PHYSICAL ACTIVITY AND AEROBIC FITNESS IN ADOLESCENCE AND BLOOD

PRESSURE IN YOUNG ADULTS BORN PRETERM WITH VERY LOW BIRTH

WEIGHT

BY

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TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

FIGURES:

TABLES:

LIST OF ABBREVIATIONS

BP	Blood Pressure
HTN	Hypertension
PT	Preterm
EPT	Early Preterm
MPT	Moderately Preterm
LPT	Late Preterm
VPT	Very Preterm
EXPT	Extremely Preterm
T	Term
VLBW	Very Low Birth Weight
LBW	Low Birth Weight
ELBW	Extremely Low Birth Weight
NBW	Normal Birth Weight
GA	Gestational Age
PA	Physical Activity
TOT-hrs	Total-Hours
VIG-hrs	Vigorous-Hours
VO_2peak	Peak Oxygen Uptake
VO_2max	Maximal Oxygen Uptake
PEPC	Prenatal Events Postnatal Consequences

ABSTRACT

Blood pressure (BP) is a common clinical parameter in determining one's risk for hypertension (HTN), coronary artery disease, renal disease and stroke. Individuals born preterm (PT) with very low birthweight (VLBW) have been found to have higher BP and greater risk for HTN in comparison to their term-born (T) normal birth weight (NBW) peers. PT or VLBW individuals have also been found to have lower levels of physical activity (PA) and aerobic fitness than T or NBW individuals in adolescence and young adulthood. Due to the well documented benefit of increased PA and aerobic fitness in reducing BP and HTN risk, the purpose of this study was to investigate the longitudinal association between adolescent PA and aerobic fitness with later BP in young adults born PT with VLBW. Total (TOT-hrs/wk) and vigorous (VIG-hrs/wk) PA for the past year was estimated using a modifiable activity questionnaire (MAQ) and aerobic fitness was determined from peak oxygen uptake (VO_2peak) in a graded maximal exercise test. Resting BP was recorded with both auscultatory and oscillometric devices and ambulatory BP monitoring was conducted to determine 24 hour BP and nocturnal dipping. A total of 142 participants (39% male) had valid data for PA measures at adolescence and young adulthood, whilst 131 had valid VO_2peak measured in adolescence. ABP was recorded in young adulthood from which valid mean 24 hour BP (n=90) and nocturnal systolic blood pressure (SBP) dipping (108) were determined. When stratified by sex, correlational analyses demonstrated that adolescent PA was not associated with resting BP or ABP outcomes in young adulthood. However, change in PA from adolescence to young adulthood was found to be inversely associated with change in diastolic blood pressure (DBP) for males (r= -0.33). Significant associations between adolescent aerobic fitness and

later SBP (males r= -0.38, females r= -0.25), DBP (females only r= -0.26) and nocturnal

dipping (females only r=0.33) were also found. These results suggest that measurement of

fitness in adolescence may provide some insight into BP in young adulthood in the at risk

VLBW preterm-born population.

INTRODUCTION

Blood pressure (BP) is defined as the force of circulating blood on the walls of the arteries. It is recorded in millimeters of mercury and measures the pressure of blood when the heart contracts (systolic) and when the heart relaxes (diastolic). [1] BP has been utilized over the years as one of the most common clinical parameters and has been demonstrated by observational and epidemiological studies to be associated with long-term diseases such as coronary artery disease, renal disease and stroke. [1] Growing evidence indicates individuals born preterm (PT) and/or very low birth weight (VLBW) have elevated BP, [2–17] and increased risk for developing hypertension (HTN). [3,4,6–9,11,13,16,17] Adolescents and adults with BP readings greater than the normal levels of <120 mmHg (systolic) and <80 mmHg (diastolic) are classified as pre-hypertensive and if their BP exceeds 140/90 mmHg they are deemed hypertensive.[18] HTN is currently the leading risk factor for morbidity and mortality on the global scale and accounted for nearly half a million deaths in the US in 2018.[19] In the general population, it is well-documented that physical activity (PA) and aerobic fitness are associated with lower BP and risk for HTN.[20–24] Some evidence indicates that aerobic fitness and PA in adolescents predicts cardio-vascular health in young adulthood.[25,26] Several studies demonstrate that persons born PT and/or with VLBW engage in less PA[27–30] and have lower aerobic fitness levels [14,31–36] which may further increase their risk for developing hypertension. To date, there have been no studies examining aerobic fitness and PA in adolescents born preterm and later BP. Thus, this study will seek to investigate the longitudinal association between PA and aerobic fitness in adolescence with BP and HTN in young adulthood in persons born PT with VLBW. .

LITERATURE REVIEW

Epidemiology

Out of the 15 million births that occur every year, the United States (US) is currently among the six countries that contribute to 50% of the total preterm (PT) births in the world.[37] In 2018, the US Centers for Disease Control reported that 3, 791,712 births occurred in the United States (US), in which 2.75% of these births were found to be early preterm (EPT), (<34 weeks) and 10.02% were preterm (PT), (<37 weeks). Data was also reported on birth weight (BW), where the percentage of infants born low birth weight (LBW) were 8.28% and VLBW were 1.38%.[38] PT birth can range from moderate/late PT (MPT; 32-37 weeks), very PT (VPT; 28-32 weeks) to extremely PT (EXPT; <28 weeks). Similarly, LBW is defined as <2500g, VLBW, <1500g and extremely low birth weight (ELBW), <1000 g.[39,40] Though the rate of infants being born with VLBW has decreased within the last decade, [38] this birth status still remains a serious public health burden. Researchers have illustrated that healthcare for the VLBW population costs the US approximately $13.4 billion annually and the average neonatal intensive care unit hospitalization for infants born with VLBW is 57.5 days.[41,42]

In general babies born VLBW or less, are likely to be born PT. There are many risk factors for PT birth which include maternal age, race, PA, obesity, nutritional status, pregnancy history, chronic disease, smoking, etc. In addition to this, most PT births take place due to spontaneous PT labor, infection, and/or premature rupture of the membranes.[43] BW can be a marker of intrauterine growth. The degree of prematurity and intrauterine growth restriction (IUGR) are associated with short and long term complications.[44] Short term complications include respiratory distress syndrome, bleeding in the brain, patent

ductus arteriosus, necrotizing enterocolitis, retinopathy of prematurity, jaundice, infections and reduced survival rates.[39,40,45] For the infants that survive, some of these complications persist into childhood and adolescence which lead to pulmonary dysfunction, cognitive/neuromotor impairments, reduced aerobic fitness and lack of physical activity (PA).[46] The existing literature shows that they have an increased risk for diabetes, heart disease, hypertension, kidney disease and obesity in young adulthood.[12,47]

Fetal Origins of Adult Disease

PT birth and VLBW have been linked to health outcomes in adult life. [48] Over the years the study on fetal origins of adult disease has developed to explain the link between what occurs during fetal development and disease risk in later life. The increased risk for adult disease among PT and VLBW individuals was first reported by David J. Barker in 1990. [44] Barker hypothesized that adverse stimuli or an insult such as undernutrition in utero may lead to adaptations in developing structures and functions which are beneficial in the short-term but may be detrimental in the long-term.[44,49] Barker's hypothesis was extended into postnatal life, referred to as the developmental origins of adult disease. It is believed that these adaptations alter phenotypic expression of affected genes.[50,51]

Epigenetics

The underlying mechanisms of fetal and developmental programming on later health have been explained in the field of epigenetics. Epigenetics suggests that during cell division methyl groups may be added or removed from regions of the DNA causing conformational changes which can interfere with binding agents and histone modifications

leading to the alteration of chromatin structure and function. The methylation and demethylation consequently regulate the phenotypic expression of genes and promote changes in cellular and tissue function.[48] These alterations can also be passed onto the next generation via the germ line resulting in inherited phenotypes.[50] Exposure to an adverse stimulus or environment (e.g. undernutrition) may result in epigenetic modifications that are beneficial for the fetus' survival but the programmed changes that persist may be detrimental in postnatal life, thus leading to increased risk of adult disease. This is demonstrated in **Figure 1**, where a mismatch occurs between the peri- and post- natal environment of the fetus. As a survival response to a poor maternal environment, genetic and phenotypic adaptations occur in the fetus to match an expected post-natal environment, similar to the one in utero. Most individuals born PT and/or VLBW in the Western hemisphere are exposed to rich, high fat diets and high levels of sedentary time. The genetic/phenotypic adaptations that occurred during uterine development therefore do not match the predicted post-natal environment of these individuals. Instead, adaptations are met with a Western lifestyle and diet which further increases and allows for the sustenance of disease risk in postnatal life.[52]
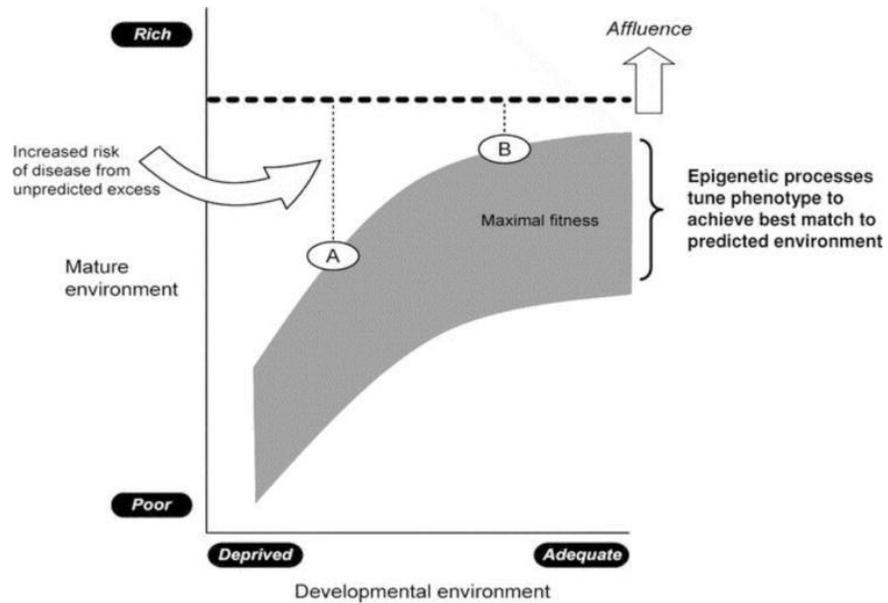
Figure 1. Reprinted from Godfrey et al. 2007 [52]

Developmental Programming and Hypertension

Developmental programming has been suggested to contribute to hypertension in later life. Adverse stimuli such as under nutrition, oxidative stress/inflammation, and excess glucocorticoid exposure can lead to epigenetic changes in utero.[51] Research has shown that an inadequate fetal environment can lead to oxidative stress which results in higher than normal lipid peroxidation and a slight increase in systolic blood pressure (SBP) among LBW offspring. [53,54] Excess amounts of glucocorticoids (cortisol-stress hormones) due to maternal physiological or psychological stressors in the intrauterine environment can result in a reduction of glucocorticoid receptors in the hypothalamus of the fetus. This can then lead to impaired negative feedback causing continuous activation of the hypothalamic-pituitary-adrenal (HPA) axis in utero. The up-regulation of the HPA axis may be sustained after birth allowing for an increased risk of elevated BP in postnatal life.

As shown in **Figure 2**, alterations in other developing systems and organs, specifically the kidneys and vasculature of the cardiovascular system, can contribute to future HTN.[55] Based on experiments done on animal models [56,57] the reduction in nephron number and arterial distensibility have been observed among neonates that undergo an intrauterine insult. These changes in homeostatic regulation affect the function of individual organs and their corresponding systems.[55] Both short and long-term changes to the function of these organ systems may lead to the development of lifetime diseases such as HTN. [58]

Altered maternal nutrition

Abnormal placenta Altered uterine blood flow

Altered fetal nutrition

Altered organ growth and maturation

Liver	Pancreas	Muscle	HPA axis	Kidney	Vasculature	Heart
↑ Gluconeogenesis ↓ Lipid metabolism	↓ Insulin secretion	↓ Insulin sensitive tissues	↑ Cortisol secretion	↓ Nephron number	↓ Distensibility ↓ Endothelial function	↓ Myocyte number

Hyperlipidaemia

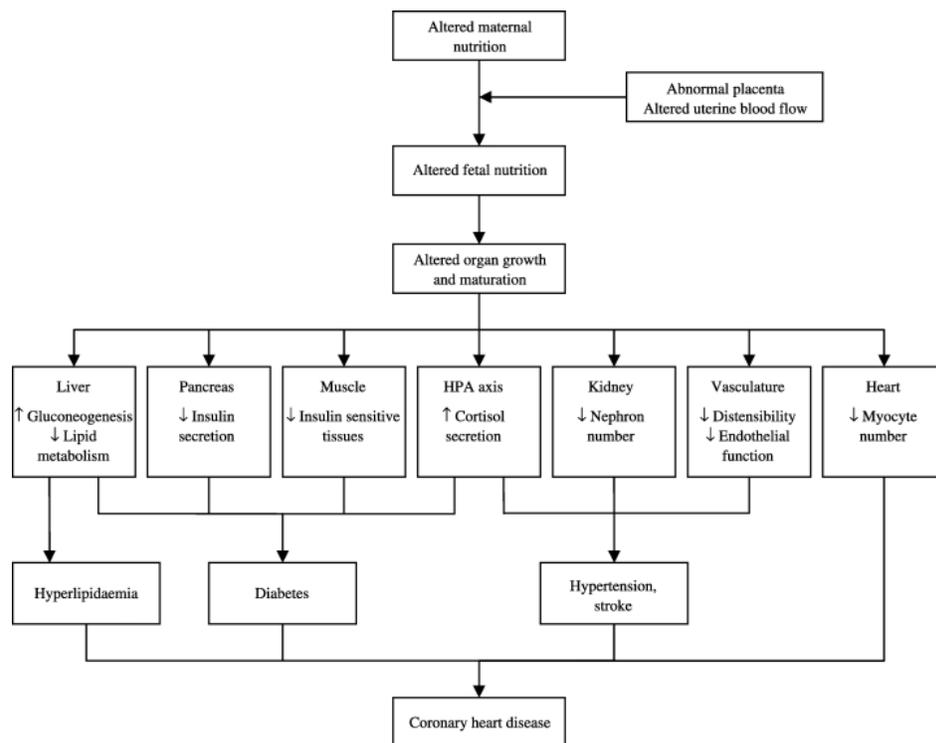Diabetes

Hypertension, stroke

Coronary heart disease

Figure 2. Reprinted from De Boo and Harding, 2006 [55]

The renal system's main organ is the kidneys. In response to fetal insult, kidney nephron loss occurs. The loss of nephrons is said to be caused by changes in the gene expression of growth factors that are important for adequate nephrogenesis. Abnormal

glomerular filtration increases neonatal risk of renal injury and disease. Hyperfiltration, glomerular rate reduction and salt sensitivity are found to be inversely associated with BW.[59] Also, poor fetal nutrition and stress can cause programmed renin-angiotensin activation which increases sympathetic activity and up-regulates sodium absorption. Thus, developmental configurations in the pressure-natriuresis function of the renal system can increase risk for HTN.[58,60]

With respect to vasculature, PT birth due to an inadequate maternal environment can interrupt the development of vascular structures. Changes in vascular structure such as arterial stiffness, reduced aortic size, narrowed coronary arteries and retinal arterioles, increase risk of elevated BP.[60] In humans peak arterial elastin synthesis occurs near birth and quickly declines thereafter. Arterial distensibility and stiffness are directly affected by the ratio between elastin and collagen at birth.[58] Studies conducted on children and adolescents (7-14 years old) born MPT or VPT have reported early signs of increased arterial stiffness.[61–63] In addition IUGR fetuses were found to have increased levels of collagen I & III messenger ribonucleic acid (mRNA) in their umbilical cord blood.[64]

In addition to stiffer arteries, endothelial function has been shown to be decreased, thus hindering flow mediated dilation in infants born PT and/or LBW.[58,60] The renin-angiotensin system plays a critical factor in vascular dysfunction as it is responsible for increased sympathetic activation via upregulation of angiotensin II (ANG II) expression.[60] In a study by Lopes et al.[65] urinary angiotensin-converting enzyme activity in PT neonates was increased in comparison to T infants. Other articles have also explained that uncontrolled responses to vasoconstrictive mechanisms (ANG II), phenylephrine and endothelin are associated with programmed HTN.[58,60]

Prematurity/Birth Weight and Blood Pressure/Hypertension Among Young Adults

Several studies in the literature have found significant differences in BP and HTN between persons born PT and/or LBW or less, compared to their term-born young peers.[2–6,8–12,14,16,17,66–68] A meta-analysis published in 2019 by Markopoulou et al.[2] consisted of 43 studies (29 longitudinal, 8 retrospective, 6 case controls) for a total of 18, 295 PT and 294, 063 T, with samples drawn from Asia, North America, Europe and Oceania continents. In this meta-analysis, significant differences in resting BP among PT and T individuals were found. This analysis was restricted to 19 studies that examined BP among these groups and included participants with a mean age of 19.4 ± 5.1 years at assessment. The overall pooled mean difference in SBP/diastolic blood pressure (DBP) difference was 4.22/2.27 mmHg higher among PT compared to terms (p<0.05).

Another meta-analysis by Mu et al.[3] examined LBW and subsequent BP. The authors included 9 longitudinal studies with a total sample size of approximately 10,000. Ages of subjects ranged from 8-84 years. For subjects with LBW, findings suggested a higher likelihood of developing HTN compared to subjects with NBW (OR:1.21, 95%CI: 1.13 to 1.30, p<0.05). Also, those with LBW had a 2.28 mmHg (95%CI: 1.24 to 3.33, p<0.0001) higher SBP than NBW subjects. The results for DBP, though significant, were not as strong as SBP (1.01 mmHg 95%CI: 0.19 to 1.83, p<0.05). More specific to young adults, another meta-analysis by De Jong et al.[4] assessed BW and BP. Seven out of the total of ten studies reported the mean age of participants to be ≥15 years. A 2.5 mmHg (95%CI: 1.7 to 3.3) higher SBP was found in VLBW subjects compared to NBW controls, and in an analysis of the 5 higher quality studies the SBP difference increased to 3.8 mm Hg (95% CI: 2.6 to 5.0).

Studies have also assessed the risk of developing HTN among young adults born PT and/or LBW compared to term-born NBW peers. A study by Haikerwal et al.[5] included 296 participants born EXPT with ELBW within the period of 1991-1992. They found the odds ratio (OR) for clinical BP between EXPT and/or ELBW and term-born NBW subjects to be non-significant. In addition to the findings of Haikerwal, Sipola-Leppanen et al.[6] (after adjusting for current participant characteristics such as, parental education, smoking status, body mass index (BMI), height, weight and PA), found that EXPT participants were almost 4 times more likely to have office measured HTN ($\geq$140/90 mmHg) when compared to T controls (OR: 3.8, 95%CI: 1.1 to 13.8, p<0.05). Similar to previous findings, an all-male study utilizing GA categories ranging from 24-41 weeks, found persons with a GA ranging from 24 to 36 weeks were 1.25 to 1.93 times more likely to have elevated SBP ($\geq$135 mmHg) than subjects who were term-born (37-41 weeks).[7] It must also be highlighted that the only GA category to have a significantly higher OR (OR:1.33, 95%CI: 1.08 to 1.64, p<0.05) for elevated DBP ($\geq$85 mmHg) was the 33-36 week GA category. In DeJong's meta-analysis, 3 out of the 8 articles that analyzed for HTN outcomes reported a statistically significant higher relative risk. Compared to T participants, young adults in the PT and/or VLBW groups had a higher risk of HTN ranging from 1.2 to 2.5 risk ratio (RR) (p<0.05). Only one study was found to report non-statistically significant results, and the other 4 did not report statistical testing; therefore authors did not report pooled analyses.[4]

As a result of the prognostic importance of BP and HTN health measures, studies have demonstrated a negative linear association between PT and/or LBW with BP.[7–11] A meta-analysis conducted by Hovi et al.[8] on 9 longitudinal cohort studies examined the BP differences between 1571 young adults born VLBW or ELBW and 777 term-born NBW

young adults (19.5-20.8 years old) born between 1977-1993. The authors found that among VLBW subjects there was a 3.0 mmHg decrease in SBP per 1 week increase in GA (95%CI: -5.1 to -0.9, p<0.01) if subjects had >1 BW standard deviation (SD) and were born <28 weeks-30 weeks. Authors also found significant mean differences in SBP (3.4 mmHg, 95%s 2.2 to 4.6, p<0.01) and DBP (2.1 mmHg, 95%CI: 1.3 to 3.0, p<0.01) between VLBW and NBW groups, with slightly higher differences being found in their analysis between ELBW and NBW groups.

Results of two studies, not included in the meta-analysis by Hovi also investigated the association between prematurity and BP in young adulthood.[7,9] The first study by Johansson et al.[7] specifically investigated the impact of the degree in prematurity at birth on BP in males. The results of this study showed that men with a mean age of 18.2 years had a 0.31/0.04 mmHg decrease in BP per 1 week increase in GA (p<0.05). The authors also reported a negative correlation between BW and BP where the regression coefficient for BP was found to be -0.67/-0.10 mmHg per 1 unit increase in BW SD score (p<0.05). A study by Skudder-Hill et al.[9] recruited an all-female sample from the Swedish military conscript (n>5000), with a similar mean age (18 years) at the time of assessment. For this study, there was no report of regression coefficients however, authors stratified by GA with <32 weeks, 33-36 weeks, 39-41 weeks and >42 weeks categories. Mean BP readings of 123.1/71.2 mmHg, 126/70.3 mmHg, 122.2/69.4 mmHg and 121/69.2 mmHg were reported for each GA category, respectively. Although a clear dose-response between SBP and GA category was not observed (there was an overlap of the 95%CI intervals for the <32 weeks (95%CI: 123.1 to 129.8) and 33-36 weeks (95%CI: 124.5 to 127.2) GA categories for SBP), both PT groups had significantly higher SBP compared to T group.

In contrast to the findings of these studies, Vohr and colleagues [10] did not find a difference in BP among PT subjects for degree of prematurity. An explanation for this finding could be that the sample size of this study was relatively small (n<400) and subjects had a lower mean age at assessment (16 years). Previous studies have shown, that BP differences are less likely to be evident among children and adolescents since their organs and organ systems related to BP regulation are still developing.[69,70] In another study by Doyle et al.[11] office BP were examined in young adults 18-19 years. Among VLBW subjects there was no significant linear correlation between office BP and BW SD score. The sample size was slightly smaller (n=194) than most studies that examined this relationship, so this could have posed as a limitation for statistical power.

Prematurity, Birth Weight and Ambulatory Blood Pressure

Most studies have reported a negative correlation between prematurity and/or BW with BP and HTN using only office/clinical BP. [7,10,66,67] Authors of other studies have indicated that clinical BP may not always be an accurate representation of a valid BP measure due to factors such as masked and white coat HTN.[71–73] These factors have been found to inhibit the ability of recording true BP in one setting. Hence, ABP has been investigated as a better marker for detecting abnormal BP and risk for hypertension. Dawes and colleagues[71] conducted a study on a cohort of 10, 129 patients from Oxford and London with a median follow up of 8 years. In this study they found that a higher level of all-cause mortality per 1000 person-years was associated with ABP monitoring of high systolic HTN compared to clinical BP monitoring. The only significant finding (p<0.0001) for risk of all-cause mortality was among ABP systolic quartiles. Individuals with a systolic ABP of

>160 mmHg were 1.5 times more likely to have all-cause mortality than those in quartile 1 (95%CI: 1.25 to 1.83).

As previously stated, it can be inferred that clinical BP may not always be an accurate representation of true BP. One study by Sipola-Leppanen et al.[13] investigated the relationship between ABP and degree in prematurity. Subjects were recruited at 23 years old from the ESTER study and born between the years 1984-1985/1987-1989. Although the sample size was relatively small (n=213) there was a significant decrease in ABP and ABP variability (reported in standard deviations) per 1 week increase in gestational age (GA) after adjusting for current confounders. It was found that per 1 week increase in GA there was a -0.5/-0.3 mmHg decrease in 24 hour ABP and a -0.6/-0.4 mmHg decrease in awake ABP ($p < 0.05$). For ABP variability similar findings were reported in addition to diastolic asleep ABP variability being reduced by -0.2 mmHg per 1 week increase in GA ($p < 0.05$). The small reduction in 24 hour and awake ABP per 1 week increase in GA may not seem significant, but the difference between 37 and 28 weeks equals 9 weeks, which yields a 4.5 mmHg for a 0.5 mmHg decrease in 24 hour ABP per week. Similarly, results for 6 studies in a meta-analysis[2] examining 24 hour ABP also found that PT individuals had a significantly higher 24 hour ABP of 4.62/1.69 mmHg compared to T individuals ($p < 0.05$).[2]

Doyle et al.[11] also examined ABP in VLBW young adults. Significant differences in systolic 24h, awake and asleep ABP were found (5.2 mmHg (95%CI: 2.1 to 8.3) 5.9 mmHg (95%CI: 2.8 to 9.1), 3.8 mmHg (95%CI: 0.4 to 7.2), respectively) between VLBW and NBW individuals. In addition, a study examining ABP at age 25, subjects born EXPT with ELBW were approximately 2-5 times more likely to have 24 hour (≥130/80 mmHg),

awake (≥135/85 mmHg) and asleep (≥120/70 mmHg) ABP HTN compared to term-born NBW controls (p<0.05). In contrast the by Leppanen et al.[13] and a study by Centra et al.[73] found no association in the comparison of both EPT and LPT to T controls for 24 hour, awake or asleep ABP HTN.

Potential Effect Modifiers and Moderators

<u>Sex</u>

A varying degree of results especially among males and females have been reported in the previously mentioned studies in which BP differences among PT and/or LBW males and females have yielded inconsistent findings. [2,3,5,8,10,11,16,67,68] In a meta-analysis by Markopoulou et al.[2] SBP/DBP differences in sex were investigated among PT men and women. Differences were found to be greater between PT women and T women compared to differences between PT men and T men (SBP; 4.94 vs 1.98 mmHg and DBP; 2.89 mmHg vs 1.29 mmHg, respectively, p<0.05). Similarly, mean 24 hour ABP was significantly higher in PT women compared to T women (SBP; 3.49 mmHg 95%CI: 1.38 to 5.60, DBP;1.55 mmHg 95%CI: 0.04 to 3.05, p<0.05) however, mean 24 hour ABP differences between PT and T men were not (SBP; 2.86 mmHg 95%CI: -3.70 to 9.43, DBP;0.05 mmHg 95%CI: -2.59 to 2.68, p>0.05). Another meta-analysis by Hovi et al.[8] found that when authors stratified by sex, a greater BP difference was also observed between VLBW women compared to NBW women (5.9/2.8 mmHg, p<0.05), whereas the difference between VLBW and NBW men was slightly lower (4.2/2.8 mmHg, p<0.05). Sexual dimorphism in developmental programming may explain the differences observed within sex group comparisons.[74] However, when comparing BP between PT and VLBW males

13

and females, Haikerwal et al.[5] found that EXPT/ELBW male subjects had a 8.3 mmHg (95%CI: 4.6 to 11.9) higher systolic 24 hour ABP than females.

Intrauterine Growth Restriction

Similar to findings regarding sex and BP among PT and/or LBW subjects, perinatal factors, in particular intrauterine growth restriction (IUGR) defined by being small for gestational age (SGA) or having a BW <-2 SD/<10th percentile has been found to be an effect mediator for the association between prematurity and BP.[68] Comparisons for BP between SGA and appropriate for gestational age (AGA; BW>-2SD/>10th percentile), PT born individuals were examined in a few articles.[15–17,67] These articles assessed the mean differences in BP among groups. For a relatively young adult population (~20 years) authors found no significant BP differences between individuals born SGA and AGA.

Year of Birth

Specific to the population of this study, a meta-analysis by De Jong et al.[4] presented pooled results of 7 studies that examined the year of birth as a potential confounder for BP among the PT and/or VLBW population. Subjects born before 1990 had a 4.2 mmHg greater SBP than term-born NBW subjects born within the same period (95%CI: 3.2 to 5, p<0.05). For subjects born after 1990 results were presented based on 3 studies. No difference between preterm-born VLBW and term-born NBW was found for subjects born after 1990. The small collection of studies examining PT populations born after 1990 could explain the lack of difference within this population sample. However, with obesity currently on the rise in modern America and the impact of BMI on moderating the effect of preterm-born VLBW on BP among young adults it is even more important to gather

14

more data on this population as they are increasingly vulnerable to the effects of their prematurity by means of an obesogenic diet and more sedentary lifestyle.

<u>Body Mass Index</u>

Due to the growing importance of BMI as a confounder in many health related studies, several authors have examined the modifying effect of BMI on the relationship between BP and HTN and PT/LBW.[5,10,66] Vohr et al.[10] found a significantly higher BMI of 3.1 kg/m^2 among PT subjects diagnosed with PreHTN/HTN than PT subjects without HTN (p<0.05). Analyses were also done including both PT and T participants, where a 1 unit increase in BMI (1 kg/m^2) was significantly associated with a 0.60/0.22 mmHg increase in BP. Likewise, Haikerwal et al.[5] demonstrated that at 25 years of age, individuals within the EPT and/or ELBW population had a 0.60/0.30 mmHg higher SBP/DBP per 1 kg increase in BMI (p<0.05). Opposite to these findings. Hack et al. [66] reported no moderation of SBP by BMI among VLBW females at 20 years old. This was also found to be true for DBP among both sexes.

<u>Race</u>

Other correlates such as race have been assessed to establish more specific risk factors for higher BP and HTN within the PT and/or LBW population. Results regarding race are found to be equivocal. Vohr et al. [10] found non-white PT subjects to have 3.77 mmHg higher SBP than whites whereas Hack et al. [66] did not find any differences between black VLBW males/females and their non-black counterparts with subsequent BP. In contrast, a meta-analysis by Mu et al. [3] reported white LBW individuals to have a 2.51 mmHg higher SBP than their NBW white peers, but no BP differences were observed for LBW and NBW in persons of Asian descent or black race. Discrepancies among studies

may be due to limited sample sizes of nonwhite participants and difference in exposure variables (e.g. BW vs. prematurity).

The presented literature supported by Barker's Hypothesis does demonstrate a dose response relationship between PT and/or LBW with BP and HTN. The majority of the studies found statistically significant differences between PT and/or VLBW and term-born NBW young adults for clinical BP. These BP differences ranged from ~2-4 mmHg for SBP and ~1-2 mmHg for DBP. Among the studies that assessed ABP differences between PT and/or VLBW and term-born NBW groups, significant results for 24 hour, awake, and asleep systolic ABP ranged from ~4-6 mmHg. HTN outcomes for BP and ABP were generally significant, with one study reporting that adolescent EPT subjects compared to controls were about 4 times more likely to have HTN in young adulthood.[13] Overall, there were few studies that did not find significant differences between PT and/or LBW and term-born NBW groups for BP, ABP and HTN. These discrepancies in the data may be due to factors such as sex, BMI and year of birth. When samples were stratified by sex the difference between in BP PT and/or LBW vs term-born NBW male groups were lower than the BP difference found when PT females were compared to T females. BMI and year of birth were also found to influence the relationship between PT and/or LBW and BP and HTN. Higher values for BMI and being born before 1990 was associated with elevated BP and risk for HTN among participants born PT with VLBW. IUGR was not found to be a significant effect modifier between SGA and AGA preterm-born VLBW groups and results regarding race were found to be equivocal and non-substantial to make conclusive results. Also, the lack of protocol standardization, random error, differences in study population, data analyses/collection, adjustments and lifestyle factors such as PA and aerobic fitness

can impact BP differences between preterm-born LBW and term-born NBW study samples.

Effect of Physical Activity and Aerobic Fitness on Blood Pressure

Physical activity (PA), described as any bodily movement produced by skeletal muscles that requires energy expenditure and aerobic fitness, defined as the body's ability to transport and utilize oxygen, both have been found to provide both protective and rehabilitative effects for lifestyle diseases.[75] The relationship between PA, aerobic fitness and blood has been well established in the existing literature.[25,26,76–79] Higher levels of PA and aerobic fitness have been found to be independently associated with improving BP.[23,80,81] Mechanisms by means of PA and aerobic exercise (usually done to achieve, maintain or improve aerobic fitness) can allow for improvements in BP autoregulation, vascular structure/function, arterial function and metabolic system processes have been found to lower BP. [21]

Whilst engaging in certain levels of PA and aerobic exercise arterial peripheral resistance decreases to allow blood to flow quicker in order for the body to meet oxygen demands.[82] The consequent reduction in sympathetic activity and arterial pressure as a result of exercise can lead to sustained reduction in BP if one exercises regularly. As shown in **Figure 3**, aerobic exercise can reduce the activation of RAS and increase the production of nitric oxide (NO; vasodilator) thereby improving endothelial function.[83,84] Reduction of intra-media wall thickness and arterial stiffness can also occur to increase arterial diameter and peak flow-mediated dilation.[85] Since BP is controlled by the autonomic nervous system and aerobic exercise uses both sympathetic and parasympathetic responses, sympathetic

17

activity can be normalized and sensitivity to the baroreflex system increased.[86] Additionally, the movement of glucose into the muscles for use during exercise improves insulin sensitivity and promotes weight loss which could lead to lower BP.[21]
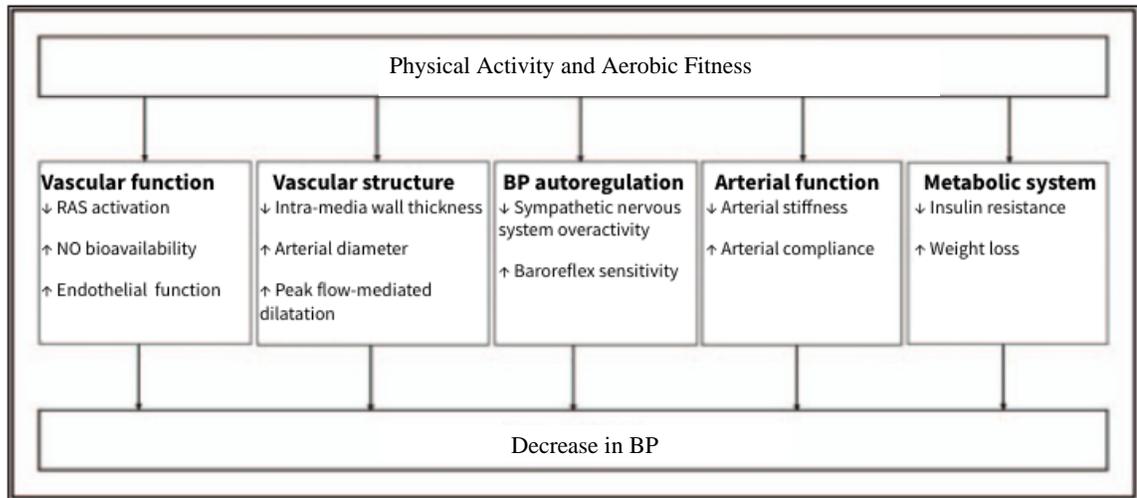
Figure 3. Mechanisms of aerobic fitness adapted from Bakker et al. 2018 **[21]**

Authors [87–91]examining the association between PA and aerobic fitness in adolescence with BP in adulthood have found significant results for aerobic fitness but not PA. Though these samples include relatively healthy adolescent populations without prematurity and low birthweight status, some researchers still found inverse associations between aerobic fitness in adolescence and later BP [25,87,90,91]. Significant inverse associations were found mostly for DBP. In a study conducted by Kvaavik et al.[87] a 1 ml/kg/min increase in VO_2 max in a sample of 716 adolescents with a mean age of 13 years was associated with a significant decrease in DBP at 25 years (-0.04 to -0.15mmHg, p<0.05). Mikkelsson et al.[90] measured aerobic fitness using a 2000m run test among Finnish adolescent males between 12-17 years old males. Authors found adolescent males who were very slow runners characterized by having a 2000m run time of 657-895 seconds to have higher BP at age 40 than those were very fast runners and had a time of 385-473

seconds (134/83mmHg vs 141/90 mmHg, p=0.05 for SBP after adjusting for BMI and p=0.013 for DBP).

In contrast to these findings a meta-analysis by Gracia-Hermoso et al.[92] found no significant findings for the pooled results of 10-12 articles that examined an association between adolescent aerobic fitness and BP in young adulthood. Two studies [89,90] that stratified by gender for the relationship between adolescent aerobic fitness and later health was found to be only significant among males which could identify males as more at risk than females for this association. It should be noted that most authors examine this association within a sample of relatively healthy adolescents and young adults. Thus, there is a need to conduct further research and analysis of other populations in order to promote higher levels of habitual and vigorous PA in adolescent PT and/or VLBW individuals. This is necessary so that they are able to reap the long term health benefits associated with increased levels of PA and aerobic fitness.

Prematurity/Birth Weight and Physical Activity/Aerobic Fitness

Aerobic fitness

Evidence of an association between PA and aerobic fitness with prematurity and BW has been discovered in the literature. Within the 21st century several studies[30,31,33,35,36,93] published results in support of this association among adolescent and young adult populations. Haraldsdottir et al. [31] performed a study on 28 subjects aged 25 years from Wisconsin and Iowa, and recruited from the Newborn Lung Project, a large prospective epidemiological study, PT participants were followed from age 5 to 26 years and compared to age matched T controls. Using cycle ergometry the authors found the

2

absolute VO_2˘ (L/min) for PT subjects to be significantly lower 2.43 ± 0.70 L/min compared to 3.46 ± 0.62 L/min for T (Cohen's d:1.63, p<0.05). Authors also examined relative maximal oxygen uptake (VO_2max, mL/kg/min), in which the weight of the subject was taken into consideration. The VO_2max of the PT subjects was 34.88 ± 9.26 mL/kg/min compared to 45.79 ± 8.71 mL/kg/min for T subjects. Additionally, the strength of the association was increased for this comparison reflected by a higher Cohen's d value of 2.15 (p<0.05). Sex differences were investigated as well. PT males were found to have significantly lower VO_2 max, mL/kg/min in comparison with T participants; however, female PT and T participants showed no between group difference for VO_2max.

A meta-analysis by Edwards et al. [33] published in 2015, included one case-control, one cross-sectional and 20 prospective studies totaling 1365 males & females in the pooled sample. Subjects were between the ages of 5-21 years from various continents. This study provided additional evidence for the association between prematurity and fitness. The pooled random effects of 20 studies (all weighted <10%) found a -2.20mL/kg/min difference (95%CI: -3.70 to 0.70, p=0.004) in VO_2max between PT and T born participants (including those with and without bronchopulmonary dysplasia). Pooled results did not change appreciably when excluding PT participants with BPD. It should be noted that only five out of twenty studies in the analysis had significant results. These five studies included subjects with ages ranging from 9-12.5 years, which may not accurately reflect PT subjects in other age groups. A sensitivity analysis of the testing modality was also conducted. With the exception of the cycle ergometer test mode, PT participants performing treadmill and 20m shuttle run tests were found to perform significantly lower than T peers. The test mode

that yielded the greatest between group difference for VO$_2$max, mL/kg/min was the 20m shuttle run test.

In corroboration with the findings by Edwards et al.[33] and Haralsdottir et al.[31] three other studies[34,35,94] presented significantly lower maximal or peak oxygen uptake (VO$_2$ peak) among persons born PT with LBW in comparison to term-born NBW controls. Two of the three studies published by Clemm et al. [34,35] examined aerobic fitness between 17-18 year old male & female EPT and/or ELBW and term-born NBW subjects in western Norway. In both studies a higher VO$_2$ peak, mL/min was reported for term-born NBW subjects when compared to EPT and/or ELBW subjects ($p<0.05$). Authors stratified by birth cohort and conducted separate analyses for 1981-1985 and 1991-1992 birth cohorts to determine if availability of medical advances such as surfactant therapy affected fitness. Although lower VO$_2$peak, mL/min values among EPT and/or ELBW were reported in both cohorts, the magnitude of the difference was slightly attenuated in the 1991-1992 birth cohort. These findings show that even with surfactant treatment and the advancement of healthcare aerobic fitness of adolescents/young adults is affected by their EPT and/or ELBW status. The third study by Evensen et al.[94] was also conducted in Norway, with a sample size of 147 subjects. In this study PT & SGA subjects were found to have a significantly lower absolute VO$_2$max than T subjects. However, differences in relative VO$_2$max were found to be insignificant for both VLBW and PT & SGA vs term-born NBW analyses. The lack of significant difference was also observed in a study performed by Vrijlandt et al.[30] in which 90 subjects recruited from the Dutch based POPS cohort performed a cycle ergometry VO$_2$peak test at the mean age of 19 years. The authors of this

study found no significant difference in VO$_2$peak, mL/kg/min among comparison groups (PT vs T).

Although assessment of VO$_2$max is considered the gold standard for assessing aerobic fitness[95], studies utilizing other measures that estimate aerobic fitness have contributed to the literature on this topic. Rogers et al.[36] examined 53 ELBW 17 year old subjects born with a BW of <800g and a mean GA of 25.8 weeks in comparison to 31 age matched term-born NBW subjects. A Modified Canadian Aerobic Fitness test was used to assess fitness (mCAFT). This test involved repeated intermittent stepping in which the step rate was progressively increased until 85% of age and gender-predicted max HR was achieved. Results were stratified by gender and showed that ELBW males had a significantly lower score than NBW males (495 vs 529.18, p<0.05). ELBW females also showed similar results with a mCAFT step score of 442.17 compared to 529.18 for NBW females (p<0.05). In another study, Svedkerans et al.[93] used data from an extremely large all male sample with a mean age of 18 at the time of Sweden military conscription. Participants were stratified by GA weeks into <27 wks, 28–31 wks, 32–36 wks, 37–41 wks and >42 wks categories. A cycle ergometer was used to obtain max Watts (Wmax) to assess aerobic fitness. Results illustrated a positive association between GA and Wmax, with a significant p for trend (p<0.001).

Physical Activity

Some of the differences in aerobic fitness may be attributed to differences in physical activity participation. Some studies comparing PA levels between preterm-born LBW and term-born NBW subjects, have yielded significant findings. One study by Vrijlandt et al.[30] including 117 young adults and another by Clemm et al.[34] with 150

adolescents found PT born individuals to engage in <1 hr/wk of PA when compared to T peers (p<0.05). Tikanmaki et al. [96] using a modified version of the Kuopio Ischemic Heart Disease Risk Factor questionnaire, similarly found early PT young adults with a mean age of 23 years from the ESTER study in Finland to have lower total leisure time PA participation (-28h MET hr/wk; 95%CI: -41.6 to -12.3) when compared to term-born young adults. Early PT males also had significantly lower frequency (times/wk) and total volume (MET hr/wk) for total, conditioning, commuting and vigorous LTPA compared to their male T counterparts (p<0.05). Another study by Spiegler and colleagues[97] compared PA between PT and T adolescents. Based on a large sample drawn from the Child Benefit Registry in England, Scotland and Wales an OR of 0.59 (95%CI: 0.40 to 0.80) for adolescents born MPT was reported. This showed that adolescents born MPT were 59% less likely to self-report moderate to vigorous PA (≥60 minutes at least 3-4 days/week) than term-born adolescents.

<u>Objectively vs Subjectively Measured PA</u>

Likewise, when Spiegler et al.[97] used wrist worn accelerometers to objectively measure PA. Males reported 18 more minutes (95%CI: 15 to 20) than females of moderate to vigorous PA defined as minutes of 5-minute windows with 80% activity (Euclidean Norm Minus One >100 mg). Authors also found that for self-reported PA, moderately PT (32-34 GA weeks) subjects were 59% less likely (95%CI: 0.40 to 0.86, p<0.05) to engage in moderate to vigorous PA than their T counterparts. In a race analyses conducted in this study, it was found that white subjects achieved 6 minutes more (95%CI: 2 to 9, p<0.05) of moderate to vigorous activity measured by accelerometry compared to non-white study subjects.

An investigation of the association between VLBW and PA by Kaseva et al.[27] found ninety four 25 year old subjects with VLBW to have significantly lower conditioning leisure time physical activity (LTPA) for frequency (times/year), total time (minutes/year), total volume (MET hr/yr) compared to 101 NBW subjects. Adjusting for SES, body composition and personality traits further strengthened the association (p<0.05). In accordance with earlier findings between PT and T participants, Kaseva also found VLBW males to engage in lower PA (-55.8 times/year, -42.3 minutes/year and -47.5 MET hr/wk) than male NBW subjects. In contrast, a meta-analysis by Anderson et al.[98] reported pooled results of 21 articles originating from 13 Nordic cohorts. When stratified by sex, no significant LTPA (hr/wk) differences were found at 14 years old among those with BW that ranged from 1.26 to 5.25 kg compared to those with BW between 3.26-3.75 kg. However, Anderson et al.[99] did present a log OR figure depicting a U-shaped association between BW groups and LTPA. The figure showed persons with a BW ranging from 1.26-2.75 kg and a BW of 5.0 kg or higher were 11-33% less likely to engage in LTPA compared to subjects included in the 3.5kg BW group (95% CI: 0.47 to 0.99). Additionally, a study by Kajantie et al.[28] conducted a similar investigation on 163 VLBW and 188 NBW male and female young adults from the Helsinki Study of VLBW adults. Authors illustrated that VLBW young adults were approximately 3 times more likely to engage in low intensity exercise (walking) and short exercise sessions (<30 minutes) when compared to NBW young adults (95%CI: 1.35 to 5.84 , p<0.05).

Notably, all studies reporting significant findings for PA utilized self-report measures via a questionnaire/survey. Three studies[100–102] examined objective measurements of PA using either hip or wrist worn accelerometers and yielded no

significant findings for the comparison of PA between preterm-born LBW subjects and term-born NBW controls. All of these studies were found to have large sample sizes of young adults and/or adolescents which include both males and females. Adherence to the proper use of the accelerometer may be a contributing factor to the non-significant results found when comparing objectively measured PA in PT and/or LBW groups. In comparison, use of self-report questionnaires as a measure for PA may entail recall error or recall bias where participants may not accurately recall their past PA or they may feel pressured to give socially appropriate answers by either over-reporting or under-reporting their PA. Speigler et al.[97] analyzed such findings from a large racially diverse sample of subjects with a mean age of 14 years in which a correlation analysis between self-reported PA and Accelerometer data among very PT, moderately PT, late PT and T groups was performed. Using the statistical Spearman rank-order correlation tool self-reported PA and accelerometer data was found to be significantly correlated within all groups except for moderately PT subjects ($p<0.05$). These findings therefore indicate that self-reported PA and accelerometry data can be used together or separately as suitable measures of PA in adolescents.

As one gets older it is natural to see a decline in PA and aerobic fitness. From the literature it is evident that PT and/or LBW subjects experience a greater decline in PA and aerobic fitness than persons born at T and/or with NBW. Elhakeem et al.[103] conducted a study on 2739 males & females born in 1946 and followed this sample from 13-68 years. PA trajectory stratified by BW was examined and included LBW (<2.50 kg) subjects as the referent group for all analyses. It was found that at 13 years of age subjects with a BW in the range of 2.50-4.0 kg were 66-91% more likely to have above average/average ability

in sports compared to participants in the referent group. At a follow-up visit, when participants were now 36-68 years old, this difference was sustained but slightly attenuated in the 3.01-3.50 kg (OR: 1.69, 95% CI: 1.19 to 2.39) and 3.51-4.00 (OR: 1.43, 95% CI: 1.01-2.03) BW categories. In the 2.51-3.0 kg BW category the OR for PA participation was non-significant at 36-68 when compared to the referent group (<2.50 kg). Additionally, Robic-Pickel and colleagues [32] assessed fitness over the adolescent to young adult life span from age 13 to 18 years among 32 VPT, 141 MPT compared to 311 T born peers. Aerobic Fitness was assessed using a timed 600 m run test and results were stratified by sex. VPT and MPT females at 15, 17 and 18 years old recorded significantly higher times ($\pm$ 21 s, $\pm$18 s & $\pm$10 s, respectively) for the 600 m run test than T born females, which indicated poorer aerobic fitness among VPT & MPT females. In contrast male VPT and MPT did not have any significant differences when compared to T born males. In fact, at 14 years old male VPT and MPT adolescents performed better than T born adolescents with a 14 and 7 s reduction in 600 m run time.

In summary, young adults PT with VLBW exhibit greater risk for higher BP and HTN when compared to their term-born NBW peers. The severity of their prematurity and/or BW status has been shown to produce a linear negative correlation with BP and HTN. Due to the rising prevalence of hypertension and hypertension-related morbidities in later adulthood and better birth/survival rates of persons born PT and/or VLBW, it is imperative to develop early lifestyle practices that provide protective effects for these later adult diseases. As predictors of health in later life, PA and aerobic fitness are found to be negatively correlated with BP and HTN outcomes in healthy term-born NBW young adults. Studies illustrating that preterm-born VLBW adolescents and young adults display lower

levels of PA and aerobic fitness, promote the importance for further examination of this population. Thus, an investigation into PA and aerobic fitness in adolescence and BP and HTN outcomes in young adulthood among PT and/or VLBW individuals, may provide evidence for promoting lifestyle changes in adolescence and/or young adulthood to protect against the long-term health issues associated with being born PT with VLBW.

PURPOSE

Based on previous research showing preterm-born VLBW adolescents and young adults to have lower PA and fitness levels and higher BP than their T counterparts, our primary aim was to examine the longitudinal association between PA and fitness in adolescence with measures of BP in young adults born prematurely with VLBW. We hypothesized that:

- PA in adolescence would be inversely associated with BP in young adulthood such that lower levels of PA in adolescence would be associated with higher BP in adulthood.

- Aerobic fitness in adolescence would be inversely associated with BP in young adulthood such that lower levels of fitness in adolescence would be associated with higher BP in adulthood.

A secondary aim was to determine if change in PA from adolescence to young adulthood was associated with change in BP over the same period. It was hypothesized that:

- A decrease in PA from adolescence to young adulthood would be associated a greater increase in BP over the same period.

METHODS

Participants

Participants born between January 1st, 1992 and June 30th, 1996 at the Forsyth Medical Center, Winston-Salem NC, were recruited via letter mail and telephone calls to be part of the first Prenatal Events-Postnatal Consequences (PEPC1) study. Addresses and phone numbers of the participants' parents were retrieved from initial contact between investigators and infants, at 1 year adjusted age. Interested parents and their children were eligible to participate if the child met the following inclusion criteria: 14 years old, BW <1500grams, singleton birth, no major congenital anomalies and evaluation at 1 year adjusted age. A second follow-up study (PEPC2) was conducted at 18-21 years of age on persons who either participated in PEPC1 or were eligible and willing, but unable to attend PEPC1 visits due to schedule conflicts. Participants in PEPC2 were excluded if they had blindness, severe cerebral palsy or diabetes requiring medication or were currently pregnant or pregnant within the past 3 months. For this investigation, participants had to have PA and aerobic fitness data at PEPC1 and PA and BP data at PEPC2 to be included. For other outcomes not related to this study, participants were also excluded from participation in PEPC2 for hypokalemic paralysis (a contraindication for oral glucose tolerance testing).

Measurements and Procedures

Participants and their parents/guardians were asked to come to the Wake Forest University School of Medicine General Clinical Research Center (GCRC) for PEPC1 and the Clinical Research Unit (CRU) of the Wake Forest School of Medicine Translational

Science Institute (TSI) for PEPC2. Informed consent was obtained from parents/guardians in PEPC1 and from the adult participants in PEPC2. Informed assent from the adolescents in PEPC1 was also obtained. Participants were asked to come for three half-day visits for PEPC1 and two half-day visits for PEPC2. Procedures and measurements relevant to this investigation are presented in **Table 1 and 2,** other study measures are also presented.

Table 1. Procedures and measurements at PEPC1 visits.

PEPC 1		
Visit 1	**Visit 2**	**Visit 3**
Measures Related to Thesis		
● Informed consent ● Anthropometric measures ● Resting BP	● Anthropometric measures ● Resting BP ● Questionnaires (general health, demographics and PA) ● Graded exercise test	● Anthropometric measures ● Resting BP
Other Measures		
● Urine sample ● Stage of sexual maturation ● Cold pressor test ● Salivary cortisol pre & post cold pressor test ● BP responsivity to stressors ● HR variability ● Food record collection	● Urine sample ● Stage of sexual maturation ● Salivary cortisol pre & post GXT ● HR variability	● Urine sample ● Stage of sexual maturation ● Motor function ● DXA assessment ● Food record collection

Table 2. Procedures and measurements at PEPC2 visits.

PEPC 2	
Visit 1	**Visit 2**
Measures Related to Thesis	
● Informed Consent ● Anthropometric measures ● Resting BP	● Anthropometric measures ● Resting BP ● Questionnaires (general health, demographics and PA) ● Ambulatory BP & diary
Other Measures	
● Urine sample ● Saliva specimen ● Indwelling venous catheter ● Questionnaires (general health, demographics and PA) ● Standardized 4 day Na diet instructions	● Urine sample ● Continuous non-invasive arterial pressure ● Pressure natriuresis ● Non-invasive vascular lab testing

Anthropometric Measures (PEPC1 & PEPC2)

During each study visit, trained study staff measured the participant's height and weight without shoes and heavy clothing (e.g. jackets, coats, sweaters etc.) using a wall mounted stadiometer and digital platform scale, respectively. Height and weight were measured in triplicate to the nearest hundredth of a centimeter and tenth of a kilogram, respectively, and the average of the three measurements were determined. The average weight and height were used to calculate body mass index (BMI; weight (kg) / height (g) ^{2}). For adolescents, overweight and obesity were defined as a BMI between the 85th and 95th percentile ≥ 95th percentile, respectively. For young adults, overweight was defined as a BMI ranging from 25 up to 30 kg/m^2 and obesity was defined as BMI ≥ 30 kg/m^2.

Resting Blood Pressure (PEPC1 & PEPC2)

For both PEPC1 and PEPC2 resting BP was measured by a trained study nurse or staff, certified in BP measurement according to AHA standards. [18] Participants were fitted with the appropriate sized cuff based on middle upper arm circumference. They were then directed to sit quietly in a room for 5 minutes with their back supported, feet flat on the floor and forearm at heart level. Resting BP was measured in the right arm using both auscultatory and oscillometric methods. A mercury sphygmomanometer and stethoscope were used to obtain three auscultatory BP measurements spaced one minute apart. A Dinamap Pro 100 was used to record five resting oscillometric BP readings (1 minute apart). Averages of the respective BP measurements were used to estimate resting BP at each visit. Study nurses/staff measuring BP were blinded to participants' aerobic fitness and PA levels at PEPC1, as well as PA levels at PEPC2. Furthermore, staff assessing PA and aerobic fitness were not aware of the participant's BP. In young adults, resting BP was considered hypertensive if measured SBP/DBP was 120-129/80mmHg (elevated), $\geq$130/>80mmHg (stage 1 HTN) and $\geq$ 140/$\geq$90mmHg (stage 2 HTN). Auscultatory and oscillometric methods were both measured because mercury sphygmomanometer is generally considered as the gold standard, but oscillometric methods eliminate measurement error by humans. [104–109] Furthermore, current AHA HTN category values are based on oscillometric BP measures. [110,111]

Ambulatory Blood Pressure (PEPC2)

Ambulatory blood pressure (ABP) was assessed using an ambulatory BP monitor (Spacelabs 90207, Redmond, WA). During the second visit of PEPC2 participants were fitted for the appropriate sized BP cuff by a study nurse or staff certified in BP

measurement. The cuff was placed on the nondominant arm. Participants were then instructed to wear the monitor for 24 hours and were given a diary to keep a log of their daily activity as well as awake and asleep times. The monitor was programmed to record daytime blood pressure every 20 minutes between 7am-9pm and nighttime blood pressure every 30 minutes from 9pm-7am. After the collection of ambulatory BP monitors and activity diaries by study coordinators, reported asleep and awake times were inserted to better reflect actual asleep and awake measurements (instead of daytime and nighttime) and results were downloaded. Variables of interest were mean 24 hour systolic and diastolic BP as well as nocturnal SBP dipping (calculated from the difference between the mean awake and asleep ABP expressed as a percentage of the awake mean). ABP was considered valid for mean 24 hour BP if $\geq$ 70% of planned readings were successful, and there were $\geq$ 20 awake and $\geq$ 7 asleep readings. If participants had $\leq$ 20 awake or $\leq$ 7 asleep readings their data for nocturnal dipping was excluded. To determine if ABP was abnormal, categories outlined by O'brien et al.[112] based on AHA definitions were used. Participants were deemed as having 24 hour HTN if the corresponding value of mean 24 hour BP was >130/80 mm Hg. Nocturnal dipping was deemed as abnormal if participants had a percent change from awake to asleep SBP that was <10%. [112]

Habitual Physical Activity (PEPC1 and PEPC2)

Habitual physical activity for the past year was assessed using Kriska's Modifiable Activity Questionnaire (MAQ). The validity and reliability of the MAQ in adolescent populations has been previously reported.[113] At PEPC1, the MAQ was administered by an investigator or trained graduate student directly to adolescent participants, in the presence of parents/guardians if assistance was needed. In both PEPC1 and PEPC2 studies,

participants were read a list of common leisure-time physical activities and asked to select

the activities they engaged in at least 5 times during the past 12 months. Activities not

included in the list could be added. For each selected activity, participants were asked to

state the number of months, average times per month or week, and average duration

(minutes) per time. The hours were summed and divided by 52 to determine the average

total hours per week (TOT-hrs/wk) of PA for the past year. Information about intensity was

obtained from the participant and assigned a MET value using the Ainsworth's

Compendium. Time spent engaging in activities with an intensity > 6 METS was summed

and divided by 52 to obtain the average participation in vigorous activities in hours per

week (VIG-hrs/wk) for the past year.

Aerobic Fitness (PEPC1)

Aerobic fitness was assessed at the 2nd visit by having participants perform a

progressive, maximal exercise test on an electronically-braked cycle ergometer following

the Godfrey protocol. After a 5 minute seated rest on the cycle ergometer, baseline BP and

HR values were recorded, and then participants were asked to begin pedaling at zero Watts

for the first minute. The work rate was increased each minute based on the participant's

height. A height of <125 cm, 125-150 cm, >150 cm resulted in a 10, 15 and 20 increase in

Watts, respectively. Participants were instructed to maintain a pedaling rate of 50-60

revolutions per minute without exceeding 70 revolutions per minute. Expired gas volumes

and concentrations were measured using the VMAX Encore Metabolic Cart (Viasys

Healthcare Incorporated). Studies have shown that very few children and adolescents

demonstrate a plateau in oxygen consumption to establish a VO_2 max during exercise tests.

[114–118] Therefore, a more reliable measure of max oxygen consumption (VO_2peak) in

adolescence was used. [114,115,119] VO_2 peak was calculated using the highest 30 second average obtained during exercise. During the test a 12 lead ECG was used with heart rate recorded every minute and BP recorded every 2 minutes. Participants were also verbally encouraged to exert maximal effort. The test was considered "maximal" 1) heart rate >195 beats per minute, 2) respiratory exchange ratio >1.05, and/or 3) two experienced testers agreed that the participant gave a maximal effort.

Neonatal Characteristics

Neonatal data such as BW, and GA, and antenatal steroid exposure were obtained from medical records at the Forsyth Medical Center and Brenner's Children Hospital (Wake Health).

Statistical Analysis

SPSS (version 27) was used to conduct statistical analyses. Normal distributions of data were determined using descriptive statistics and measures of central tendency. Between-group differences for BP variables were analyzed using a Student's t-test, or Mann-Whitney U test if data were not normally distributed. Chi-squared analysis was performed to compare frequencies and proportions for categorical variables. Pearson's correlation coefficients were determined to examine the longitudinal association between PA and aerobic fitness in adolescence and BP and HTN in young adulthood. If data were not normally distributed or linearly related, the Spearman's rank-order analysis was used.

RESULTS

Participant Recruitment

As shown in **Figure 4**, at 14 years old 193 participants enrolled in the PEPC1 study. Five participants were excluded for not meeting eligibility criteria. Out of the remaining 188 participants at PEPC-1, 28 had no visit two and 12 were lost to follow-up at PEPC2. In the current analyses, six participants were excluded for missing (3) or unreliable PA data (3) at adolescence. A total of 142 participants with PA data at 14 years of age and BP measures in young adulthood were included.

701 PT/VLBW infants born between 1/1/ 1992 – 6/30/1996

222 Did not meet inclusion criteria
153 No follow-up
21 Died
19 Anomalies
15 Adopted /ward of state
12 Current health problems
1 Non english speaking
1 Requested no contact

479 Met inclusion criteria

286 Not enrolled
166 Not located
95 Interested but not able to be enrolled
25 Not interested

5 Excluded
2 Twins
1 Chromosomal abnormality
1 Polycystic Kidney Disease
1 Severe CP

193 Enrolled

188 Included at 14 years

40 Excluded
28 No PEPC1 visit
12 Lost to follow-up

PA data at 14 years
3 No V2
3 unreliable report

Exercise test data at 14 years
7 No V2
5 tech problems
4 abnormal ECG
3 submax effort

148 participated in PEPC1 and PEPC2

142 with valid PA data at 14 yrs and resting BP in adulthood
- - - - - - - - - - - - -
131 with valid aerobic fitness data at 14 years

90 with valid 24h ABP data in young adulthood
- - - - - - - - - - - - -
108 with valid ABP dipping data in young adulthood

24h ABP data in young adulthood
26 Successful readings <70%
21 No V2 or ABP not measured
5 Sleep readings < 7

BP dipping data
21 No V2 or ABP not measured
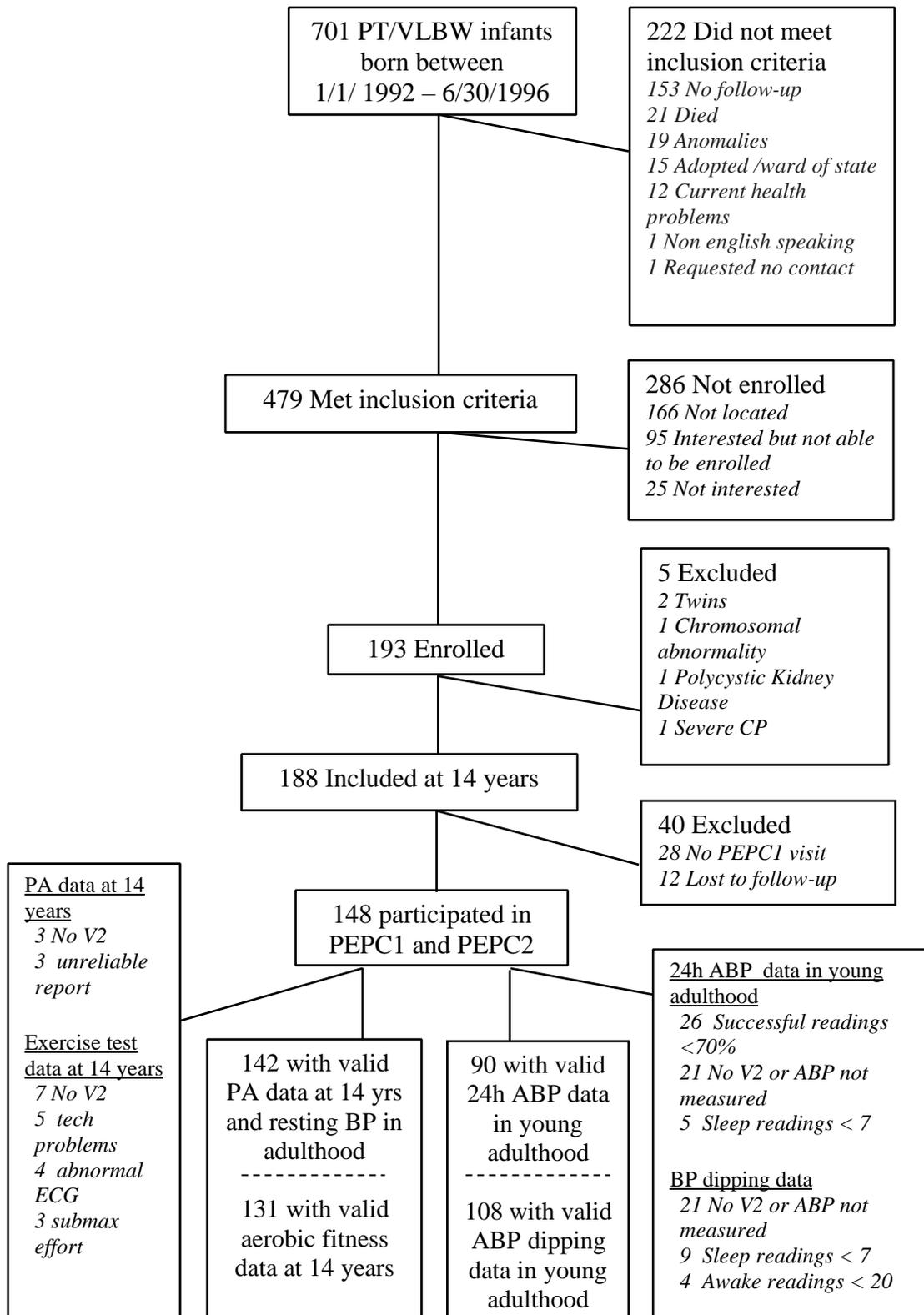*9 Sleep readings < 7*
4 Awake readings < 20

Figure 4. Consort Diagram

Participant Characteristics

Participant characteristics are shown in **Table 3.** Although participants were required to be VLBW for inclusion, all were also PT. At birth, the mean gestational age was 27.8 ± 2.8 weeks and the mean birthweight was 1048.9 ± 274.0 grams with no sex differences. At 14 years of age, males were significantly taller but not heavier than females ($p<0.05$). Thirty-five percent of participants were found to be overweight (BMI $\geq$85th percentile) or obese (BMI $\geq$95th percentile) with no significant difference between sexes. Males had significantly higher resting SBP (both auscultatory and oscillometric) than females (mean difference, 4.6mmHg CI:1.5 to 7.7 and 5.6mmHg, CI:2.5 to 8.8, respectively). Diastolic BP did not differ significantly between males and females ($p>0.05$). There were 14 participants (10 male, 4 female) found to have elevated SBP (120-129 mmHg) at adolescence. Chi-squared analysis showed that males had a significantly higher proportion of elevated SBP ($X^2=6.66$; $p<0.05$). No participants at adolescence were found to have diastolic HTN.

Table 3. Participants' characteristics at birth and at 14 years of age by sex [†].

	Total Sample (n=142)	Male (n=56)	Female (n=86)
Birth			
Black Race, n (%)	64 (45.1)	27 (48.2)	37 (43.0)
Gestational age, weeks	27.8 ± 2.8	28.1 ± 2.9	27.7 ± 2.8
Birth weight, g	1048.9 ± 274.0	1089.0 ± 261.4	1022.7 ± 280.3
Birth weight, z-score	-0.296 ± 0.860	-0.400 ± 0.943	-0.228 ± 0.801
Adolescence			
Age, years	14.5 ± 0.3	14.5 ± 0.3	14.5 ± 0.3
Height, cm*	160.7 ± 8.7	165.9 ± 8.5	157.3 ± 7.1
Height, z-score*	-0.427 ± 1.082	-0.147 ± 1.020	-0.609 ± 1.088
Weight, kg	59.8 ± 17.6	63.1 ± 19.1	57.7 ± 16.3
Weight, z-score	0.360 ± 1.294	0.494 ± 1.367	0.27 ± 1.24
BMI, kg/m^2	23.1 ± 6.1	22.8 ± 6.0	23.3 ± 6.2
BMI, percentile	62.95 ± 31.74	61.78 ± 32.28	63.71 ± 33.49
Auscultatory BP			
SBP, mmHg*	104.0 ± 9.3	106.8 ± 9.5	102.2 ± 8.8
DBP, mmHg	60.1 ± 9.4	59.6 ± 10.1	60.4 ± 9.0
Oscillometric BP			
SBP, mmHg*	107.9 ± 9.2	111.31 ± 10.0	105.7 ± 8.1
DBP, mmHg	59.2 ± 5.7	58.6 ± 5.8	59.6 ± 5.6

[†]Values presented are means ± (SD) or n (%).

*$p < 0.05$ from independent t-test comparison between males and females.

Physical Activity and Aerobic Fitness in Adolescence

Adolescent PA and aerobic fitness data are reported in **Table 4.** As previously stated, PA data were summed and averaged for the previous 52 weeks to reflect total PA (TOT-hrs/wk), as well as average time spent engaging in vigorous (> 6 METs) PA (VIG-hrs/wk) in the past year. Data were not normally distributed, even after various transformations, so the Mann-Whitney U test was used to make between-group comparisons. For males, participation in both total and vigorous PA was significantly higher when compared to females (11.59 vs 5.45 TOT-hrs/wk and 3.61 vs 0.24 VIG-hrs/wk; $p<0.05$).

Aerobic fitness was measured using VO_2peak expressed in mL/kg/min. Eleven participants were excluded in the aerobic fitness analyses due to missing data (7), technical problems (5), cardiac related contraindications to testing (4) or submaximal effort (1). Data for VO_2peak measures were normally distributed and comparisons between groups were conducted using the independent t-test. A significant difference between males and females was reported for VO_2peak, with males having a 10.7 mL/kg/min higher mean VO_2peak compared to females.

Table 4. PA and Aerobic Fitness at 14 years of age by sex.

	Total (n = 142)	**Male** (n = 56)	**Female** (n = 86)
Physical Activity[†]			
Total PA, TOT-hrs/wk*****	8.46 (4.00, 14.37)	11.59 (7.76, 20.16)	5.45 (2.61, 12.90)
Vigorous PA, VIG-hrs/wk*	0.77 (0.00, 3.30)	3.61 (0.70, 8.12)	0.24 (0.00, 1.62)
Aerobic Fitness[‡ §]			
VO$_2$ peak, mL/kg/min*****	36.89 ± 10.02	43.61 ± 10.20	32.87 ± 7.47

[†]PA variables presented as medians (25th, 75th percentile).

[‡] VO$_2$ peak presented as means ± (SD).

[§]VO$_2$peak total n=131, male n=49, female n=82.

[*]$p<0.05$ from comparison between males and females.

Characteristics in Young Adulthood

Participants' characteristics in young adulthood are presented in **Table 5.** Males were taller and weighed more than females, but BMI did not differ. A total of 61 participants (43% of final sample) were found to be either overweight (16.2%) or obese (26.8%). When stratified by sex, percent overweight or obese did not differ between males and females.

Table 5. Participants' characteristics at young adulthood by sex [†].

	Total (n=142)	**Male** (n=56)	**Female** (n=86)
Age, years*	19.7 ± 0.8	19.6 ± 0.5	19.8 ± 0.9
Height, cm*	164.2 ± 10.1	172.3 ± 8.9	159.0 ± 6.9
Weight, kg*	70.1 ± 21.2	76.0 ± 21.6	66.2 ± 20.0
BMI, kg/m^2	25.9 ± 7.3	25.5 ± 6.5	26.2 ± 7.8

[†]Values presented are means ± (SD).

*$p < 0.05$ from independent t-test comparison between males and females.

Resting BP in Young Adulthood

Participants' resting and ambulatory BP measured in young adulthood are presented in **Table 6.** Resting BP data was also found to be normally distributed using the Shapiro-Wilk test. Males had significantly higher auscultatory (mean difference: 4.8mmHg) and oscillometric (mean difference: 4.7mmHg) SBP than females. In contrast, DBP did not differ between sexes using either method. Although mean auscultatory and oscillometric BP data for the total sample and stratified by sex were found to be within normotensive range, some participants were found to have elevated BP or HTN according to the categories outlined by AHA. Using oscillometric BP readings (upon which AHA cut points are based)[110,120] 23 participants (16 males and 7 females) were found to have elevated SBP (120-129 mmHg). In addition, four males and two females exhibited stage 1 HTN for SBP and one male had stage 2 systolic HTN. Results of the X^2 analysis showed that males had a higher proportion of abnormal SBP ($\geq$120 mmHg) than females ($X^2 = 14.88$; $p < 0.05$). There was only one case of abnormal DBP ($\geq$80 mmHg)in the sample, for a female participant, therefore, no sex differences were found.

Table 6. Resting BP in young adulthood [†].

	Total	**Male**	**Female**
Auscultatory BP			
Sample, n	141	56	85[‡]
SBP, mmHg*	110.2 ± 8.7	113.1 ± 9.0	108.25 ± 8.0
DBP, mmHg	71.1 ± 7.6	72.0 ± 8.7	70.5 ± 6.8
Oscillometric BP			
Sample, n	142	56	86
SBP, mmHg*	112.1 ± 10.2	115.0 ± 11.0	110.3 ± 9.3
DBP, mmHg	64.8 ± 5.9	64.2 ± 6.0	65.1 ± 5.8

[†]Values presented are means ± (SD).
[‡]Participant arm too large for auscultatory BP cuff.
*p<0.05 from independent t-test comparison between males and females.

Ambulatory BP in Young Adulthood

For ambulatory BP, we examined mean 24 hour SBP and DBP and nocturnal dipping, derived from percent change from awake to asleep for SBP. As shown in Figure 4, for 24 hour BP, 31 participants did not meet the criteria for inclusion (>70% successful ABP readings, n=26 and <7 asleep ABP readings, n=5), and 21 did not have data. Mean 24 hour SBP values were found to be higher among males when compared to females (121.7mmHg vs 114.9mmHg, p<0.05) as shown in **Table 7.** Based on AHA guidelines,[18] 8 cases (4 males and 4 females) of 24 hour SBP HTN (≥130 mmHg) and 2 cases (all males) of 24h DBP HTN (>80 mmHg) were found. The proportion of participants with 24 hour SBP and DBP HTN did not differ by sex (24 hour SBP; X^2=0.80, 24 hour DBP; X^2=1.13, p>0.05). One hundred and eight participants (43 male) had valid awake and asleep readings

(see **Figure 4** for nocturnal dipping exclusion criteria). Percent change in SBP from awake to asleep was < 10% in 14 males (13%) and 30 females (28%) classifying them as non-dippers. However, when using Chi-squared analysis, mean percent change and the proportion of non-dippers vs. dippers did not differ by sex ($X^2=1.98$, $p>0.05$).

Table 7. 24 hour ambulatory BP and nocturnal BP dipping in young adulthood[†].

	Total	**Male**	**Female**
24 Hour Ambulatory BP			
Sample, n	90	32	58
SBP, mmHg*	117.3 ± 8.4	121.7 ± 7.4	114.9 ± 8.0
DBP, mmHg	68.1 ± 5.5	67.3 ± 5.2	68.6 ± 5.6
Nocturnal BP Dipping			
Sample, n	108	43	65
SBP % change	10.8 ± 5.0	11.4 ± 5.3	10.4 ± 4.9

[†]Values presented are means ± (SD).
*$p<0.05$ from independent t-test comparison between males and females.

Longitudinal Analyses

PA and Aerobic Fitness with Resting BP

In view of the sex differences in PA, aerobic fitness, and resting BP, we stratified our analyses by sex. Due to the non-normal distribution of the PA data, we examined the associations between adolescent PA and resting BP in young adulthood using Spearman's rank-order correlational analysis. There were no significant associations between PA and resting BP variables ($p<0.05$) measured by either auscultatory or oscillometric methods. In contrast, Pearson correlational analysis revealed significant associations between VO_2peak

and auscultatory BP as shown in **Figure 5.** (p<0.05). For both males and females, VO$_2$peak was inversely associated with auscultatory SBP (r= -0.38 and r= -0.25 for males and females respectively). However, the association between VO$_2$peak and auscultatory DBP was significant in females (r= -0.26, p<0.05) but not in males (**Figure 6**). Similarly, for oscillometric measures of SBP, the correlation with VO$_2$peak was significantly associated in females (r= -0.37, p<0.05) , but not in males (r= -0.12, p>0.05).
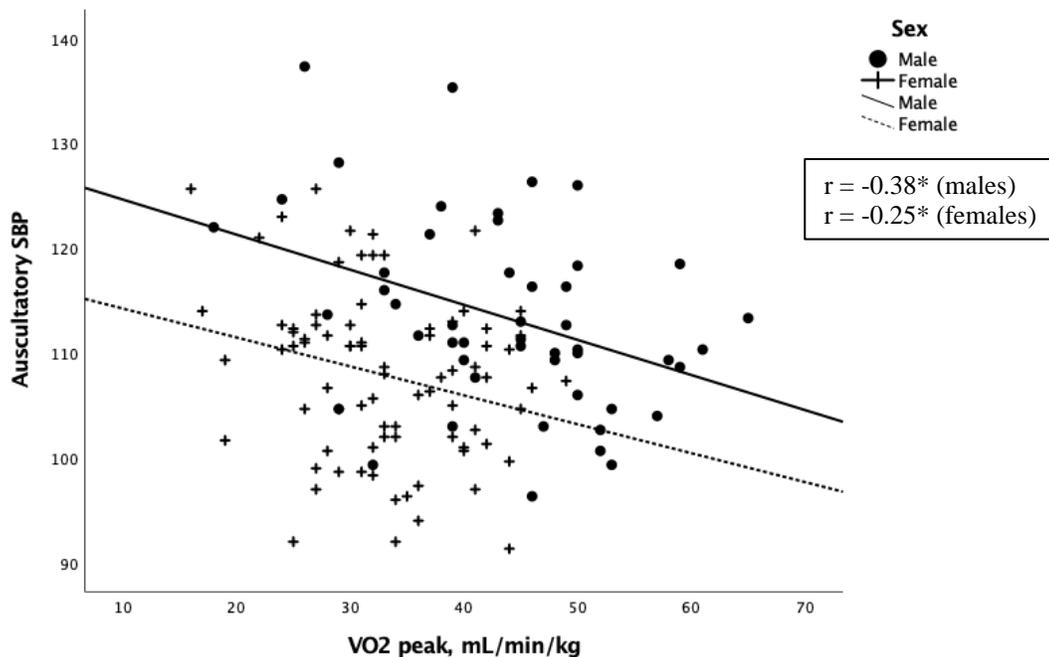

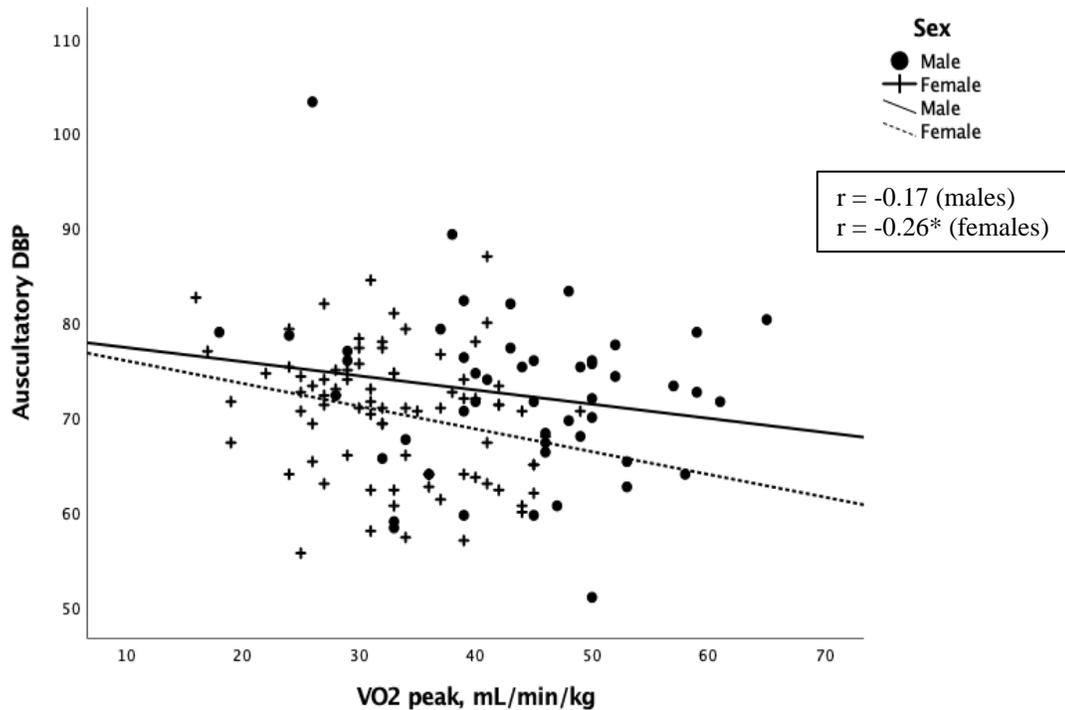**Figure 5.** Correlation between adolescent VO2 peak and auscultatory SBP in young adulthood. *p<0.05

Figure 6. Correlation between adolescent VO2 peak and auscultatory DBP in young adulthood. *p<0.05

<u>PA and Aerobic Fitness with ABP</u>

We also examined the associations between adolescent PA and aerobic fitness with ambulatory BP in young adulthood stratified sex. For both males and females, neither total nor vigorous PA were associated with 24 hour BP or nocturnal dipping. Similarly, VO_2peak was not associated with mean 24 hour SBP or DBP for either sex. However, in females, but not males (r= 0.23, p>0.05), VO_2peak was directly associated with SBP dipping (r= 0.33, p<0.05), in that higher fitness was associated with greater nocturnal dipping for SBP, shown in **Figure 7.**
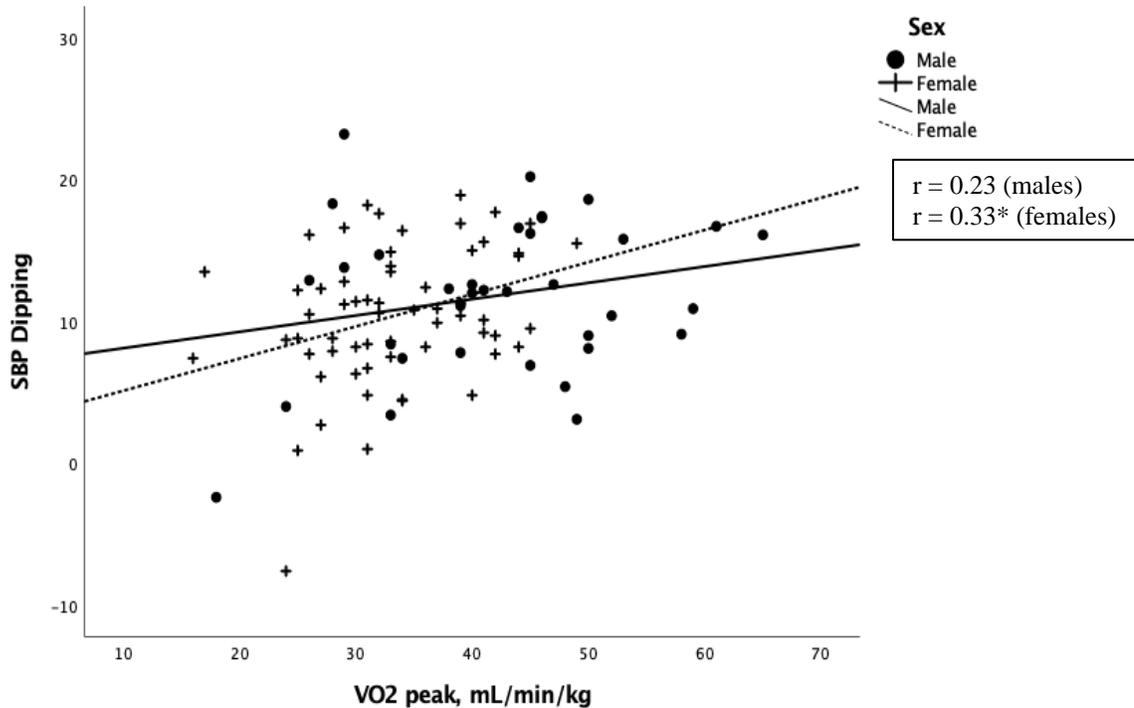
Figure 7. Correlation between adolescent VO2 peak and nocturnal SBP dipping in young adulthood. *p<0.05

Associations Between Change in Habitual PA (Δ PA) and Change in Resting BP (Δ BP)

We also wanted to determine if Δ PA was associated with Δ BP. In both males and females, participation in total PA decreased significantly (p<.05) from adolescence to young adulthood (median, 25th to 75th percentile; -4.84, -9.37 to -1.58 and -2.07, -7.23 to 1.14 for males and females, respectively). As shown in **Figure 8**, a decrease in total PA was significantly associated with an increase in oscillometric DBP but only in males (r= -0.332, p<0.05). As shown in **Figure 9**, there was also a trend for the decrease in total PA to be associated with an increase in SBP in males only (r= -0.25, p=0.08). In females, no associations between change in ΔPA and Δ BP were significant (SBP r= -0.05, DBP r= -0.01; p>0.05).

30

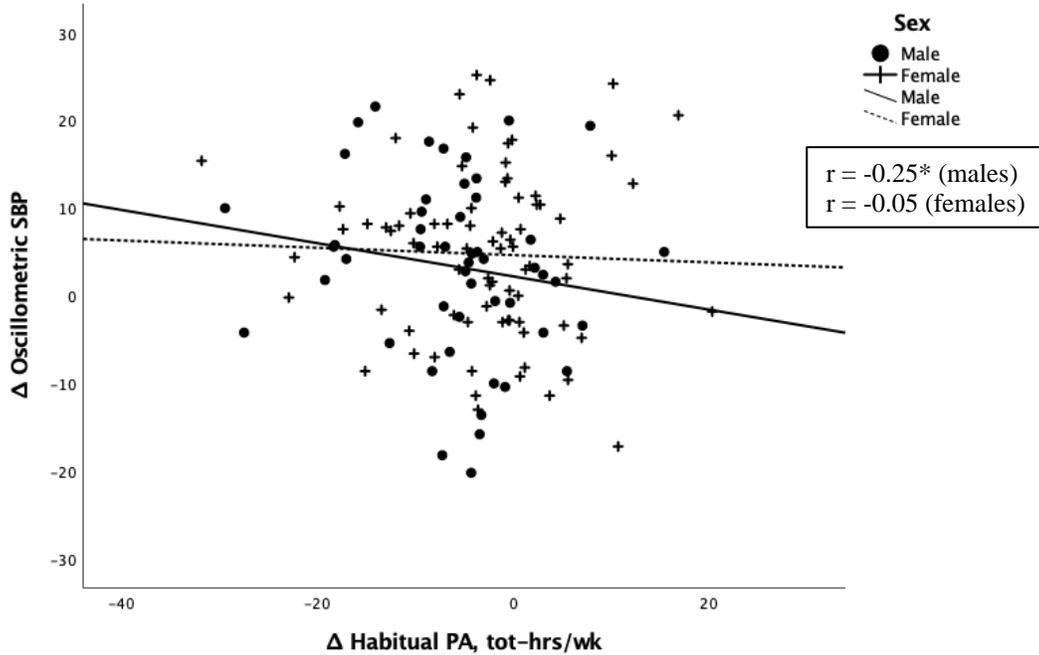**Figure 8.** Correlation between Δ total PA and Δ oscillometric SBP from adolescence to young adulthood. *p<0.05
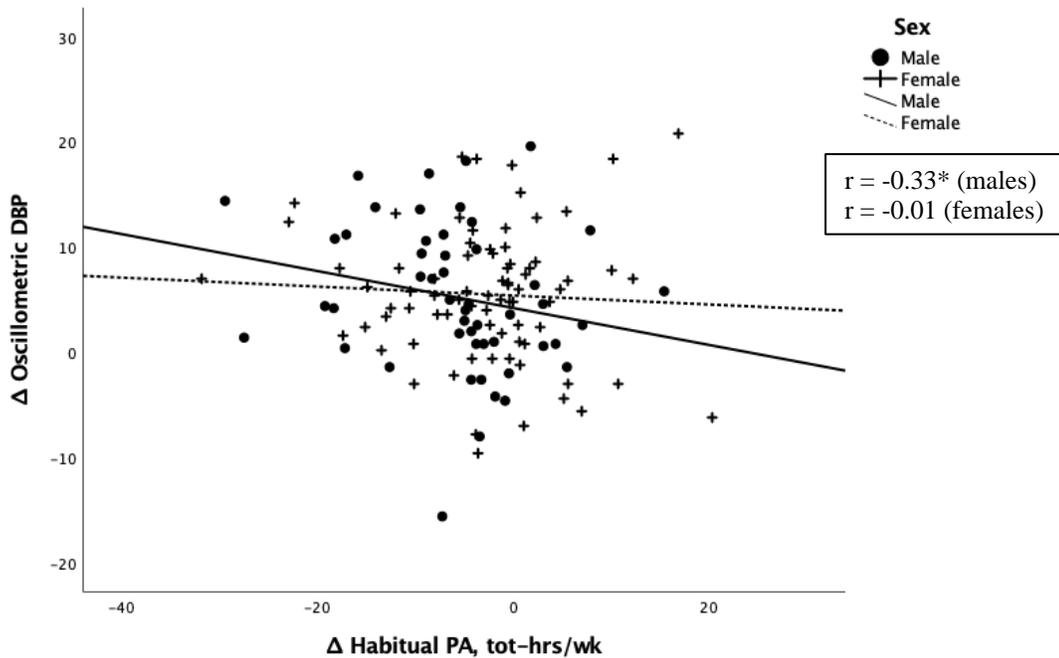

Figure 9. Correlation between Δ total PA and Δ oscillometric DBP from adolescence to young adulthood. *p<0.05

DISCUSSION

Our study demonstrated a significant association between adolescent aerobic fitness and blood pressure in young adulthood, such that higher aerobic fitness was associated with lower SBP in both males and females, and DBP in females only. In contrast, we found no association between PA levels in adolescence and later BP. To our knowledge, this is the first study to examine the longitudinal associations between fitness and PA with later BP in a sample of young adults born preterm-born VLBW who have increased risk for developing hypertension.

The results of our study showing an inverse correlation between fitness in adolescence and blood pressure in young adulthood is inconsistent with some,[89,121] but not all [87,91,92] studies examining this association in the general (not PT) population. A meta-analysis by Garcia-Hermoso et al. [92] with pooled results of 7 studies (n=3895) reported no association between lab-tested fitness with SBP and DBP(-0.02 and r= -0.03, respectively; p>0.05). Likewise, Hasselstrom et al.[121] found no association between adolescent aerobic fitness and later BP at ~25 years of age. Somewhat contrary, to the findings of these authors and our study, Twisk et al.[89] found a positive association (β= 0.25) such that higher aerobic fitness in adolescence was associated with higher SBP at 32 years of age in both males and females.

Our results are consistent with other studies in the existing literature. Hamer et al.[91] found aerobic fitness (estimated at 10 years of age) to be inversely associated with SBP at 46 years of age in females (β= -0.3, 95%CI: -4.3 to -1.7) but not males (β= -0.2, 95%CI: -1.5 to 1.0). In contrast, Kvaavik et al. [87] found an inverse association (r=-0.15) between VO$_2$peak in early adolescence and BP at age 25 years old, but only for DBP. Statistical

significance found in these studies likely reflects the larger sample sizes, in view of the relatively weaker correlation coefficients. Despite our smaller sample size and enrollment of males and females compared to previous studies, the correlations found in our study (SBP; r=-0.38 for males, r= -0.25 for females and DBP; r=-0.37 for females) were relatively stronger.

The higher correlations we observed between aerobic fitness and BP may be due to their relatively higher BP. There is evidence that the protective effect of aerobic fitness is greater in subjects that are already hypertensive, [122] and the beneficial effects of having lower BP within normal limits is not known. As PT and VLBW adolescents and young adults are more likely to have higher BP and greater risk for HTN compared to their term-born NBW peers[3,4,8], the association between fitness and later BP may appear stronger and earlier in adulthood. A study by Carnethon et al.[26] found that at 18 years old, relatively healthy/normal participants (2029 men, 2458 women) with low aerobic fitness (0.2 - ≤6.4 and 1.9 - ≤10 treadmill minutes in men and women, respectively) were 2-3 times more likely to have HTN defined by a SBP >140mmHg and a DBP >90mmHg as middle aged adults (43-45 years old) with high aerobic fitness (>8.6 and >10 treadmill minutes in men and women, respectively). Additionally, participants in the study by Carnethon et al.[26] had diverse backgrounds and ethnicities similar to our cohort. In comparison to our findings, this study shows that associations between aerobic fitness and HTN may track more closely from young adulthood to middle-age. Since, 21% (n=30) of our sample had elevated systolic blood pressure (>120mmHg) at approximately 20 years old, based on the well documented findings of BP trajectory [123] their BP is only expected to increase as they get

older. This makes the protective effect/inverse association even more important to reduce HTN risk in our study population.

The apparent sex differences found in our study are possibly due to the timing of the fitness assessment, relative to growth and development. It has been shown that girls reach their peak VO_2 around age 14, whereas males generally reach their peak around age 16-18. [124] This may be explained by the fact that, at 14 years of age, most girls will have gone through puberty, whilst puberty in boys is in the early stages. [125] Consequently, 14 years of age may not be the best time to assess the association between aerobic fitness and later BP in males.

We also examined 24-hour ambulatory BP in our sample. Neither PA nor aerobic fitness in adolescence was found to be associated with the mean 24 hour SBP or DBP in young adult males or females. This may be due to other factors that influence blood pressure throughout the day such as PA, stress from work, alcohol consumption, smoking etc. In contrast, we did observe a significant positive correlation between aerobic fitness and nocturnal SBP dipping; however, the association (r=0.30) was only significant in females. Nocturnal dipping < 10% is considered abnormal and associated with increased risk for CVD and kidney disease.[126,127] A primary contributing factor to this association is increased sympathoadrenal activity. A study by Sherwood et al.[128] found that catecholamines were significantly higher in non-dippers compared to dippers (norepinephrine dippers= 9.3 vs 13.1 g/mg, epinephrine dippers= 2.7 vs 4.0 g/mg). The vasoconstrictive effect of increased sympathoadrenal activity results in high systemic vascular resistance during asleep.[128] Additionally, other studies[129,130] have found non-dipping to be associated with greater left ventricular mass and wall thickness in adults and

34

adolescents, presumably due to the persistently elevated BP at night. [129] In view of the findings that 13% of males and 28% of females in our sample dipped less than 10%, further evaluation of their heart structure may be warranted.

The beneficial effects of aerobic fitness on later BP may be partially explained by its effects on systems involved with BP regulation. As previously mentioned elevated sympathoadrenal activity is associated with higher BP. Several studies suggest that higher aerobic fitness is associated with lower circulating levels of catecholamines at rest and during submaximal PA. [131–133] Higher aerobic fitness has also been found to be associated with lower levels of circulating Ang II. [134,135] Ang II is a product of the RAS and is known to have potent vasoconstrictive effects, increasing BP. Ang II also stimulates the release of anti-diuretic hormone (increasing water reabsorption by kidney) as well as the release of aldosterone (increasing sodium reabsorption by kidney) both increasing blood volume and subsequently BP.[136,137] Ang II is also associated with endothelial dysfunction mediated by an increase in reactive oxygen species and a decrease in NO bioavailability.[138] Several studies show the beneficial effects of aerobic PA and fitness on endothelial function associated with higher levels of NO resulting in vasodilation and lower BP. [83–85] Additionally, aerobic fitness has also been found to promote glucose uptake by the muscles during exercise, thereby increasing insulin sensitivity.[21] These biological adaptations associated with higher aerobic fitness may help to explain the inverse association between fitness and BP that we observed in our study sample.

In contrast to aerobic fitness, PA in adolescence was not associated with BP in young adulthood. This is consistent with the studies of Kvaavik et al.[87] and Hasselstrom et al.[121] who found no correlation between adolescent PA and BP in young adulthood. The

lack of associations in findings may be due to the subjective nature of self-report PA questionnaires. It is very likely that recall error for PA over the past year will occur as this is a long time-frame. The lack of association we found between adolescent vigorous PA and later BP in our study may be due to the fact that many participants (>50%), especially females, reported not engaging in any vigorous PA. However, we did find an association between change in total PA and change in BP in males only. Increase in PA from adolescence to young adulthood was associated with a decrease in DBP (r= -0.32, p <0.05), and a trend towards a decrease in SBP (-0.25, p =0.08). This finding is inconsistent with those of Hasseltrom and colleagues[121] who reported no association between change in PA and change in BP at 15-19 years to ~25 years of age in both males and females.

In our sample, based on oscillometric measures of BP and standard criteria, forty of our participants (27 male) had abnormal readings (either resting BP or ABP), and 17 (11 males) met criteria for hypertension for resting (n=7) and 24 hour HTN (n=10). As BP has been shown to track fairly well [123], the incidence of HTN is likely to increase as our participants mature. This is supported by the study by Carthenon et al.[26] in which lower fitness at 18 years of age was associated with a 2-3 times greater likelihood of developing HTN in middle age.

The strengths of our study include the longitudinal design and a sample that is racially and ethnically diverse. Based on their birth occurring between 1992-1996 they benefited from more modern advances in their neonatal care (e.g. surfactant and antenatal steroid therapies), but are also exposed to an obesogenic environment, making more generalizable to current day cohorts born PT with VLBW. Furthermore, 79% of the participants at PEPC1 (adolescence) returned for evaluation at PEPC2 (young adulthood).

We also followed AHA guidelines [18] and trained study nurses and other research personnel for the measurement of BP. Our use of multiple measurements of BP over multiple days as well as ABP monitoring, provided a more accurate representation of their BP and classification of HTN status. We also used the gold standard for determining aerobic fitness by measuring peak oxygen consumption. Furthermore, study personnel were blinded to the participants' PA and aerobic fitness levels when assessing BP, and personnel measuring PA and fitness were blinded to the participants' BP.

Despite the many strengths, this study is not without limitations. As previously stated self-reported PA is subject to recall error, especially for longer recall time frames (≥ 1 year). The use of an objective measure of PA such as accelerometry might provide a better picture of short-term PA but may not reflect an accurate reflect their habitual PA. The measurement of fitness only in adolescence limits our ability to observe dynamic changes in fitness and subsequent associations with BP as they mature. Although our study retention was listed as a strength, the 21% attrition in our study may introduce some lost-to-follow-up bias. Regarding ABP, only 90 out of 142 participants had valid 24 hour data, consequently the results for that outcome may not be representative of the population from which the sample was drawn. Lastly, our analyses did not include measures of other potential confounders such as maternal HTN and socio-economic status which may affect the association between adolescent aerobic fitness and later BP.

CONCLUSION

Our findings provide evidence of early development of elevated BP in a young adult sample born PT with VLBW. As BP tracks over time, the likelihood of developing HTN increases as they mature, thus warranting closer clinical follow-up. We also demonstrated an inverse association between aerobic fitness in adolescence and BP in young adulthood. As fitness can be improved via regular participation in vigorous PA, future research should employ a randomized control trial to determine the effects of PA and aerobic fitness on BP and other health outcomes in this at risk preterm-born VLBW population.

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ANTENATAL STEROIDS AND BLOOD PRESSURE IN CHILDHOOD

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INTRODUCTION

Your child is being invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. Your child may or may not receive any benefit from being part of the study. There may also be risks associated with being part of research studies. Your child is being asked to take part in this study because of being born either prematurely or close to their due date. Your participation is voluntary. Please take your time to make your decision, and ask your study doctor or the study staff to explain any words or information 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 is to study the long term effects of antenatal steroids (a steroid shot given to pregnant mothers to help the baby's lungs mature) on blood pressure during childhood.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 230 prematurely born children and 50 children born near their due date will take part in this study. This study is being done at Wake Forest University Health Sciences.

WHAT IS INVOLVED IN THE STUDY?

This study involves 3 visits during a 12 month period.

Each visit will begin in the General Clinical Research Center and will include the following:
1. Your child's arm circumference (the measured distance around the arm), height and weight will be measured.
2. Your child's blood pressure will be measured multiple times while seated in a chair.
3. You will be asked to complete questionnaires.
4. Your child will be asked to complete questionnaires.

5. Your child will be asked to complete a form with pictures of the different stages of puberty to identify the stage of sexual development that he or she is in. This will be done in private and placed in a sealed envelope to avoid any embarrassment.

The visits will last about 1/2 day and are outlined as follows:

Visit 1

1. Your child will be asked to provide a sample of urine during the visit. If your child needs to use the restroom prior to obtaining consent from you and assent from your child, we will collect the urine but hold it until you consent and your child assents to participate in the study.
2. A sample of saliva (spit) will be obtained by asking your child to spit into a container.
3. Another sample of saliva (spit) will be obtained by asking your child to chew a piece of sugarless gum and then spit into a container.
4. Then we will ask your child to lie on a bed and we will monitor his/her heart rate, breathing, and blood pressure. Next, a plastic bag of ice and water will be placed on your child's forehead for one minute. We will continue to measure your child's blood pressure response with an arm cuff until it returns to the resting level. While measuring your child's blood pressure change in response to the cold, we will also monitor his/her heart rate with an EKG and monitor the respiratory rate with a strap around your child's stomach. (The way a person's blood pressure responds to the cold sensation may be predictive of their blood pressure in later life.)
5. Another sample of saliva (spit) will be obtained by asking your child to chew a piece of sugarless gum and then spit into a container.
6. You and your child will meet with a nutritionist in the General Clinical Research Center to learn how to keep the 3 day food record. (This may be moved to the second or third visit if necessary.)
7. At the end of Visit 1, we will give your child supplies and instructions for collecting their first morning urine. Your child will collect this urine in the morning of a subsequent study visit and bring this urine sample to that appointment.

Visit 2

1. Your child will collect their first morning urine and bring this sample with them to Visit 2.
2. **If** your child was unable to provide a urine sample at Visit 1, your child will be asked to provide a sample of urine during Visit 2.
3. A sample of saliva (spit) will be obtained by asking your child to chew a piece of sugarless gum and then spit into a container.
4. We will ask your child to lie on a bed while we monitor heart rate with an EKG, blood pressure with an arm cuff and finger strap, and breathing with a strap around your child's stomach.

5. Your child will be escorted to the lab where the exercise test will take place. Prior to the exercise test we will obtain baseline lung function or breathing tests. Your child will then perform the exercise test on a stationary bicycle. The test will start out very easy like riding on level ground. Each minute the test will get progressively harder, like riding up a steeper and steeper hill. Your child will be encouraged to give a maximal or best effort. During the test you child will breathe through a mouthpiece and wear nose clips so that we will measure the air your child breathes out. Your child's heart rate will be monitored with an EKG and oxygen levels in the blood will also be monitored using a pulse oximeter, which is a plastic clip with a red light that sees through the skin on the finger. (No blood is drawn.)
6. After the exercise test is over, your child will lie on a bed while we monitor their heart rate. Next we will have your child repeat the breathing tests. We will give your child a breathing treatment with a bronchodilator, Albuterol, a medicine that opens airways. This will treat any bronchoconstriction (tightening of the airways) that may have occurred with exercise.
7. We will repeat the breathing tests to make sure they return to the baseline levels.
8. Another sample of saliva (spit) will be obtained in the same way.

Visit 3

{Your child will need to collect a first morning urine sample and bring it with them to the Visit 3 appointment **IF** this was not done at Visit 2.}

1. Your child will be asked to provide a sample of urine at the beginning of the visit. If your child is female, she will be required to provide a urine sample before the DXA scan (described below) to rule out pregnancy. Even though the radiation is very small, it may be harmful to an unborn baby. The results of the pregnancy test that is performed on your child will be kept confidential and you will not be told the results unless your child agrees to share this information with you, unless there is a medical problem for which we need to receive parental consent to treat, or if medical care is needed from another physician.
2. Your child will have measurements made of skin thickness with calipers and a measurement of the waist with a tape measure.
3. Your child will be asked to perform several game-like tasks assessing coordination such as throwing and catching a ball, walking on line, balancing on one leg on a low (2 ½ inch high) balance beam, and copying a square. These tasks will take about 15 minutes to complete.
4. Your child's body composition will also be measured by a dual energy x-ray absorptiometry (DXA) scan. You will be escorted to the Sticht Center (a 5 minute indoor walk) for this test. During the DXA scan, your child will be asked to lie very still on a table for approximately 5 minutes while the machine makes an image of your child's total body. The scan exposes your child to a very small amount of radiation, similar to the radiation from playing outside on a couple of sunny days.
5. Your child will have approximately 2 Tablespoons of blood withdrawn from a vein at this visit. To decrease the pain often felt with a needle stick, a numbing cream will be

applied 30 minutes prior to the needle stick. Your child can still participate in the study if he/she doesn't want to participate in the blood sampling part.

6. Some people have elevated blood pressure when they are in the doctor's office or clinic but normal blood pressure at home. This is called "White Coat" hypertension. To check your child's blood pressure during normal activities your child will be fitted with an ambulatory blood pressure monitor. This monitor will be worn home and kept on for 24 hours (all day and all night) if possible. It consists of a blood pressure cuff and a small box that is worn on a strap like a purse or clipped onto the belt. The cuff will inflate every 20 minutes during the day and every 30 minutes at night. We will ask you and your child to keep a record of the activities your child participates in while wearing the monitor. The ambulatory blood pressure monitor will have to be returned to the GCRC after use. You may pull your car into a special drop off area that we will point out to you or if you live outside of Winston-Salem you may mail it back.

(The order of Visit 2 and Visit 3 study appointments may be reversed if needed to accommodate scheduling.)

The records surrounding your child's birth (mother and child) will be reviewed to obtain information about the pregnancy and your child's nursery stay. If your child was born at term, you will be asked to provide authorization for release of medical records information so that we may obtain information about early growth from your child's primary healthcare provider.

FUTURE USE OF BLOOD, URINE AND SALIVA SAMPLES

If you agree, your child's leftover blood, saliva, and urine will be kept and may be used in future research to learn more about hypertension and other diseases. The blood and urine will be stored by the Hypertension Core Laboratory at Wake Forest University Health Sciences. The saliva will be stored in the GCRC Molecular Lab. An Institutional Review Board (IRB) must also approve any research study using your child's blood, saliva, and urine. Sometimes blood, saliva, and urine samples are used for genetic research that may provide information about diseases that are passed on in families. Even if your child's blood, saliva, or urine is used for this kind of research, the results will not be told to you or members of your family and will not be put in your health records. The choice to let your child's blood, saliva, and urine be kept for future research is up to you. No matter what you decide to do, it will not affect your child's participation in this study. If you decide now that your child's blood, saliva, and urine can be kept for research, you can change your mind at any time. Just contact Dr. Washburn and let her know that you do not want your child's blood, saliva, and urine kept. Otherwise, the blood, saliva, and urine may be kept until it is used up, or until it is destroyed.

I agree that my child's blood, saliva, and urine samples and health records may be kept for use in future research to learn about, detect, prevent, treat, or cure high blood pressure and other health problems.

_____

Signature of parent or legal guardian   Date of signature

As part of this study, a saliva (spit) sample will be obtained from your child and DNA from your child's saliva (spit) 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 child's 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 child's individual health, the results of the research will not be given to your child's doctor without your permission. These results will also not be placed in your child's medical records.

HOW LONG WILL I BE IN THE STUDY?

Each study visit will last about half of a day. There will be three visits scheduled within 1 year. You will be asked to keep a 3 day food record of what your child eats. The ambulatory blood pressure monitor is worn for 24 hours and you must drop it off at the GCRC or put it in the mail the next day. Your child will be asked to record his/her activities during the ambulatory blood pressure monitoring. You or your child 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 opportunities for follow-up evaluations.

_____

Signature of parent or legal guardian   Date of signature

WHAT ARE THE RISKS OF THE STUDY?

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

<u>**Visit 1**</u>

The bag of ice placed on the forehead will feel very cold and uncomfortable but similar to what you would feel when placing an ice pack on a minor injury.

Visit 2

Your child may experience wheezing, shortness of breath, tightening of the airways (bronchoconstriction), muscle soreness, and fatigue from the exercise testing. A bronchodilator will be administered to reverse any exercise induced airway tightening. A possible side effect of the bronchodilator, Albuterol, is a rapid or irregular heart rate and tremor that may last for 4 to 6 hours. Your child will be monitored closely during the tests. Trained personnel will be present in the unlikely event that any medical emergency arises. Your child may have sore muscles 1 to 2 days from the exercise test.

Visit 3

The DXA scan involves exposure to radiation. The risk of the DXA procedures is small and is similar to that received from a clinical x-ray or nuclear medicine study. The scan exposes your child to a very small amount of radiation, similar to the radiation from playing outside on a couple of sunny days. The amount of radiation exposure that your child will receive from this procedure is equivalent to a uniform whole body exposure of 0.7 millirem. This is equal to 0.23% of the amount of background radiation that the average person in the United States receives each year. In the United States, the background radiation is 300 millirem per year.

When having their blood sample taken, your child 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.

The ambulatory blood pressure monitoring may be inconvenient.

All Visits

One of the study questionnaires involves asking your child about his/her stage of puberty or sexual development. This may cause embarrassment to some children but this will be minimized by picture identification done in private and placed in a sealed envelope.

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.

A Data Safety and Monitoring Committee, an independent group of experts, will be reviewing the data from this research throughout the study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If your child agrees to take part in this study, there may or may not be direct benefit to him/her. We hope the information learned from this study will benefit children in the

future. The benefits of participating in this study may be: Identification of elevated blood pressure.

WHAT OTHER CHOICES ARE THERE?

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

What about the Use, Disclosure and Confidentiality of Health Information?

By taking part in this research study, you and your child's personal health information, as well as information that directly identifies you and your child, may be used and disclosed. Information that identifies you and your child includes, but is not limited to, such things as your name, address, telephone number, and date of birth. You and your child's personal health information includes all information about you and your child which is collected or created during the study for research purposes. It also includes you and your child's personal health information that is related to this study and that is maintained in your medical records at this institution and at other places such as other hospitals and clinics where you may have received medical care. Examples of your personal health information include your health history, your family health history, how you respond to study activities or procedures, laboratory and other test results, medical images, and information from study visits, phone calls, surveys, and physical examinations.

You and your child's personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.
Some of the people, agencies and businesses that may receive and use your health information are the Institutional Review Board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; LabCorp; representatives from government agencies.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You and your child will not be directly identified in any publication or presentation that may result from this study.

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. As a participant in this study, a copy of this signed informed consent 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.

If this research study involves the treatment or diagnosis of a medical condition, then information collected or created as part of the study may be placed in your child's medical record and discussed with individuals caring for your child who are not part of the study. This will help in providing you with appropriate medical care. In addition, all or part of your child's research related health information may be used or disclosed for treatment, payment, or healthcare operations purposes related to providing you with medical care.

Laboratory test results and other medical reports created as a result of your child's participation in the research study may be entered into the computer systems of Wake Forest University Health Sciences, North Carolina Baptist Hospital, and LabCorp, an independent laboratory. 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.

When you sign this consent and authorization form you authorize or give permission for the use of your health information as described in the consent form. This authorization does not have an expiration date. You can revoke or take away your authorization to use and disclose your health information at any time. You do this by sending a written notice to the investigator in charge of the study at the following address:

Lisa Washburn, MD
Medical Center Blvd.
Winston-Salem, NC 27104

If you withdraw your authorization you will not be able to be in this study. If you withdraw your authorization, no new health information that identifies you will be gathered after that date. Your health information that has already been gathered may still be used and disclosed to others. This would be done if it were necessary for the research to be reliable. You will not have access to your health information that is included in the research study records until the end of the study.

WHAT ARE THE COSTS?

There are no costs to you for taking part in this study.

WILL YOU BE PAID FOR PARTICIPATING?

Your child will receive $50 for participating in Visit 1, $75 for participating in Visit 2 and $100 for participating in Visit 3. If your child participates in all three visits he/she will get a total of $225. In addition, you will receive $25 for participation in each visit, a total of $75 for participating in all three visits. To receive payment you must provide yours and your child's 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 and

your child have been paid. If you do not wish to provide this information you can still take part in this study but you and your child will not be paid.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by National Institutes of Health.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should your child experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at (336) 716-3467.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call Lisa Washburn at 336-716-5987.   If there is no answer or a problem arises in the evening, please call the hospital operator at 336-716-2011 and ask for Dr. Washburn in Neonatology to be paged.

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. This could be because new information becomes available or because the entire study has been stopped.

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 in the evening, 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, you should contact the Chairman of the IRB at (336) 716-4542.

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

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 sent important medical findings from our child's study to your child's personal physician?

[   ] Yes   [   ] No   _____ Initials

SIGNATURES

I agree to let my child take part in this study. I authorize the use and disclosure of my child's 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 my child's participation 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)

_____

  Legally Authorized Representative Name (Printed)

The above named Legally Authorized Representative has legal authority to act for the research subject based upon (specify: parent, legal guardian, health care power of attorney, etc.):

_____

_____   _____   _____
Legally Authorized Representative (Signature)   Date   Time

_____   _____   _____
Person Obtaining Consent   Date   Time

WAKE FOREST UNIVERSITY HEALTH SCIENCES DEPARTMENT OF PEDIATRICS

PATIENT ASSENT FORM

ANTENATAL STEROIDS AND BLOOD PRESSURE IN CHILDHOOD

Principal Investigators: Lisa Washburn, MD and Patricia Nixon, PhD

Co- Investigators:T. Michael O'Shea, MD, MPH; Jen-Jar Lin, MD;
Leon Lenchik, MD; Paula Sisk, PhD

WHY AM I HERE?
We want to tell you about a research study about blood pressure in children. We want to see if you would like to be in this research study. Dr. Washburn and some other people at this medical center are doing this study.

WHY IS THIS STUDY BEING DONE?
By doing this study you will help us learn more about the medicines we give to help premature babies and about how blood pressure changes as children grow up.

WHAT WILL HAPPEN TO ME?
This study is made up of three visits. You do not have to do everything in the study to participate. Only if you want to be in the study, the following things will happen:

This is what will happen on every visit:
1.   We will weigh you, see how tall you are, and measure your arm muscle.
2. We will check your blood pressure while you are sitting down.   To take your blood pressure we will put a band around your arm that gets a little tight for a second or two but it doesn't hurt.
3. We will ask you some questions about your health, habits, and activities. We will also ask you to look at some drawings of the stages of puberty and ask you to circle the pictures that look the most like your body looks now. So that you won't be too embarrassed you will do this in private and put the form in a sealed envelope and it won't even have your name on it.

This is what will happen on your first visit:
1. We will ask you to pee in a cup. You can do this all by yourself in the bathroom. So, if you need to use the bathroom when you get here let us know! We will save the sample until you have time to decide if you want to do the study. This urine sample will be sent to the lab to check how your kidneys are working.

2. We will collect some of your spit three times! First, we will ask you to spit into a container. Then, we will ask you to chew a piece of sugarless gum and spit into a container. We will ask you to chew gum and spit into a container two times.
3. We will check your blood pressure after we put a bag of ice on your forehead! How your blood pressure changes when you get the cold feeling on your head will tell us more about how your blood pressure may be when you get older. You will be asked to lie on a bed and we will take your blood pressure with a cuff around your arm. Then we will put a bag of ice on your forehead. This will last for 1 minute. We will take the bag of ice off your forehead and then we will take your blood pressure while you lie on the bed. You will have 3 sticky pads called electrodes attached to your chest so we can see how fast your heart beats during the test. You will also have a strap around your stomach so we can see how fast you are breathing. The bag of ice will feel very cold, probably like an ice pack you may have put on your head when you bumped your head! You can stop the test at any time.
4. We want to know what you've been eating. We want you to keep a record of what you eat for three days. A nutritionist will show you how to do this. We may move this part to your second or third visit.
5. We will ask you to pee in a cup at home on the morning of a next visit. You will be given supplies and instructions. You will bring this urine to the GCRC.

This is what will happen on your second visit:
1. You will collect your urine (pee) in the morning and bring it to the GCRC.
2. If you were unable to provide a urine (pee) sample at Visit 1, we will ask you to pee in a cup when you get to the GCRC. You can do this by yourself in a bathroom. We will send this urine to the lab to check how your kidneys are working.
3. We will also ask you to chew gum and spit in a tube.
4. We will also ask you to lie on a bed while we monitor your heart rate, blood pressure, and breathing. We will do some breathing tests. For the breathing tests, you will be asked to blow into a mouthpiece with nose clips on your nose. You will have to take deep breaths in and blow out hard and fast.
5. We will ask you to do the exercise test. For the exercise test, you will also have to blow into a mouthpiece and wear nose clips while you ride an exercise bicycle. You will have sticky pads called electrodes attached to your chest so we can see how fast your heart beats during the test. You will have a strap around your stomach to see how fast you are breathing. A plastic clip with a red light will be loosely attached to your finger so we can see how much oxygen is in your blood while you exercise. Your ride on the bike will start out very easy like riding on flat ground. Every minute it will get harder and harder, like going up a steeper and steeper hill. It is important that you give your best effort and we will cheer you on. The bike ride will only take 5 to 10 minutes. You may feel tired or short of breath or may even cough or wheeze during or after the test. You can stop the test at any time.
6. After the exercise test, we will ask you to lie on a bed while we monitor your heart rate and breathing. Next you will do some more breathing tests while sitting in a chair. We will ask you to breathe in some medicine called a bronchodilator or Albuterol. You may have breathed in this medicine as part of testing you have had in the past or may even use this medicine at home. Several minutes later, you will do

the breathing tests one more time to see if the medicine made a difference in your breathing. This medicine sometimes causes people to have a fast heartbeat or feel jittery. If this happens it usually only lasts 4 to 6 hours.

7. During the breathing test and exercise test, you may also feel short of breath, tired, lightheaded, or it may make you wheeze or cough. However, the doctor will be nearby and all of the people involved have done many of these tests and know how to take care of these problems quickly.

8. We will ask you to chew gum and spit into a container again.

This is what will happen on your third visit:
 (You will need to collect and bring a morning urine sample IF you did not do this at Visit 2.)

1. We will ask you to pee in a cup. You can do this all by yourself in the bathroom. This urine sample will be sent to the lab to check how your kidneys are working. (If you are a female, we will need to do a pregnancy test on your urine sample before you have the DXA scan on this visit.)

2. We will measure around your waist with a measuring tape and measure the thickness of your skin on your arm, below your shoulder blade, and at your hip bone.

3. We will ask you to do some game-like tasks like throwing and catching a ball, walking on a line, balancing on one leg on a low (2 ½ inch high) balance beam, and copying a square. These tasks will take about 15 minutes to do.

4. We will ask you to have a DXA scan which is a good way for measuring your body composition – or how much of your body is made of bones, muscle, and fat.   For the scan, you lie very still on a table while a metal x-ray arm passes above you from your head to your toes. Your feet may be held in place with tape to help you lie still. You will not feel any pain or discomfort, and the scan only lasts about 5 minutes.

5. For young women we are required to do a urine pregnancy test before the DXA scan. Even though the radiation from the DXA scan is very low, it might be harmful to an unborn baby if you were pregnant. Prior to the DXA scan we will ask you to provide a urine sample in a cup. If the test is positive (meaning you are pregnant), you will not be able to do the DXA scan. We also will not tell anyone, including your parents, that you are pregnant, but we will be happy to help you tell them if you wish.

6. We will get a sample of blood. First we can put some numbing cream on the inside of your arm at the elbow (the best place for getting to the vein) so you won't feel the needle stick so much. Then we will place a small needle into a vein in your arm and take out about 2 Tablespoons of blood. This may hurt and you may have a small amount of bleeding and a bruise where the needle goes in. We will hold pressure on the spot until it stops bleeding and you will be given a band aid. If you have any tenderness, pain or redness in that spot that is getting worse instead of better- let your parent know!

7. We will measure your blood pressure when you are at home or doing your regular activities. We will give you a special blood pressure cuff to wear for 24 hours (all day and all night). It is connected to a small box that you will wear on a strap or on your belt. This monitor will measure your blood pressure every 20 minutes during the day and every 30 minutes during the night. We understand that wearing this monitor all

day and all night may bother you some but it will give us very important information about your blood pressure.

We may ask you to do the second visit and the third in reverse (backwards) order if needed for scheduling your study appointments.

WILL THE STUDY HURT?
The stick from the needle will hurt but the hurt will go away after a while.
The bag of ice on your forehead will feel cold but will only be on for 1 minute and we will remove it sooner if you ask us to.
The exercise test may cause you to have sore muscles for 1 to 2 days.
You may be tired after the exercise testing.
The exercise testing may cause you to breathe harder. You will be given a medicine through an inhaler to help you breathe easier. This medicine may make you feel jittery and cause your heart to beat faster. There will be a doctor nearby if you have any problems.

WILL I GET BETTER IF I AM IN THE STUDY?
This study is not being done because you are sick. But the doctors might find out if you are having certain health problems. The doctors hope to find out something that will help other children in the future.

WHAT IF I HAVE QUESTIONS?
You can ask questions any time. You can ask questions now, or later. You can talk to the doctors or others helping with the study. You can also talk with your parents or other adults about being in the study if you want to.

DO I HAVE TO BE IN THE STUDY?
You do not have to be in the study. No one will be mad at you or unhappy if you don't want to do this. If you don't want to be in this study, you just have to tell the study doctor or study nurse. And if you want to be in the study, just let the study doctor or study nurse know. You can decide that you want to leave out part of this study. For example, you may not want to give a sample of blood or wear the blood pressure monitor all day and all night. You can say yes now and change your mind later. It's up to you.

_____   _____   _____
      Signature of Subject   Age   Date

_____   _____
      Person Obtaining Assent   Date

Adult Consent Form

Version: 05.30.2016

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.
5. Have your blood pressure measured multiple times.
6. Answer questions about your general health, any medications and supplements that you
take, use of alcohol and tobacco, and your family's general health.
7. Answer questions asked about your physical activity level.

8. Drink 8 ounces (1 cup) of room temperature water.
9. Provide two urine samples by voiding (peeing) in a container, in a bathroom, in private.
10. Have your blood pressure monitored by a cuff that wraps around two of your fingers.
11. Have your heart rate monitored by three electrodes (sticky pads) placed on your trunk.
12. Have your breathing monitored by a belt around your waist and perform 5 minutes of paced (steady) breathing.
13. Perform mental tasks and video games while your heart rate, blood pressure, and breathing are monitored.
14. 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:
<u>Visit 1</u>
- 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.

<u>Visit 2</u>
- 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.

71

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
WFU School of Medicine

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)

Antenatal Steroids and Cardiometabolic Risk   Study ID _____
PEPC-1   Date _____
IRB 00017340   Interviewer _____

PHYSICAL ACTIVITY QUESTIONNAIRE (MAQ)

"Please tell me any sports or leisure time activities you did in the past 7 days – from last _____   up through last night _____." *Fill in days.*

Activity	Times per week	Minutes per time

"Was this a normal work week? (If no, how different?)"

PAST YEAR LEISURE-TIME PHYSICAL ACTIVITY

"I am going to read you a list of activities people your age might do. Please let me know any that you have done at least 5 or more times in the past year (from _____ to _____)." *(If 15th of month or less, count back from previous month. If >15th of month, include current month as last).* (*Check to left of any indicated 5 or more times*).

Aerobics	Ice Skating	Tennis
Band/Drill Team	Racquetball	Ultimate Frisbee
Baseball/softball	Rock climbing	Volleyball
Basketball	Roller	Walking for
Bicycling	Skating/Blading	Exercise
Bowling	Running for	Water Skiing
Cheerleading	Exercise	Weight Training
Dance Class	Skateboarding	Wrestling
Football	Snow skiing	Yoga
Garden/yard work	Snow boarding	Others: *(ask "if do*
Golf	Soccer	**activities not on**
Gymnastics	Street Hockey	**list"**)
Hiking	Swimming (Laps)	_____
Home/video	Swimming (other)	_____
workout		_____

For each indicated activity ask **"which months in the past 12 did you do *(the activity)*, and on average, how many times per month or week, and how many minutes per time?"**
For sports, ask if team or pickup game or just shooting, throwing, etc. and how many people (if pickup or by self). If report both team and pickup, list separately. For garden/yardwork, ask to specify (mowing grass --push or riding or self-propelled, raki

Activity	Jan	Feb	Mar	Apr	May	Jun	Jly	Aug	Sep	Oct	Nov	Dec	Months per Year	Days per Wk or Mon	Min per Day

Ishawn J. Francis

EDUCATION: Claflin University, Orangeburg, SC   **Graduated May 2019**
Bachelor of Science, Major: Biology, Minor: Chemistry   **GPA 3.86/4.00**

Wake Forest University, Winston-Salem, NC   **Graduated May 2021**
Master of Science, Health and Exercise Science   **GPA 3.57/4.00**

RESEARCH EXPERIENCE:
Wake Forest University Health and Exercise Science   January 2020-Present
Graduate Research
 •Work under the direction of a graduate advisor
 •Conduct research using data from the PEPC-1 and PEPC-2 studies
 •Read and analyze research grants
 •Review literature of various studies on the topic of Prematurity and Low Birth Weight
 •Utilize statistical analyses to test hypothesis

Advanced Diversity in Aging Research   May 2017- November 2018
Bio-medical Engineering Research Assistant
 •Worked alongside graduate student under direction of mentor
 •Learnt, understood and performed techniques to conduct cellular research on
  Alzheimer's Disease
 •Read and analyzed articles based on the research
 •Researched and implemented troubleshooting methods
 •Created and presented research poster

Claflin University's School of Natural Sciences and Mathematics   May 2016- March 2017
Biochemistry Research Intern
 •Carried out efficient and effective use of lab equipment
 •Followed guidelines of the assigned mentor
 •Solved and analyzed problems that occurred
 •Studied scientific material on Global Warming and Cellulase DNA mutation
 •Developed new and innovative ways to conduct the research

PROFESSIONAL EXPERIENCE:
Wake Forest Health and Exercise Science Department   August 2019-May 2021
Teaching Assistant-Exercise for Health (1st year)
and Human Physiology Lab (2nd year)
 •Create and source class content
 •Effectively communicate class instructions and information
 •Develop teaching strategies and ways to get students engaged
 •Conduct laboratory sessions
 •Grade and administer assignments and tests

Homestead Hills Senior Living Home   June 2020- January 2021
Concierge
- •Assist residents age 65+ with tasks relating to their well-being
- •Greet family members and visitors of residents
- •Ensure safety of residents and enforced COVID 19 policies
- •Manage and sign up residents for exercise classes and events during the week
- •Respond to emergency situations and contact necessary personnel

LEADERSHIP EXPERIENCE:

Claflin University Writing Center   August 2018-May 2019
Writing Center Consultant
- •Prompted students to engage in active and critical thinking
- •Instructed students on ways to communicate ideas effectively
- •Ensured that students' papers have structure, purpose and are relevant to the topic
- •Conducted sessions where students learned to cite using APA or MLA

Claflin University Student Success Center   August 2017-December 2017
Panther STEPS Peer Mentor
- •Guided and instructed students on how to solve Algebraic Equations
- •Ensured that students were informed about class activities and assignments
- •Mentored students on proper studying habits and test taking skills
- •Developed relationships and built a good rapport with students

TUTORING EXPERIENCE:

Claflin University Student Support Service   August 2018- May 2019
TRIO Tutor
- •Provided academic assistance to first generation college students
- •Suggested effective learning tools for Genetics and Chemistry college courses
- •Assisted students in developing self-learning and researching skills
- •Helped students to understand course materials, assignments and projects

COMMUNITY SERVICE:

Healthy Exercise and Lifestyle Programs   August 2019-September 2020
Clinical Exercise Assistant
- •Assist in prescribing exercise for older adults in person and virtually
- •Conduct exercise tests to ensure participant cardiovascular health is suitable for exercise
- •Perform skin fold, pulmonary function, glucose and body height and weight assessments
- •Communicate with participants to ensure that they feel safe and comfortable in the exercise setting
- •Administer blood pressure and electro-cardiogram readings prior to exercise

Orangeburg Habitat For Humanity   May 2016-March 2017
Volunteer
•Helped repair and build houses
•Cleaned up around newly built houses
•Worked in large teams

TECHNOLOGICAL SKILLS & SPECIALTIES:
•CITI Certification, CPR Certification, Silver Sneakers Certification
•Anthropometric Measures, Glucose and Lipid Measurement, Blood Pressure
  Measurement, Electro-cardiogram interpretation, Cardiovascular and Pulmonary
  Function Testing, SPSS Statistical Program Analyses
•NanoDrop and Image Lab Software, PCR Machine, Pipetting, Fluorescence and
  Compound Microscopy, Hemocytometer, Western blotting technique and BCA Analysis
•Microsoft Word, Excel, PowerPoint, Web Applications
•Team Building, Collaboration, Communications, Problem Solving, Service Oriented
•Regular involvement in volunteer and community service

AFFILIATIONS & HONORS:
Wake Forest University HES Graduate Assistantship   August 2019-May 2021
Hearst Scholar Award   August 2019-May 2021
Wake Forest University Archery Club   September 2020-May 2021
Silver Medallion for 3.7-3.9 G.P.A.   February 2017, 2018 & 2019
Claflin University Honors College   August 2017-May 2019
Friends of the Earth Club   January 2017-May 2019
Ernest E. Just Science Club   August 2016-May 2019
Coach's Award   April 2016
Certificate for 4.0 Fall Semester G.P.A   February 2016
Academic Incentive Award   August 2015-May 2019
Claflin University Track and Cross Country   August 2015-May 2019