PRETERM BIRTH, PHYSICAL ACTIVITY, AND ARTERIAL STIFFNESS IN
YOUNG ADULTS

BY

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LIST OF ABBREVIATIONS

AG	Augmentation
AGA	Appropriate for Gestational Age
AI	Aortic Augmentation Index
AI75	Augmentation Index Standardized @ 75 bpm
BMI	Body Mass Index
BP	Blood Pressure
BW	Birth Weight
CHD	Coronary Heart Disease
Cm	Centimeter
CRF	Cardiorespiratory Fitness
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DNA	Deoxyribonucleic Acid
ELBW	Extremely Low Birth Weight
FEV_1	Forced Expiratory Volume
FVC	Forced Vital Capacity
GA	Gestational Age
HR	Heart Rate
Kg	Kilogram
LTPA	Leisure Time Physical Activity
MAP	Mean Arterial Pressure
MAQ	Modifiable Activity Questionnaire
MVPA	Moderate to Vigorous Physical Activity
MET	Metabolic Equivalent of Task
NO	Nitric Oxide
P2/P1	Peripheral Augmentation Index
PA	Physical Activity
PEPC	Prenatal Exposures Postnatal Consequences
PP	Pulse Pressure
PT	Preterm Birth
PWA	Pulse Wave Analysis
PWV	Pulse Wave Velocity
rAI	Radial Augmentation Index
RNA	Ribonucleic Acid
SGA	Small for Gestational Age
SBP	Systolic Blood Pressure
SD	Standard Deviation
SpO_2	Peripheral Capillary Oxygen Saturation
T	Term birth
T2D	Type II Diabetes
VLBW	Very Low Birth Weight

ABSTRACT

PURPOSE: To compare arterial stiffness and physical activity (PA) between preterm (PT) and term-born (T) young adults and determine if PA is a partial mediator of arterial stiffness. **METHODS**: 68 PT (31 M) and 33 T (15 M), 18-23 yrs old, participated. Arterial stiffness was assessed via applanation tonometry from which augmentation index (AI) and AI at heart rate of 75 (AI75) were examined. Physical activity (PA) was assessed via questionnaire and past year average total hours per week (TOT-hrs), vigorous hours per week (Vig-hrs; PA > 6 METs), MET-hrs per week were determined. Between group differences were examined with independent samples t-tests or Mann-Whitney U tests, and regression analysis was used to examine relationships and potential mediation. **RESULTS**: AI did not differ between PT and T ($1.38 \pm 11.04\%$ vs. $-2.33 \pm 8.25\%$), however, AI75 was significant ($p<.01$) ($0.21 \pm 11.15\%$ vs. $-5.64 \pm 8.08\%$). TOT-hrs per week were similar between PT and T, but Vig-hrs (1.98 ± 3.66 v. 2.90 ± 3.63 hrs/wk) and MET-hrs (36.36 ± 43.50 v. 45.08 ± 32.41 hrs/wk) were significantly lower in PT v. T. PT and T differences in AI75 were no longer significant after adjusting for height differences. **CONCLUSIONS**: Earlier pulse wave reflection associated with shorter stature likely accounted for greater SBP augmentation observed in PT versus T. Less participation in vigorous PA by PT was not associated with arterial stiffness, but is concerning and may contribute to CVD risk.

<u>**REVIEW OF LITERATURE**</u>

According to the CDC, in 2014, 1 in every 10 live births in the United States was preterm (PT; < 37 weeks gestational age).[1] In the same year, 1.4% of infants were born with very low birth weight (VLBW; <1500 grams), and nearly all VLBW infants are born PT.[1] Both VLBW and PT are associated with short term and long term consequences. Some short term consequences include respiratory distress, neurodevelopmental issues, necrotizing enterocolitis, retinopathy, and intraventricular hemorrhage, as well as increased infant mortality.[1] Some of the short term consequences persist in that people born PT with VLBW are at increased risk for asthma, cerebral palsy, neurocognitive limitations, as well as vision and/or hearing impairments.[1] Furthermore, growing evidence suggests these persons have increased risk for developing cardiovascular disease (CVD) in adulthood, one of the leading causes of death in the United States.[2]

Fetal Origins Hypothesis

One of the more widely accepted hypotheses for the increased risk for CVD is the "fetal origins hypothesis". This hypothesis, originally proposed by Barker, suggests that chronic diseases may have their origins in fetal life. Structural and functional adaptations to adverse fetal environments may be beneficial in the short term, promoting survival; however, in later life, when the environment changes and is no longer threatening, these adaptations become detrimental and increase risk for development of chronic diseases.[3,4] This hypothesis is supported by Barker's observation that men who were born with the lowest birth weight, and continued to weigh the least after one year of life, had the highest mortality rate from ischemic heart disease.[5] Standardized mortality rates dropped significantly from men who were 12.3 kg at one year compared to those who were 8.2 kg

in 5654 men born between 1911-1930. Barker also observed that mortality rates were highest in those infants born at the lowest weights.

The fetal origins hypothesis has been extended to include critical periods of growth after birth and labeled the "developmental origins hypothesis."[4] For instance Eriksson et al. examined the medical records of 4630 men who were born in the Helsinki University Hospital during 1934-44 and had multiple measures of height and weight from birth to 12 years of age.[6,7] This study found that in addition to an association between lower birth weight and later development of coronary heart disease (CHD), risk was further increased by slow growth during the first year of life. They also noted that rapid weight gain after 1 year of age increased risk for CHD, but only among boys who were thin at birth. Consequently, those born with lower birth weight adapted to fetal undernutrition, but the adaptations persisted in postnatal life affecting growth patterns. Infancy and the early childhood years are considered plastic, developmental periods.[3,4] These adaptations then potentially could have led to the increased development of CHD in adulthood.[6]

The second study completed by Eriksson and colleagues also supports the fetal and developmental origins hypotheses.[7] The researchers once again used a sample of people born in Helsinki during a similar time period with 8790 participants including both men and women. Their goal was to examine the effect of income of the parents during gestation, BW, and weight gain during and after infancy. The authors found that those born into low income families tended to be smaller, as well as, despite slow weight gain for first year after birth, exhibited more rapid weight gain after infancy. These participants then went on to exhibit an increased risk for developing CHD as well as

higher prevalence of type II diabetes (T2D) in adulthood. Based on the results, it can be suggested that lower birth weight, as well as slow growth during the first year followed by rapid growth after infancy led to poor health in adulthood, thus supporting the fetal and developmental origins hypotheses.[3,4]

Epigenetics

Epigenetics might explain some of the fetal and/or developmental origins of disease. Epigenetics has shown that in response to adverse environments, changes are made to genes of the person without affecting the DNA sequence. These changes can be due to changes in methyl or histone groups, functioning of RNA, and other mechanisms.[8]Such mechanisms result in phenotypic changes, which are often permanent.

The degree to which the childhood and adult environment matches the predicted environment from development will determine the susceptibility of the individual to chronic diseases, such as CVD.[8] As phrased by Godfrey and colleagues, this mismatch can be due to a more rich postnatal environment, or a poorer development environment, or a combination of both.[8] There is some research, as summarized in reviews by Godfrey et al. and Martinez et al. that suggest that these changes can potentially be carried on to future generations.[8,9] This would suggest that an individual who experienced an adverse fetal environment could have grandchildren with an elevated risk for CVD. With the potential generational alteration in DNA makeup, and poor fetal environments, epigenetic regulations come into effect due to more than just the individual's own developmental

environment. The epigenetic effect and its relationship to the fetal origins hypothesis is shown in Figure 1.
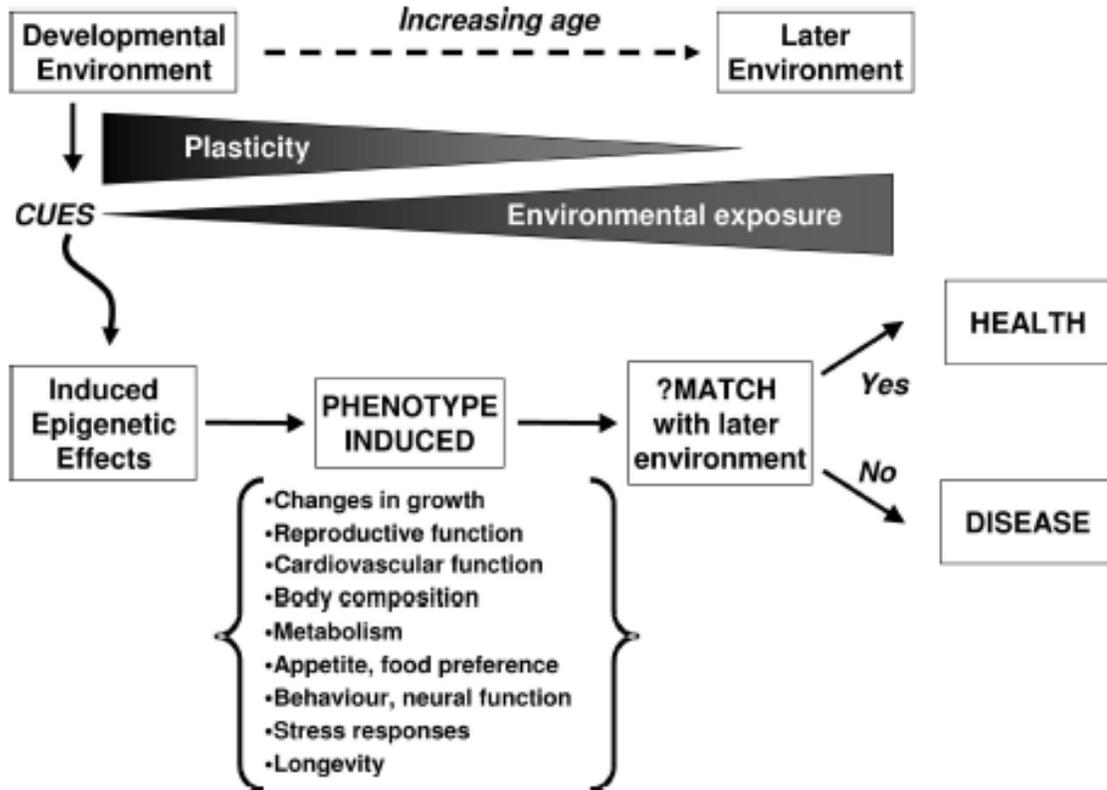
Figure 1. A diagram following epigenetic effects throughout lifetime. From Godfrey et al.[8]

Cardiovascular Development

There are many stages to vascular development. First, most of the development of the heart occurs during the 4th to 5th weeks of gestation.[10] From here, the heart continues to grow, with much of the vascular tree beginning to develop. This development continues into 28th to 32nd weeks of gestation, where many of the blood vessels surrounding the heart are considered functional.[11] However, more development of the heart and cardiovascular system occurs later in fetal life, such as around 37 weeks GA.[12,13] Preterm birth and low BW, as well as the associated adaptations, can lead to changes in heart development. There is a theoretical critical window potentially seen

during fetal growth and ending just prior to or after birth during which the different developmental mechanisms of the heart determine the cell population from which the heart will continue to grow.[14] At this time, the development of the heart switches from primarily hyperplastic to hypertrophic.[14] If PT occurs during this critical period, the cell population may be reduced, thus affecting future cardiac development. This altered cardiac development can result in smaller vessel size.[15] Smaller size of the arteries can lead to reduced blood flow during fetal and infant development, thus causing deficits in development, and possibly future cardiovascular disease risk.[14,15]

Along with the delayed growth of the heart, vascular development may also be impaired with premature birth.[12,13,16] The vessel wall is comprised of tunica intima, media, and adventitia. The tunica intima is the deepest layer of the artery, and contains primarily the endothelium. The tunica media is located between the intima and adventitia and contains smooth muscle as well as elastin fibers. Finally, the tunica adventitia is comprised of both elastin and collagen fibers, and provides the primary structure of the artery. Potentially, due to the smooth muscle and connective tissue found in these layers, each layer of the artery may be affected by PT birth.

The alterations associated with PT birth mainly occur with the synthesis and deposition of elastin and collagen. Collagen is a stiff fibrous tissue which is found throughout the body, especially in major arteries. It helps build arteries during fetal development, and is responsible for the strength of the vessels at high amounts of pressure.[17] Elastin is less stiff, and accounts for much of the vasodilation that occurs during various physiological actions. During fetal development, it has been suggested that collagen is synthesized before elastin.[12] Therefore, during early periods, such as prior

to just before the 37th week of gestation, the vascular tree is quite stiff. While elastin is synthesized throughout much fetal development, the critical period for elastin occurs primarily during the last trimester.[13] If the primary period of elastin development is altered by PT birth, collagen is synthesized quickly to make up for the lack of elastin, adding to the already fibrous makeup of the vessel.[12,13] With more collagen, there is less arterial compliance.[12] Therefore, PT birth may be associated with reduced elastin deposition and greater collagen synthesis, resulting in stiffer arterial walls, especially compared to infants who complete their gestation in utero.

Along with alteration of elastin and collagen deposition, PT birth may disrupt development of the endothelium.[12,13,18] The endothelium plays a large role in vasodilation and arterial wall distension by releasing vasoactive substances that result in the dilation of the artery.[13,18] During normal physiological functioning, these substances interact with the smooth muscle found in the intima media. If endothelial dysfunction seen in people born PT limits the release of these substances, arterial wall distension may be affected, increasing stiffness.[13,18] An example of a substance that may be affected by PT birth is nitric oxide (NO), which is synthesized by endothelial cells and promotes vasodilation.[19] Development of smooth muscle may also be affected by PT birth and lead to stiffer arteries, however, this occurrence is mostly seen in small arteries which have more smooth muscle than large arteries.[12] Deficits in vasoactive substance release is only one known mechanism of endothelial dysfunction in those born PT. The other effects of PT birth on endothelial dysfunction, as well as the exact mechanisms through which they occur, are not well known, and warrant further study.[13] Ultimately, endothelial dysfunction has been associated with hypertension and CVD.[12,13] Norman reviewed the

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literature surrounding endothelial dysfunction and PT birth.[13] According to his research,

some literature supports the idea that those born PT have lasting endothelial dysfunction

that can result in stiffer arteries in adulthood.

Measurement of Arterial Stiffness

Various methods have been employed to examine arterial properties. Two of the

most common techniques include pulse wave velocity (PWV) and pulse wave analysis

(PWA).[20,21] Both measure the stiffness of an artery based on a waveform initiated by

contraction of the heart. Figure 2, from London and Pannier, demonstrates a sample

waveform and derived measures.[20] Figure 2, part A represents a waveform of an

individual with less stiff arteries, while part B shows a waveform indicative of elevated

arterial stiffness. The dashed line is the forward pulse wave, while the dotted line is the

pulse wave reflection, which occurs when the forward pulse wave reaches the end of the

extremities. PWV is determined by the speed of the pulse wave. A faster PWV indicates

stiffer arteries. If the pulse wave reflection is quick, it can return to the heart during

systole, causing it to augment the waveform and increase systolic blood pressure (SBP).

This can be seen in B on the figure.
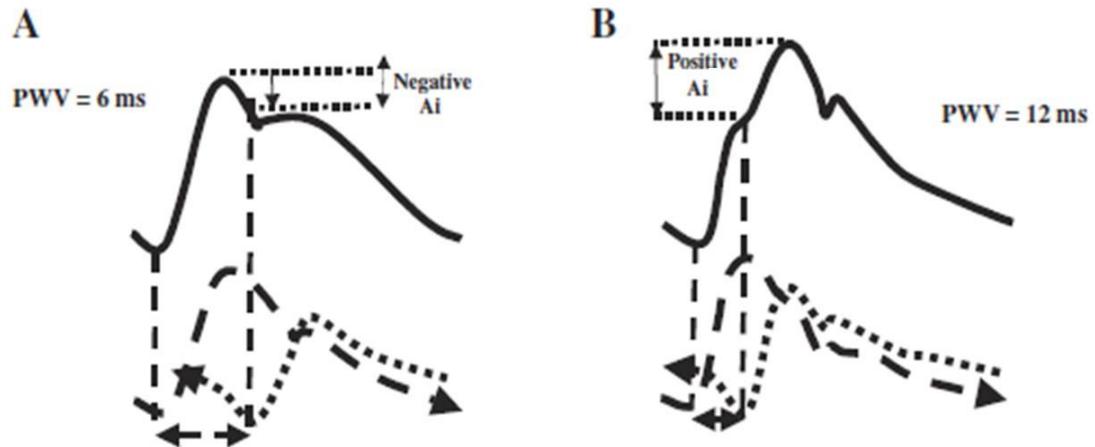
Figure 2. This figure presents the pulse wave of an individual with less stiff arteries (A) and an individual with stiffer arteries (B). The solid lines show the SBP, while the dashed line indicates the forward pulse wave, and the dotted line represents the pulse wave reflection. Person A has a negative AI (P2 – P1), and person B has a positive AI. Larger numbers are indicative of elevated arterial stiffness. From London & Pannier.[20]

Pulse wave velocity is commonly assessed via applanation tonometry using the carotid-femoral, brachioradial, or radial tonometry methods. Each technique is slightly different, and they vary in accuracy. However, they all provide information regarding PWV and PWA. Radial applanation tonometry uses a captured waveform from the radial artery to obtain variables such as peripheral augmentation and augmentation index (AI), and uses a transfer function to create an aortic waveform. This waveform is then used to estimate measures of central stiffness.

Augmentation is an absolute measure of how much the SBP has been augmented by the reflected wave. This variable can be either negative or positive, which is determined by the peaks in the pulse wave. Each waveform has two peaks, peak one (P1) and peak two (P2). P1 is whichever peak comes first, and it can be larger or smaller than

P2, as shown in Figure 2, part A and B, respectively depending on whether or not the pulse wave reflection returns during systole (larger) or diastole (smaller). Augmentation (AG) is determined by subtracting P1 from P2 (P2-P1). Augmentation index is a relative value of how much SBP has been augmented, and can be represented as either peripheral or central (aortic). Peripheral AI is determined by P2/P1, and is represented as a percentage. An equation, AG/PP, is used to create an AI that is representative of central arterial stiffness, and is also expressed as a percentage, but can also be either negative or positive. Studies have shown that HR can linearly alter AI.[22,23] Consequently, Aortic AI is often standardized at a HR of 75 bpm to account for potential variation different HR (AI75).[22,23] Higher values in all variables reflect stiffer arteries. There have been some studies that have referenced the good validity and reliability of the transfer function in determining the central measurements from peripheral waveforms.[21,24,25] These same papers mentioned the feasibility of using PWA compared to other arterial stiffness measures, citing how PWA methods are quick, non-invasive, and accurate.

In addition to HR, there are several other physiologic parameters that affect PWA and PWV. In general, age is directly associated with PWV and males tend to have lower values than females.[26,27] A study completed in children found that height significantly affected PWV, with short persons having elevated numbers.[26] This may be due to a shorter travel distance for the pulse wave, resulting in a faster PWV as well as faster and earlier reflection. However, higher values due to height are not representative of elevated stiffness, which can be misleading. These findings were supported by McGrath et al. who showed AI differences between healthy young adults of different heights.[27] Blood pressure is another measure commonly adjusted for, as those with hypertension tend to

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have stiffer arteries.[28] However, the temporal sequence of BP and arterial stiffness is somewhat cloudy, as it has not been fully determined whether BP causes stiffer arteries, or elevated arterial stiffness causes higher BP, thus so some do not adjust for this measures. Consequently, it is important to take these factors into consideration when examining PWV and PWA.

Preterm Birth and Arterial Stiffness

As it has been suggested that arterial development is affected by PT and/or VLBW, there has been some research to determine if stiffer arteries are observed in these populations as well. Details of these studies are presented in Appendix A. Most of the research suggests that PT and/or VLBW affect arterial stiffness, especially in children.[15,29,30] One study examined the association among gestational age (GA) and birth weight (BW) on AI75 and PWV in PT and T adolescents using radial applanation tonometry.[29] Seventy-one adolescents were stratified into quartiles by GA and BW based on gender-specific birth weight percentage by GA as determined by Australian national data from 1991-1994. It was found that AI75 was elevated in those adolescents who were both PT and small for GA (children born anywhere below the national average of weight for their GA; SGA) adolescents compared to those born PT and appropriate for their GA (AGA), and those born at T, both SGA and AGA.

Cheung et al. used brachioradial PWV to study arterial stiffness in 86 children (avg. age 8.2 ± 1.7 yrs.).[30] Once the children were categorized based on GA, they were further stratified by whether or not their BW was appropriate for gestational age (AGA) or SGA. SGA was classified as BW<10th percentile for GA on a growth chart from 1989 for average Chinese births. Similar to other studies, PWV was elevated in children born

PT with SGA compared to PT with AGA and all T participants. However, PT AGA had slightly but not statistically significant higher PWV than T participants. There was also an inverse association between z-score of birth weight and PWV (β=-0.43, p<0.001).

Other studies showed similar results for the association between PT or BW and elevated arterial stiffness when examining pulse wave augmentation.[31,32] Lurbe et al. studied the relationship between BW and various measures of arterial stiffness in 219 children and adolescents between the ages of 7-18.[31] Participants were stratified into quartiles based on BW. The authors found that AI, as well AI represented as a percentage of PP (AI/PP), were both elevated in the two lower quartiles (<2.5kg and 2.5-2.99kg) compared to the higher two quartiles (3.0kg-3.5kg and >3.5kg). These findings suggest that in addition to low birth weight, lower but normal birth weight can potentially have an effect on arterial stiffness.

When examining extremely PT ($\leq$25 wks, 6 days) participants, McEniery and colleagues studied arterial stiffness in children using both radial pulse wave recording as well as carotid-femoral PWV.[32] As hypothesized, the extremely PT children had elevated AI and augmentation pressure (AP), even when the data was adjusted for sex, height, heart rate, BP, and weight. This finding is congruent with previous studies, as extremely PT may be at even higher risk for stiffer arteries than those born less PT.

While the studies in children and adolescents generally support a relationship between lower gestational age and birth weight and greater arterial stiffness, there have been mixed findings in studies of young adults. Boardman and colleagues compared arterial stiffness in 102 young adults born PT (GA<37 weeks) with their T peers.[15] By assessing the carotid-femoral & brachial femoral PWV, the authors found that PWV was

elevated in PT when compared to T adults. Augmentation index standardized at a heart

rate of 75 bpm was also elevated in PT when compared to T. Both of these results are

indicative of elevated arterial stiffness in PT adults. Adjustment for BP attenuated the

group differences, but they remained statistically significant. It should be noted that the

PT were shorter than T, but height was not considered in their analysis. Consequently,

some of the greater arterial stiffness observed in the PT may due to shorter stature and

earlier reflection of the pulse wave. Kerkhof et al. also studied the relationship between

PT and arterial stiffness in young adults, but reported no significance difference from

AGA T controls.[33] The relationship between SGA and PWV was significant in a linear

regression model, but became non-significant when adjusting for adult height.

Ultimately, the majority of the research supports an association between lower

birth weight and stiffer arteries in children and adolescents. However, the inconsistencies

among studies may be explained by the age, gender, and stature, as well as other

covariates not adjusted for consistently. Further research is needed to determine if PT/

VLBW do in fact have stiffer arteries than their T peers, and if these differences persist

into adulthood.

Arterial Stiffness and Cardiovascular Disease Risk

The evidence suggesting arterial stiffness is elevated in those born PT or with

VLBW is important when considering long term consequences of children born

PT/VLBW, especially with respect to CVD risk. It has been suggested that arterial

stiffness can contribute to the development of CVD. A review by Tauzin summarized the

impact arterial stiffness has on CVD risk.[12] The primary mechanism of this increased risk

is through hypertension and atherosclerosis. Over time stiff arteries elevate systolic blood

pressure (SBP). This increase in SBP is partially due to the decrease in arterial distension caused by reduced presence of elastin in the arterial wall. With less vasodilation and adjustments to extreme environments, SBP increases, which can lead to scaring of the endothelium. This scaring starts the cascade which eventually leads to a build-up of plague and, therefore, the development of atherosclerosis. Atherosclerosis can lead to ischemia and ultimately myocardial infarction and stroke.

According to the same review, SBP and, in turn, PP and MAP which are elevated through increased SBP, as well as decreased distensibility of the aorta and arterial walls, increase cardiac afterload.[12] Afterload is considered the aortic pressure the ventricle must overcome during systole to eject blood. With elevated blood pressure, there is more pressure within the arteries, specifically within the aorta and applied on the ventricle walls due to the elevated afterload. An elevated afterload causes the heart to work harder during systole in order to eject blood. When the heart applies more effort, left ventricular hypertrophy may develop, which can lead to other diseases such as heart failure. These are just some of the many long term complications of elevated arterial stiffness in terms of CVD and heart disease.

Physical Activity and Arterial Stiffness

It is well-accepted that higher levels of physical activity (PA) are associated with reduced risk for CVD.[34] However, few studies have examined the influence of PA on arterial stiffness.

The details of several cross-sectional studies are presented in Appendix B, most of which suggest people who are less active have stiffer arteries.[35–38] Sakuragi and colleagues used examined PA using pedometers and arterial stiffness using carotid-

femoral PWV in 615 healthy children.[35] Cardiorespiratory fitness (CRF) was also measured using the 20-meter shuttle run, as the authors suggested that those who were more active would have higher CRF. Univariate analysis showed an inverse association between pedometer counts and PWV. However, the results raised the question of clinical significance, as β=-0.003, and p=0.046. Children who exhibited lower CRF had higher PWV in a univariate analysis, suggesting stiffer arteries. The relationship between PWV and CRF was attenuated after controlling for BMI (p=0.054). After further adjusting for waist circumference and then body fat percentage, both individually, the relationship was attenuated even further to suggest that there was not a significant association between the two measures. Therefore, the authors speculated the findings may not be reliable, specifically due to high measurement error and low face validity of both pedometer usage and CRF methods.

In a sample of young adults, Edwards et al. examined the association between PA and brachial artery distensibility, PWV, and AI in 548 adults, 156 of whom were type II diabetic, 191 were obese (≥95th percentile for BMI), and 201 were lean (5th-85th percentile for BMI).[36] By measuring PA using an accelerometer, it was determined that both AI and PWV were elevated in less active young adults of all groups, including diabetic, obese, and lean, although there was greater significance in the diabetic group. All of these findings were determined after adjusting for age, sex, body size, MAP, obesity, and type II diabetes status. Similarly, a study of 1241 slightly older adults (avg. age 30 yrs), using accelerometry to assess PA, found that carotid-femoral PWV was significantly higher in less active participants.[37]

In one of the largest studies to date, the EVIDENT trial examined the role of PA as well as physical inactivity on both central and peripheral vascular measures in 1365 adults ranging in age from 20-80 years old.[38] These measures included blood pressure (BP), pulse pressure (PP), radial augmentation index (rAI), and ambulatory arterial stiffness index. Accelerometers were used to determine PA and sedentary time. While many of the measures more commonly associated with arterial stiffness (rAI, ambulatory arterial stiffness index) were not significantly related to PA or sedentary time, there was a positive relationship between sedentary time and central and peripheral PP, suggesting that those participants who were more sedentary had elevated PP, which is potentially associated with increased stiffness, specifically in the aorta. However, this relationship disappeared when controlling for moderate-vigorous PA (MVPA) and also number of breaks in sedentary time. This finding suggests that, although a person may have a high amount of sedentary time, if they have some MVPA and take breaks to be physically active during the day, their PP and arterial stiffness may not be affected as much as if they were completely sedentary. The previous studies mentioned, two of which included similar age groups, also showed some evidence to suggest that those participants with lower PA may have elevated arterial stiffness, or at least warrant further research into the relationship.[35–37]

The mechanisms by which PA may alter arterial stiffness have been speculated by several authors.[12,35,37] It has been suggested that those born PT but who are less sedentary have more efficient endothelial function and therefore have less impaired arterial vasodilation than other PT born, but sedentary, individuals.[12,35,37] The effect of increased PA on endothelial function could be through altered cytokine release including

interleukin-6 and tumor necrosis factor α, as well as decreased inflammation.[35,37] Authors have also suggested that PA may delay the inevitable stiffening of arteries due to aging and, although this hypothesis would most likely be true in T young adults, it may be more important in PT whose arteries are stiffer at the start, in hope of retarding the progression.[37]

PA and sedentary behavior may act on arterial stiffness via adiposity. Greater adiposity is associated with insulin resistance, dyslipidemia, and inflammation which may affect arterial stiffness. Sedentary lifestyles may increase adiposity, and conversely, active lifestyles may decrease adiposity, thereby affecting arterial stiffness.[35] It is not clear if high PA or a decreased sedentary lifestyle is more important, or if the combination has even greater effects on arterial stiffness.

There is a growing number of studies examining whether or not exercise interventions improve arterial stiffness (as shown in Appendix C).[39–42] These studies encompass a wide range of ages, and much of the research has examined chronic disease populations. Although most training studies have been completed on older adults, there have been a few completed in young adults. However, most of the young adult studies are based in unhealthy populations. Yuan and colleagues examined the effects of an eight-week swimming protocol on arterial stiffness in young overweight adults, and found reductions in arterial stiffness from baseline to post-intervention.[39] Beck et al. also found decreased PWV and PWA measures when examining eight weeks of aerobic or resistance exercise in prehypertensive young adults.[40] Goldberg and colleagues found similar reductions in AI after four weeks of aerobic exercise in young men with a family history of hypertension.[41] However, most of the field focuses on older, disease populations. For

example, Kim et al. found that moderate intensity, continuous aerobic exercise improved arterial stiffness in older adults.[42] Despite the varying age and health status of the populations, most the studies have shown aerobic training to reduce arterial stiffness.

While most of the studies have examined the effects of aerobic training on arterial stiffness, some authors have ventured into other training modalities. Ashor and colleagues completed a detailed review and meta-analysis on randomized controlled trials involving the effect of exercise on arterial stiffness. The authors found that aerobic exercise appeared to reduce measures of arterial stiffness, while resistance training, as well as combined aerobic and resistance training, did not significantly alter arterial stiffness in various populations.[43] Montero et al. completed a similar review on various age groups and populations, but found that both aerobic and combined aerobic plus resistance training reduced arterial stiffness, the reduction did not differ between groups.[44]

In opposition to the studies, Montero et al. completed a detailed review and meta-analysis regarding aerobic training and arterial stiffness in an obese population.[45] All of the studies included had examined populations of older adults. Study results were inconsistent. Some studies showed reductions in arterial stiffness, whereas most of the publications reported little to no changes after training, with an estimated total standard mean difference of -0.17 (95% CI: -0.39, 0.06) which was not statistically significant. Consequently, more training studies examining different exercise modalities are warranted.

Birthweight, Prematurity, and Physical Activity

There is some evidence suggesting that young adults born PT or VLBW are less active than their T normal BW peers.[46–49] Details of these studies are presented in Appendix D. Three studies examined physical activity in cohorts of young adults born PT and/or with VLBW. Kajantie and colleagues examined the association between VLBW and PA levels in 351 young adults (163 VLBW, 188 T).[46] The authors determined that the adults who were born with VLBW had lower levels of conditioning (i.e. more intense) leisure-time PA (LTPA) as determined by a PA questionnaire.

Another study with a similar sample (94 VLBW unimpaired adults and 101 T matched controls) also used a questionnaire to assess PA (occupational, commuting, and LTPA).[47] This study also had the goal of determining the relationship between VLBW and PA. The results suggested that those born VLBW likewise had lower levels of conditioning LTPA (running, swimming, etc.) compared to T born controls. PA of the VLBW participants was also, on average, of a lower intensity, supporting the results of the previous study. However, when the authors gave a slightly smaller subset of the same cohort (57 VLBW, 47 controls) wrist accelerometers, the findings were a little different.[48] Compared to the controls, VLBW participants had similar total PA, as well as when PA was split between weekday total PA and weekend total PA. These findings are not congruent with the two previous studies mentioned, suggesting PA measured in a similar cohort by accelerometer presents slightly different results than questionnaire. However, although not significant, the authors did find that T controls had slightly higher MVPA and vigorous PA (p=0.1), as well as less sedentary time (p=0.06) than VLBW participants.

Lowe and colleagues found slightly different results when using accelerometry.[49] Instead of using birth weight criterion, the authors studied the relationship between GA age and PA in healthy 7-year old children, both girls and boys stratified by gestational age into 4 groups (25-32, 33-34, 35to <37, and $\geq$ 37 wks).[49] Using data from an accelerometer that collected information such as MVPA, total PA, and sedentary time, it was determined that boys who were born at $\leq$32 weeks GA, had lower levels of MVPA compared to T controls. This study is slightly different from the two previously mentioned in that the exposure variable included is GA instead of VLBW. The average birth weights corresponding to the GA groups were 1619 g for 25-32 wks, 2147 g for 33-34 weeks, 2683 g for 35-36 wks, and 3452 g for T participants. The authors reported that people born $\leq$32 weeks were less active than T (GA $\geq$ 37wks), but no differences were observed among any other PT GA and T groups.

There are several explanations for lower PA participation in PT. As previously mentioned, people born PT are at high risk for long term consequences persisting into young adulthood. These consequences include asthma, cerebral palsy, neurocognitive limitations, as well as vision, hearing, and motor impairments, all of which may limit a person's ability or desire to participate in PA.[1]

Reduced PA may be due to abnormal lung development, as seen in bronchopulmonary dysplasia, as well as reduced lung function and greater prevalence of exercise induced bronchoconstriction.[50] The reduced lung function may reflect fewer alveoli, impaired diffusion capacity, exercise-induced bronchoconstriction, and smaller airways, all of which have been reported in those born PT. This occurrence can be seen in McLeod et al.[51] The authors reported that VLBW children were more likely to show

outcomes indicative of obstructive pulmonary disease, such as decrease FVC, compared to normal BW children, suggesting poor lung development.[51]

Several studies have examined pulmonary function, exercise capacity, and PA.[52,53] In young adults, Vrijlandt and colleagues studied lung function in those born very PT had decreased FEV_1 and exercise capacity compared to T born peers.[52] In younger populations, Kilbride and colleagues examined pulmonary function and exercise capacity in children born with extremely low birth weight (ELBW).[53] These children showed lower peak oxygen uptake ($VO_{2\ peak)}$ and peripheral capillary oxygen saturation (SpO_2) than the normal BW control group, and the parents of ELBW reported less PA in their children than the parents of normal BW participants. These decrements can result in decrements in exercise capacity, as shown in Kilbride et al., as well as a study completed on Swedish young adults enrolled for military service.[53,54] Those participants born PT performed worse on cycle ergometer tests, with a steady decline for each week of GA, supporting decreased exercise capacity in young adults born PT.

It has been speculated that lower PA may also be associated with deficits in skeletal musculature, such as strength and coordination.[50] These issues could, by leading to lower PA in childhood, delay normal strength and coordination development, causing even more deficits in adulthood. Previous speculations are supported by a group of Finnish researchers.[55] The authors determined through modified push-ups in 40 seconds and maximal handgrip strength that muscular fitness was decreased in 23-year-olds born PT compared to T controls, and grip strength was reduced in those born early PT (<34 weeks GA).[55]

Ultimately, all of these factors can potentially combine to create low confidence in their ability to participate in PA. As reported in the previous study, those who were born PT, especially those born at less than 34 weeks GA, perceived themselves to be less physically capable compared to T peers. Saigal and colleagues also looked at physical activity self-efficacy and perceived PA performance, and found that ELBW reported lower self-efficacy in both compared to T peers.[56] Overall, PA levels may be reduced in PT/VLBW due to physiologic limitations as well as altered perceptions about their abilities to participate in PA.

PURPOSE

If people born PT or VLBW are less physically active and lower levels of PA are associated with elevated arterial stiffness, it may be that the some of the higher levels of arterial stiffness observed in PT/VLBW could be mediated via lower PA levels. To date, no study has examined the influence of PA on arterial stiffness in persons born PT with VLBW. Therefore, the purpose of this thesis was to compare arterial stiffness and PA between PT and T young adults, as well as determine if PA is a partial mediator of arterial stiffness. It was hypothesized that compared to their term-born normal BW peers, persons born PT/VLBW will have higher arterial stiffness and lower PA. It was further hypothesized that some of the association between PT and arterial stiffness would be partially mediated by PA level. If these hypotheses are proven to be true, then increasing PA may provide an avenue for decreasing arterial stiffness and ultimately CVD risk in young adults who were born PT/VLBW.

METHODS

Participants

Both PT and T were recruited from subjects who participated or expressed interest in participating in the first Prenatal Events – Postnatal Consequences (PEPC1) study at 14 years of age. For PEPC1, the PT participants were recruited from a cohort of infants born with VLBW between 1/1/1992 and 6/30/1996 at Forsyth Medical Center. Inclusion criteria were: 14 years of age, singleton birth without major congenital anomalies, clinical evaluation at 1 year adjusted age, and cognitive and physical ability to participate in the assessments. For PEPC2, follow up evaluation occurred between July 1, 2012 and August 31, 2016, and the participants were between the ages of 18-23 years old.

The T participants were recruited via various media for PEPC1, including newspaper ads and general word of mouth. These subjects were also born at Forsyth Medical Center, singleton birth with no major congenital anomalies, 14 years of age for PEPC1, no antenatal exposure to glucocorticords, and possessed the cognitive and physical ability to participate in the assessments. At the PEPC2 follow-up visit, their age ranged between 18 and 23 years of age. For PEPC2, participants were first sent a letter explaining the study and asked to return a post card indicating their interest in participating. They were then contacted by the study coordinator who explained the study in more detail. Participants were compensated for completing both PEPC2 study visits. The staff of the study were blinded to the birth status of the participants.

Measurements and Procedures

Participants reported for two visits and the measurements obtained at each visit are listed in Table 1. At the first visit, the study was explained in detail and written

informed consent was obtained (Appendix E). Measurements relevant to this thesis were

taken at the second visit and are denoted in bold in Table I. Height and weight (in light

clothing without shoes) were obtained in triplicate upon arrival using a wall-mounted

stadiometer and digital platform scale, respectively. They underwent several assessments

for the larger PEPC2 study. After testing in the morning and before lunch, physical

activity was assessed. After lunch, subjects were escorted to the vascular lab in the

Hypertension and Vascular Research Center where the measurements of arterial stiffness

were made.

Table I. Description of study visits; data important to this thesis in **bold**

Visit 1	Visit 2
Informed Consent	**Height, weight**, MUAC
Urine Sample	Blood pressure
Height, weight, body composition, MUAC	Urine samples
	Continuous non-invasive arterial blood pressure
Blood pressure	Heart rate variability
Saliva specimen	Pressure Natriuresis tests
Indwelling venous catheter	Health status questionnaires
Fasting blood labs	**Physical activity questionnaires**
Oral glucose tolerance test	**Non-invasive vascular lab testing**
Health status questionnaires	Provided with accelerometer and
Given instructions for overnight urine sample & 4 day standardized sodium diet	ambulatory BP monitor, with diary for each

Physical Activity Measurement

Habitual leisure time PA was assessed using the Modifiable Activity

Questionnaire (MAQ) and administered by a trained graduate student. Participants were

read a list of common leisure time activities (such as soccer, football, basketball, running,

swimming, yard work, and walking for exercise) and asked to identify those in which

they participated at least 5 times in the past 12 months. Then, for each of the identified

activities, the subjects were asked which months in the past year they participated in the

activity, as well as the number of times per month or week, and the number of minutes each time. The participants were asked to elaborate on each activity to help with determination of the appropriate MET value for that activity.

From the information provided, the average hours per week of PA (Tot-hrs) for the past year was determined. Activities with MET values deemed > 6 were considered vigorous, and the average hours per week spent in vigorous PA was determined (Vig-hrs) for the past year. Additionally, time spent in each activity was multiplied by its respective MET value to derive average MET-hours/wk (MET-hrs) for the past year. The validity and reliability of the MAQ has been established in other young adult and adolescent populations.[57–59] Physical activity data were also stratified based on meeting or not meeting the 2008 National Physical Activity Guidelines for total PA per week $\geq$ 150 min or < 150 min per week (Tot-grp), and also for time spent in vigorous PA $\geq$ 75 min or < 75 min per week (Vig-grp).[60]

Arterial Stiffness

Arterial stiffness was determined using the Sphygmocor SCOR-PX model. Each participant rested in a supine position for 10 minutes prior to measurements being taken. A graduate student trained in the Sphygmocor device collected the data by resting a tonometer over the radial artery on the left arm near the wrist until valid continuous waveforms were present. The waveforms collected were considered valid with an operator index greater than 75 as determined by Sphygmocor. The Sphygmocor device used a transfer function to determine aortic augmentation measures from the peripheral waveforms obtained. These measures included augmentation (AG), aortic augmentation index (AI), AI standardized at a HR of 75bpm (AI75), and peripheral augmentation index

(P2/P1). As previously mentioned, PWA is considered easier and less time consuming than carotid-femoral or brachioradial PWV, and is correlated with both of those measures.[21,24,25]

Statistical Analysis

Descriptive statistics were performed using SPSS version 24.0 to examine measures of central tendency and dispersion. Independent t-tests were used to make between-group (PT v. T) comparisons for subject characteristics as well as arterial stiffness parameters. Physical activity data were not normally distributed (based on Shapiro-Wilk Test with $p<.05$). Various log transformations were made but did not improve distributional characteristics of the PA data. Consequently, between group PA comparisons were made using nonparametric Mann-Whitney U tests. Pearson correlational analysis was used to examine associations among variables that met parametric criteria, and Spearman rank-order correlation analysis was used to examine associations with PA data. Chi-squared statistic was used to examine frequency distributions of categorical variables. Logistic regression analysis was completed for associations between dichotomous variables. Multivariate regression analysis was utilized to examine the independent association between PT birth and arterial stiffness measures adjusting for potential a priori confounders and mediators such as sex, race, BP, BW z-score, and height. Potential mediation by PA was examined using multiple regression and the steps specified by Kenny (2008).[61]

RESULTS

As shown in Figure 3, 176 of 193 PT and 35 of 56 T participated in the follow-up evaluation at 18-23 years of age resulting in 211 total subjects. Of the 211, 101 PT participants, all PT, were evaluated prior to addition of vascular measures to the PEPC2 study, and eight (2 T) who underwent vascular testing had an operator index < 75. One person was excluded due to unreliable PA data. Ultimately 101 participants were included in the final analysis, consisting of 68 PT and 33 T.

Sample Characteristics

Table II shows the neonatal characteristics of the 68 PT and 33T included in the final analysis. There were no significant differences between PT and T groups for proportion of males and nonblacks. Mean GA, BW, and BW z-score were significantly lower in PT compared to T. As shown in Table III, weight and BMI in adulthood were also not significantly different between PT and T groups; however, those born PT were significantly shorter than T participants. Systolic blood pressure did not differ between PT and T groups, but diastolic blood pressure tended (p=0.07) to be higher the PT group.
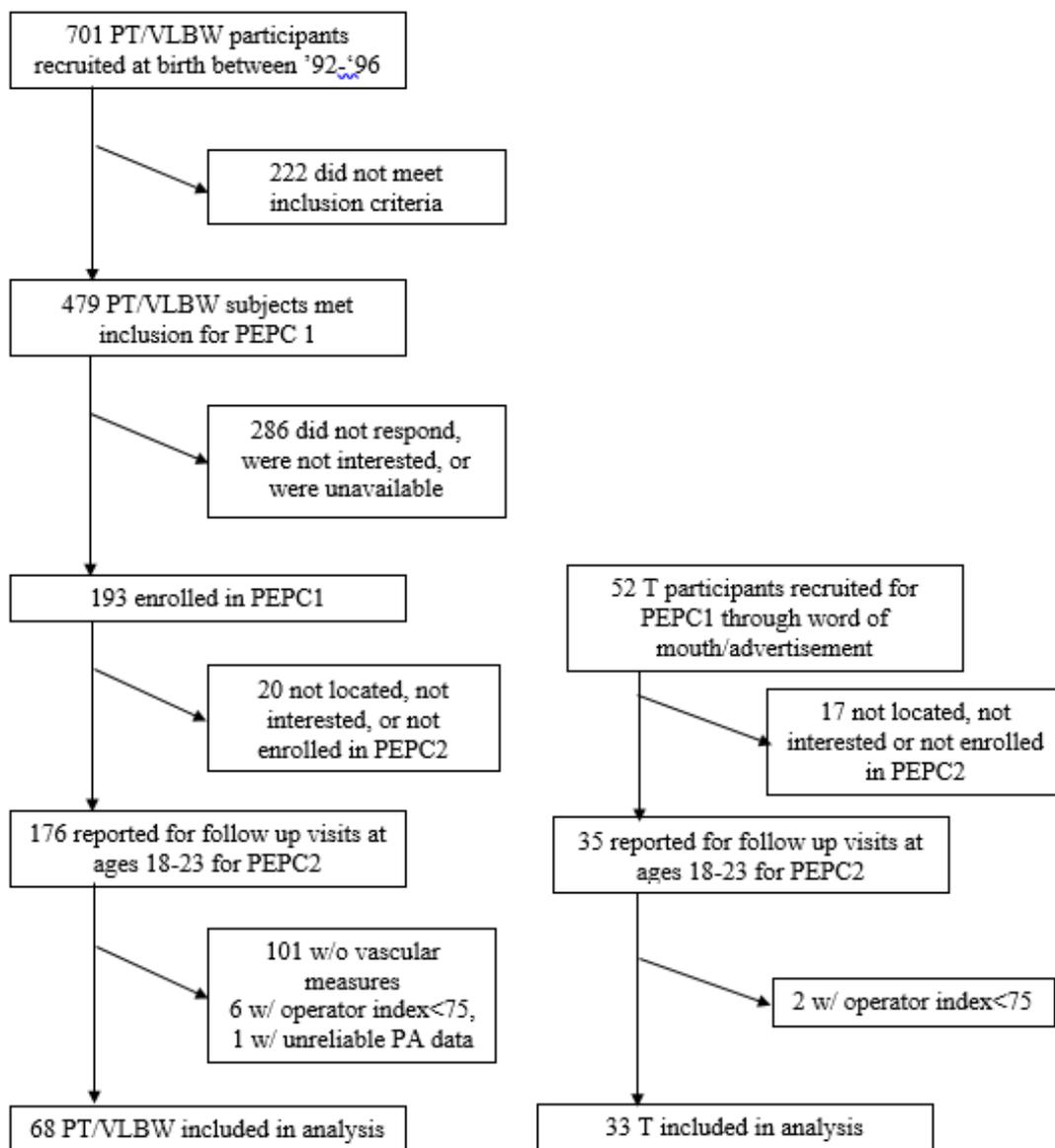
Figure 3. Flow chart reporting recruitment of participants.

Table II. Participants' neonatal characteristics expressed as Mean $\pm$ SD (5th,95th percentile) or n (%).

	Preterm	**Term**
n	68	33
Male, n (%)	31 (46)	15 (46)
Nonblack, n (%)	41 (61)	21 (64)
Gestational age, wks	27.7 $\pm$ 2.9 (24.0, 32.6)	39.6 $\pm$ 1.1* (37.7, 41.3)
Birth weight, g	1024.7 $\pm$ 287.7 (601.3, 1487.8)	3490.8 $\pm$ 471.1* (2796.7, 4572.3)
Birth weight z-score	-0.373 $\pm$ 0.936 (-2.576, 1.109)	0.058 $\pm$ 1.007† (-1.651, 2.145)
ANCS exposure, n (%)	36 (52.9)	0

*p<.01
†p<.05

Table III. Participants' adult characteristics expressed as Mean $\pm$ SD (5th, 95th percentile)

	Preterm	**Term**
Age, years	20.0 $\pm$ 1.1 (18.7, 21.9)	20.2 $\pm$ 0.6 (19.0, 21.4)
Weight, kg‡	74.0 $\pm$ 23.1 (40.9, 133.0)	73.7 $\pm$ 15.0 (53.3, 107.5)
Height, cm	165.46 $\pm$ 9.87 (148.57, 181.14)	171.62 $\pm$ 14.98* (158.14, 190.94)
BMI, kg·cm^{2}‡	26.99 $\pm$ 7.71 (17.89, 42.63)	24.99 $\pm$ 4.19 (19.11, 34.52)
Systolic blood pressure, mmHg‡	126.8 $\pm$ 12.2 (109.4, 152.8)	122.2 $\pm$ 8.9 (108.70, 145.10)
Diastolic blood pressure, mmHg‡	67.0 $\pm$ 8.6 (53.5, 83.6)	64.3 $\pm$ 6.8† (55.4, 81.8)
Pulse pressure, mmHg‡	59.9 $\pm$ 9.5 (44.9, 78.6)	57.9 $\pm$ 8.7 (40.5, 76.6)

*p<.01
†p<.10
‡Comparisons made with Mann-Whitney U test

Physical Activity

Physical activity data are presented in Table IV. None of the PA variables was normally distributed. Various transformations were attempted but none improved the distributional characteristics of the parameters, so group comparisons were made using Mann-Whitney U tests. PT reported slightly less Tot-hrs per week than T (p=0.075).

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However, a similar percentage of PT and T participants met the guidelines for total PA of 150 min (2.5 hrs) per week (70.6 and 78.8%, respectively; $X^2 = 0.763$, p=0.27). In contrast, PT engaged in significantly less Vig-hrs per week than T subjects, and fewer met the national recommendations for vigorous PA of 75 min (1.25 hrs) per week (33.8 and 60.6% for PT and T respectively; $X^2 = 6.519$, p=0.01). Furthermore, PT had lower MET-hrs per week than T, and a greater proportion (57.4%) of the PT had values below the median of 28 MET-hrs per week ($X^2 = 5.128$, p = .02) compared to T (33.3%).

Sex differences in PA were evident in the PT but not T group. Preterm females had significantly lower (p<.01) Tot-hrs, MET-hrs, and Vig-hrs than PT males, and fewer met the national guidelines of 150 min of PA per wk (54.1 v. 90.3% for females and males, respectively) as well as participation in vigorous PA of $\geq$ 75 minutes per week (10.8 v. 61.3% for females and males respectively). No sex differences were observed in the T, although T females were less likely than males to meet the national guidelines for vigorous (44.4 vs. 80% for females and males, respectively; p=0.072).

Table IV. Habitual physical activity levels for 68 PT and 33 T participants expressed as mean $\pm$ SD (5th, 95th percentile)

	Preterm	Term
Physical Activity		
Tot-hrs, hrs·wk^{-1}	6.72 $\pm$ 7.67 (0.09, 25.83)	7.79 $\pm$ 5.57 (0.69, 22.60)
MET-hrs, hrs·wk^{-1}	36.36 $\pm$ 43.50 (0.19, 124.43)	45.08 $\pm$ 32.41* (3.04, 114.39)
Vig-hrs, hrs·wk^{-1}	1.98 $\pm$ 3.66 (0, 9.97)	2.90 $\pm$3.63* (0.00, 12.91)

*p<0.05, comparisons made with Mann-Whitney U test

Arterial Stiffness

Arterial stiffness measures are presented in Table V. Both augmentation and aortic augmentation index corrected for a heart rate of 75 (AI75) were significantly

different between the two groups, with PT having higher values. PT also had slightly

higher values than T for peripheral AI (p=0.054) and central AI (p=0.06).

Sex differences were apparent in both PT and T groups. Males also generally had

lower values than females on measures of arterial stiffness in both PT and T, with AI75

showing the most significant difference (p<0.01 for both PT and T).

Table V. Vascular measures for preterm and term participants. Values are mean $\pm$ SD
(5th, 95th percentiles).

	Preterm	Term
Augmentation, mmHg	0.82 $\pm$ 4.18 (-6.55, 7.00)	-0.85 $\pm$ 2.92* (-6.00, 6.00)
Central AI (AG/PP), %	1.38 $\pm$ 11.04 (-20.10, 18.55)	-2.33 $\pm$ 8.25 (-17.50, 14.90)
Peripheral AI (P2/P1), %	102.19 $\pm$ 12.17 (79.90, 123.00)	97.97 $\pm$ 8.76 (82.80, 117.90)
Aortic Aix (AG/PP) @ HR75	0.21 $\pm$ 11.15 (-17.10, 16.55)	-5.64 $\pm$ 8.08* (-17.60, 8.60)

*p<0.05, comparisons made with independent t-tests

Correlation Analysis

Univariate relationships among measures of arterial stiffness and participants'

anthropometric and blood pressure measures are presented in Table VI. Of note, height

was negatively correlated with all measures of arterial stiffness in the PT group and T

group, as shown in Table VI. None of the associations between BP and arterial stiffness

measures were significant in either group, except for PP, which had a small significant

negative relationship with AI75 in the T group.

Table VI. Spearman correlation coefficients for arterial stiffness measures and participants' blood pressure and anthropometric characteristics.

	Preterm				Term			
	Aug.	**AG/PP**	**P2/P1**	**AI75**	**Aug.**	**AG/PP**	**P2/P1**	**AI75**
SBP	0.124	0.104	0.106	0.191‡	-0.312†	-0.295†	-0.298†	-0.298†
DBP	-0.012	-0.003	-0.004	0.203†	-0.278‡	-0.318†	-0.313†	0.018
PP	0.105	0.070	0.072	0.027	-0.237‡	-0.177	-0.182	-0.391*
Height	-0.280*	-0.304*	-0.301*	-0.450*	-0.328†	-0.291‡	-0.291†	-0.567*
BMI	0.031	-0.006	-0.006	0.139	0.325†	0.326†	0.325†	0.356*
BWz	-0.128	-0.129	-0.129	-0.056	-0.097	-0.128	-0.128	-0.129

*p<0.05
†p<0.10
‡p<0.20

Physical activity variables were also not normally distributed, so Spearman's rho coefficients were determined to assess univariate relationships among PA and arterial stiffness parameters as well. As shown in Table VII for the PT group, positive correlations were observed for Tot-hrs and augmentation as well as both central and peripheral AI. MET-hrs was directly associated with central and peripheral AI for the PT group. Similar associations were observed in the T group, although none approached statistical significance (p>.10). In contrast, Vig-hrs was inversely related, but not significantly, to AI75 in either group.

Table VII. Spearman correlation coefficients for PA and arterial stiffness measures in PT and T groups.

	Preterm			Term		
	Tot-hrs	**MET-hrs**	**Vig-hrs**	**Tot-hrs**	**MET-hrs**	**Vig-hrs**
Augmentation	0.253*	0.235	0.061	0.211	-0.200	-0.113
Central AI	0.260*	0.246*	0.078	0.245	0.257	-0.043
Peripheral AI	0.261*	0.247*	0.081	0.245	0.257	-0.043
AI75	0.118	0.068	-0.149	-0.016	-0.015	-0.267

*p<0.05

Figure 4. This figure shows a scatter plot presenting Tot-hrs/wk, and AI75 for both PT (triangles) and T (cross). Fit lines were applied to examine potential patterns in the data.
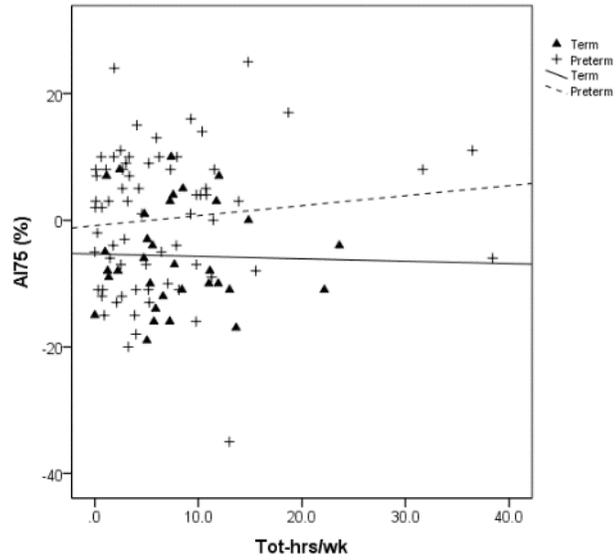

Figure 5. This figure shows a scatter plot presenting MET-hrs/wk, and AI75 for both PT (triangles) and T (cross). Fit lines were applied to examine potential patters in the data.

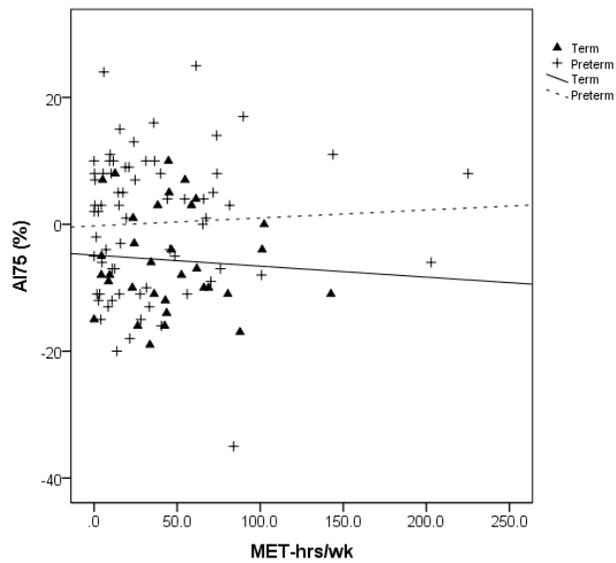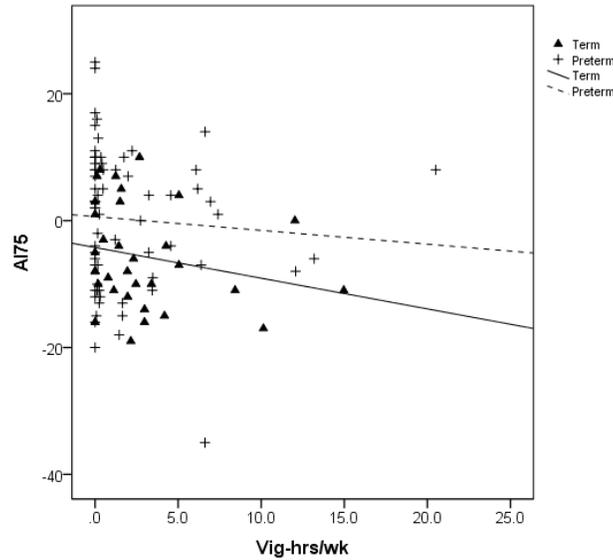**Figure 6**. This figure shows a scatter plot presenting Vig-hrs/wk, and AI75 for both PT (triangles) and T (cross). Fit lines were applied to examine potential patters in the data.

The unexpected direct and lack of inverse associations observed between PA and some of the arterial stiffness measures prompted us to examine the relationships more closely by creating scatterplots (Figures 4-6). Given the number of subjects who reported little or no PA, especially vigorous PA, we decided to stratify the data based on meeting or not meeting the 2008 National PA Guidelines, and then used regression analysis with the dichotomous PA variables as predictors of arterial stiffness measures. The β-coefficients for these associations are presented in Table VIII. As shown, meeting the guidelines for TOT-hrs was not a significant predictor of any of the arterial stiffness measures. In contrast, meeting the guidelines for vigorous PA was significantly (p=.017) associated with a 5.503 lower AI75.

Table VIII. Univariate Regression analysis in reference to aortic augmentation index @ HR 75 (AI75)

	β-coefficient	**Significance**
Preterm birth	5.842	p=0.009*
Tot hrs $\geq$ 2.5 hrs/wk	-1.263	p=0.240
MET-hrs $\geq$ 28.0/wk	-1.273	p=0.548
Vig-hrs $\geq$ 1.25 hrs/wk	-5.053	p=0.017*

*Significant at p<.05

Multiple Regression Analysis

      Multiple regression analysis was performed to examine if some of the PT – T differences in AI75 might be mediated by meeting the national guidelines for vigorous PA. As shown in Figure 7, engaging in Vig PA $\geq$ 1.25 hrs/wk attenuated the PT – AI75 association by 20% from β=5.842 (C) to β=4.665 (C^1).

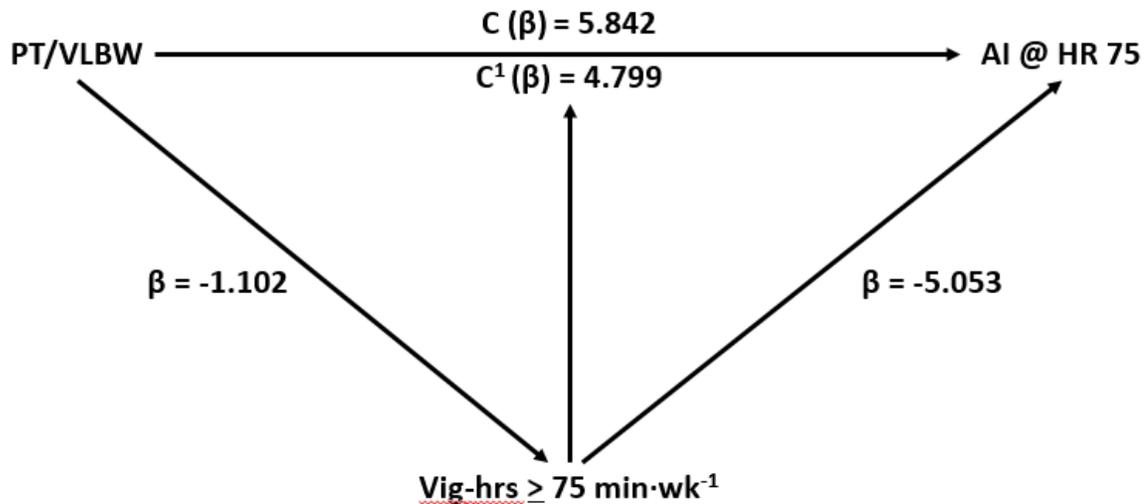**Figure 7**. Mediational analysis with β-coefficients obtained from regression analysis.

      Inclusion of birth weight z-score, sex, or race did not alter the PT – AI75 association appreciably as shown in Table IX. However, addition of height and BP abolished the significant difference in AI75 between T and PT, negating the use of examining the mediational effect of vigorous PA in that relationship.

Table IX. Multivariate regression analyses examining association between PT and AI75 with adjustment for covariates

	β	95% CI	p	Δβ
PT	5.842	1.523, 10.161	0.009	-
PT + BW z-score	5.518	1.091, 9.946	0.012	0.324
PT + Sex	5.854	1.903, 9.804	0.004	0.012
PT + Race	5.736	1.443, 10.029	0.009	0.106
PT + Height	2.734	-1.273, 6.740	0.179	3.108
PT + SBP + Height	1.124	-2.870, 5.117	0.578	4.718
PT + DBP + Height	2.158	-1.835, 6.151	0.286	3.684
PT + PP + Height	1.985	-2.057, 6.026	0.332	3.857

DISCUSSION

The purpose of this thesis was to compare arterial stiffness and PA between PT/VLBW and T young adults, as well as determine if PA was a partial mediator of the PT – arterial stiffness association. Although initial findings were consistent with our hypotheses, adjusting for height and BP abolished the PT – arterial stiffness relationship. Without this relationship, there was no reason to examine the mediational effect of PA.

Greater arterial stiffness in PT/VLBW compared to their T born peers has been reported in several studies conducted in children[30,32] and adolescents[29,31]. The results of these studies suggest those born PT have stiffer arteries, which may be explained by the impact of premature birth on the developing vasculature, including greater collagen and less elastin deposition, as well as reduced number of smooth muscle cells.[12,13,18] More collagen leads to stiffer structure of the artery, making it more difficult for the artery to adjust to physiological circumstances. Furthermore, endothelial dysfunction can lead to deficits in arterial wall distension and compliance, as well as affect smooth muscle function via altered release of vasoactive substances. However, it is important to note that only one of these studies adjusted for height and other covariates (sex, HR, BP and weight), and the PT –T differences persisted.[32]

In contrast to the studies of children and adolescents, studies in young adults have seen mixed results.[15,62] Kerkhof and colleagues (2012) reported no difference in PWV in PT (AGA & SGA) compared to T (AGA), with height being a significant independent predictor of PWV, supporting the abolishment of significance seen in our results after adjusting for height.[33] However, another study did not adjust for height, but saw the PT – T differences in AI75 attenuated (but remained significant) when adjusting for BP.[15]

Tauzin and colleagues likewise reported greater arterial stiffness as reflected in faster PWV in PT compared to T young adults.[62] The authors examined growth patterns in different periods of infancy, childhood, adolescence, up to young adulthood, and reported no association with PWV. Despite PT being significantly shorter than the T controls, the authors did not adjust for adult height in their PT – T comparisons.

The effect of height on PWV can be explained simply in that taller persons have longer arteries, and thus greater distance that the pulse wave must travel from the heart to the tonometer, resulting in a slower PWV. Conversely, PT, who tend to be shorter, would have a faster PWV than their T counterparts, who are taller. Similarly, in shorter people, the pulse wave is reflected earlier and faster, thus augmenting SBP and giving the appearance of stiffer arteries. The influence of height on PWV and PWA has been demonstrated in children as well as adults.[26,27] Our analysis indicated that the arterial stiffness differences between PT and T groups were abolished when adjusted for height differences.

Similar to our study, many publications examining the effect of PT on arterial stiffness adjust for BP due to its strong relationship with the outcome.[15,29,30,32,33] Boardman and colleagues, as well as the authors of the EPICURE study, suggested that their findings showing elevated arterial stiffness in PT born participants were due to higher BP.[15,32] The authors referenced previous studies which have determined direct relationships between BP and PWV, with rises in PWV for specific elevations in various BP measures.[63,64] However, in a publication examining temporal relationships between arterial stiffness and BP, Kaess and colleagues suggested that the relationship between the two variables is bidirectional.[28] We found mixed results when examining correlations

between BP and arterial stiffness measures, with both direct and inverse relationships, however, it was still important to adjust for BP. While we did find that adjusting for both BP and height abolished the relationship between PT and arterial stiffness, the cross-sectional design of our study cannot elucidate temporal sequence. Future studies should employ longitudinal designs to determine if arterial stiffness leads to higher BP or vice versa.

Our study showed that PT participated in less PA, specifically vigorous PA, than their T born peers. Few studies have assessed PA in PT and/or VLBW populations but generally suggest lower PA in more vigorous activities including conditioning[46,47] and sports participation[65] in PT and/or VLBW compared to their T peers. The lower PA participation may be attributed to greater prevalence of airway obstruction, lower aerobic fitness, neuromotor limitations (including cerebral palsy), and reduced muscle strength which have been reported in other studies of persons born preterm and/or with VLBW. All of these physiologic factors may impede participation in PA, especially more vigorous PA.[50,52,54–56] Furthermore, PT and/or VLBW report lower self-efficacy in their ability to participate in PA which makes them less motivated to be active which in turn will lessen their ability to participate.[56,65]

However, despite seeing differences between groups in vigorous PA, Spearman's rank-order correlations showed weak but direct correlations between some measures of arterial stiffness and PA. This is a surprising result, but has been seen in one other study examining the relationships between CRF and many arterial stiffness measures including PWA and PWV.[66] It was suggested that the accuracy of non-invasive arterial stiffness measures may play a role. Also, since the correlations were weak, the fact that stiffness is

easier to assess in older populations due to a natural increase in arterial stiffness with aging may create such results. Along with these potential explanations, we partially attribute these unexpected results to the unusual distribution of data, which led us to examine whether or not the participants met the national guidelines for PA, and if stratifying the data in such a way would affect the results.

Lack of participation in Vig-hrs $\geq$ 1.25 hours per week was observed in a greater proportion of PT compared to T and was also was associated with higher AI75. However, adjustment for height made the vigorous PA associations with PT and AI75 nonsignificant, and abolished the relationship between vigorous PA and AI75. Using self-report questionnaires has limitations such as increased risk for recall error and bias. The unusual distributions of the PA data limited our ability to make PT-T comparisons using more robust parametric statistics. Our questionnaire attempted to examine intensity by assigning MET values and calculating time spent in more vigorous PA (> 6 METs) as well as Tot-hrs of PA and MET-hrs per week. It is difficult to examine participation in lighter PA from questionnaires. Use of a more objective PA measurement such as accelerometry would permit better examination of different levels of PA (e.g. light, moderate, light) as well as time spent in sedentary behaviors. Kaseva et al. used accelerometry to objectively measure PA and found no differences in PA between VLBW and T normal BW young adults.[48] However, participation in more vigorous PA tended (p=.10) to be lower in VLBW compared to T controls. Further research is warranted using object measures (e.g. accelerometry) to determine if PA participation is lower in PT/VLBW persons compared to their T peers and associated with CV health outcomes.

Although the association between PA level and AI75 was nullified by adjusting for height, studies in other populations suggest that aerobic training may lessen arterial stiffness.[36–38] This improvement could be due to the potential positive effects of PA on endothelial function, inflammatory mediators, and indirectly and through decreases in adiposity.[12,35,37] Vigorous PA may be effective at decreasing adiposity, reducing inflammation, and, therefore, arterial stiffness. These mechanisms may be more effective in those who participate in vigorous PA compared to moderate PA.

Our study differed from others with respect to adjustments for potential confounders and mediators. As previously mentioned, few studies adjusted for height which has been shown to affect PWV and PWA.[26,27] Other studies also adjust for sex as males have been shown to exhibit slower PWV and lower augmentation, although some of the sex differences could be explained by differences in height.[27] Similarly, racial differences have been reported with African Americans having greater stiffness.[27] While we did adjust for race and sex, we did not find that they altered the association between PT and AI75.

Our results may have been affected by the measurement of arterial stiffness using the Sphygmocor SCOR-PX model. Although PWA has been validated[21,23,24], and has been shown to correlate with other measures of arterial stiffness, it is not without drawbacks. Many PWV techniques collect pulse waves at multiple points (carotid-femoral, brachioradial, etc.), and measure the time it takes the pulse wave to travel from one point to another. These measures are often gated by electrocardiography in order to ensure accuracy. One of the most criticized aspects of PWA is the transfer function that is utilized to create an aortic pulse wave, which is then used to estimate central vascular

measures. Hope and colleagues report that, when compared to direct central aortic measures, the transfer function is quite variable and may not hold as much clinical value.[67] There are a number of factors, such as LV ejection, PWV, timing of reflection, arterial tone, BP, age, gender, height, and HR, that may affect the final AI measurement. Two reviews cite that, due to these reasons, PWA may not be suitable for clinical settings.[68,69] However, PWA was the best measure for the overall scope of the PEPC2 study for a number of reasons such as ease of use, small time commitment, and that it was one of the more widely used techniques at the beginning of the study, and was therefore used.

Lack of significant associations in our study (and those of other studies) may be related to the relatively small sample sizes. Although the PEPC2 study included 176 PT and 52 T, vascular measures were added after 101 participants from the original cohort had already undergone testing for the larger PEPC2 study. Future studies should include larger numbers of PT and T to have sufficient statistical power to detect differences in arterial stiffness if they exist.

Despite these limitations, there are several strengths of our study. This is the first study to examine the influence of PA on the association between PT birth and arterial stiffness. Our cohort is more similar to PT infants born today with respect to availability of such medical advances surfactant and antenatal steroid therapy (the latter being true for 50% of our sample). The sample is also racially diverse, represents both sexes, and was raised in an obesogenic environment (i.e. low PA compared to others, bad diet).

Conclusions and Future Directions

The results of our study suggest that the PT – T differences in arterial stiffness may be due to differences in height. The partial mediation by vigorous PA participation was nullified by inclusion of height and BP in the regression model. However, it is important to note that arterial stiffness increases with age and differences between PT and T may become more apparent as they mature.

Our results do add further evidence that PT young adults engage in less PA, particularly vigorous PA, as compared to their T peers. The health benefits of PA are well documented, and growing evidence suggests that PT individuals have increased risk for developing cardiometabolic disease. Future research should examine if increasing PA may help to improve cardiometabolic profiles, and ultimately reduce risk for developing chronic disease in this at risk population.

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Design: Cross-sectional		Definition of exposure variable	Definition of outcome measures			
Population, Investigator, Purpose	Sample Characteristics	Preterm birth	Arterial measurements	Main findings	Dose-response	Adjustments
-Boardman et al. 2016 -Population: Adults born btwn '82-'85, both term & preterm -Purpose: To determine the effect of preterm birth on central/conduit artery size & arterial stiffness in adults	-Recruited at birth for randomized feeding intervention trial -Initial study: 926 participants -240 agreed contact for future studies during fu @ adolescents -Part of initial cohort w/ birthweight < 1850g -102 preterm, 102 matched term (age & sex) -Age 23-28 yo -Avg. age: 25.1 (preterm), 25 (term) -GA: 30.3 (preterm), 29.6 (term) -47 males/55 females (per group) -Avg. bw: 1297g (preterm), 3460g (term)	-Preterm data from med recs during 1st weeks of life -Term data from maternal recall	-BP: avg. of 2 measurements after 10 min supine rest **Cardiovascular magnetic resonance** -"Free breathing & retrospectively ECG-gated w/ spoiled gradient echo sequence" **Non-invasive arterial stiffness** -Carotid-femoral pwv -Applanation tonometry -Sphygmacor -Brachial-femoral pwv -sphygmomanometer-derived indices -timed pulse arrival w/ cuffs on brachial and femoral -Augmentation index @ 75bpm recorded from radial pulse **Cardio-ankle vascular index (CAVI)**	<u>Table 2</u>: Arterial Stiffness (m/s) in preterm vs. term **Sphygmacor (m/s (sd))** Preterm: 5.82 (.80) Term: 5.47 (.59) *p<.01* Multivariate analysis: p=.07 **Augmentation index** Preterm: 6.85 (9.64) Term: -4.01 (11.83) *p<.001* Multivariate analysis: p<.001 CAVI not sig (indep. of bp)	-Only possibly in multivariate analysis, due to only two groups	-Table 2 multivariate analysis: mean blood pressure

Design: Retrospective cohort			Definition of exposure variable	Definition of outcome measures			
Population, Investigator, Purpose	Sample Characteristics	Preterm birth/IUGR	Cardiovascular function (arterial stiffness)	Main findings		Dose-response	Adjustments
-Chan et al. 2010 -Population: Term & preterm periadolescent children born btwn '92-'95 -Purpose: To determine relative influence of IUGR & preterm birth on cardio, renal, & metabolic functions	-Children born @ RNS Hospital, Sydney, Australia btwn 1/1/92 & 12/31/95 -Study done '06-'08 -Aimed 25 children per group (100 overall) w/ 80% power -71 participants -32 femaile, 39 male -Age (avg. range for each group): 13.5-14.1 yo	-Preterm birth: ≤32 wks GA -<1500g bw -Identified from neonatal intensive care records -Term: ≥37 wks GA -Ads & "word of mouth" -Split into quartiles based on gender-specific bw % by GA – Australian national data '91-'94: Q1: preterm & SGA Q2: preterm & approp. For GA Q3: term & SGA Q4: term & AGA --Q1-14; **Q2-25**, Q-7, **Q4-25** -BW converted to z-score -SGA: small for gestational age	-Augmentation index (AI) -standardized @ hr 75 bpm -Estimated from pwv -Pwv measured reclined by applanation tonometry -SphygmoCor -Right radial -Blood pressure: SBP, DBP -Mercury sphygmomanometry -Avg. 2 measures, 5 min apart -BP performed by unblind investigator	**Augmentation index (AI)** Q1 sig high than other groups; 9.7% mean, *p<.011* Table 1: Clinical characteristics Median GA (wks): Q1-31, Q2-30, Q3-39, Q4-40 Median BW (g): Q1-980, Q2-1635, Q3-2750, Q4-3302 BW z-score: Q1: -1.59, Q2: .30, Q3: 1.58, Q4: -.30 SBP (mmHg (IQR)) Q1: 107 (90-114.5), Q2: 101 (95-107.5), Q3: 105 (95-110), Q4: 103 (103-105), p=.6 DBP (mmHg (IQR)) Q1: 65 (58-70.5), Q2: 61 (60-70), Q3: 65 (55-66), Q4: 60 (60-65) Table 2: Maternal characteristics @ birth -pre-eclampsia during pregnancy: Q1-86% vs. Q4-16% *p<.001* Table 3: SBP multivariate analysis SGA sig risk for increase SBP *p=.002*, preterm not sig risk *p=.4*, SGA avg. SBP higher than AGA (4.6 mmHg, *p=.002*)		-Yes: BW -Although Q1 is sig higher in AI, the other groups do not seem to show a dose-response	-Table 3 controlled for current BMI & DBP

Design:		Definition of exposure variable	Definition of outcome measures			
Population, Investigator, Purpose	Sample Characteristics	Birth weight/gestational age	Arterial stiffness/blood pressure	Main findings	Dose-response	Adjustments
-Cheung et al. 2004 -Population: Children born btwn '90-'96 -Purpose: Determine if children born preterm w/ IGR are predisposed to cardiovascular disease	-Children born btwn '90-'96 -Recruited through mailing -650 sent, 110 responded -Children from Hong Kong -86 children initially -Avg. age 8.2 -39 male, 47 female -Exclusion: free of chronic disease/disability	-Birth weight recorded from medical records -GA estimated from mother's last menstrual period -SGA: weight below 10th percentile -Premature: GA<37wk -Three groups: G1-preterm/SGA, G2-preterm/normal bw, G3-term/normal bw -G1-15; G2-36; G3-35	-Supine, rested 15 min prior -Brachioradial measurement -Non-invasive photoplethysmographic technique -Measured both brachial and radial arteries simultaneous -Divide distance btwn arteries by wave reflection transit time -Automated BP (Dinamap) -Average of 2 BP	Table 1: Anthropometric G1: 32.3 wk GA (adjusted bw -2.29) G2: 29.4 wk GA (adjusted bw -.01) G3: Term (adjusted bw -.04) Figure 2: PWV of 3 groups (box plot) [m/s] *G1: 9.45 (1.79)* G2: 7.29 (1.85) G3: 7.09 (1.20) P<.001 G1 vs. G2 P<.001 G1 vs. G3 **P=1.00 G2 vs. G3** Table 3: Assoc. btwn pwv & variables **Univariate** (R, p) *SBP (.31, p=.004); DBP (.38, <.001), MBP (<.001), bwz (-.43, <.001),* GA (.03, .81), bw (-.12, .28) **Multivariate** (sig univ var) (β, p) R^2=.39 bwz (-.61, <.001), MBP (.11, <.001)	-Yes, birth weight & MBP	-None on tables or figures shown

Design: Observational		Definition of exposure variable	Definition of outcome measures			
Population, Investigator, Purpose	Sample Characteristics	Preterm birth	CVD Risk	Main findings	Dose-response	Adjustments
-Kerkhof et al. 2012 -Healthy young adults (18-24) from PROgramming factors for Growth And Metabolism, Prematurity and Small for Gestational Age studies -Purpose: Investigate effect of preterm birth on risk factors for CVD, independent of birth size	-PROgramming factors for Growth And Metabolism (PROGRAM): 323 -Prematurity an Small for Gestational Age (PREMS): 169 -Total: 492 healthy 18-24y -Diff btwn cohorts: PREMS born preterm (GA<36 wks) -Recruited from hospitals in Netherlands -Registered b/c small birth size, short stature, or preterm -Recruit AGA (healthy) w/ adverts -Q about SES, smoke, alc use -SES det using ed level -Final #: 406 – incomplete data for BP, carotid intima media thickness (cIMT), or PWV	-Birth data from med recs from hospitals, community health services, general practitioners -Three groups: SGA-S, SGA-CU (catch up), AGA -SD-scores for BL & BW to correct for GA & sex	-Participants fasted 12 hrs w/o alc or smoke for 16 hrs -PWV: carotid-femoral (SphygmoCor) -Assessed w/ SBP, DBP, PP, BP variability, HR, PWV, & cIMT -BP & HR: 10min rest supine,, nondominant arm, Accutorr Plus, every 5min for 1hr, mean of 13 measurements -BP used for PP (SBP-DBP) & coefficient of variation (CV) -cIMT: supine, ultrasonographic images of left & right carotid artery w/ 7.5 MHz linear array transducer -Mean of mean near & far wall measurement of left & right com. carotid	Table 3 -GA inverse assoc w/ SBP, PP – @ most adjust model (add HR), remain sig for PP, but SBP nonsig -GA positive assoc w/ DBP Table 4 – MR for PWV & cIMT in EA β(%) **PWV Model D** GA: β=.261 (p=.145) BW SDS: β=-.173 (p=.787) Adult height SDS β=1.574 **(p=.029)** More sig w/ more adjust Table 5 – Subgroup analyses of BP, PP, BP variability, HR, PWV, cIMT compared w/ AGA term controls (β%) **PWV model 3** SGA-S preterm β=2.48 (p=.691) SGA-S term β=-6.41 (p=.145) SGA-CU preterm β=-4.48 (p=.114) SGA-CU term β=-4.18 (p=.106) AGA preterm β=-3.22 (p=.163) PWV was sig @ model 2 for SGA-S term w/ β=-11.2 (p<.001) but became non-sig after adjust for adult height SDS	-None for PWV, potentially assoc. btwn BP & GA	All adjust for BL SDS, BW SDS, AH SDS, age, sex SES, smoke, alc, interaction term BL SDS x AH SDS Table 3 – model C: weight SDS (B add), HR (C add) Table 4 – model D: MAP (B add), interaction term sex x weight SDS & age x weight SDS (C add), HR (D add) Table 5 – Model 3: AH SDS

Design: Cross-sectional			Definition of exposure variable	Definition of outcome measures			
Population, Investigator, Purpose	Sample Characteristics	Birth weight	Aortic Derived Parameters	<u>Main findings</u>		Dose-response	Adjustments
-Lurbe et al. 2003 -Population: 7-18 y, from large BP study (not mentioned) -Purpose: Study relationship btwn bw, central aortic pressure (cap), & wave reflection in children/ adolescents	-219 children & adolescents age 7-18 y -Born at term, normotensive pregnancy (>37 wks) -Selected from not mentioned BP study -Pediatric Outpatient Clinic of the General Hospital of the University of Valencia -126 female, 93 male -All white -Exclusion: systemic & renal disease -Avg. age btwn 11-11.5 y -Low bw (<2.5kg) n=17 -Largest group: >3.5kg (n=91)	-Birth weight & gestational age obtained from obstetrical records @ Hospital of University of Valencia -Quartiles: <2.5kg (Q1), 2.5-2.999kg (Q2), 3.0-3.5kg (Q3), >3.5kg (Q4)	Pulse wave -radial artery of wrist of dominant hand -Radial/aortic -SphygmoCor -High-fidelity micromanometer -Estimated aortic pressure waveform – averaged 8-seconds of radial/aortic waveforms to make single waveform -Estimated aortic waveforms from radial waveforms -Aortic derived parameters: aortic BP, AI, AI/PP%, radial/aortic PP -3 consecutive BPs after 5 min rest -Measured w/ mercury sphygmo in sitting position -Korotkoff pI for SP, pIV in <13 y/pV in >13 y for DP -Mean of 3 used, calculated PP	<u>Table 1:</u> Lower birth weight trend toward higher SBP, DBP <u>Table 2:</u> ADP by bw SBP: Q1-93.3+/-2.5, Q2-90.7+/-1.5, Q3-86.1+/-1.2, Q4-8.2+/-1.1 DBP: Q1-65.6+/-2.0, Q2-59.9+/-1.3, Q3-58.1+/-1.3, Q4-60.1+-1.0 AI: Q1-3.9+/-1.3, Q2-3.7+/-0.8, Q3-0.9+/-0.6 (p<.05), Q4-0.7+/-0.5 (p<.01) (still sig. after control for HR, DBP (p=.007; fig. 1) AI/PP (%): Q1-11.1+/-3.5, Q2-11.7+-2.5, Q3-3.4+/-2.1 (p<.05), Q4-2.5+/-1.6 (p<.01) (still sig. after control for HR, DBP (p=.039; fig. 1) <u>Table 3:</u> Factors related to AI estimated by MR BW: β=-1.123 (p=.024) Gender (f vs. m): β=1.303 (p=.044) <u>Partial Correlations</u> BW sig neg relationship w/ aortic BP (r=-.17; p=.015), AI (r=-.19; p=.006); overall model explained 21% of AI variability		-Could potentially be dose-response in Table 2, w/ those of lower weight @ birth having higher SBP, DBP, and AI	

Design: Cross-sectional			Definition of exposure variable	Definition of outcome measures			
Population, Investigator, Purpose	Sample Characteristics		Extreme prematurity	Haeomdynamic characteristics (PVW, Aix)	Main findings	Dose-response	Adjustments
-McEniery et al. 2012 -Population: EPICURE study - $\leq$ 25 wks 6 days GA -Purpose: Examine cardiovascular consequences of extreme prematurity in children	-11 yo -219 extremely premature children -153 matched classmates -11 yo -UK & Ireland -cohort examined @ 2.5, 6, & 11 yo – only used 11 yo data -schools identified 3 potential comparison children w/in 3 mo age, matched for sex/ethnic origin – selected one at random -Term matched controls excluded if <37 wks GA -Height & weight measured, converted to z scores -Q's administered for perinatal history, current health, therapy, maternal smoking – for parents -Exclusion: severe physical disability -Full data on 68 prem & 90 matched		-$\leq$25 wks GA	-Not added until "latter part of data collection" -9/'06 and on -No initial start date given -Measured by 1 specially trained pediatrician -Recorded at radial artery – high-fidelity micromanometer -SphygmaCor program used for central (aortic) waveform (CAW) generation -Used CAW for central systolic pressure (CSP), nonaugmented systolic pressure (NSP), mean BP (MBP) -Central augmentation pressure (CAP): 1st systolic peak – 2nd systolic peak -Central augmentation index (CAix): AP as % of CSP -Radial augmentation index (RAix): 1st systolic peak/2nd systolic peak -From actual waveform, not calculated waveform -Aortic pulse wave velocity (aPWV) w/ ecg-gated carotid & femoral -Divide distance btwn two sites by wave transit time -Distance w/ tape measure -Techs blinded -BP w/ oscillometric sphygmomanometer -mean of 3 consecutive measurements, supine	Table 2: Haemodynamic characteristics of preterm vs. control **CAP** (mmHg (sd)) EP: 2.1 (2.8) C: .6 (2.8) *p=.002* **CAix** (% (sd)) EP: 7.3 (9.4) C: 2.4 (8.7) *p=.002* **RAix** (% (sd)) EP: 47.1 (10.5) C: 51 (11) *p=.02* **aPWV** (m/s (sd)) EP: 4.5 (.75) C: 4.72 (.76) CI: -.46-.02	-Only two groups, so tough to say dose response	-CAP, CAix, RAix adjusted for sex, height, hr, BP, weight -aPWV adjusted for sex & MAP

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Design: Cross-sectional						
Population, Investigator, Purpose	Sample Characteristics	Definition of exposure variable	Definition of outcome measures			
		Physical activity measurement	Arterial stiffness	Main findings	Dose-response	Adjustments
-Edwards et al. 2012 -Population: adolescents and young adults -Purpose: Determine if PA is independent predictor of measures of arterial stiffness in adolescents & young adults (ya)	-1/3 of participants from T2DM & cv system study (156) -Matched w/ obese w/o T2DM & lean subjects -Obese: $\geq$95th% BMI (191) -Lean: 5th-85th% BMI (201) -Also matched by age, race, sex -Exclusion: pregnant, T2DM requiring insulin in basal state -Collected anthropometrics (height, weight, BMI), BP, arterial stiffness, fasting blood levels -Tertiles based on PA: Low (T1), middle (T2), high (T3) -Participants per group: T1-183, T2-182, T3-183 -Each group 62% persons of color -BMI sig higher in T! & T2 than T3 -Average age: T1-19, T2-18, T3-17 -T3 younger (p<.0001) & more boys (p<.0001	-Multidirectional accelerometer (Actical, Phillips Respironics) -Wore accel 7 consec days, excluding sleep, bathing, harmful activities -Split by mean counts per minute (cpm) over 7 days (valid days) -Valid days: 1st min w/ $\geq$60 counts followed by 4 consec min w/ $\geq$10cpm, stopped when 7-10 consec min w/ $\geq$10 counts proceeded 120 consec min w/ <10cpm – 10-20 hrs wear time -Average PA (cpm (sd)): T1-127 (35), T2-216 (25), T3-377 (106)	-3 measures: Brachial artery distensibility (BrachD), pwv, AI -pwv – carotid-femoral (SphygmoCor) -AI adjusted to 75 bpm	Table 1: Hemodynamics by PA level **AI (% (sd))** T1: 6.2 (12) T2: 2.6 (11) T3: .7 (11) T1 higher than T2/T3 p<.0001 **PWV (m/s (sd))** T1: 6.4 (1.5) T2: 6.2 (1.2) T3: 5.6 (.9) T3 lower than T1/T2 p<.0001 Adjust for age, sex, body size, MAP, obesity, T2Dm status: PA sig independent predictor of AI (-.011, p<.05); PA greater effect on PWV in T2DM (p=.009) **SBP (mmHg (sd))** T1: 116 (12) T2: 117 (13) T3: 112 (12) p=.005 T3 less than T1/T2	-Most obvious dose response in AI (higher AI in lower PA), w/ potential dose response in pwv (higher pwv in lower PA)	-mentioned in findings

Design: Cross-sectional			Definition of exposure variable	Definition of outcome measures			
Population, Investigator, Purpose	Sample Characteristics	Physical Activity/sedentary behavior	Arterial Stiffness		<u>Main findings</u>	Dose-response	Adjustments
-Garcia-Hermoso et al. 2015 -Population: Spanish adult population from EVIDENT trial -Purpose: Analyze relationship btwn sedentary behavior & arterial stiffness	-Taken from EVIDENT trial -20-80 y.o. -Selected by random sampling from general practitioner's offices from 6 primary care centers in Spain -Exclusion: CVD, COPD, heart failure, respiratory, renal, or hepatic disease, limiting musculoskeletal disease, severe mental disease, oncological disease w/in past 5 yrs, terminal status, and pregnancy -Originally 1553; 188 excluded for data -Final: 1365	-ActiGraph GT3X accelerometers -Worn @ waist right side for 7 days -Worn from wake to bed -Taken off for water activities -Wear time: 24hr minus non-wear -Non-wear: >60 consecutive min w/ 0 counts -Valid day: wear time >600 min; >4 days -Intensity: light (100-2019 cpm), moderate (2020-5998 cpm), vigorous (>5999 cpm); MVPA (mean daily min >2020 cpm) -Sedentary variables: sed time (total times <100 cpm), sed time in bouts >10 20, & 60 min, # sed breaks	Ambulatory arterial stiffness index (AASI) -1 minus regression slope of DBP/SBP -DBP/SBP from 24 hr BP recordings -AASI close to 1 – stiff Radial augmentation index (rAIx) -Pulse Wave Application Software (APulse) -Applanation tonometry @ radial artery -Patient sitting Central & Peripheral Pulse Pressure (PP) -SBP – DBP for all BP measures		Table 3: Regression models btwn sed behavior & arterial stiffness (β, p) **Model 1** Sed time (min/day) rAIx: -0.095, p=0.136 AASI: 0.272, **p=0.001** 24 hr PP: 0.195, **p=0.001** Sed time bouts >10 min rAIx: 0.001, p=0.987 AASI: 0.006, p=0.884 24 hr PP: 0.056, **p=0.023** Breaks per sed hr (n/hr) rAIx: -0.091, **p=0.012** AASI: -0.172, **p<0.001** 24 hr PP: -0.149, **p<0.001** **Model 3** Sed time (min/day) rAIx: -0.031, p=0.742 AASI: 0.032, p=0.724 24 hr PP: 0.034, p=0.719 Sed time bouts >10 min rAIx: 0.0003, p=0.918 AASI: 0.004, p=0.984 24 hr PP: 0.041, p=0.123 Breaks per sed hr (n/hr) rAIx: -0.069, p=0.147 AASI: -0.163, **p=0.034** 24 hr PP: -0.057, **p=0.032**	Can be suggested due to regression analyses before adjustments	Model 1: age, sex, accelerometer worn time Model 3: Model 1, plus MVPA, breaks in sed time or total sed time, mean arterial BP, HR, BMI, smoke, alcohol, statins, diabetes, LDL, HDL, TG

Design: Cross-sectional			Definition of exposure variable	Definition of outcome measures			
Population, Investigator, Purpose	Sample Characteristics	Physical activity measurement		Pulse wave velocity (PWV)	Main findings	Dose-response	Adjustments
-Lessa Horta et al. 2015 -Population: Brazilian adults followed since birth -Purpose: determine associations btwn objective measure PA, sedentary time, & pwv	-Born @ hospitals in Pelotas, Brazil, in '82 -Followed throughout life -Initially 5914 -Current study 6/12-2/13 -Avg. 30 yrs -FU w/ 3701 participants (68%), complete data collect on 1241 -325 known deaths from initial 5914 -633 men (51%), 608 female (49%) -919 white (74%), 322 non-white (26%) -Exclusion: disabled, living in other cities, labor activities not allowed w/ accelerometer, pregnant (825)	-GENEActiv accelerometer -Worn on non-dominant wrist -Acceleration measured in three axes (x, y, z) -4-7 days of activity, including at least 1 wknd -Excluded first 10 hrs (maximum period observed btwn initialization & attachment of monitors) -Considered valid if data present for every 15min period per 24hr cycle -Results in mg -60min window classified as non-wear if at least two out of three axes sd<13mg & range <50mg -MVPA (moderate-vigorous): threshold of 100mg per $\geq$10min -Sedentary: <50mg (not btwn 11pm-7am) -Calculate % of participants w/ $\geq$30min/day -Sed quartiles (min/d): Q1: 317.8-623.9, Q2: 624-684.8, Q3: 684.8-739.7, Q4: 739.8-952.1 -MVPA quartiles (min/d): Q1: 0-5.3, Q2: 5.3-16.3, Q3: 16.3-34.6, Q4: **34.6-379.6**		-Carotid-femoral pwv (m/s) -Measured twice in one visit using Sphygmocor -Measured in supine on right side -Distance of pulse wave transit measured as distance from suprasternal notch to femoral point of app, & from carotid point of app to suprasternal notch -Pwv: distance btwn sites/transit time delay btwn femoral & carotid pw -Trained volunteers	Table 2: Assoc. btwn PA, sed time, & pwv (β, 95%CI) **Acc** (mg, model 1, Q1 ref) Q2: -.06 (-.24; .13) Q3: -.24 (-.42; -.06) Q4: -.37 (-.56; -.19) p<.001 **MVPA** (min, Q1 ref) Model 1 sig, Q3&Q4 sig (p=.001) Model 2 Q2: .02 (-.16; .2) Q3: -.18 (-.36; -.01) Q4: -.18 (-.37; .01) p=.05 **Sed time** (min, Q1 ref) Model 1 sig, Q4 sig (p=.001) Model 2 Q2: .06 (-.12; .23) Q3: .12 (-.06; .29) Q4: .28 (.09; .47) p=.03 Table 3: total, direct, indirect effects of PA & sed time on pwv consid BMI, wc, & BP as mediators DBP captured about 46% of effect of accel on pwv; 44% of MVPA & pwv assoc explained by wc; DBP 27% of assoc btwn sed & pwv	Yes, acc, mvpa (model 1), potentially sed time	Table 2: Model 1 – sex, skin color, family income @ birth, NEI score, smoke Model 2: 1+MVPA/sed time

Design: Cross-sectional		Definition of exposure variable	Definition of outcome measures			
Population Investigator, Purpose	Sample Characteristics	Physical activity measurement	Arterial Stiffness	Main findings	Dose-response	Adjustments
-Sakuragi et al. 2009 -Population: Taken from Lifestyle of Our Kids Study -Purpose: Determine relationship btwn adiposity, pa, & arterial stiffness in healthy children	-Lifestyle of Our Kids Study: prospective cohort study investigating pa on health & development -Recruited from local primary schools (2005) -Initially 830 kids -CV exams in 2007 -Age 9-10 -615 healthy children -Exclusion: diabetes, hypertension, evidence of CVD -573 completed full examinations -Mean age: 10.1 yo -51% boys -Tertiles by %BF T1: 12.7-23% (n=193) T2: 23.1-29.4% (n=189) T3: 29.6-46.5% (n=191)	-7-day pedometer assessments -AT pedometers -Those w/o at least 3 days of pedometer data retested -Q for parents about family & community-based activities -Analyzed PE classes Cardiorespiratory fitness (CRF): 20-m shuttle run -Adiposity determined through BMI, waist circumference (wc), and DXA	-PWV – Sphygmocor, ECG-gated carotid/femoral -Applanation tonometry -Carotid-femoral path length/carotid-femoral transit time -Supine brachial BP -Avg 2 measurement @ 1 min intervals	Table 1: Characteristics of pop. By tertiles of %BF **PWV (m/s (sd))** T1: 4.2 (.4)**;** T2: 4.4 (.4)**;** T3: 4.6 (.5) $p<.0001$ (clinically sig?) **SBP (mmHg (sd))** T1: 102 (7); T2: 105 (8); T3: 109 (9) $p<.0001$ (clinically sig?) **DBP (mmHg (sd))** T1: 60 (5); T2: 62 (6); T3: 64 (6) $p<.0001$ (clinically sig?) Table 2: Univariate analysis btwn PWV & characteristics CRF (stage): r=-.233, β=-.064, $p<.0001$ Pedometer counts (half steps): r=-.083, β=-.003, p=.046 (clinically sig?) Figure 2: PWV by tertiles of %BF & CRF (bivariate analysis) PWV increased by increasing tertile of %BF ($p<.0001$) & decreased by decreasing tertile of CRF (p=.054) Table 3: Assoc. btwn PWV & CRF (multivariate) Model 1: β=-.047, $p<.0001$ Model 2a: β=-.024, p=.054 Model 2b: β=-.022, p=.127 Model 2c: β=-.023, p=.094	-Dose response seen in pwv & %BF in table 1, but clinically significant? -Also seen in pwv & CRF stage/pedometer counts, but also clinically sig? -Also seen in model 1 of table 3 before adjustments	Table 3 Model 1: age, sex, SBP, MAP, HR Model 2a: 1+BMI Model 2b: 1+WC Model 2c: 1+&BF

Design: Randomized Case Control		Definition of exposure variable	Definition of outcome measures			
Population, Investigator, Purpose	Sample Characteristics	Resistance or endurance exercise training	Arterial stiffness	Main findings	Dose-response	Adjustments
-Beck et al. 2013 -Population: Unmedicated prehypertensive young adults Purpose: Examine effect of resistance and endurance exercise training on arterial stiffness and hemodynamics in young prehypertensive adults	-43 prehypertensive adults (18-35 y.o.) -University of Florida and surrounding area -Avg. age 21 -Prehypertensive: 120-139 mmHg SBP/80-89 mmHg DBP -15 normotensive (<120/<80) -9 men, 6 women -Inclusion: nonsmokers, no exercise in past 6 months	-Randomly assigned to group -G1: resistance exercise; G2: endurance exercise; G3: nonexercise; G4: healthy control -G1: 15; 11 men, 4 women -G2: 13; 9 men, 4 women -G3: 15; 10 men, 5 women -G4: 15; 9 men, 6 women -Exercise 3 days/wk for 60 min for 8 wks -Resistance: 2 sets, 8-12 reps on 7 machines for major muscles -Endurance: intervals on treadmill at 65-85% MHR -G3/G4: sedentary	-Pulse wave analysis (PWA) & pulse wave velocity (PWV) PWA -Radial applanation tonometry w/ Sphygmocor -Obtained AI & AI75 PWV -Carotid-femoral, carotid-radial, carotid-dorsalis pedis	Figure 2: PWA before & after training **AI** -G1, G2, & G3 lower after training ($p<0.05$) -G1 & G2 sig different than G3 after training ($p<0.05$) **AI75** -G1, G2, & G3 lower after training ($p<0.05$) -G1 & G2 sig diff than G3 after training ($p<0.05$) Figure 3: PWV before & after training **Carotid-Radial** -G1, G2, & G3 lower after training ($p<0.05$) -G1, G2 sig diff than G3 after training ($p<0.05$) **Femoral-Distal** -G1, G2, & G3 lower after training ($p<0.05$) -G1, G2 sig diff than G3 after training ($p<0.05$) **Carotid-Femoral** -No sig diff btwn grps or w/in grps before & after training	-Outcome measures did not allow for dose-response to be assessed	-No known adjustments

Design: Randomized Controlled Trial		Definition of exposure variable	Definition of outcome measures			
Population, Investigator, Purpose	Sample Characteristics	Aerobic exercise	Arterial stiffness	Main findings	Dose-response	Adjustments
-Goldberg et al. 2012 -Population: Young men w/ family history (FHx) of hypertension -Purpose: Examine effect of short-term aerobic exercise on vascular function of young men w/ FHx of hypertension	-30 young men (18-25) assigned exercise or control -Healthy, normotensive (BP<140/90 mmHg), medication-free, non-smokers, BMI<25 -Did not participate in PA > 3 times/wk at light-moderate intensity -FHx hypertension: diagnosed hypertension or antihypertensive treatment in > 1 parent/grandparent	-12 exercise sessions -Cycle ergometer @ 65% VO_2max -30 min sessions -3 times/wk, 4 wks	**AI** -Radial applanation tonometry **PWV** -Carotid-femoral PWV	Figure 2: AI pre and post exercise **Exercise** Pre: -9.2 $\pm$ 2.4% Post: -15.2 $\pm$ 3.9% **Control** Pre: -10.6 $\pm$ 2.8% Post: -3.4 $\pm$ 3.4% Between grp diff at post: p=0.03 Table 2: Pre and post variables of exercise and control groups **Exercise PWV (m/s (SD))** Pre: 5.1 (0.30) Post: 4.8 (0.2) **Control PWV (m/s (SD))** Pre: 5.0 (0.2) Post: 5.2 (0.2) No difference between groups and within groups both pre and post exercise for PWV	Dose response hard to assess due to only two levels, control and exercise	-No known adjustments

Design: Randomized Controlled Trial		Definition of exposure variable	Definition of outcome measures			
Population, Investigator, Purpose	Sample Characteristics	Prematurity, VLBW	Fitness & lung function	Main findings	Dose-response	Adjustments
-Vrijladnt et al. 2006 Population: Preterm and SGA children and young adults Purpose: To determine effects of premature birth on lung function and exercise capacity in children and young adults	-Original cohort 1338 infants -998 survived hospital stay, 379 died -959 available; 99 invited back -Final sample: 42 PT & SGA born '83 -<32 wk GA and/or BW < 1500g -19 y.o. -48 controls -healthy friend brought by PT participants for age-matched control	-<32 wk GA -<1500g BW	**Maximal exercise test** -Cycle ergometer -HR, V_e, VO_2, VCO_2 -30 avg. calc -Pedaled at 60-70rpm -3 min unloaded cycling, followed by 15W increase in load every min -Peak values: last 20s of completed max work -AT obtained **Lung function testing** -FVC, FEV_1, $FEF_{25-75\%}$, PEF	-No sig dif in VO_2max btwn preterm and term (p=0.143) -V_{Emax}, Max HR sig lower in preterm compared to controls -No diff in ventilator reserve, oxygen uptake-work relationship, and Borg scale -No sig. diff in lung function & exercise parameters found btwn BPD- & BPD+ groups (both PT) -$FEF_{25-75\%}$ abnormally low for PT -FVC, FEV_1, FEV_1/FVC, PEF, and -sGaw of preterms sig lower than controls -Total lung capacity slightly smaller in PT, but not sig -Diffusion capacity sig lower in PT	-Due to measures, difficult to assess dose-response	-No noticeable adjustments

Design: Cohort Study		Definition of exposure variable	Definition of outcome measures			
Population, Investigator, Purpose	Sample Characteristics	8-week swimming; 4-week detraining	Carotid hemodynamics	Main findings	Dose-response	Adjustments
-Yuan et al. 2016 -Overweight young adults -Purpose: Determine effects of 8-week swimming training and 4-week detraining on arterial stiffness and hemodynamics in young overweight adults	-20 male volunteers -19-21 y.o. -Recruited from area surrounding Chinese University -Inclusion: Overweight, no regular exercise program -Exclusion: History of CVD, other medical disorder, BP/CV meds -3 withdrew during study; lack of interest -2 withdrew during detraining; did not stop training	Swimming -Indoor swimming pool -5 min stretch, 5 min warm up, 30 min swim, 10 min cool down, 5 min stretch -Interval training; rest declining w/ improved fitness -50% MHR first 2 wks, 65-80% MHR 3-8 wks -HR by HR monitor	-Calculated blood flow velocity waveforms w/ high-resolution Doppler ultrasound -Completed in left upper arm -Obtained BP, flow rate (FR), β-stiffness index (β), peripheral resistance (R_p), wall shear stress (WSS), Oscillatory shear index (OSI)	Figure 2: Changes in arterial stiffness before/after swimming training -No differences at 4 wks, but sig difference btwn baseline and 8 wks -No diff btwn baseline & after 4 wks detraining (12 wks post)	-Could be suggested due to significance being seen at 8 wks but not 4 wks	-No known adjustments

Design: Retrospective cohort		Definition of exposure variable	Definition of outcome measures			
Population, Investigator, Purpose	Sample Characteristics	Very low birth weight	Physical Activity	Main findings	Dose-response	Adjustments
-Kajante et al. 2010

-Population: Term and VLBW young adults (Helsinki Study of Very Low Birth Weight Adults)

-Purpose: To study effects of VLBW birth on PA | -Taken from Helsinki Study of VLBW Adults
-351 healthy adults
-163 VLBW, 188 T
-Born between '78-'85 @ Helsinki University Central Hospital
-Selected next available singleton T birth, same sex and not SGA (bw>-2SD)
-Age range 18.5-5-27.1 y.o.
-Avg. 22.3 y.o.
-Invited 255 VLBW & 314 T for f.u.
-F.u. on 188 VLBW & 190 T
-Excluded 27 for cerebral palsy, blindness, developmental delay, or severe hearing deficit
-Male: 69 VLBW, 75 T | -Perinatal/neonatal data from hospital charts
-VLBW: bw<1500g
-BW SD from Finnish birth records btwn '79-'83 | -PA questionnaire (Q)
-occupational, commuting, LT non-conditioning (LTNC), LT conditioning (LTC)
-LTNC: min spent gardening, cleaning, household chores, etc. – split into low (<1 hr) and high ($\geq$1 hr)
-LTC: continuous and dichotomous
-Continuous: How much do you exercise and stress yourself physically in LT?
-Dichotomous: 4 categories | Table 1: OR (95% CI) for low level LTC in VLBW vs. T
Model 1
Physically inactive: 1.61 (1.01-2.55)*
Low frequency (<1/wk): 1.61 (1.05-2.46)*
Low intensity (walking): 2.75 (1.63-4.65)*
Short session duration (<30min): 3.11 (1.44-6.75)*
*significant CI
Model 4
Physically inactive: 1.66 (0.90-3.08)
Low frequency: 1.30 (0.74-2.27)
Low intensity: 2.81 (1.35-5.84)
Short session: 3.07 (1.14-8.24) | Not noticeable, only two groups | Model 1 – age and sex
Model 4 – m1, height, parental education, maternal pregnancy smoking, currently smoke of subject, lean bm, % body fat |

Design: Retrospective cohort			Definition of exposure variable	Definition of outcome measures			
Population, Investigator, Purpose	Sample Characteristics		Very low birth weight	Physical Activity	Main findings	Dose-response	Adjustments
-Kaseva et al. 2012 -Population: Term and VLBW young adults (Helsinki Study of Very Low Birth Weight Adults) -Purpose: To study PA in VLBW & T participants	-Taken from Helsinki Study of VLBW Adults -335 VLBW, 373 T in original cohort -Born between '78-'85 @ Helsinki University Central Hospital -Matched VLBW w/ T singleton birth for sex & appropriate for gestational age (AGA) -569 invited back; 338 attended f.u. from '04-'05 -Data from '07-'08 f.u. -25 not invited bc developmental delay, refusal to return, abroad, not found, ineligible for extra glucose study @ f.u. -Age range 21-29 -Invited 159 VLBW & 154 T for f.u.; 113 VLBW & 105 T participated -Excluded 12 VLBW & 3 T w/o PA, 7 VLBW & 1 T w/ cerebral palsy, developmental delay, blind, hearing deficit or disability -Final: 94 VLBW, 101 T		-Perinatal/ neonatal data from hospital charts -VLBW: bw<1500g	-PA questionnaire (Q): modified Kuopio Ischemic Heart disease Risk Factor Study Q -30-item list -conditioning LTPA (LTC), non-conditioning LTPA (LTNC), commute, "other" -LTNC: gardening, cleaning, household chores, etc -LTC: running, skiing, swimming, etc. -monthly frequency & duration of PA for past 12 months -Avg. intensity: 0 (light), 1 (moderate), 2 (strenuous), 3 (very strenuous) -Times/yr, min/yr, & MET for intensity -vig PA: MET $\geq$ 5	Table 3: Diff in frequency (times/yr), tot-time (min/yr), tot-volume (METh/yr), energy expend (kcal/yr). of diff subtypes of PA btwn VLBW & T [% mean diff (95% CI)] **Model 3** LTC freq: -38.5 (-58.9, -7.7)* LTC tot-time: -47.4 (-71.2, -4.1)* LTC tot-vol: -44.3 (-65.8, -9.2)* LTC enrg expend: -55.9 (-78.6, -9.4)* No sig. for LTNC, commute, or vig PA **Model 4** (LTC) Freq: -48.1 (-64.8, -23.6)* Tot-time: -60.5 (-77.7, -30.2)* Tot-vol: -54.9 (71.6, -28.4)* Enrg expend: -68.4 (-84, -37.2)* *p<.05	Not noticeable, only two groups	Model 3 – age, sex, BMI, smoke, parent education Model 4 – age, sex, BMI, smoke, parent education, extraversion, openness to experience, neuroticism, agreeableness, and conscientiousness

Design: Retrospective cohort		Definition of exposure variable	Definition of outcome measures			
Population, Investigator, Purpose	Sample Characteristics	Very low birth weight	Objective Physical Activity	Main findings	Dose-response	Adjustments
-Kaseva et al. 2015 -Population: Term and VLBW young adults (Helsinki Study of Very Low Birth Weight Adults) Purpose: Examine objectively measured PA differences in VLBW and T young adults	--Taken from Helsinki Study of VLBW Adults -335 VLBW, 373 T in original cohort -Born between '78-'85 @ Helsinki University Central Hospital -Matched VLBW w/ T singleton birth for sex & appropriate for gestational age (AGA) -569 invited back; 338 attended f.u. from '04-'05 -Data from '07-'08 f.u. -Final 57 VLBW, 47 T -Excluded w/ developmental delay, cerebral palsy, blindness, hearing deficit, or condition affecting mobility	-Perinatal/ neonatal data from hospital charts -VLBW: bw<1500g -BW SD from Finnish birth records btwn '79-'83	-Given accelerometer at f.u. -Actiwatch A24 -Minute-by-minute activity counts -Worn on nondominant wrist for at least 3 days -Only removed for water activities -Recorded bedtime & waking up -Excluded bed & when monitor was not worn -Minimum 600 min/day, $\geq$ 3 days -Divided PA by intensity for some analyses -Sedentary (<1.5 METs, <320 cpm), moderate (3-6 METs, 1048-624 cpm), vigorous (>6 METs, >1624 cpm), moderate-to-vigorous ($\geq$3 METs, $\geq$1048 cpm)	Table 1: PA characteristics [min/day (SD)] **Sedentary time**, p=0.6 VLBW: 521.3 (114.0) T: 507.5 (149.4) **Moderate PA**, p=0.7 VLBW: 30.3 (30.2) T: 32.4 (25.6) **Moderate-to-vigorous PA**, p=0.4 VLBW: 37.3 (38.2) T: 44.5 (43.1) **Vigorous PA**, p=0.1 VLBW: 7.0 (13.1) T: 12.1 (20.6) Table 2: Daily PA (mean cpm) differences btwn VLBW & T [mean diff (95% CI)] **Model 3** Daily PA: -18.9 (-77.3, 39.5) Weekday PA: -15.5 (-76.8, 45.9) Weekend PA: -40.4 (-109.3, 28.6) *Next variables min/day* Sedentary time: 14.1 (-40.4, 68.5) Moderate PA: -2.5 (-14.6, 9.6) Moderate-to-vigorous: -8.3 (-25.7, 9.1) Vigorous: -5.8 (-13.1, 1.5)	No, only two groups	Model 3: age, sex, season, BMI, smoke, parent education

Design: Cross-sectional		Definition of exposure variable	Definition of outcome measures			
Population, Investigator, Purpose	Sample Characteristics	Preterm birth	Objective Physical Activity	Main findings	Dose-response	Adjustments
-Lowe et al. 2016

-Population: Millennium Cohort Study – healthy children

-Purpose: Compare objective PA in PT & T children | -Taken from Millennium Cohort Study (MCS) -Based in UK -Original cohort sampled from ethnic minority and lower socioeconomic status areas -Original cohort: 18.818 -Recruited btwn '00-'02 -F.u. @ 3, 5, & 7 yrs -14043 had f.u. @ 7 yrs; 12781 consented to PA monitor -6675 valid PA data (52%) -Excluded 253 for missing birth GA -Final 6422 (50%) -46.8-49.1% male (dependent on group) -Q1: 79, Q2: 119, Q3: 275, Q4: 5949 | -BW, NICU admission & length of stay from hospital records -GA from mother based on due date and actual birth -4 GA groups (quartiles): Q1 – 25-32 wks; Q2 – 33-34 wks; Q3 – 35-36 wks; Q4 – 37-43 wks (T control) | -Uniaxial accelerometer -Worn @ waist for 7 consec. days -Valid data: minimum of 7 $\geq$10 hrs on $\geq$ 2 days -Calculated total PA (mean counts per minute (cpm)), MVPA (min/day @ >224 2241 cpm), sedentary time (min/day @ <100 cpm) | Table 3: General linear models for PA relation to GA split by sex (min/day) (Q4 ref) [β (95% CI)] **Model 4** *Males MVPA (square root transformed)* Q1: -0.58 (-1.12, -0.03), **p=0.04** Q2: -0.04 (-0.49, 0.41), p=0.87 Q3: -0.20 (-0.49, 0.08), p=0.16 *Males Total PA* Q1: -58.7 (-120, 2.81), p=0.06 Q2: 6.93 (-44.1, 58.0), p=0.79 Q3: -13.9 (-46.2, 18.5), p=0.40 *Males Sedentary Time* Q1: 14.6 (-4.85, 34.0), p=0.14 Q2: -0.36 (-16.5, 15.8), p=0.97 Q3: 0.05 (-10.2, 10.3), p=0.99 *Females MVPA (square root transformed)* Q1: -0.29 (-0.81, 0.23), p=0.27 Q2: 0.002 (-0.43, 0.43), p=0.99 Q3: 0.13 (-0.14, 0.40), p=0.36 *Females Total PA* Q1: -35.2 (-92.9, 22.6), p=0.23 Q2: 0.38 (-47.2, 47.9), p=0.99 Q3: 8.00 (-22.1, 38.1), p=0.60 *Females Sedentary Time* Q1: 16.9 (-3.11, 36.9), p=0.10 Q2: 6.36 (-10.1, 22.8), p=0.45 Q3: 0.40 (-10.1, 10.9), p=0.94 | -Not a noticeable dose-response, due to only Q1 showing significance | Model 4: single/multiple births, IUGR status, admission to NICU, pregnancy smoke, BMI, season of data collect., ethnicity, maternal educ., socio-econ. status, current wheeze, atopy |

Design: Cross-sectional			Definition of exposure variable	Definition of outcome measures			
Population, Investigator, Purpose	Sample Characteristics		Extremely low birth weight	Physical activity questionnaire, hand-grip strength	Main findings	Dose-response	Adjustments
-Saigal et al. 2007 -Surviving ELBW young adults -Purpose: Compare health status, PA, functional limitations, and health care use of ELBW and NBW young adults	-144 ELBW survivors -ELBW – 501-1000g -Born btwn '77-'82 -23 y.o. @ study ELBW survivors Avg. BW: 841 + 124g Avg. GA: 27.1 + 23 wks SGA: 36 + 24 NBW (133) BW: 3584 + 487 -Born at term SGA: 4 + 3		-ELBW -BW < 1000g	-SF 36 measured physical functioning and physical health -Physical self-efficacy scale -Hand grip dynamometer w/ dominant hand	Sig. Findings -ELBW more functional limitations than NBW (clumsiness & dexterity) -More ELBW's than NBW's w/ limitation in normal daily activities -Physical self-efficacy and perceived physical ability lower in ELBW -Lower proportions of ELBW vs. NBW reported regular participation in sports & strenuous activity Table 6: Physical self-efficacy, participation in PA, & hand-grip (ELBW, NBW) Physical self-efficacy scale -Total score, mean (SD): 88 (16), 97 (14)* -Perceived physical ability, mean (SD): 39 (9), 43 (8)* Participation in PA -Regular part. In sports/stren active, n (%): 57 (38), 78 (59)* -Unable to part b/c of health, n (%): 32 (22), 12 (9)* Hand-grip strength Mean (SD), kg: 32 (10), 38 (10)* *p<0.01	-Due to stratification, dose-response is not available	-No noticeable adjustments

Wake Forest™
School of Medicine

Department/Section of Pediatrics/Neonatology

ANTENATAL STEROIDS AND CARDIOMETABOLIC RISK
Informed Consent Form to Participate in Research
Lisa Washburn MD, Principal Investigator

Introduction

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because at 14 years of age you participated in or expressed interest in participating in research to study the health of former premature infants. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

Why Is This Study Being Done?

The purpose of this research study is to continue studying the long term effects of antenatal steroids, a medication given to mothers in preterm labor to help the baby's lungs mature. This study will investigate how exposure to antenatal steroids affects the health of young adults.

How Many People Will Take Part in the Study?

About 200 young adults who were born prematurely and 52 young adults who were born at term (normal length of pregnancy) will take part in this study being done at Wake Forest University Health Sciences.

What Is Involved in the Study?

This study involves two study visits (appointments). Each study visit lasts approximately

one half day and will take place in the Clinical Research Unit (CRU), formerly the General Clinical Research Center (GCRC), at Wake Forest University Health Sciences.

AT YOUR FIRST STUDY VISIT, YOU WILL:
1. Have your weight, height, and upper arm measured.
2. Have your waist and the skin thickness on your arm, below your shoulder blade, and at your hip bone measured.
3. Have your blood pressure measured multiple times.
4. Provide a sample of your saliva (spit).
5. Have a small catheter (tube) inserted into a vein in your arm or hand. You will have numbing cream applied to the area first. This catheter will remain in place for approximately two hours for obtaining blood samples. The total amount of blood drawn during the study will be approximately 3 tablespoons. If we are unable to insert the catheter, you will have blood withdrawn twice from a vein in your arm or hand; then the amount of blood drawn for the study will be approximately 1 Tablespoon. If we are unable to obtain the last sample from your vein, we will obtain blood from your finger.
6. *Have an oral glucose tolerance test (OGTT). The purpose of the OGTT is to check how the body breaks down the sugar in your blood. This test involves having your blood taken from the catheter when it is first inserted and then at 30, 60 and 120 minutes after you have been given a sweet beverage to drink. This sweet drink (glucose) tastes like a soda with a lot of sugar. We will check your blood glucose (sugar) level to make sure it is okay for you to do the oral glucose tolerance test.*
7. Answer questions about your general physical and psychological health, any medications and supplements that you take, use of alcohol and tobacco, your family's general health, social and economic factors, your sleep habits and your stress level.
8. Receive instructions on how to maintain a diet with a standard amount of salt for the four days prior to your next visit and be asked to complete a provided checklist for the standardized salt diet.
9. Receive instructions on how to collect and return a urine sample at your next visit.

AT YOUR SECOND STUDY VISIT, YOU WILL:
1. Arrive at the CRU after having nothing to eat or drink (except for water) since midnight.
2. Return the urine that you collected at home. **IF you do not return the home urine, the second study visit will be rescheduled.**
3. Return the completed standardized salt diet checklist.
4. Have your weight, height, and upper arm measured.
3. Have your blood pressure measured multiple times.
4. Answer questions about your general health, any medications and supplements that you take, use of alcohol and tobacco, and your family's general health.
5. Answer questions asked about your physical activity level.
6. Drink 8 ounces (1 cup) of room temperature water.
7. Provide two urine samples by voiding (peeing) in a container, in a bathroom, in private.
8. Have your blood pressure monitored by a cuff that wraps around two of your fingers.
9. Have your heart rate monitored by three electrodes (sticky pads) placed on your trunk.
10. Have your breathing monitored by a belt around your waist and perform 5 minutes of paced (steady) breathing.
11. Perform mental tasks and video games while your heart rate, blood pressure, and

breathing are monitored.
12. Have measurements to determine the stiffness of your blood vessels. These measurements will be taken in the Hypertension Clinic located in the Clinical Science Building at Wake Forest University Health Sciences. Study staff will accompany you to this clinic. For this testing, we will place electrodes and sensors on your neck, chest and wrists. We will also place blood pressure cuffs on your arms and ankles. This testing will take approximately 45 minutes. You will be provided with lunch before the testing.
13. Wear a blood pressure monitor for 24 hours. You will wear the blood pressure cuff on your arm and the monitor will be attached to a belt around your waist. The cuff will inflate every 20 minutes during the day and every 30 minutes during the night. You will keep a diary of your activities and medications while you are wearing the monitor.
14. Wear a physical activity monitor on your wrist and keep a diary of your activities for 7 days. This monitor is the size of a pager.

The records surrounding your birth, your hospital nursery stay and early growth may be reviewed for information important to this study.

We can send copies of your test results to your personal physician. Even if you do not wish to have any of your medical information sent to your physician, you can still participate in this research study.

Do you request that we send important medical findings from your study tests/exams to your personal physician?

[ ] Yes   [ ] No   _____ Initials

As part of this study, a saliva sample will be obtained and DNA from your saliva sample will be purified. DNA, or deoxyribonucleic acid, stores and transmits inherited traits, such as eye color or blood type. As part of this research project, your DNA will be studied in an effort to find out if there are genes that contribute to medical conditions that are part of this study. Because we do not know how the results of this DNA study relate to your individual health, the results of the research will not be given to you or your doctor without your permission. These results will also not be placed in your medical records.

STORAGE OF BIOLOGICAL TISSUES

If you agree to participate in this study, your leftover blood, urine and saliva will be kept and may be used in future research to learn more about other diseases. Your samples will be obtained in the CRU (Clinical Research Unit) at Wake Forest University Baptist Medical Center. The samples will be stored at Wake Forest University Baptist Medical Center and will be given only to researchers approved by Dr. Lisa Washburn. An Institutional Review Board (IRB) must also approve any future research study using your blood, urine and saliva samples. In order to

participate in this study, you must be willing to allow storage of your leftover blood, urine and saliva samples for future research.

Your blood, urine and saliva samples will be stored with a unique identifier and will not include any identifiable information about you such as your name, address, telephone number, social security number, medical record number or any of the identifiers outlined in the HIPAA Privacy Rule. The unique identifier will be a number and only the principal investigator will have access to the code that links the unique identifier to you. Your name, address, social security number, etc., will never be disclosed to future researchers and neither will the code that links your identifiers to the sample.

The research that may be performed with your blood, urine and saliva samples is not designed to help you specifically. There is no personal benefit to you from taking part in this aspect of the research study. It might help people who have diseases at some point in the future, but it is not known if this will happen. The results of the research performed with your blood, urine and saliva will not be given to you or your doctor. The results will not be put in your medical record. The research using your blood, urine and saliva samples will not affect your care.

Your blood, urine and saliva samples will be used only for research and will not be sold. The findings from this research may result in the future development of products that are of commercial value. There are no plans to share any of the profits with you which may occur as a result of the research.

How Long Will I Be in the Study?

You will be in the study for two visits (appointments). Each study visit will last about half a day. You will eat a standardized amount of salt in your diet for four days before your second visit. You will wear an ambulatory blood pressure monitor for 24 hours and keep a record of your activities during that time. You will also wear a physical activity monitor for seven days and keep a record of your activities during that time. You will need to return the blood pressure monitor and the physical activity monitor to the CRU unless arrangements have been made for you to return these items per insured mail.

You may decide to stop participating at any time.

In the future, we may wish to invite our study participants to return for a follow-up assessment. Your signature on the line below indicates that you give permission for us to contact you about any follow-up evaluations.

_____   _____

Subject Signature   Date

What Are the Risks of the Study?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff. Risks and side effects related to the study include:

Visit 1
- The numbing cream may cause a rash or irritation to the skin.

- You may experience discomfort, bruising and/or bleeding where the needle is inserted. Occasionally some people become dizzy, lightheaded or feel faint. Infection may occur on rare occasions. Frequent donation of blood can result in low iron in your blood (iron deficient anemia).

- The sweet drink may make you feel nauseated or sweaty.

- Maintaining a four day standardized salt diet could be inconvenient.

Visit 2
- Wearing the ambulatory blood pressure monitor and keeping an activity diary for 24 hours could be inconvenient.

- Wearing the physical activity monitor and keeping an activity diary for seven days could be inconvenient.

There also may be other side effects that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks.

Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

Are There Benefits to Taking Part in the Study?

If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will benefit other people in the future. The benefits of participating in this study may be: Identification of health conditions such as high blood pressure, obesity, or diabetes.

What Other Choices Are There?

This is not a treatment study. Your alternative is to not participate in this study.

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you and/or information we get from your medical records about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes**:** height, weight, skinfold measurements, blood pressure, urine and blood tests, health history, medications and supplements, alcohol and tobacco use, family's general health, physical activities, food record, heart rate, response to stress tasks, social and economic factors, sleep habits and physical activity monitoring.

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study will be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer. Only the following people or organizations will be granted access to your Protected Health Information:

1) The study investigator and his/her staff, or others at Wake Forest University Health Sciences who oversee research

2) Other people or laboratories providing services for this research project on behalf of Wake Forest University Health Sciences and Wake Forest University Baptist Medical Center

3) The study sponsor, The National Institutes of Health

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it might no longer be protected by federal or state privacy rules.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for an indeterminate period of time. This authorization does not expire. Any research information entered into your medical record will be kept for as long as your medical record is kept by the Medical Center. You will not be able to obtain a copy of your Protected Health Information in the research records until all activities in the study are completely finished.

You can tell Dr. Lisa Washburn that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Lisa Washburn, MD
Department of Pediatrics
Medical Center Boulevard
Winston-Salem, NC 27157

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

Laboratory test results and other medical reports created as a result of your participation in the research study may be entered into the computer systems of Wake Forest University Health Sciences and North Carolina Baptist Hospital. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. Information about your participation in the study will be placed in the NCBH medical record, along with any routine medical test results that were obtained at NCBH as part of this study.

What Are the Costs?

There are no costs to you for taking part in this study. All study costs will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

Will You Be Paid for Participating?

You will be paid $200 for participating in Visit 1 and $200 for participating in Visit 2. We will process payment for Visit 2 after the blood pressure and physical activity monitors have been returned. If you live greater than 90 miles away from the CRU, we will offer you overnight accommodations for the night before Visit 1 and Visit 2, approximately a $72 value. You will be provided lunch at Visit 2.

To receive payment, you must provide your social security number, name and address so that we can comply with IRS (Internal Revenue Service) reporting requirements. When payments are reported to the IRS we do not let them know what the payment is for, only that you have been paid. If you do not wish to provide this information you can still take part in this study but you will not be paid.

Who is Sponsoring this Study?

This study is being sponsored by the National Institutes of Health. The sponsor is providing money or other support to Wake Forest University Health Sciences to help conduct this study. The researchers do not, however, hold a direct financial interest in the sponsor.

What Are My Rights as a Research Study Participant?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, Lisa Washburn, MD at 336-716-5987. If there is no answer or a problem arises after hours, please call the hospital operator at 336-716-2011 and ask for Dr. Washburn in Neonatology to be paged.

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at (336) 716-4542.

You will be given a copy of this signed consent form.

Signatures

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered.   By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

_____

Subject Name (Printed)

_____   _____ _____

Subject Signature   Date   Time (military)

_____   _____ _____

Person Obtaining Consent   Date   Time (military)

JORDAN COTTLE

<u>*Education*</u>

Master of Science in Health and Exercise Science   May 2017
Wake Forest University (WFU), Winston-Salem, NC

Bachelor of Science in Exercise Science   May 2015
Minor in **Neuroscience**
Elon University, Elon, NC
Honors: *3.68 GPA; Trey Halker Memorial Scholarship for Sport/Exercise Science; Southeast American College of Sports Medicine Undergraduate Student Research Award Finalist*

<u>*Research Experience*</u>

Graduate Research Assistant, PEPC-2   October 2015 – May 2017
Departments of Health & Exercise Science and Pediatrics, WFU

Undergraduate Research Assistant, Elon BrainCARE   September 2012 – May 2015
Department of Exercise Science, Elon University

<u>*Publications*</u>

Cottle, J.E., Hall, E.E., Ketcham, C.J., Patel, K., Barnes, K.F. (2017). Pre-existing factors influence neurocognitive performance and symptoms on concussion baseline testing. *Journal of Athletic Training*, *52*(2), 77-81.

<u>*Professional Affiliations*</u>

Kappa Omicron Nu, Health Science Honor Society   2015 – Present

American College of Sports Medicine   2014 – Present

Southeast American College of Sports Medicine Chapter   2013 – Present

Society for Neuroscience   2014 – 2015

<u>*Certifications*</u>

SilverSneakers Classic Fitness Instructor   September 2015

American Heart Association CPR and AED for Health Care Providers   August 2015