composition

Body composition was determined with conventional bioelectrical impedance analysis (BIA) by a single trained investigator with a single frequency (50 kHz) analyzer (BodyStat1500, BodyStat Ltd., Isle of Man, UK). This tetrapolar, hand-to-foot technique required the subject to be in the supine position. The

electrodes were placed on the dorsal surface of right foot and ankle, and right wrist and hand. Subjects were evaluated after voiding the bladder, and were asked to refrain from strenuous exercise and consumption of caffeinated beverages the twelve hours preceding the measurements.

Body composition variables measured included relative and absolute fat and fat free (lean) mass, total body water, impedance, resistance, and reactance at 50 kHz. Height was recorded with a wall-mounted stadiometer to the nearest 0.1 cm and body mass was measured to the nearest 0.1 kg with a calibrated digital scale. Anthropometric measures such as the circumference of the waist and hip were obtained according to current ACSM Guidelines for Exercise Testing and Prescription using a flexible measuring tape (100). Each anatomical location for girth measurements was taken in duplicate to the nearest 0.1 cm, and the data were subsequently averaged. Test, re-test reliability by the single investigator was optimal, with an r^2 between measures at 0.99.

Dietary Quality

Each subject completed a 140 item, web-based National Institute of Health Diet History Questionnaire, addressing food frequency that was used for determination of overall dietary quality and adherence to the U.S. Dietary Guidelines regarding the previous one year. The composite Healthy Eating Index (HEI) score ranges from 0 to 100, with higher scores representing higher dietary quality. The HEI score is a composite of the 12 subcomponents, which

include: 1) Total vegetables, 2) Dark green vegetables and beans and peas, 3) Total fruit, 4) Whole fruit, 5) Refined grains, 6) Whole grains, 7) Total dairy, 8) Total protein foods, 9) Seafood and plant proteins, 10) Fatty acids, 11) Sodium, and 12) Empty calories (46). Nutritional analyses were conducted on Diet*Calc 1.5 (Diet*Calc Analysis Program, National Cancer Institute, Silver Spring, MD) and HEI component and composite scores were performed on SAS 9.4 (SAS Institute, Cary, NC).

Large Elastic Artery (Aortic) Stiffness and Central Hemodynamics

Aortic pulse wave velocity *(*aPWV) is considered the "gold standard" measure of arterial stiffness that uses non-invasive arterial tonometry, a commonly performed clinical technique (89). Importantly, these noninvasive estimations of central (aortic) blood pressure and pulse wave velocity correlate well with invasive catheter-derived measurements acquired at the ascending aorta with a correlation coefficient of 0.91, demonstrated with the SphygmoCor device (32). Subsequently, the radial, carotid, and femoral artery locations were located and the pressure-sensing device, tonometer, was placed directly on the skin surface above the site of the strongest palpable pulse. The non-invasive SphygmoCor pulse wave analysis (PWA) and pulse wave velocity (PWV) system (AtCor Medical, Sydney, Australia) were used to measure central blood pressure and hemodynamics and arterial stiffness, respectively, during resting conditions. Each subject was placed in the supine position and allowed to rest quietly for 10-15 minutes prior to data acquisition. PWA measures are reported as mmHg and

the speed of the pulse wave (PWV) from the carotid to femoral artery were calculated and presented in meters/second (145). Test, re-test reliability by the single investigator was optimal, with an r^2 between measures at 0.98.

STATISTICAL ANALYSIS

Shapiro-Wilk tests were run on all variables to determine normality. Levene tests were used to determine equal variances. Pearson product-moment correlation analyses examined the association between lifestyle factors to CVD risk (S/DAY, SRT, GRIP/BW, FAT%, and HEI) and the primary health-related outcome measure, aPWV. Partial correlation testing examined the age-adjusted associations between lifestyle factors and aPWV. Multivariable linear regression analyses analyzed the predictive abilities of the lifestyle factors on aPWV. Backward stepwise regression analysis was run on all lifestyle factors to determine the strongest predictor of aPWV.

Analysis of covariance (age as covariate) tested the association of lifestyle factors (expressed as categorical variables) with the continuous variable, aPWV, using the equal slopes test. Two levels for quantiles were created based around (above and below) the median, whereas three levels for tertiles were divided from the ordered distribution of values, which were split into (nearly) equal parts (low, N = 17; moderate, N = 18; high, N = 17). All pairwise multiple comparison procedures used the Holm-Sidak method. The alpha level was set as $P < 0.050$. Pearson-product moment correlations are described as weak if r = 0.0 to 0.29,

moderate if r = 0.30 to 0.69, and strong if greater than or equal to 0.70. All data were analyzed with SigmaPlot 12.3 (Systat Software Inc., San Jose, CA) and SPSS 23 (IBM SPSS Statistics, Armonk, NY).

CHAPTER FOUR: RESULTS

The descriptions of study variables used in this study are presented in Table 1A and statistical variables in Appendix A. Descriptive statistics of the study population are presented in Table 1B. Pearson product-moment correlation matrix representing the association of lifestyle factors with aortic stiffness and age is presented in Table 2A. Specifically, S/DAY was not associated with aPWV ($r = -0.02$; $P = 0.875$), demonstrating no association between physical activity and aortic stiffness. However, SRT and GRIP/BW were inversely associated with aPWV ($r = -0.51$; $P = 0.000$, $r = -0.56$; $P = 0.000$, respectively), demonstrating that greater physical function is associated with reduced CVD risk. FAT% was strongly associated with aPWV ($r = 0.62$; $P = 0.000$) and reflects the negative impact of obesity on large elastic artery stiffness. HEI was associated with aPWV ($r = -0.30$; $P = 0.033$), demonstrating an important link between overall dietary quality and a novel risk factor for CVD risk. Age was associated with aPWV ($r = 0.56$; $P = 0.000$), SRT ($r = -0.30$; $P = 0.29$), GRIP/BW ($r = -0.45$; $P = 0.001$), FAT% ($r = 0.41$; $P = 0.003$), but not HEI ($r = 0.14$; $P = 0.337$). Due to the impact of aging on lifestyle factors and aortic stiffness, an age-adjusted partial correlation matrix was created, and is presented in Table 3. Age and body fat-adjusted correlations are presented in Table 3. Regarding the primary health outcome measure, aPWV, bivariate correlation adjusting for age is presented in Table 4.

Several age-adjusted multivariable linear regression models are presented in Table 5, which demonstrate the predictive power and relative contribution of each of the lifestyle factors on aPWV. All models present the *adjusted* coefficient of determination (r^2). Model 1 used SRT and GRIP/BW as predictor variables and explained 44% of the variation in aortic stiffness; model 2 used FAT% and HEI as predictor variables and explained 50% of the variation in aortic stiffness; model 3 used SRT and FAT% as predictor variables and explained 49% of the variation in aortic stiffness; model 4 used GRIP/BW and HEI as predictor variables and explained 47% of the variation in aortic stiffness; last, model 5 used SRT, GRIP/BW, FAT%, and HEI as predictor variables and explained 51% of the variation of aortic stiffness.

The association of dietary quality and aPWV is presented in Table 6. Specifically, after age-adjustment, two sub-components of the HEI-2010 that were associated with aPWV include refined grains (r = -0.36; P = 0.010) and fatty acids (r = -0.46; P = 0.001). To clarify, reduced intake of refined grains resulted in a higher score on the refined grains sub-component. Whereas, for fatty acids, greater consumption of unsaturated fatty acids relative to saturated fatty acids resulted in a higher score for this sub-component. There was a trend for significance for total protein (r = -0.27; P = 0.057) and empty calories (r = -0.26; P = 0.065).

Age-adjusted ANCOVA results for all categorical variables on aPWV are presented in conjunction with their associated figures. For S/DAY, there was no

significant association to aPWV for any category (“quantiles, Table 7” “10,000 steps, Table 8” and “groups, Table 9”; P = 0.678; P = 0.587; P = 0.253, respectively). However, for the category “groups,” there was a significant age vs aPWV interaction (P = 0.010). For SRT, the category “quantiles, Table 10” there was a significant difference between groups (P = 0.018), independent of age. Additionally, there was a significant difference for the category “groups, Table 11” (P = 0.020), independent of age. Pairwise comparison analysis revealed a significant difference only between those who scored a 10 on SRT vs. < 9 (P = 0.024). For GRIP/BW, the category “quantiles, Table 12” there was a significant difference between groups (P = 0.042), independent of age. Additionally, there was a significant difference for the category “tertiles, Table 13” (P = 0.012), independent of age. A *post hoc* pairwise comparison analysis revealed a significant difference only between the lowest and highest tertile (P = 0.009). This technique compared the entities in pairs to judge specifically which groups were statistically different from one another. For FAT%, the category “quantiles, Table 14” there was a significant difference between groups (P = 0.000), independent of age. Last, for HEI, the category “quantiles, Table 15” there was a significant difference between groups (P = 0.003), independent of age.

For all figures, the primary health outcome (dependent) measure is aPWV. Figure 1 represents the non-significant relationship of S/DAY, expressed as values above and below the median value of 7.372 steps per day. Figure 2 represents the non-significant relationship of S/DAY, expressed as above and

below 10,000 steps per day. Figure 3 represents the non-significant relationship of steps per day, expressed in categories of 1) 4,999 steps or less per day, 2) 5,000 to 9,999 steps per day, 3) 10,000 steps or more per day. Figure 4 represents the significant relationship of SRT, expressed as values above and below the median value of 9.5. Figure 5 represents the significant relationship of muscular function, expressed in categories of 1) Less than 9 on SRT, 2) 9 on SRT, 3) 9.5 on SRT, and 4) 10 on SRT. Figure 6 represents the significant relationship of GRIP/BW, expressed as values above and below the median value of 1.20 (or 120% of muscular strength relative to body weight). Figure 7 represents the significant relationship of relative muscular strength, expressed in categories of 1) 88 to 112% of body weight, 2) 113 to 127% of body weight, and 3) 128 to 156% of body weight. Figure 8 represents the significant relationship of FAT%, expressed as values above and below the median value of 18.2% body fatness. Figure 9 represents the significant relationship of HEI, expressed as values above and below the median of 70.6 on the diet history questionnaire II.

Age-adjusted correlation coefficients for all hemodynamic variables are presented in Appendix B. Specifically, after adjusting for age, SRT was inversely associated with A-AIx75 ($r = -0.30$; $P = 0.032$). GRIP/BW was inversely associated with A-AIx75 ($r = -0.35$; $P = 0.012$). FAT% was associated with A-SBP ($r = 0.33$; $P = 0.17$), A-DBP ($r = 0.32$; $P = 0.23$), A-AIx75 ($r = 0.35$; $P = 0.011$), B-SBP ($r = 0.29$; $P = 0.036$), B-DBP ($r = 0.28$; $P = 0.044$), MP ($r = 0.35$; $P = 0.011$), and MAP ($r = 0.32$; $P = 0.023$). HEI was inversely associated with RHR

(r = -0.36; P = 0.010). Backward stepwise regression results are presented in Appendix C and indicate that AGE and FAT% are the strongest independent factors associated with aPWV.

Table 1A. Description of variables used in this study.

Variables	Description
AGE	Chronological age (years)
WT	Body weight (kg)
HT	Height/stature (cm)
BMI	Body mass index (kg/m2)
WHR	Waist-to-hip circumference ratio (%)
FAT%	Body fatness (%)
LEAN%	Fat-free mass (%)
RHR	Resting heart rate (bpm)
B-SBP	Brachial (peripheral) systolic blood pressure (mmHg)
B-DBP	Brachial (peripheral) diastolic blood pressure (mmHg)
B-PP	Brachial (peripheral) pulse pressure (mmHg)
MP	Arithmetic mean pressure (mmHg)
MAP	Mean arterial pressure (1/3rd B-PP + B-DBP)
PP-AMP%	Pulse pressure amplification (%)
SEVR	Subendocardial viability ratio (%) – also called Buckberg ratio
A-SBP	Aortic (central) systolic blood pressure (mmHg)
A-DBP	Aortic (central) diastolic blood pressure (mmHg)
A-PP	Aortic (central) pulse pressure (mmHg)
A-AP	Aortic (central) augmentation pressure (mmHg)
A-AIx	Aortic (central) augmentation index (%)
A-AIx75	Aortic (central) augmentation index (@ heart rate 75 bpm)
A-PWV	Aortic (central) pulse wave velocity (m/s)
S/DAY	Average step counts per day (7 day average)
GRIP/BW	Peak L+R handgrip strength/body weight (%)
SRT	Sitting-rising test score (0 to 10)
HEI	Healthy eating index score (0 to 100)
T-VEG	Total vegetables (0-5) [adequacy]
DRK-GRNS-BNS	Dark greens and beans (0-5) [adequacy]
T-FRUIT	Total fruit (0-5) [adequacy]
W-FRUIT	Whole fruit (0-5) [adequacy]
R-GRAINS	Refined grains (0-10) [moderation]
W-GRAINS	Whole grains (0-10) [adequacy]
T-DAIRY	Total dairy (0-10) [adequacy]
T-PRO	Total protein (0-5) [adequacy]
SEA-PLNT-PRO	Seafood and plant protein (0-5) [adequacy]
F-ACIDS	Fatty acids (0-10) [adequacy]
SODIUM	Sodium (0-10) [moderation]
EMPTY	Empty calories (0-20) [moderation]

Table 1B. Descriptive statistics of the study population (N = 52 men).

	Mean	±	Std. Dev	Std.Err	Min	Max	Median
AGE	41.48	±	8.49	1.18	30.00	59.00	40.00
WT	83.21	±	12.98	1.80	59.60	123.90	80.70
HT	178.79	±	7.14	0.99	164.20	195.50	178.40
BMI	25.91	±	3.31	0.46	19.90	40.00	25.40
WHR	0.88	±	0.06	0.01	0.79	1.00	0.87
FAT%	18.41	±	4.75	0.66	7.90	31.50	18.20
LEAN%	81.56	±	4.75	0.66	68.50	92.10	81.60
RHR	63.25	±	10.45	1.45	42.00	91.00	62.00
B-SBP	119.23	±	9.59	1.33	100.00	138.00	119.50
B-DBP	72.67	±	6.99	0.97	58.00	86.00	72.00
B-PP	46.56	±	8.41	1.17	30.00	73.00	45.00
MP	87.67	±	7.51	1.04	69.00	106.00	88.00
MAP	88.18	±	6.89	0.96	71.99	103.32	88.48
PP-AMP%	148.48	±	15.90	2.21	111.00	178.00	147.50
SEVR	171.81	±	36.38	5.04	107.00	281.00	161.50
A-SBP	105.06	±	8.54	1.18	85.00	126.00	105.00
A-DBP	73.56	±	7.01	0.97	58.00	88.00	73.00
A-PP	31.60	±	4.94	0.68	24.00	44.00	31.00
A-AP	3.57	±	3.63	0.50	-5.00	11.00	3.25
A-AIx	10.96	±	10.62	1.47	-14.00	32.00	10.50
A-AIx75	5.35	±	11.58	1.61	-18.00	32.50	3.75
A-PWV	6.82	±	0.87	0.12	5.60	9.40	6.60
S/DAY	8158.70	±	3758.03	521.14	2339.14	18086.86	7372.64
GRIP/BW	1.21	±	0.17	0.02	0.88	1.57	1.20
SRT	9.34	±	0.84	0.12	6.00	10.00	9.50
HEI	70.87	±	11.38	1.58	30.88	90.61	70.54
T-VEG	4.20	±	1.15	0.16	1.00	5.00	5.00
DRK-GRNS-BNS	4.17	±	1.49	0.21	0.00	5.00	5.00
T-FRUIT	3.81	±	1.34	0.19	0.17	5.00	4.24
W-FRUIT	4.49	±	0.99	0.14	0.09	5.00	5.00
R-GRAINS	8.32	±	2.46	0.34	0.47	10.00	9.77
W-GRAINS	2.82	±	1.96	0.27	0.04	8.06	2.34
T-DAIRY	6.36	±	2.57	0.36	0.71	10.00	6.18
T-PRO	4.77	±	0.72	0.10	1.16	5.00	5.00
SEA-PLNT-PRO	4.33	±	1.21	0.17	0.60	5.00	5.00
F-ACIDS	6.00	±	2.96	0.41	0.00	10.00	6.20
SODIUM	4.66	±	2.99	0.42	0.00	10.00	4.30
EMPTY	16.93	±	4.64	0.64	0.00	20.00	19.19

Table 2A. Correlation matrix representing the association of lifestyle factors with aortic stiffness and age.

	A-PWV	S/DAY	SRT	GRIP/BW	FAT%	HEI	
AGE	0.56	0.05	-0.30	-0.45	0.41	0.14	**r**
	0.000	0.722	0.029	0.001	0.003	0.337	**P**
A-PWV		-0.02	-0.51	-0.56	0.62	-0.30	**r**
		0.875	0.000	0.000	0.000	0.033	**P**
S/DAY			0.02	0.03	0.01	-0.10	**r**
			0.881	0.831	0.969	0.496	**P**
SRT				0.58	-0.62	0.17	**r**
				0.000	0.000	0.228	**P**
GRIP/BW					-0.74	0.28	**r**
					0.000	0.042	**P**
FAT%						-0.40	**r**
						0.003	**P**

Table 2B. Age-adjusted correlation matrix representing the association of lifestyle factors with aortic stiffness.

	S/DAY	SRT	GRIP/BW	FAT%	HEI	
A-PWV	-0.06	-0.44	-0.41	0.51	-0.45	**r**
	0.669	0.001	0.003	0.000	0.001	**P**
S/DAY		0.04	0.06	-0.02	-0.11	**r**
		0.789	0.676	0.908	0.465	**P**
SRT			0.52	-0.57	0.22	**r**
			0.000	0.000	0.114	**P**
GRIP/BW				-0.68	0.39	**r**
				0.000	0.005	**P**
FAT%					-0.50	**r**
					0.000	**P**

Table 3. Age and body fat-adjusted correlation matrix representing the association of lifestyle factors with aortic stiffness.

	S/DAY	SRT	GRIP/BW	HEI	
A-PWV	-0.06	-0.20	-0.10	-0.26	**r**
	0.671	0.160	0.505	0.065	**P**
S/DAY		0.04	0.07	-0.13	**r**
		0.807	0.647	0.365	**P**
SRT			0.22	-0.09	**r**
			0.132	0.540	**P**
GRIP/BW				0.08	**r**
				0.602	**P**

Table 4. Age-adjusted relationship of lifestyle factors with aortic stiffness.

Factor	Outcome	Bivariate correlation			Age-adjusted		
		r	r^2	P	r	r^2	P
S/DAY	aPWV	-0.02	0.00	0.875	-0.06	0.00	0.669
SRT	aPWV	-0.51	0.26	0.000	-0.44	0.19	0.001
GRIP/BW	aPWV	-0.56	0.31	0.000	-0.41	0.17	0.003
FAT%	aPWV	0.62	0.38	0.000	0.51	0.26	0.000
HEI	aPWV	-0.30	0.09	0.033	-0.45	0.21	0.001

Table 5. Age-adjusted multivariable linear regression models predicting aortic stiffness with lifestyle factors.

Model	P (ANOVA)	Adj r^2	Predictors	Outcome	B	SE B	P	SEE
1	0.000	0.44	*Constant*	aPWV	9.258	1.345	0.000	0.649
			SRT		-0.274	0.133	0.044	
			GRIP/BW		-1.212	0.709	0.094	
2	0.000	0.50	*Constant*	aPWV	4.931	0.809	0.000	0.615
			FAT%		0.063	0.023	0.008	
			HEI		-0.017	0.008	0.065	
3	0.000	0.49	*Constant*	aPWV	5.863	1.602	0.000	0.624
			SRT		-0.190	0.133	0.160	
			FAT%		0.065	0.025	0.010	
4	0.000	0.47	*Constant*	aPWV	7.926	1.048	0.000	0.634
			GRIP/BW		-1.317	0.644	0.046	
			HEI		-0.022	0.009	0.013	
5	0.000	0.51	*Constant*	aPWV	7.684	2.031	0.000	0.610
			SRT		-0.208	0.134	0.128	
			GRIP/BW		-0.155	0.799	0.847	
			FAT%		0.037	0.031	0.242	
			HEI		-0.018	0.009	0.050	

Table 6. Age-adjusted relationship of dietary quality with aortic stiffness.

HEI-2010 Scores	Outcome: aPWV			Age-adjusted		
HEI	-0.30	0.09	0.033	-0.45	0.21	0.001
T-VEG	-0.12	0.01	0.398	-0.13	0.02	0.377
DRK-GRNS-BNS	-0.08	0.01	0.556	-0.09	0.01	0.510
T-FRUIT	0.07	0.00	0.625	-0.11	0.01	0.460
W-FRUIT	-0.03	0.00	0.824	-0.15	0.02	0.305
R-GRAINS	-0.25	0.06	0.072	-0.36	0.13	0.010
W-GRAINS	0.16	0.03	0.253	-0.08	0.01	0.589
T-DAIRY	-0.11	0.01	0.446	0.01	0.00	0.923
T-PRO	-0.14	0.02	0.319	-0.27	0.07	0.057
SEA-PLNT-PRO	-0.10	0.01	0.497	-0.17	0.03	0.236
F-ACIDS	-0.31	0.10	0.026	-0.46	0.21	0.001
SODIUM	-0.18	0.03	0.201	-0.21	0.04	0.137
EMPTY	-0.20	0.04	0.160	-0.26	0.07	0.065
	r	***r²***	**P**	***r***	***r²***	**P**

Figure 1. Age-adjusted relationship of physical activity (quantiles) with aortic stiffness.

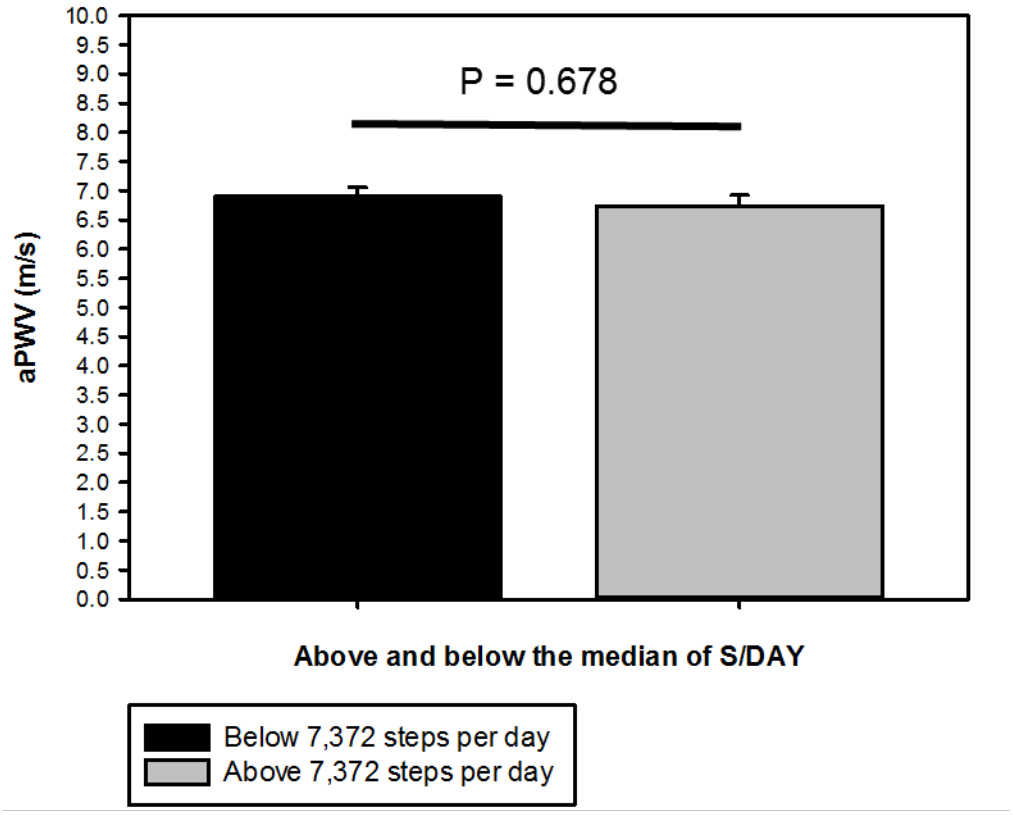

Table 7. ANCOVA results showing age-adjusted aPWV means for S/DAY on quantiles.

Factor	Category	Level	Adj means	SE	P	P (age x aPWV)
S/DAY	Quantiles	1) Above median	6.779	0.144	0.678	0.417
		2) Below median	6.864	0.144		

Figure 2. Age-adjusted relationship of physical activity (10,000 steps) with aortic stiffness.

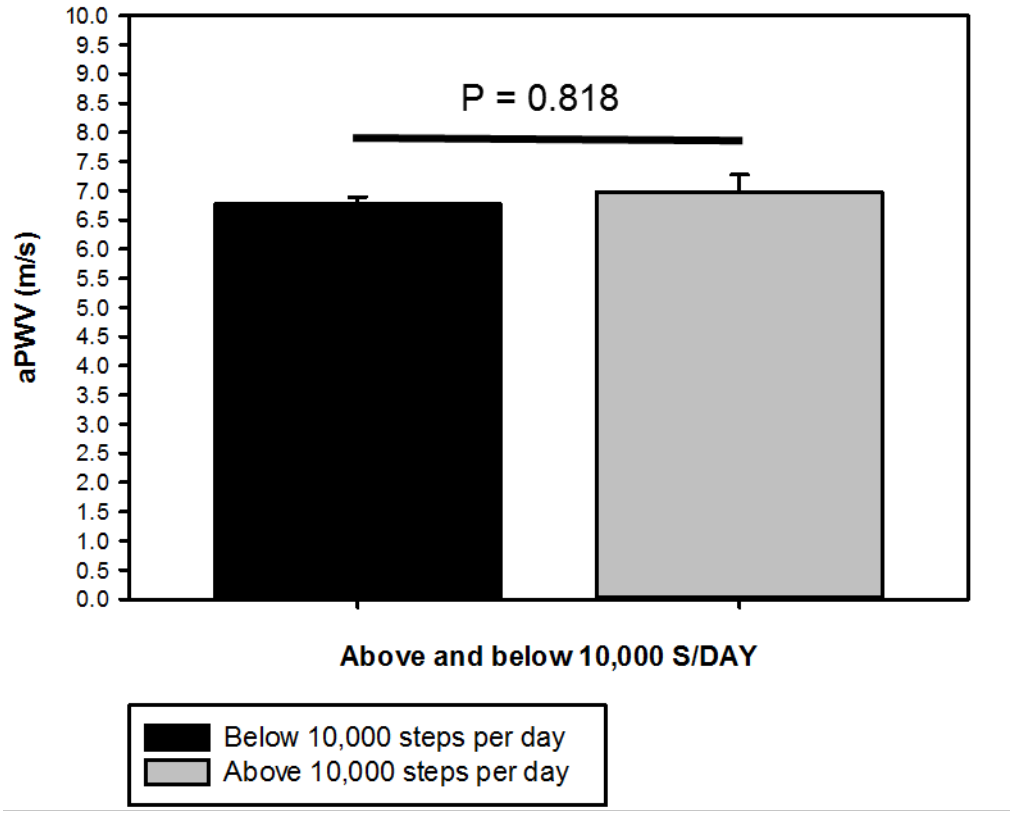

Table 8. ANCOVA results showing age-adjusted aPWV means for S/DAY on 10,000 steps.

Factor	Category	Level	Adj means	SE	P	P (age x aPWV)
S/DAY	10,000 steps	1) Above	6.860	0.198	0.818	0.547
		2) Below	6.807	0.119		

Figure 3. Age-adjusted relationship of physical activity (groups) with aortic stiffness.

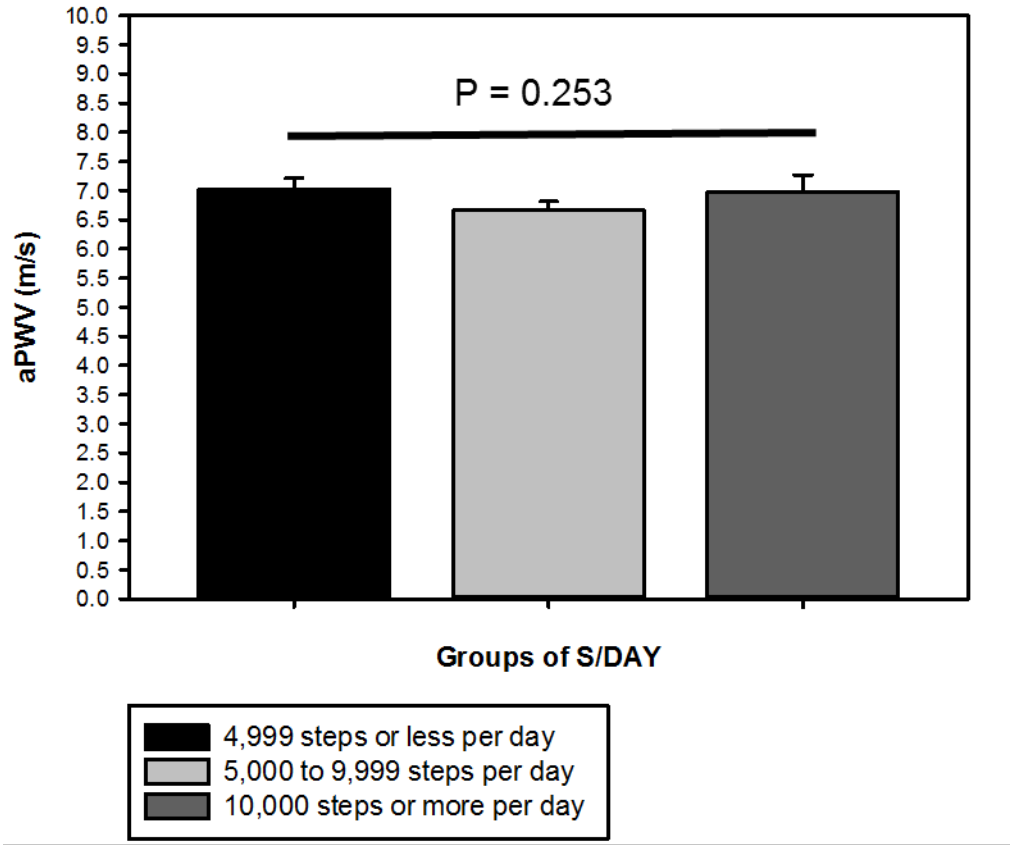

Table 9. ANCOVA results showing age-adjusted aPWV means for S/DAY on groups.

Factor	Category	Level	Adj means	SE	P	P (age x aPWV)
S/DAY	Groups	1) ≤ 4,999	7.113	0.218	0.253	0.010
		2) 5,000 to 9,999	6.683	0.139		
		3) ≥ 10,000	6.858	0.194		

Figure 4. Age-adjusted relationship of physical function (quantiles) with aortic stiffness.

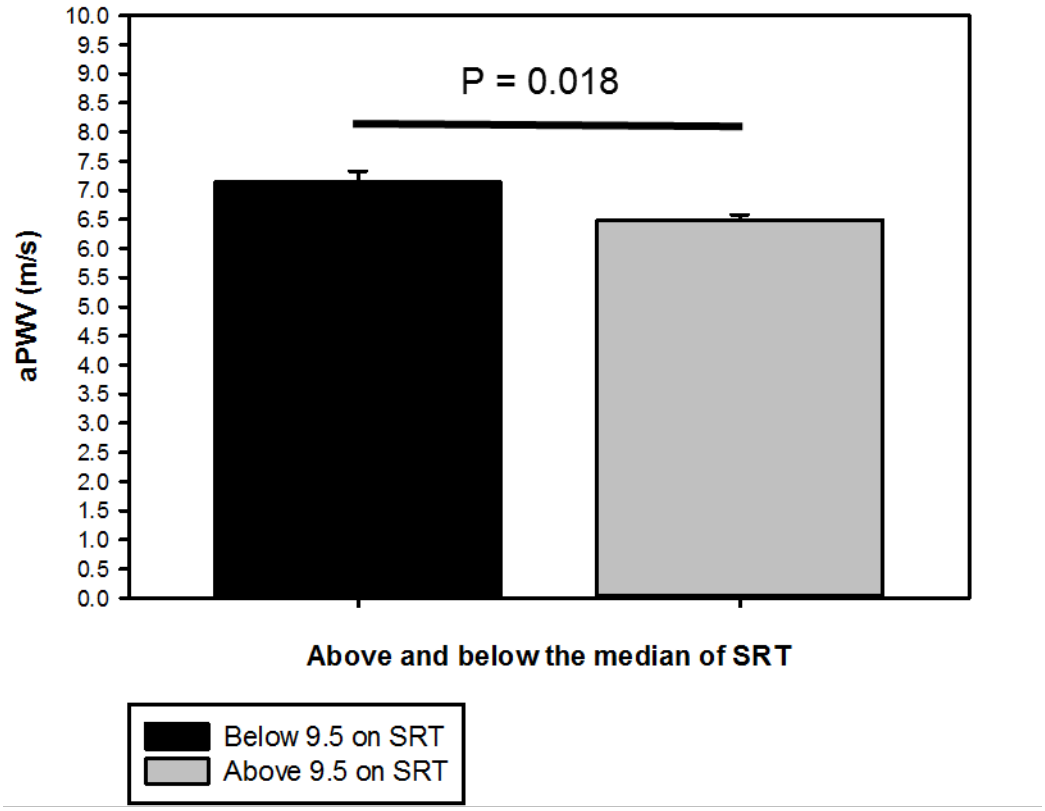

Table 10. ANCOVA results showing age-adjusted aPWV means for SRT on quantiles.

Factor	Category	Level	Adj means	SE	P	P (age x aPWV)
SRT	Quantiles	1) Above median	6.571	0.140	0.018	0.167
		2) Below median	7.053	0.135		

Figure 5. Age-adjusted relationship of physical function (groups) with aortic stiffness.

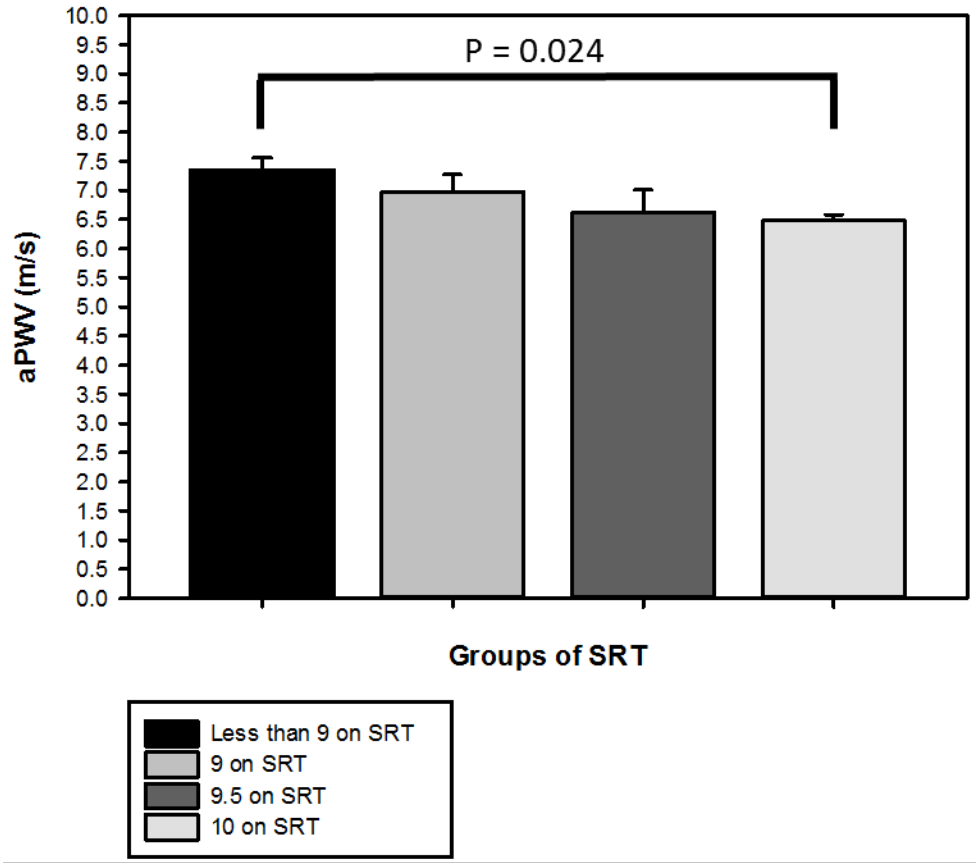

Table 11. ANCOVA results showing age-adjusted aPWV means for SRT on groups.

Factor	Category	Level	Adj means	SE	P	P (age x aPWV)
SRT	Groups	1) < 9 on SRT	7.341	0.212	0.020	0.321
		2) 9 on SRT	7.021	0.214		
		3) 9.5 on SRT	6.608	0.276		
		4) 10 on SRT	6.563	0.137		

Figure 6. Age-adjusted relationship of relative muscular strength (quantiles) with aortic stiffness.

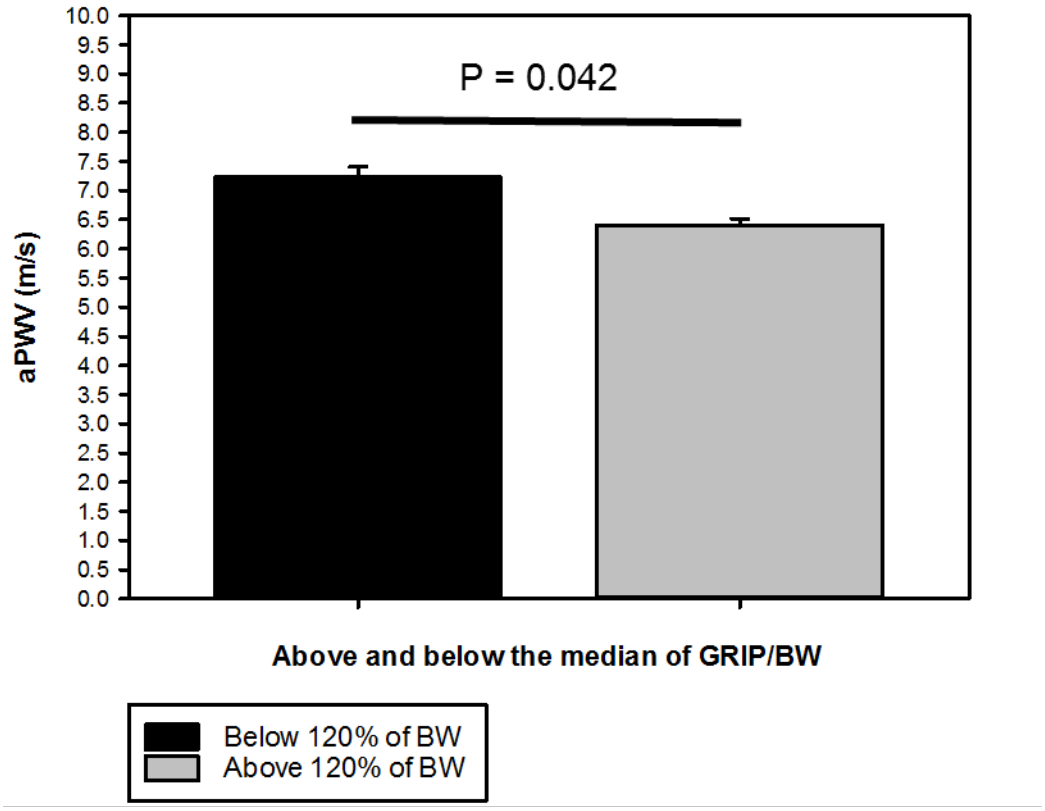

Table 12. ANCOVA results showing age-adjusted aPWV means for GRIP/BW on quantiles.

Factor	Category	Level	Adj means	SE	P	P (age x aPWV)
GRIP/BW	Quantiles	1) Above median	6.589	0.148	0.042	0.155
		2) Below median	7.053	0.148		

Figure 7. Age-adjusted relationship of relative muscular strength (tertiles) with aortic stiffness.

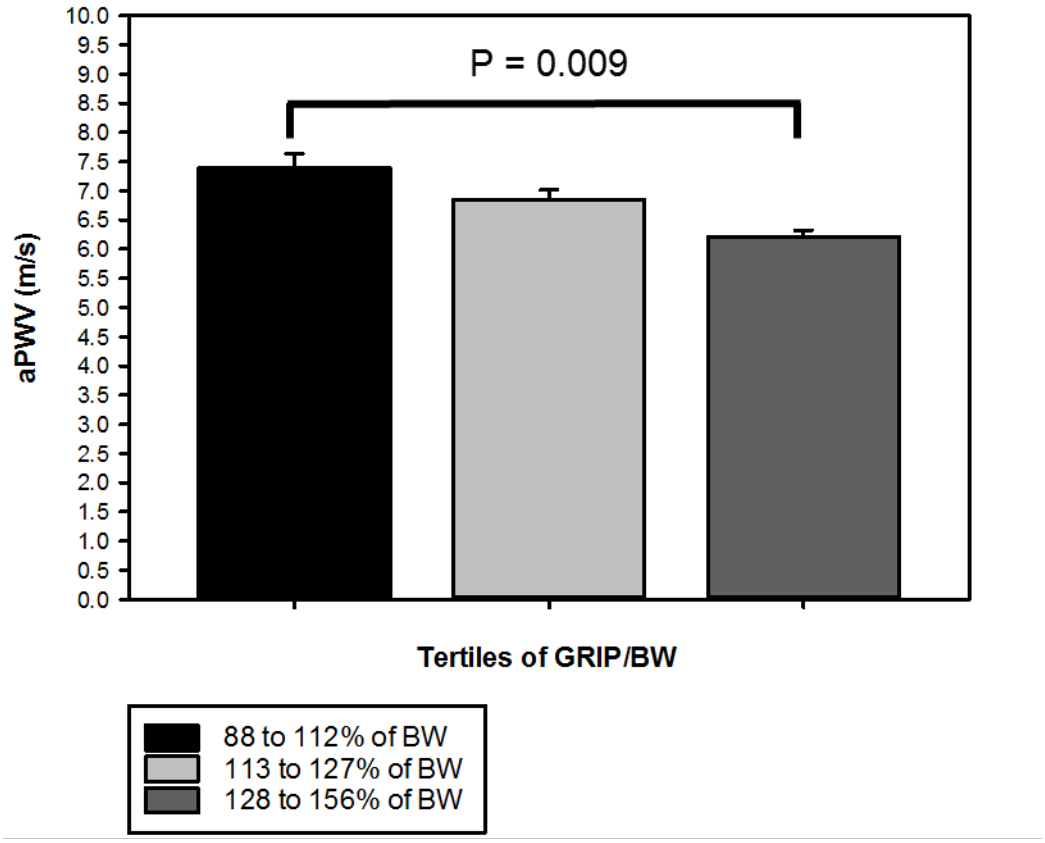

Table 13. ANCOVA results showing age-adjusted aPWV means for GRIP/BW on tertiles.

Factor	Category	Level	Adj means	SE	P	P (age x aPWV)
GRIP/BW	Tertiles	1) Low	7.221	0.172	0.012	0.438
		2) Moderate	6.823	0.160		
		3) High	6.419	0.175		

Figure 8. Age-adjusted relationship of body composition (quantiles) with aortic stiffness.

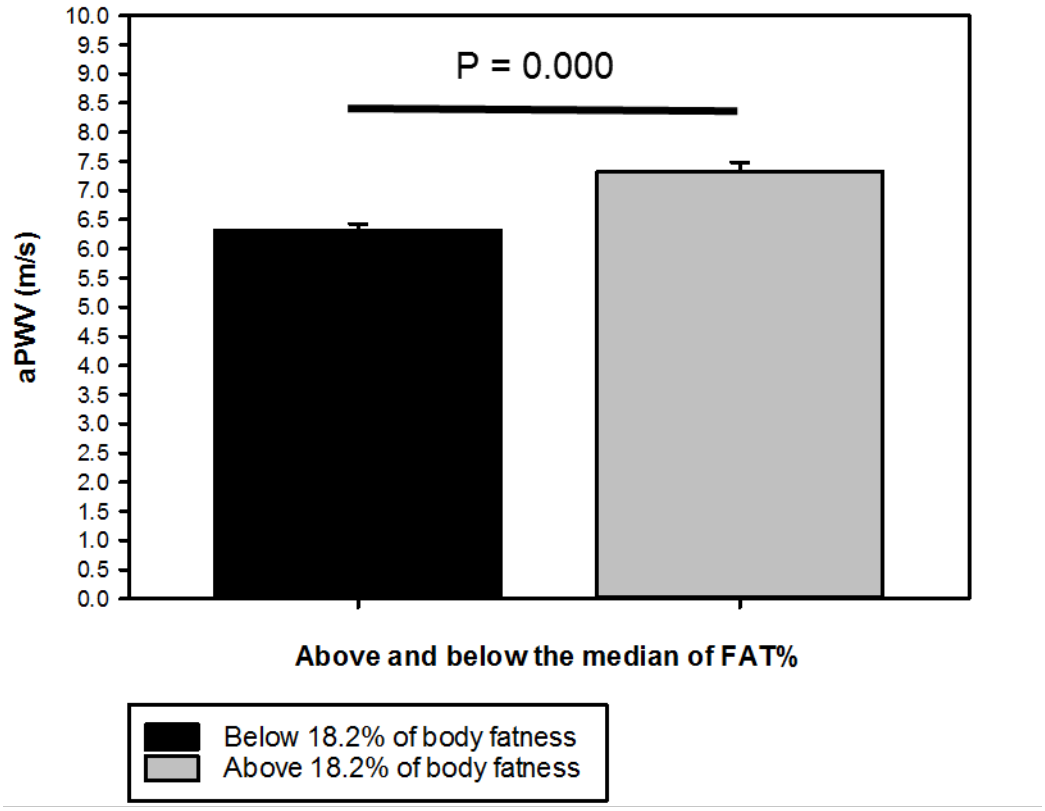

Table 14. ANCOVA results showing age-adjusted aPWV means for FAT% on quantiles.

Factor	Category	Level	Adj means	SE	P	P (age x aPWV)
FAT%	Quantiles	1) Above median	7.214	0.126	0.000	0.579
		2) Below median	6.429	0.126		

Figure 9. Age-adjusted relationship of dietary quality (quantiles) with aortic stiffness.

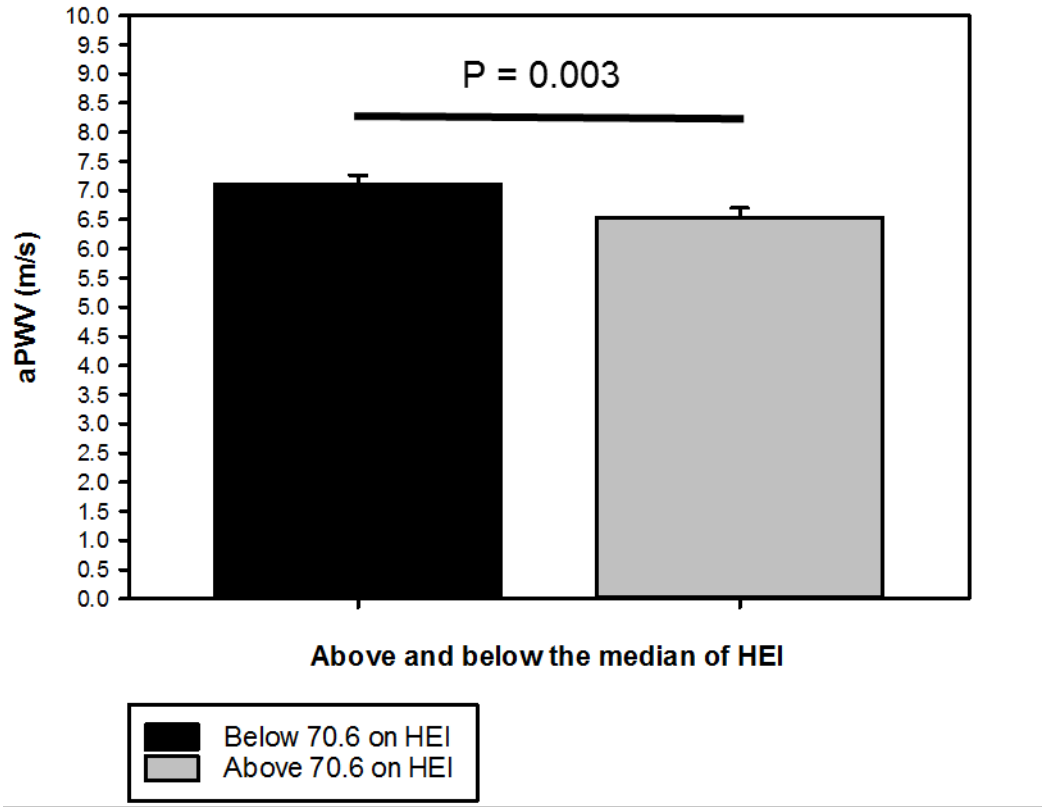

Table 15. ANCOVA results showing age-adjusted aPWV means for HEI on quantiles.

Factor	Category	Level	Adj means	SE	P	P (age x aPWV)
HEI	Quantiles	1) Above median	6.527	0.131	0.003	0.169
		2) Below median	7.115	0.131		

CHAPTER FIVE: DISCUSSION

The utility of aortic stiffness as a biomarker has been clearly established in large population-based, follow-up studies that control for traditional CVD risk factors (11). The focus of the present study was to control for the normal and gradual aortic stiffening process caused with advancing age, and to examine global contributors of early vascular aging that may provide insight into key health-related behaviors associated with its presence. Due to the confounding influence of gender on aortic stiffness, women were excluded from participation in this investigation (40, 80).

In the present study, greater muscular strength and function were associated with reduced aortic stiffness, after statistically adjusting for age. In addition, after age adjustment greater dietary quality was associated with reduced aortic stiffness. Perhaps most interesting was that physical activity was not associated with any measure of CVD risk including aortic stiffness in the present study. Thus, in an apparently healthy, physically active population, a large percentage of the variation in aPWV was able to be explained with a novel measure of physical function and by assessing adherence to the United States Dietary Guidelines. There is research that suggests in a physically inactive population achieving greater step counts per day positively influences measures of CV health, such as biomarkers of the metabolic syndrome including total and HDL cholesterol, insulin resistance, and body fatness (23).

The total number of step counts per day (averaged over 7 days) was directly assessed with a tri-axial accelerometer mounted on the right hip. We showed that physically active, apparently healthy middle aged men who stepped more per day were not those who had reduced aortic stiffness. In fact, the total number of step counts per day was not associated with aortic stiffness, and was unable to explain any of the variation of aPWV in this study. While the recommendation of acquiring greater than or equal to 10,000 steps per day has been associated with positive cardiometabolic health improvements, it may be a worthwhile target for a physically *inactive* population (23).

Step-based activity is undoubtedly important for breaking up periods of physical inactivity, which has been associated with elevated CVD risk (52). Yet, the differences in aPWV between men who stepped less than 5,000 steps per day compared with those who stepped more than 10,000 steps per day were not significant. To reiterate, the men in this study were physically *active*, hence increasing the number of step counts per day was not correlated with reduced aortic stiffness. Tracking the total number of step counts per day is an indicator of physical activity, and a metric that has been associated with aortic stiffness. The Busselton Health Study, a large prospective, follow-up investigation, showed that increased physical activity (measured with a questionnaire) was associated with reduced CVD risk and all-cause mortality in middle aged and older adults (47). Moreover, several studies have demonstrated that more total physical activity is associated with reduced aortic stiffness, both in young and elderly

populations (57, 66, 115). For example, in young children who wore a pedometer for 7 days, more step counts per day was inversely associated with aPWV (115). In older adults, inverse associations between pedometer step counts (worn for 3 days) were also demonstrated with aPWV (57). And, a research-grade accelerometer worn for 7 days showed greater caloric expenditure per day was inversely associated with aPWV (66). For middle aged men and women greater step counts per day was associated with the attenuation of aortic stiffness (3, 44, 61, 74, 93). To clarify, in each of these 5 studies that used both men and women, physical activity levels were determined with an accelerometer that was worn for 7 consecutive days, which was associated with reduced aortic stiffness.

However, the population in this study was an apparently healthy, middle aged male cohort. Because men and women present different CVD etiologies and disease courses, controlling for gender as a confounding variable is essential to examine the relationship of physical activity and aortic stiffness in a single isolated population (80). To date, there has only been one study that has examined the relationship of physical activity (measured with a questionnaire) and aPWV in middle aged men (99). In their study, physical activity expressed as greater than or equal to 4 METs (hours per week) was not statistically associated with aPWV. These data parallel our findings, indicating that among middle aged men neither intensity nor step counts was able to predict aPWV in otherwise healthy adults. Furthermore, the central limitation in the study that

indicated no relationship between exercise intensity and aortic stiffness, was that physical activity was not measured directly but rather was estimated from a questionnaire. Tracking physical activity with an accelerometer provides dissimilar results when compared with estimations drawn from pencil-and-paper responses (70). Therefore to determine free-range step counts, exercise intensity, and energy expenditure, it is paramount that each individuals' actual day-to-day movements and levels of physical activity are accounted for directly, not estimated.

Another significant finding in the present study was that physical function is a key determinant of aortic stiffness. Physical function is typically measured by the VO_{2MAX} (cardiorespiratory fitness) and muscular strength/endurance, and in general is associated with greater longevity and reduced CVD risk (53). Furthermore, when physical function is optimized, the perceived level of difficulty of functional tasks and activities of daily living are reduced (30). Regarding CVD risk, however, there is a shortage of research that has related novel measures of physical function that incorporate both aerobic and anaerobic components of fitness with aortic stiffness. For instance, one study showed reduced aortic stiffness was associated with greater maximal walking speed and more total distance covered in a functional walking test in apparently healthy older adults (45). Increased walking speed and covering more total distance may be not tantamount to VO_{2MAX} per se, but the functional system involved with gait performance is reflected in maximal oxygen consumption (21). For older adults,

assessments that are geared at improving activities of daily living will directly benefit the quality of life (97).

Interestingly, increased grip strength has been associated with greater maximal walking speed and leg strength (36). The use of handgrip strength has also been used as a predictor of future disability, CVD risk, and all-cause mortality appears to be a viable metric of physical function that has clinical utility and prognostic value (67, 105). Increased grip strength is associated with greater lean muscle mass in older years, which is associated with reduced aortic stiffness (116). The use of handgrip strength in the present study was chosen as a measure of upper body muscular strength that is well established and clinically relevant.

Furthermore, peak handgrip strength values from both hands averaged by body weight allowed inter-subject comparison, and therefore reflected relative muscular strength. In this study, individuals in the highest tertile, or those at or above 128% of handgrip power relative to body weight, had significantly reduced aortic stiffness compared with those in the lowest or middle tertile. The relation of greater muscular strength and reduced aortic stiffness was independent of age.

While greater muscular strength in early adulthood has been correlated with increased aortic stiffness (13, 87, 96), there exists one well-designed study that has shown greater relative muscular strength (measured with 1RM bench press/body weight) is associated with reduced aortic stiffness (34). In older

adulthood, for example, greater muscular strength appears to be definitively cardio-protective, and is particularly associated with reduced aortic stiffness (116). Because the current study population was middle aged, thus it appears that greater muscular strength is a favorable physical adaptation that is associated with reduced aortic stiffness. This is the first time that the association of greater handgrip strength in middle aged men has been associated with reduced aortic stiffness, indicating improved vascular health among those with higher levels of relative muscular strength. Perhaps the underlying mechanism explaining the strength-related differences and increased aortic stiffness is the inflammatory status. For example, in older men, higher serum C-reactive protein levels, an important biomarker associated with greater CVD risk, were independently related to lower handgrip strength and reduced walking speed (78). Because skeletal muscle operates as a secretory organ, the cytokine and peptide profile is strongly dependent upon physical activity, specifically, muscular contractions (98). In that way, it is plausible that individuals with greater physical function and strength, and reduced aortic stiffness, were those who had an optimized myokine response that favorably interacted with the vasculature (147). Taken together, perhaps the reduction in aortic stiffness in apparently healthy middle aged men was due to reduced serum and myokine pro-inflammatory expression.

In the present study, greater handgrip strength was associated with a novel test of physical function, the SRT Because the sitting-rising test score was

associated with relative muscular strength, we demonstrated internal validity between the two chosen independent measures of physical function. The SRT is unique in that it assesses overall musculoskeletal function such as strength, balance, coordination, and flexibility (19, 20). In that way, the SRT is a safe and simple assessment tool that integrates the traditional measures of physical function such as cardiorespiratory fitness with muscular strength and endurance. In addition, the sitting-rising test score is a strong predictor of all-cause mortality that adds relevant information regarding functional capabilities and outcomes in adults with low CVD risk (20). In this study, a greater SRT score was associated with reduced aortic stiffness, independent of age, indicating a functional relationship between the cardiovascular and muscular nexus.

In conjunction with greater physical activity and function, focusing on nutrition, specifically dietary quality, is another first-line therapy used to minimize CVD risk. While the obesity trend is continually climbing, the overall dietary quality of American adults has been improving over the last 20 years (150). Data from the Framingham Heart Study has indicated that younger adults, in particular, benefit from greater adherence to the United States Dietary Guidelines in terms of reduced peripheral blood flow velocity and reduced arterial wave reflection (119). This study indicated that overall dietary quality, measured with the validated and reliable HEI score (46), was associated with reduced aortic stiffness independent of age. These data coincide with meta-analyses and systematic reviews that have shown a higher Healthy Eating Index score was associated with reduced

all-cause, and CVD related mortality (121). In fact, middle aged adults can expect approximately a 1/3rd reduction in CVD risk with greater adherence to the United States Dietary Guidelines (110). Furthermore, two sub-components of the dietary analysis that largely contributed to the relationship of Healthy Eating Index and reduced aortic stiffness were refined grains and fatty acids. Previous research has indicated that greater fruit and vegetable consumption is associated with reduced aortic stiffness in early adulthood (1). This study is the first to indicate that a reduction in refined grain consumption is associated with reduced aortic stiffness. And, the fatty acid profile – specifically, greater than or equal to 2.5 grams of unsaturated to 1 gram of saturated fatty acid ratio – was associated with reduced aortic stiffness. Prior investigations have shown that greater consumption of unsaturated fatty acids, particular the omega-3 variety, is associated with reduced CVD risk (49, 75). Well designed, long-term clinical trials have shown the favorable effects of omega-3 fatty acids on aortic stiffness is through a reduction in vascular inflammation (128, 140). For instance, the first study showed that 12 weeks of omega-3 fatty acids supplementation at 2 grams per day in young adults reduced circulating levels of TNF alpha, IL-6, and was able to reduce aortic stiffness (128). Whereas, in the second study, 12 weeks of omega-3 fatty acid supplementation at 2 grams per day in middle aged adults, was successful in reducing circulating levels of IL-6 in conjunction with aortic stiffness (140). This study is the first to demonstrate an observational link between the composition of fatty acids within the diet over the last 1 year and aortic stiffness. The explanation accounting for the association of reduced

refined grain consumption and reduced aortic stiffness may be due to a reduction in risk of type 2 diabetes – a proposed contributor of AGEs formation within the artery leading to greater aortic stiffness (7, 148).

Traditionally, first-line therapies that are used to minimize CVD risk are exercise-based. For example, modifying undesirable health-related behaviors such as reducing physical inactivity and improving physical dysfunction favorably improves CVD risk stratification. Although obesity trends in the United States have leveled off (129), it is worthwhile to assess the utility of traditional first-line approaches as prophylactic therapy against CVD risk. For instance, promoting greater physical activity and adherence to habitual exercise is the foundation of ACSM's "exercise is medicine" agenda (139). Exercise scientists and physiologists understand the potential benefits of adherence to regular physical activity and structured exercise as it relates to improved CVD risk stratification. However, the fundamental evaluation of any approach that involves modifying public health should be results-based. For example, although it is evident that exercise *is* medicine, according to the agenda of the ACSM, most aging Americans are simply not motivated to actually *do* exercise (58). In that regard, simply promoting more (and more) physical activity does not appear to be effective in directly addressing the obesity epidemic, physical fitness, or CVD risk stratification for millions of Americans. In brief, the promotion of exercise is only worthwhile if the American public actually recognizes and changes their

undesirable health-related lifestyle behaviors, leading to an objective reduction in CVD risk.

Results from the stepwise regression analysis indicated that after age, body fatness was the strongest predictor of aPWV in this study cohort. Given that the primary risk factor for CVD risk is age, the results of this study confirm that obesity is a powerful indicator of aortic stiffness (142). Interestingly, elevated body fatness in early adulthood has been associated with reduced aortic stiffness; however, this paradoxical association continues until approximately 50 years of life, after which time the relationship becomes proportional, not inverse (26). It appears as though the location of excessive fat mass (ie the fat depot) has a differing influence of aortic stiffness. For instance, results from the Amsterdam Growth and Health Longitudinal Study demonstrated among healthy adults that increases in trunk mass and decreases in peripheral fat mass were associated with accelerated arterial stiffening (120). Although in its infancy, one proposed mechanism explaining vascular disease in the context of the fat depot is enhanced autocrine communication between the perivascular adipose regions and local vasculature, which appears to increase the vasoconstrictive phenotype of the arterioles (154).

CONCLUSION

Novel lifestyle contributors to aortic stiffness include physical function and overall dietary quality. For example, the sitting-rising test score which determines

overall musculoskeletal fitness by integrating aspects of muscular strength, balance, coordination, and flexibility may be used as a cardiovascular health screen in apparently healthy, middle aged men. And, greater adherence to the United States Dietary Guidelines, assessed with the validated and reliable Healthy Eating Index score is associated with reduced aortic stiffness, in part due to reduced refined grain consumption and greater unsaturated fatty acid intake. For apparently healthy, active middle aged men, focusing on improving physical function (fitness) and improving overall dietary quality is essential to reducing CVD risk.

STUDY LIMITATIONS

The Fitbit Zip as an objective measure of step counts has been previously validated (141). However, this model of the Fitbit does not track metabolic data such as energy expenditure or heart rate. Due to the influence of resistance-based exercise on these variables, but not step counts, it is possible that the men in this study who had stepped very minimally were those who had participated in stationary exercise such as weightlifting. In fact, anecdotally, several of the participants directly informed study personnel that this was the case. Additionally, cardiovascular exercise such as cycling or yoga would not register as moderate-intensity physical activity or greater step counts on the accelerometer used in this study. Therefore, the attribution of step counts as a metric representing actual physical activity levels is not justified in all participants. It would have been worthwhile to incorporate metabolic data such as energy expenditure or heart

rate into physical activity determination. Given the scope of this project, the need was unable to be justified.

FUTURE DIRECTIONS

Exploring the differences in gender for the same outcome measures would help to clarify the isolated associations of aortic stiffness and key health-related behaviors associated with CVD risk. Because younger populations are able to maintain relatively low CVD risk in spite of unfavorable lifestyle habits, it would be worthwhile to explore novel measures of physical function in an effort to explain the variation of aortic stiffness independent of body composition. Molecular study should focus on the relationship between inflammation and vascular health. Last, it is important to consider the relationship of fat free (lean) muscle mass on aortic stiffness. Unpublished data from our lab indicate that in young adult men with greater levels of fat free mass are those who have increased aortic stiffening. One possible cause may be a skeletal muscle phenotypic difference due to excessive hypertrophy. The relationship between muscle hypertrophy and aortic stiffness would be an interesting area for further exploration, and possibly one contributor to early vascular aging seen in otherwise healthy young populations such as weightlifters.

APPENDICES

APPENDIX A: DESCRIPTION OF STATISTICAL VARIABLES

Variables	Description
r	Pearson's correlation coefficient
r^2	Coefficient of determination
Delta r^2	Relative change in r^2 with each step of multiple linear regression
Adj r^2	Adjusted coefficient of determination for # of variables in the equation
P	Probability of obtaining an effect, alpha (α) level ≤ 0.050
Factor	Lifestyle factor of CVD disease, predictor or independent variable
Outcome	Response or dependent variable
B	Unstandardized regression coefficient
SE B	Standard error of the unstandardized regression coefficient
SEE	Standard error of the estimate
ANCOVA	Analysis of covariance
Constant	The y-intercept is the expected mean value of Y when all X=0
Adj aPWV	Age-adjusted mean values of aPWV
P (age x aPWV)	Probability of obtaining an interaction effect

APPENDIX B: LIFESTYLE FACTORS AND HEMODYNAMICS

Factor	Outcome	Bivariate correlation			Age-adjusted		
		r	r^2	P	r	r^2	P
S/DAY	PP-AMP%	0.09	0.01	0.509	0.19	0.04	0.193
SRT	PP-AMP%	0.30	0.09	0.032	0.12	0.01	0.387
GRIP/BW	PP-AMP%	0.39	0.15	0.004	0.11	0.01	0.457
FAT%	PP-AMP%	-0.32	0.10	0.020	-0.05	0.00	0.732
HEI	PP-AMP%	-0.28	0.08	0.048	-0.26	0.07	0.069
Factor	**Outcome**	**Bivariate correlation**			**Age-adjusted**		
		r	r^2	P	r	r^2	P
S/DAY	SEVR	0.27	0.07	0.052	0.27	0.07	0.057
SRT	SEVR	0.23	0.05	0.105	0.27	0.07	0.059
GRIP/BW	SEVR	0.17	0.03	0.225	0.24	0.06	0.096
FAT%	SEVR	-0.15	0.02	0.283	-0.20	0.04	0.150
HEI	SEVR	0.26	0.07	0.068	0.25	0.06	0.080

Factor	Outcome	Bivariate correlation			Age-adjusted		
		r	r^2	P	r	r^2	P
S/DAY	A-SBP	-0.13	0.02	0.360	-0.14	0.02	0.319
SRT	A-SBP	-0.27	0.07	0.051	-0.23	0.05	0.107
GRIP/BW	A-SBP	-0.27	0.07	0.052	-0.21	0.04	0.141
FAT%	A-SBP	0.38	0.14	0.006	0.33	0.11	0.017
HEI	A-SBP	-0.12	0.02	0.385	-0.15	0.02	0.280
Factor	**Outcome**	**Bivariate correlation**			**Age-adjusted**		
		r	r^2	P	r	r^2	P
S/DAY	A-DBP	-0.12	0.01	0.401	0.14	0.02	0.326
SRT	A-DBP	-0.19	0.04	0.175	-0.11	0.01	0.438
GRIP/BW	A-DBP	-0.33	0.11	0.018	-0.23	0.05	0.110
FAT%	A-DBP	0.40	0.16	0.004	0.32	0.10	0.023
HEI	A-DBP	-0.15	0.02	0.278	-0.21	0.04	0.150
Factor	**Outcome**	**Bivariate correlation**			**Age-adjusted**		
		r	r^2	P	r	r^2	P
S/DAY	A-PP	-0.06	0.00	0.648	-0.06	0.00	0.667
SRT	A-PP	-0.22	0.05	0.121	-0.25	0.06	0.077
GRIP/BW	A-PP	-0.02	0.00	0.913	-0.05	0.00	0.722
FAT%	A-PP	0.09	0.01	0.518	0.13	0.02	0.363
HEI	A-PP	0.00	0.00	0.976	0.01	0.00	0.925

Factor	Outcome	Bivariate correlation			Age-adjusted		
		r	r^2	P	r	r^2	P
S/DAY	A-AP	-0.02	0.00	0.900	-0.07	0.00	0.633
SRT	A-AP	-0.36	0.13	0.010	-0.22	0.05	0.126
GRIP/BW	A-AP	-0.44	0.19	0.001	-0.21	0.04	0.141
FAT%	A-AP	0.45	0.20	0.001	0.27	0.07	0.059
HEI	A-AP	0.13	0.02	0.362	0.05	0.00	0.715
Factor	**Outcome**	**Bivariate correlation**			**Age-adjusted**		
		r	r^2	P	r	r^2	P
S/DAY	A-AIx	0.01	0.00	0.950	-0.04	0.00	0.791
SRT	A-AIx	-0.36	0.13	0.009	-0.22	0.05	0.125
GRIP/BW	A-AIx	-0.47	0.22	0.000	-0.23	0.05	0.100
FAT%	A-AIx	0.45	0.20	0.001	0.25	0.06	0.076
HEI	A-AIx	0.13	0.02	0.349	0.05	0.00	0.718
Factor	**Outcome**	**Bivariate correlation**			**Age-adjusted**		
		r	r^2	P	r	r^2	P
S/DAY	A-AIx75	-0.09	0.01	0.530	-0.15	0.02	0.281
SRT	A-AIx75	-0.41	0.17	0.002	-0.30	0.09	0.032
GRIP/BW	A-AIx75	-0.53	0.28	0.000	-0.35	0.12	0.012
FAT%	A-AIx75	0.51	0.26	0.000	0.35	0.12	0.011
HEI	A-AIx75	-0.04	0.00	0.803	-0.15	0.02	0.280

Factor	Outcome	Bivariate correlation			Age-adjusted		
		r	r^2	P	r	r^2	P
S/DAY	RHR	-0.25	0.06	0.079	-0.24	0.06	0.086
SRT	RHR	-0.19	0.03	0.188	-0.22	0.05	0.117
GRIP/BW	RHR	-0.20	0.04	0.161	-0.27	0.07	0.060
FAT%	RHR	0.20	0.04	0.161	0.26	0.07	0.071
HEI	RHR	-0.37	0.13	0.008	-0.36	0.13	0.010
Factor	**Outcome**	**Bivariate correlation**			**Age-adjusted**		
		r	r^2	P	r	r^2	P
S/DAY	B-SBP	-0.07	0.00	0.624	-0.06	0.00	0.670
SRT	B-SBP	-0.14	0.02	0.339	-0.21	0.04	0.144
GRIP/BW	B-SBP	-0.05	0.00	0.730	-0.16	0.02	0.272
FAT%	B-SBP	0.19	0.03	0.190	0.29	0.09	0.036
HEI	B-SBP	-0.25	0.06	0.077	-0.23	0.05	0.109
Factor	**Outcome**	**Bivariate correlation**			**Age-adjusted**		
		r	r^2	P	r	r^2	P
S/DAY	B-DBP	-0.13	0.02	0.366	-0.15	0.02	0.286
SRT	B-DBP	-0.16	0.03	0.257	-0.07	0.01	0.623
GRIP/BW	B-DBP	-0.32	0.10	0.021	-0.21	0.04	0.146
FAT%	B-DBP	0.38	0.14	0.006	0.28	0.08	0.044
HEI	B-DBP	-0.12	0.01	0.403	-0.17	0.03	0.228

Factor	Outcome	Bivariate correlation			Age-adjusted		
		r	r^2	P	r	r^2	P
S/DAY	B-PP	0.03	0.00	0.850	0.06	0.00	0.682
SRT	B-PP	-0.02	0.00	0.879	-0.20	0.04	0.155
GRIP/BW	B-PP	0.21	0.04	0.138	-0.02	0.00	0.919
FAT%	B-PP	-0.10	0.01	0.477	0.12	0.01	0.395
HEI	B-PP	-0.18	0.03	0.193	-0.14	0.02	0.342
Factor	**Outcome**	**Bivariate correlation**			**Age-adjusted**		
		r	**r^2**	**P**	**r**	**r^2**	**P**
S/DAY	MP	-0.16	0.02	0.268	-0.17	0.03	0.232
SRT	MP	-0.22	0.05	0.125	-0.17	0.03	0.246
GRIP/BW	MP	-0.29	0.08	0.039	-0.23	0.05	0.113
FAT%	MP	0.40	0.16	0.004	0.35	0.12	0.011
HEI	MP	-0.21	0.04	0.135	-0.25	0.06	0.083
Factor	**Outcome**	**Bivariate correlation**			**Age-adjusted**		
		r	**r^2**	**P**	**r**	**r^2**	**P**
S/DAY	MAP	-0.12	0.01	0.401	-0.13	0.02	0.377
SRT	MAP	-0.17	0.03	0.226	-0.14	0.02	0.325
GRIP/BW	MAP	-0.24	0.06	0.089	-0.21	0.04	0.148
FAT%	MAP	0.34	0.11	0.014	0.32	0.10	0.023
HEI	MAP	-0.20	0.04	0.167	-0.22	0.05	0.129

APPENDIX C: STEPWISE REGRESSION RESULTS

Step #	Vars. Entered	Vars. Removed	r^2	Delta r^2	P
0	Intercept		0.52		0.002
	AGE				0.003
	FAT%				0.079
	S/DAY				0.694
	HEI				0.440
	GRIP/BW				0.822
	SRT				0.191
1	Intercept	GRIP/BW	0.52	0.001	0.001
	AGE				0.002
	FAT%				0.031
	S/DAY				0.679
	HEI				0.409
	SRT				0.160
2	Intercept	S/DAY	0.52	0.002	0.001
	AGE				0.002
	FAT%				0.029
	HEI				0.414
	SRT				0.152
3	Intercept	HEI	0.52	0.007	0.001
	AGE				0.002
	FAT%				0.010
	SRT				0.160
4	Intercept	SRT	0.50	0.021	0.000
	AGE				0.002
	FAT%				0.000

REFERENCES

1. **Aatola H, Koivistoinen T, Hutri-Kahonen N, Juonala M, Mikkila V, Lehtimaki T, Viikari JS, Raitakari OT, and Kahonen M**. Lifetime fruit and vegetable consumption and arterial pulse wave velocity in adulthood: the Cardiovascular Risk in Young Finns Study. *Circulation* 122: 2521-2528, 2010.

2. **AlGhatrif M, Strait JB, Morrell CH, Canepa M, Wright J, Elango P, Scuteri A, Najjar SS, Ferrucci L, and Lakatta EG**. Longitudinal trajectories of arterial stiffness and the role of blood pressure: the Baltimore Longitudinal Study of Aging. *Hypertension* 62: 934-941, 2013.

3. **Andersson C, Lyass A, Larson MG, Spartano NL, Vita JA, Benjamin EJ, Murabito JM, Esliger DW, Blease SJ, Hamburg NM, Mitchell GF, and Vasan RS**. Physical activity measured by accelerometry and its associations with cardiac structure and vascular function in young and middle-aged adults. *J Am Heart Assoc* 4: e001528, 2015.

4. **Anoop S, Misra A, Bhardwaj S, and Gulati S**. High body fat and low muscle mass are associated with increased arterial stiffness in Asian Indians in North India. *J Diabetes Complications* 29: 38-43, 2015.

5. **Antoniades C, Tousoulis D, Vasiliadou C, Marinou K, Tentolouris C, Ntarladimas I, and Stefanadis C**. Combined effects of smoking and hypercholesterolemia on inflammatory process, thrombosis/fibrinolysis system, and forearm hyperemic response. *Am J Cardiol* 94: 1181-1184, 2004.

6. **Aoyagi Y, Park H, Kakiyama T, Park S, Yoshiuchi K, and Shephard RJ**. Yearlong physical activity and regional stiffness of arteries in older adults: the Nakanojo Study. *Eur J Appl Physiol* 109: 455-464, 2010.

7. **Aune D, Norat T, Romundstad P, and Vatten LJ**. Whole grain and refined grain consumption and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of cohort studies. *Eur J Epidemiol* 28: 845-858, 2013.

8. **Avolio AP, Van Bortel LM, Boutouyrie P, Cockcroft JR, McEniery CM, Protogerou AD, Roman MJ, Safar ME, Segers P, and Smulyan H**. Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. *Hypertension* 54: 375-383, 2009.

9. **Ayabe M, Park S, Shephard RJ, and Aoyagi Y**. Associations of activity monitor output and an estimate of aerobic fitness with pulse wave velocities: the Nakanojo study. *J Phys Act Health* 12: 139-144, 2015.

10. **Babu AS, Veluswamy SK, Arena R, Guazzi M, and Lavie CJ**. Virgin coconut oil and its potential cardioprotective effects. *Postgrad Med* 126: 76-83, 2014.

11. **Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, Boutouyrie P, Cameron J, Chen CH, Cruickshank JK, Hwang SJ, Lakatta EG, Laurent S, Maldonado J, Mitchell GF, Najjar SS, Newman AB, Ohishi M, Pannier B, Pereira T, Vasan RS, Shokawa T, Sutton-Tyrell K, Verbeke F, Wang KL, Webb DJ, Willum Hansen T, Zoungas S, McEniery CM, Cockcroft JR, and Wilkinson IB**. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol* 63: 636-646, 2014.

12. **Benetos A, Zervoudaki A, Kearney-Schwartz A, Perret-Guillaume C, Pascal-Vigneron V, Lacolley P, Labat C, and Weryha G**. Effects of lean and fat mass on bone mineral density and arterial stiffness in elderly men. *Osteoporos Int* 20: 1385-1391, 2009.

13. **Bertovic DA, Waddell TK, Gatzka CD, Cameron JD, Dart AM, and Kingwell BA**. Muscular strength training is associated with low arterial compliance and high pulse pressure. *Hypertension* 33: 1385-1391, 1999.

14. **Borlaug BA, Olson TP, Abdelmoneim SS, Melenovsky V, Sorrell VL, Noonan K, Lin G, and Redfield MM**. A randomized pilot study of aortic waveform guided therapy in chronic heart failure. *J Am Heart Assoc* 3: e000745, 2014.

15. **Boutouyrie P, Laurent S, Girerd X, Benetos A, Lacolley P, Abergel E, and Safar M**. Common carotid artery stiffness and patterns of left ventricular hypertrophy in hypertensive patients. *Hypertension* 25: 651-659, 1995.

16. **Brazier J, Cooper N, and Buckberg G**. The adequacy of subendocardial oxygen delivery: the interaction of determinants of flow, arterial oxygen content and myocardial oxygen need. *Circulation* 49: 968-977, 1974.

17. **Brenna JT**. Efficiency of conversion of alpha-linolenic acid to long chain n-3 fatty acids in man. *Curr Opin Clin Nutr Metab Care* 5: 127-132, 2002.

18. **Breslow JL**. n-3 fatty acids and cardiovascular disease. *Am J Clin Nutr* 83: 1477S-1482S, 2006.

19. **Brito LB, de Araujo DS, and de Araujo CG**. Does flexibility influence the ability to sit and rise from the floor? *Am J Phys Med Rehabil* 92: 241-247, 2013.

20. **Brito LB, Ricardo DR, Araujo DS, Ramos PS, Myers J, and Araujo CG**. Ability to sit and rise from the floor as a predictor of all-cause mortality. *Eur J Prev Cardiol* 21: 892-898, 2014.

21. **Brown M, and Holloszy JO**. Effects of walking, jogging and cycling on strength, flexibility, speed and balance in 60- to 72-year olds. *Aging (Milano)* 5: 427-434, 1993.

22. **Celermajer DS, Sorensen KE, Georgakopoulos D, Bull C, Thomas O, Robinson J, and Deanfield JE**. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. *Circulation* 88: 2149-2155, 1993.

23. **Cocate PG, de Oliveira A, Hermsdorff HH, Alfenas Rde C, Amorim PR, Longo GZ, Peluzio Mdo C, Faria FR, and Natali AJ**. Benefits and relationship of steps walked per day to cardiometabolic risk factor in Brazilian middle-aged men. *J Sci Med Sport* 17: 283-287, 2014.

24. **Cook JN, DeVan AE, Schleifer JL, Anton MM, Cortez-Cooper MY, and Tanaka H**. Arterial compliance of rowers: implications for combined aerobic and strength training on arterial elasticity. *Am J Physiol Heart Circ Physiol* 290: H1596-1600, 2006.

25. **Cooper JN, Buchanich JM, Youk A, Brooks MM, Barinas-Mitchell E, Conroy MB, and Sutton-Tyrrell K**. Reductions in arterial stiffness with weight loss in overweight and obese young adults: potential mechanisms. *Atherosclerosis* 223: 485-490, 2012.

26. **Corden B, Keenan NG, de Marvao AS, Dawes TJ, Decesare A, Diamond T, Durighel G, Hughes AD, Cook SA, and O'Regan DP**. Body fat is associated with reduced aortic stiffness until middle age. *Hypertension* 61: 1322-1327, 2013.

27. **Crichton GE, Elias MF, and Robbins MA**. Cardiovascular health and arterial stiffness: the Maine-Syracuse Longitudinal Study. *J Hum Hypertens* 28: 444-449, 2014.

28. **Czernichow S, Bertrais S, Oppert JM, Galan P, Blacher J, Ducimetiere P, Hercberg S, and Zureik M**. Body composition and fat repartition in relation to structure and function of large arteries in middle-aged adults (the SU.VI.MAX study). *Int J Obes (Lond)* 29: 826-832, 2005.

29. **de Oliveira Otto MC, Mozaffarian D, Kromhout D, Bertoni AG, Sibley CT, Jacobs DR, Jr., and Nettleton JA**. Dietary intake of saturated fat by food source and incident cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. *Am J Clin Nutr* 96: 397-404, 2012.

30. **den Ouden ME, Schuurmans MJ, Brand JS, Arts IE, Mueller-Schotte S, and van der Schouw YT**. Physical functioning is related to both an impaired physical ability and ADL disability: a ten year follow-up study in middle-aged and older persons. *Maturitas* 74: 89-94, 2013.

31. **Dengo AL, Dennis EA, Orr JS, Marinik EL, Ehrlich E, Davy BM, and Davy KP**. Arterial destiffening with weight loss in overweight and obese middle-aged and older adults. *Hypertension* 55: 855-861, 2010.

32. **Ding FH, Fan WX, Zhang RY, Zhang Q, Li Y, and Wang JG**. Validation of the noninvasive assessment of central blood pressure by the SphygmoCor and Omron devices against the invasive catheter measurement. *Am J Hypertens* 24: 1306-1311, 2011.

33. **Drawz PE, Abdalla M, and Rahman M**. Blood pressure measurement: clinic, home, ambulatory, and beyond. *Am J Kidney Dis* 60: 449-462, 2012.

34. **Fahs CA, Heffernan KS, Ranadive S, Jae SY, and Fernhall B**. Muscular strength is inversely associated with aortic stiffness in young men. *Med Sci Sports Exerc* 42: 1619-1624, 2010.

35. **Fantin F, Rossi AP, Cazzadori M, Comellato G, Mazzali G, Gozzoli MP, Grison E, and Zamboni M**. Central and peripheral fat and subclinical vascular damage in older women. *Age Ageing* 42: 359-365, 2013.

36. **Fragala MS, Alley DE, Shardell MD, Harris TB, McLean RR, Kiel DP, Cawthon PM, Dam TT, Ferrucci L, Guralnik JM, Kritchevsky SB, Vassileva MT, Gudnason V, Eiriksdottir G, Koster A, Newman A, Siggeirsdottir K, Satterfield S, Studenski SA, and Kenny AM**. Comparison of Handgrip and Leg Extension Strength in Predicting Slow Gait Speed in Older Adults. *J Am Geriatr Soc* 64: 144-150, 2016.

37. **Franklin SS, Gustin Wt, Wong ND, Larson MG, Weber MA, Kannel WB, and Levy D**. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation* 96: 308-315, 1997.

38. **Gando Y, Yamamoto K, Murakami H, Ohmori Y, Kawakami R, Sanada K, Higuchi M, Tabata I, and Miyachi M**. Longer time spent in light physical activity is associated with reduced arterial stiffness in older adults. *Hypertension* 56: 540-546, 2010.

39. **Gebel K, Ding D, and Bauman AE**. Volume and intensity of physical activity in a large population-based cohort of middle-aged and older Australians: prospective relationships with weight gain, and physical function. *Prev Med* 60: 131-133, 2014.

40. **George J, Rapsomaniki E, Pujades-Rodriguez M, Shah AD, Denaxas S, Herrett E, Smeeth L, Timmis A, and Hemingway H**. How Does Cardiovascular Disease First Present in Women and Men? Incidence of 12 Cardiovascular Diseases in a Contemporary Cohort of 1,937,360 People. *Circulation* 132: 1320-1328, 2015.

41. **Gepner AD, Korcarz CE, Colangelo LA, Hom EK, Tattersall MC, Astor BC, Kaufman JD, Liu K, and Stein JH**. Longitudinal effects of a decade of aging on carotid artery stiffness: the multiethnic study of atherosclerosis. *Stroke* 45: 48-53, 2014.

42. **Gepner AD, Young R, Delaney JA, Tattersall MC, Blaha MJ, Post WS, Gottesman RF, Kronmal R, Budoff MJ, Burke GL, Folsom AR, Liu K, Kaufman J, and Stein JH**. Comparison of coronary artery calcium presence, carotid plaque presence, and carotid intima-media thickness for cardiovascular disease prediction in the multi-ethnic study of atherosclerosis. *Circ Cardiovasc Imaging* 8: 2015.

43. **Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, and Turner MB**. Executive summary: heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation* 129: 399-410, 2014.

44. **Gomez-Marcos MA, Recio-Rodriguez JI, Patino-Alonso MC, Agudo-Conde C, Lasaosa-Medina L, Rodriguez-Sanchez E, Maderuelo-Fernandez JA, and Garcia-Ortiz L**. Relationship between objectively measured physical activity and vascular structure and function in adults. *Atherosclerosis* 234: 366-372, 2014.

45. **Gonzales JU**. Gait performance in relation to aortic pulse wave velocity, carotid artery elasticity and peripheral perfusion in healthy older adults. *Clin Physiol Funct Imaging* 33: 245-251, 2013.

46. **Guenther PM, Kirkpatrick SI, Reedy J, Krebs-Smith SM, Buckman DW, Dodd KW, Casavale KO, and Carroll RJ**. The Healthy Eating Index-2010 is a valid and reliable measure of diet quality according to the 2010 Dietary Guidelines for Americans. *J Nutr* 144: 399-407, 2014.

47. **Gunnell AS, Knuiman MW, Divitini ML, and Cormie P**. Leisure time physical activity and long-term cardiovascular and cancer outcomes: the Busselton Health Study. *Eur J Epidemiol* 29: 851-857, 2014.

48. **Hale SA, Weger L, Mandala M, and Osol G**. Reduced NO signaling during pregnancy attenuates outward uterine artery remodeling by altering MMP expression and collagen and elastin deposition. *Am J Physiol Heart Circ Physiol* 301: H1266-1275, 2011.

49. **Hall WL**. Dietary saturated and unsaturated fats as determinants of blood pressure and vascular function. *Nutr Res Rev* 22: 18-38, 2009.

50. **He FJ, and MacGregor GA**. A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. *J Hum Hypertens* 23: 363-384, 2009.

51. **He FJ, Marciniak M, Visagie E, Markandu ND, Anand V, Dalton RN, and MacGregor GA**. Effect of modest salt reduction on blood pressure, urinary albumin, and pulse wave velocity in white, black, and Asian mild hypertensives. *Hypertension* 54: 482-488, 2009.

52. **Heffernan KS, Tarzia BJ, Kasprowicz AG, Lefferts WK, Hatanaka M, and Jae SY**. Self-reported sitting time is associated with higher pressure from wave reflections independent of physical activity levels in healthy young adults. *Am J Hypertens* 26: 1017-1023, 2013.

53. **Heir T, Erikssen J, and Sandvik L**. Life style and longevity among initially healthy middle-aged men: prospective cohort study. *BMC Public Health* 13: 831, 2013.

54. **Heller R, Werner-Felmayer G, and Werner ER**. Alpha-Tocopherol and endothelial nitric oxide synthesis. *Ann N Y Acad Sci* 1031: 74-85, 2004.

55. **Huynh Q, Blizzard L, Sharman J, Magnussen C, Schmidt M, Dwyer T, and Venn A**. Relative contributions of adiposity in childhood and adulthood to vascular health of young adults. *Atherosclerosis* 228: 259-264, 2013.

56. **Jablonski KL, Fedorova OV, Racine ML, Geolfos CJ, Gates PE, Chonchol M, Fleenor BS, Lakatta EG, Bagrov AY, and Seals DR**. Dietary sodium restriction and association with urinary marinobufagenin, blood pressure, and aortic stiffness. *Clin J Am Soc Nephrol* 8: 1952-1959, 2013.

57. **Jennersjo P, Ludvigsson J, Lanne T, Nystrom FH, Ernerudh J, and Ostgren CJ**. Pedometer-determined physical activity is linked to low systemic inflammation and low arterial stiffness in Type 2 diabetes. *Diabet Med* 29: 1119-1125, 2012.

58. **Justine M, Azizan A, Hassan V, Salleh Z, and Manaf H**. Barriers to participation in physical activity and exercise among middle-aged and elderly individuals. *Singapore Med J* 54: 581-586, 2013.

59. **Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan RS, and Mitchell GF**. Aortic stiffness, blood pressure progression, and incident hypertension. *JAMA* 308: 875-881, 2012.

60. **Kawano H, Tanimoto M, Yamamoto K, Sanada K, Gando Y, Tabata I, Higuchi M, and Miyachi M**. Resistance training in men is associated with increased arterial stiffness and blood pressure but does not adversely affect endothelial function as measured by arterial reactivity to the cold pressor test. *Exp Physiol* 93: 296-302, 2008.

61. **Kozakova M, Palombo C, Mhamdi L, Konrad T, Nilsson P, Staehr PB, Paterni M, and Balkau B**. Habitual physical activity and vascular aging in a young to middle-age population at low cardiovascular risk. *Stroke* 38: 2549-2555, 2007.

62. **Lahti J, Rahkonen O, Lahelma E, and Laaksonen M**. Leisure-time physical activity and disability retirement: a prospective cohort study. *J Phys Act Health* 10: 669-675, 2013.

63. **Laurent S**. Defining vascular aging and cardiovascular risk. *J Hypertens* 30 Suppl: S3-8, 2012.

64. **Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, and Benetos A**. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 37: 1236-1241, 2001.

65. **Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, and Struijker-Boudier H**. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 27: 2588-2605, 2006.

66. **Laursen AS, Hansen AL, Wiinberg N, Brage S, Sandbaek A, Lauritzen T, Witte DR, Jorgensen ME, and Johansen NB**. Higher physical activity is associated with lower aortic stiffness but not with central blood pressure: the ADDITION-Pro Study. *Medicine (Baltimore)* 94: e485, 2015.

67. **Leong DP, and Teo KK**. Predicting cardiovascular disease from handgrip strength: the potential clinical implications. *Expert Rev Cardiovasc Ther* 13: 1277-1279, 2015.

68. **Leopold JA**. Cellular and molecular mechanisms of arterial stiffness associated with obesity. *Hypertension* 62: 1003-1004, 2013.

69. **Levy MN, and Pappano AJ**. *Cardiovascular Physiology*. Philadelphia, PA: Mosby Inc., 2007.

70. **Lim S, Wyker B, Bartley K, and Eisenhower D**. Measurement error of self-reported physical activity levels in New York City: assessment and correction. *Am J Epidemiol* 181: 648-655, 2015.

71. **Lindstrom PJ, Suni JH, and Nygard CH**. Associations of leisure-time physical activity with balance and lower extremity strength: a validation of the neuromuscular part of the Physical Activity Pie. *J Phys Act Health* 6: 493-502, 2009.

72. **Logan JG, and Barksdale DJ**. Pulse wave velocity in Korean American men and women. *J Cardiovasc Nurs* 28: 90-96, 2013.

73. **London GM, Pannier B, Guerin AP, Marchais SJ, Safar ME, and Cuche JL**. Cardiac hypertrophy, aortic compliance, peripheral resistance, and wave reflection in end-stage renal disease. Comparative effects of ACE inhibition and calcium channel blockade. *Circulation* 90: 2786-2796, 1994.

74. **Mac Ananey O, McLoughlin B, Leonard A, Maher L, Gaffney P, Boran G, and Maher V**. Inverse Relationship Between Physical Activity, Adiposity and Arterial Stiffness in Healthy Middle-aged Subjects. *J Phys Act Health* 2015.

75. **Marklund M, Leander K, Vikstrom M, Laguzzi F, Gigante B, Sjogren P, Cederholm T, de Faire U, Hellenius ML, and Riserus U**. Polyunsaturated Fat Intake Estimated by Circulating Biomarkers and Risk of Cardiovascular Disease and All-Cause Mortality in a Population-Based Cohort of 60-Year-Old Men and Women. *Circulation* 132: 586-594, 2015.

76. **McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, and Cockcroft JR**. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). *J Am Coll Cardiol* 46: 1753-1760, 2005.

77. **Meaume S, Benetos A, Henry OF, Rudnichi A, and Safar ME**. Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. *Arterioscler Thromb Vasc Biol* 21: 2046-2050, 2001.

78. **Meng Y, Wu H, Yang Y, Du H, Xia Y, Guo X, Liu X, Li C, and Niu K**. Relationship of anabolic and catabolic biomarkers with muscle strength and physical performance in older adults: a population-based cross-sectional study. *BMC Musculoskelet Disord* 16: 202, 2015.

79. **Mero AA, Hulmi JJ, Salmijarvi H, Katajavuori M, Haverinen M, Holviala J, Ridanpaa T, Hakkinen K, Kovanen V, Ahtiainen JP, and Selanne H**. Resistance training induced increase in muscle fiber size in young and older men. *Eur J Appl Physiol* 113: 641-650, 2013.

80. **Mikkola TS, Gissler M, Merikukka M, Tuomikoski P, and Ylikorkala O**. Sex differences in age-related cardiovascular mortality. *PLoS One* 8: e63347, 2013.

81. **Mitchell GF**. Arterial Stiffness and Hypertension: Chicken or Egg? *Hypertension* 2014.

82. **Mitchell GF**. Central pressure should not be used in clinical practice. *Artery Res* 9: 8-13, 2015.

83. **Mitchell GF, Guo CY, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, and Levy D**. Cross-sectional correlates of increased aortic stiffness in the community: the Framingham Heart Study. *Circulation* 115: 2628-2636, 2007.

84. **Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, and Benjamin EJ**. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation* 121: 505-511, 2010.

85. **Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, and Levy D**. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension* 43: 1239-1245, 2004.

86. **Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson O, Garcia M, Aspelund T, Harris TB, Gudnason V, and Launer LJ**. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility--Reykjavik study. *Brain* 134: 3398-3407, 2011.

87. **Miyachi M, Kawano H, Sugawara J, Takahashi K, Hayashi K, Yamazaki K, Tabata I, and Tanaka H**. Unfavorable effects of resistance training on central arterial compliance: a randomized intervention study. *Circulation* 110: 2858-2863, 2004.

88. **Miyaki A, Maeda S, Yoshizawa M, Misono M, Saito Y, Sasai H, Endo T, Nakata Y, Tanaka K, and Ajisaka R**. Effect of weight reduction with dietary intervention on arterial distensibility and endothelial function in obese men. *Angiology* 60: 351-357, 2009.

89. **Najjar SS, Scuteri A, Shetty V, Wright JG, Muller DC, Fleg JL, Spurgeon HP, Ferrucci L, and Lakatta EG**. Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. *J Am Coll Cardiol* 51: 1377-1383, 2008.

90. **Nichols WW, and O'Rourke MF**. *McDonald's Blood Flow in Arteries: Theoretical, Experimental, and Clinical Principles*. Philadelphia, PA: Edward Arnold, 1990.

91. **Nordstrand N, Gjevestad E, Dinh KN, Hofso D, Roislien J, Saltvedt E, Os I, and Hjelmesaeth J**. The relationship between various measures of obesity and arterial stiffness in morbidly obese patients. *BMC Cardiovasc Disord* 11: 7, 2011.

92. **North BJ, and Sinclair DA**. The intersection between aging and cardiovascular disease. *Circ Res* 110: 1097-1108, 2012.

93. **O'Donovan C, Lithander FE, Raftery T, Gormley J, Mahmud A, and Hussey J**. Inverse relationship between physical activity and arterial stiffness in adults with hypertension. *J Phys Act Health* 11: 272-277, 2014.

94. **O'Rourke MF, and Hashimoto J**. Mechanical factors in arterial aging: a clinical perspective. *J Am Coll Cardiol* 50: 1-13, 2007.

95. **Orr JS, Gentile CL, Davy BM, and Davy KP**. Large artery stiffening with weight gain in humans: role of visceral fat accumulation. *Hypertension* 51: 1519-1524, 2008.

96. **Otsuki T, Maeda S, Iemitsu M, Saito Y, Tanimura Y, Ajisaka R, and Miyauchi T**. Vascular endothelium-derived factors and arterial stiffness in strength- and endurance-trained men. *Am J Physiol Heart Circ Physiol* 292: H786-791, 2007.

97. **Palgi Y, Shrira A, and Zaslavsky O**. Quality of life attenuates age-related decline in functional status of older adults. *Qual Life Res* 24: 1835-1843, 2015.

98. **Pedersen BK, and Febbraio MA**. Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nat Rev Endocrinol* 8: 457-465, 2012.

99. **Perkins GM, Owen A, Swaine IL, and Wiles JD**. Relationships between pulse wave velocity and heart rate variability in healthy men with a range of moderate-to-vigorous physical activity levels. *Eur J Appl Physiol* 98: 516-523, 2006.

100. **Pescatello LS, and American College of Sports M**. *ACSM's guidelines for exercise testing and prescription*. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health, 2014.

101. **Pichler G, Martinez F, Vicente A, Solaz E, Calaforra O, and Redon J**. Pulse pressure amplification and its determinants. *Blood Press* 25: 21-27, 2016.

102. **Pierce GL, Zhu H, Darracott K, Edet I, Bhagatwala J, Huang Y, and Dong Y**. Arterial stiffness and pulse-pressure amplification in overweight/obese African-American adolescents: relation with higher systolic and pulse pressure. *Am J Hypertens* 26: 20-26, 2013.

103. **Plantinga Y, Ghiadoni L, Magagna A, Giannarelli C, Franzoni F, Taddei S, and Salvetti A**. Supplementation with vitamins C and E improves arterial stiffness and endothelial function in essential hypertensive patients. *Am J Hypertens* 20: 392-397, 2007.

104. **Quan HL, Blizzard CL, Sharman JE, Magnussen CG, Dwyer T, Raitakari O, Cheung M, and Venn AJ**. Resting heart rate and the association of physical fitness with carotid artery stiffness. *Am J Hypertens* 27: 65-71, 2014.

105. **Rantanen T, Guralnik JM, Foley D, Masaki K, Leveille S, Curb JD, and White L**. Midlife hand grip strength as a predictor of old age disability. *JAMA* 281: 558-560, 1999.

106. **Rasool AH, Rahman AR, Yuen KH, and Wong AR**. Arterial compliance and vitamin E blood levels with a self emulsifying preparation of tocotrienol rich vitamin E. *Arch Pharm Res* 31: 1212-1217, 2008.

107. **Rauramaa R, Tuomainen P, Vaisanen S, and Rankinen T**. Physical activity and health-related fitness in middle-aged men. *Med Sci Sports Exerc* 27: 707-712, 1995.

108. **Recio-Rodriguez JI, Gomez-Marcos MA, Patino-Alonso MC, Sanchez A, Agudo-Conde C, Maderuelo-Fernandez JA, and Garcia-Ortiz L**. Association between fat amount of dairy products with pulse wave velocity and carotid intima-media thickness in adults. *Nutr J* 13: 37, 2014.

109. **Redheuil A, Yu WC, Wu CO, Mousseaux E, de Cesare A, Yan R, Kachenoura N, Bluemke D, and Lima JA**. Reduced ascending aortic strain and distensibility: earliest manifestations of vascular aging in humans. *Hypertension* 55: 319-326, 2010.

110. **Reidlinger DP, Darzi J, Hall WL, Seed PT, Chowienczyk PJ, and Sanders TA**. How effective are current dietary guidelines for cardiovascular disease prevention in healthy middle-aged and older men and women? A randomized controlled trial. *Am J Clin Nutr* 101: 922-930, 2015.

111. **Roman MJ, Devereux RB, Kizer JR, Okin PM, Lee ET, Wang W, Umans JG, Calhoun D, and Howard BV**. High central pulse pressure is independently associated with adverse cardiovascular outcome the strong heart study. *J Am Coll Cardiol* 54: 1730-1734, 2009.

112. **Roman MJ, Saba PS, Pini R, Spitzer M, Pickering TG, Rosen S, Alderman MH, and Devereux RB**. Parallel cardiac and vascular adaptation in hypertension. *Circulation* 86: 1909-1918, 1992.

113. **Rubanyi GM, and Vanhoutte PM**. Superoxide anions and hyperoxia inactivate endothelium-derived relaxing factor. *Am J Physiol* 250: H822-827, 1986.

114. **Safar ME, and O'Rourke MF**. *Arterial Stiffness in Hypertension*. Amsterdam: Elsevier, 2006.

115. **Sakuragi S, Abhayaratna K, Gravenmaker KJ, O'Reilly C, Srikusalanukul W, Budge MM, Telford RD, and Abhayaratna WP**. Influence of adiposity and physical activity on arterial stiffness in healthy children: the lifestyle of our kids study. *Hypertension* 53: 611-616, 2009.

116. **Sampaio RA, Sewo Sampaio PY, Yamada M, Yukutake T, Uchida MC, Tsuboyama T, and Arai H**. Arterial stiffness is associated with low skeletal muscle mass in Japanese community-dwelling older adults. *Geriatr Gerontol Int* 14 Suppl 1: 109-114, 2014.

117. **Sanders TA**. Plant compared with marine n-3 fatty acid effects on cardiovascular risk factors and outcomes: what is the verdict? *Am J Clin Nutr* 100 Suppl 1: 453S-458S, 2014.

118. **Saneei P, Salehi-Abargouei A, Esmaillzadeh A, and Azadbakht L**. Influence of Dietary Approaches to Stop Hypertension (DASH) diet on blood pressure: a systematic review and meta-analysis on randomized controlled trials. *Nutr Metab Cardiovasc Dis* 24: 1253-1261, 2014.

119. **Sauder KA, Proctor DN, Chow M, Troy LM, Wang N, Vita JA, Vasan RS, Mitchell GF, Jacques PF, Hamburg NM, and West SG**. Endothelial function, arterial stiffness and adherence to the 2010 Dietary Guidelines for Americans: a cross-sectional analysis. *Br J Nutr* 113: 1773-1781, 2015.

120. **Schouten F, Twisk JW, de Boer MR, Stehouwer CD, Serne EH, Smulders YM, and Ferreira I**. Increases in central fat mass and decreases in peripheral fat mass are associated with accelerated arterial stiffening in healthy adults: the Amsterdam Growth and Health Longitudinal Study. *Am J Clin Nutr* 94: 40-48, 2011.

121. **Schwingshackl L, and Hoffmann G**. Diet quality as assessed by the Healthy Eating Index, the Alternate Healthy Eating Index, the Dietary Approaches to Stop Hypertension score, and health outcomes: a systematic review and meta-analysis of cohort studies. *J Acad Nutr Diet* 115: 780-800 e785, 2015.

122. **Scoditti E, Capurso C, Capurso A, and Massaro M**. Vascular effects of the Mediterranean diet-part II: role of omega-3 fatty acids and olive oil polyphenols. *Vascul Pharmacol* 63: 127-134, 2014.

123. **Scuteri A, Morrell CH, Orru M, Strait JB, Tarasov KV, Ferreli LA, Loi F, Pilia MG, Delitala A, Spurgeon H, Najjar SS, AlGhatrif M, and Lakatta EG**. Longitudinal perspective on the conundrum of central arterial stiffness, blood pressure, and aging. *Hypertension* 64: 1219-1227, 2014.

124. **Scuteri A, Orru M, Morrell CH, Tarasov K, Schlessinger D, Uda M, and Lakatta EG**. Associations of large artery structure and function with adiposity: effects of age, gender, and hypertension. The SardiNIA Study. *Atherosclerosis* 221: 189-197, 2012.

125. **Seals DR, Tanaka H, Clevenger CM, Monahan KD, Reiling MJ, Hiatt WR, Davy KP, and DeSouza CA**. Blood pressure reductions with exercise and sodium restriction in postmenopausal women with elevated systolic pressure: role of arterial stiffness. *J Am Coll Cardiol* 38: 506-513, 2001.

126. **Sesso HD, Buring JE, Christen WG, Kurth T, Belanger C, MacFadyen J, Bubes V, Manson JE, Glynn RJ, and Gaziano JM**. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *JAMA* 300: 2123-2133, 2008.

127. **Shimizu M, Hoshide S, Ishikawa J, Yano Y, Eguchi K, and Kario K**. Correlation of Central Blood Pressure to Hypertensive Target Organ Damages During Antihypertensive Treatment: The J-TOP Study. *Am J Hypertens* 2014.

128. **Siasos G, Tousoulis D, Oikonomou E, Zaromitidou M, Verveniotis A, Plastiras A, Kioufis S, Maniatis K, Miliou A, Siasou Z, Stefanadis C, and Papavassiliou AG**. Effects of Omega-3 fatty acids on endothelial function, arterial wall properties, inflammatory and fibrinolytic status in smokers: a cross over study. *Int J Cardiol* 166: 340-346, 2013.

129. **Smith KB, and Smith MS**. Obesity Statistics. *Prim Care* 43: 121-135, 2016.

130. **Steed MM, Tyagi N, Sen U, Schuschke DA, Joshua IG, and Tyagi SC**. Functional consequences of the collagen/elastin switch in vascular remodeling in hyperhomocysteinemic wild-type, eNOS-/-, and iNOS-/- mice. *Am J Physiol Lung Cell Mol Physiol* 299: L301-311, 2010.

131. **Stenholm S, Koster A, Valkeinen H, Patel KV, Bandinelli S, Guralnik JM, and Ferrucci L**. Association of Physical Activity History With Physical Function and Mortality in Old Age. *J Gerontol A Biol Sci Med Sci* 2015.

132. **Strasser B, Arvandi M, Pasha EP, Haley AP, Stanforth P, and Tanaka H**. Abdominal obesity is associated with arterial stiffness in middle-aged adults. *Nutr Metab Cardiovasc Dis* 25: 495-502, 2015.

133. **Suni JH, Oja P, Miilunpalo SI, Pasanen ME, Vuori IM, and Bos K**. Health-related fitness test battery for middle-aged adults: associations with physical activity patterns. *Int J Sports Med* 20: 183-191, 1999.

134. **Sutton-Tyrrell K, Newman A, Simonsick EM, Havlik R, Pahor M, Lakatta E, Spurgeon H, and Vaitkevicius P**. Aortic stiffness is associated with visceral adiposity in older adults enrolled in the study of health, aging, and body composition. *Hypertension* 38: 429-433, 2001.

135. **Taddei S, Virdis A, Ghiadoni L, Magagna A, and Salvetti A**. Vitamin C improves endothelium-dependent vasodilation by restoring nitric oxide activity in essential hypertension. *Circulation* 97: 2222-2229, 1998.

136. **Tanaka H, DeSouza CA, and Seals DR**. Absence of age-related increase in central arterial stiffness in physically active women. *Arterioscler Thromb Vasc Biol* 18: 127-132, 1998.

137. **Tanaka H, and Safar ME**. Influence of lifestyle modification on arterial stiffness and wave reflections. *Am J Hypertens* 18: 137-144, 2005.

138. **Tarumi T, Gonzales MM, Fallow B, Nualnim N, Pyron M, Tanaka H, and Haley AP**. Central artery stiffness, neuropsychological function, and cerebral

perfusion in sedentary and endurance-trained middle-aged adults. *J Hypertens* 31: 2400-2409, 2013.

139. **Tipton CM**. The history of "Exercise Is Medicine" in ancient civilizations. *Adv Physiol Educ* 38: 109-117, 2014.

140. **Tousoulis D, Plastiras A, Siasos G, Oikonomou E, Verveniotis A, Kokkou E, Maniatis K, Gouliopoulos N, Miliou A, Paraskevopoulos T, and Stefanadis C**. Omega-3 PUFAs improved endothelial function and arterial stiffness with a parallel antiinflammatory effect in adults with metabolic syndrome. *Atherosclerosis* 232: 10-16, 2014.

141. **Tully MA, McBride C, Heron L, and Hunter RF**. The validation of Fibit Zip physical activity monitor as a measure of free-living physical activity. *BMC Res Notes* 7: 952, 2014.

142. **Vaitkevicius PV, Fleg JL, Engel JH, O'Connor FC, Wright JG, Lakatta LE, Yin FC, and Lakatta EG**. Effects of age and aerobic capacity on arterial stiffness in healthy adults. *Circulation* 88: 1456-1462, 1993.

143. **Vasu S, Morgan TM, Kitzman DW, Bertoni A, Stacey RB, Hamilton C, Chiles C, Thohan V, and Hundley WG**. Abnormal stress-related measures of arterial stiffness in middle-aged and elderly men and women with impaired fasting glucose at risk for a first episode of symptomatic heart failure. *J Am Heart Assoc* 4: e000991, 2015.

144. **Vigen R, Maddox TM, and Allen LA**. Aging of the United States population: impact on heart failure. *Curr Heart Fail Rep* 9: 369-374, 2012.

145. **Vlachopoulos C, Aggelakas A, Ioakeimidis N, Xaplanteris P, Terentes-Printzios D, Abdelrasoul M, Lazaros G, and Tousoulis D**. Music decreases aortic stiffness and wave reflections. *Atherosclerosis* 240: 184-189, 2015.

146. **Vrablik M, Prusikova M, Snejdrlova M, and Zlatohlavek L**. Omega-3 fatty acids and cardiovascular disease risk: do we understand the relationship? *Physiol Res* 58 Suppl 1: S19-26, 2009.

147. **Walsh K**. Adipokines, myokines and cardiovascular disease. *Circ J* 73: 13-18, 2009.

148. **Wang H, Weihrauch D, Kersten JR, Toth JM, Passerini AG, Rajamani A, Schrepfer S, and LaDisa JF, Jr.** Alagebrium inhibits neointimal hyperplasia and restores distributions of wall shear stress by reducing downstream vascular resistance in obese and diabetic rats. *Am J Physiol Heart Circ Physiol* 309: H1130-1140, 2015.

149. **Westerhof BE, and Westerhof N**. Magnitude and return time of the reflected wave: the effects of large artery stiffness and aortic geometry. *J Hypertens* 30: 932-939, 2012.

150. **Wilson MM, Reedy J, and Krebs-Smith SM**. American Diet Quality: Where It Is, Where It Is Heading, and What It Could Be. *J Acad Nutr Diet* 116: 302-310.e301, 2016.

151. **Wilson PW, D'Agostino RB, Parise H, Sullivan L, and Meigs JB**. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation* 112: 3066-3072, 2005.

152. **Wykretowicz A, Adamska K, Guzik P, Krauze T, and Wysocki H**. Indices of vascular stiffness and wave reflection in relation to body mass index or body fat in healthy subjects. *Clin Exp Pharmacol Physiol* 34: 1005-1009, 2007.

153. **Yannoutsos A, Rinaldi ER, Zhang Y, Protogerou AD, Safar ME, and Blacher J**. Central hemodynamics in risk assessment strategies: additive value over and above brachial blood pressure. *Curr Pharm Des* 21: 719-729, 2015.

154. **Yudkin JS, Eringa E, and Stehouwer CD**. "Vasocrine" signalling from perivascular fat: a mechanism linking insulin resistance to vascular disease. *Lancet* 365: 1817-1820, 2005.

155. **Zhu W, Hooker SP, Sun Y, Xie M, Su H, and Cao J**. Associations of cardiorespiratory fitness with cardiovascular disease risk factors in middle-aged Chinese women: a cross-sectional study. *BMC Womens Health* 14: 62, 2014.

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