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MATERNAL EXERCISE, OFFSPRING BLOOD PRESSURE, AND GROWTH

By

James M. Pivarnik

A THESIS

Submitted to
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ABSTRACT

MATERNAL EXERCISE, OFFSPRING BLOOD PRESSURE, AND GROWTH

By

James M. Pivarnik

Despite numerous studies designed to explore the fetal origins hypothesis, none have addressed the issue of maternal physical activity and its relationship to subsequent outcomes in the offspring. We recently completed a detailed study designed to evaluate physical activity measurement techniques during pregnancy and the postpartum period. Study participants (N=51) were evaluated for two consecutive days, at both 20 and 32 weeks gestation. We found that maternal physical activity during pregnancy was inversely related to birth weight and fetal growth ratios ($r=-0.45$; $P<0.001$), even when controlling for maternal weight gain. We propose to expand our study of these women and evaluate their offspring who are now 6-7 years of age. The specific aims of the present investigation are as follows: 1) to determine the effect of maternal physical activity in pregnancy on later blood pressure and body mass index in children born to women in whom physical activity and weight gain were determined during pregnancy; 2) to assess whether the generally found inverse relationship between birth weight and blood pressure is modified by maternal physical activity, in a cohort in whom we have shown that birth weight is inversely related to maternal physical activity, 3) to determine the relationship between maternal physical activity and change in children's body mass index (from birth to six years of age), and in children's fat deposition in this cohort.

ACKNOWLEDGEMENTS

Special thanks to all those who helped me through this degree. In particular, I would like to thank my committee members (Nigel Paneth, Mat Reeves, and Mike Collins), the many wonderful students I have had the pleasure to work with over the years, and of course, my wife Linda and "the girls".

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INTRODUCTION AND SPECIFIC AIMS:

That cardiovascular disease (CVD) risk factors in general, and blood pressure specifically, can be traced to fetal origins, is thought to be related to the phenomenon known as "programming" (5). Programming posits that critical developmental periods for the heart and blood vessels exist during embryonic and fetal life. If, during these periods, the maternal-fetal unit is unduly stressed, permanent developmental alterations can occur. This has been shown experimentally in animal models (29,41,83)

The fetal origins hypothesis states that coronary heart disease is associated with specific patterns of disproportionate fetal growth in middle to late gestation (27). The proposed mechanism of action is that undernutrition, malnutrition or other stressors have a negative effect on cell division during crucial periods of fetal growth. The hypothesis further asserts that the crucial periods may be different for different organ systems, resulting in disproportionate growth. Further, small birth weight may be an indicator of lack of oxygen to fetal tissues during pregnancy; and this hypoxia may cause other problems related to CVD. For obvious reasons, experimental data in humans is lacking.

While most early investigations of the role of birth weight and subsequent blood pressure in offspring have been performed on adult cohorts, several recent studies have focused on children. David Barker, one of the major proponents of the fetal origins hypothesis, suggests that since associations between birth weight and CVD risk factors are found in childhood, we should

initiate studies assessing the link between fetal growth and the emergence of these risk factors early in life (6).

Despite numerous studies designed to explore the fetal origins hypothesis, none have addressed the issue of maternal physical activity and its relationship to subsequent offspring outcomes. It is well known that maternal physical activity may affect birth weight, but the results have been conflicting (59). Most have found maternal physical activity during pregnancy results in babies who are smaller at birth. Recent evidence shows that this difference in birth weight is mostly in the form of fat mass (15,17). How this may affect subsequent CVD risk in offspring is unknown.

We recently completed a detailed study designed to evaluate physical activity measurement techniques during pregnancy and the postpartum period (66,76). Physical activity was measured via continuous heart rate monitoring and motion sensor accelerometry, as well as recall surveys. Study participants (N=51) were evaluated for two consecutive days, at 20 and 32 weeks gestation, and 12 weeks postpartum. Birth weight averaged 3695±517 g (range 2753-4943 g). We found that maternal physical activity during pregnancy was inversely ($r=-0.45$; $P<0.001$) related to both birth weight and fetal growth ratio (birth weight adjusted to the 50^{th} %tile by parity, gender, and gestational length) as shown in Figure 1 (84). This relationship held after controlling for gestational weight gain (58).

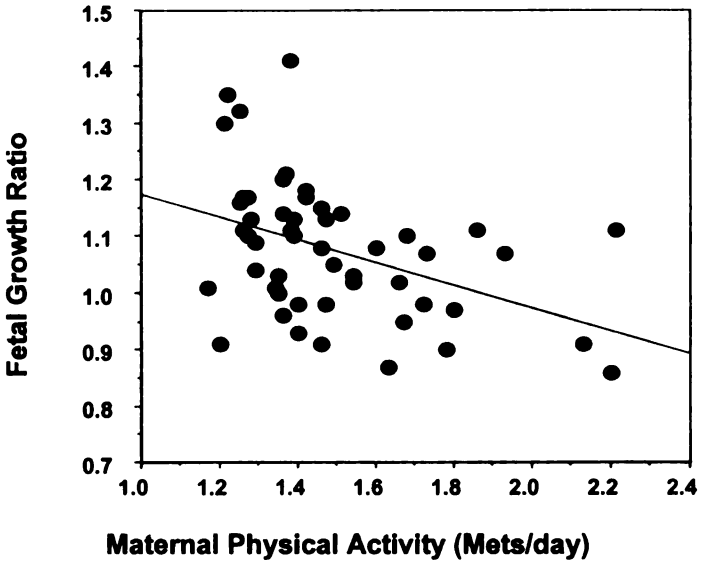

Figure 1 Fetal growth ratios plotted as a function of maternal physical activity performed during second and third trimesters of pregnancy.

We propose to expand our study of these women and evaluate their offspring who are now 5-7 years of age. This cohort is largely intact, and all women contacted have agreed to follow-up evaluation of their children. The specific aims of the present investigation are as follows:

Specific Aim 1

To determine the effect of maternal physical activity in pregnancy on later blood pressure and body mass index in children born to women in whom physical activity and weight gain were determined during pregnancy.

We hypothesize that there will be no relationship between maternal physical activity and child blood pressure and an inverse relationship between maternal physical activity and child body mass index.

Specific Aim 2

To assess whether the generally found inverse relationship between birth weight and blood pressure is modified by maternal physical activity, in a cohort in whom we have shown that birth weight is inversely related to maternal physical activity

We hypothesize that entering maternal physical activity into a statistical model will diminish the inverse relationship between birth weight and blood pressure in the children.

Specific Aim 3

To determine the relationship between maternal physical activity and change in children's body mass index (from birth to six years of age), and in children's fat deposition in this cohort.

We hypothesize that there will be no relationship between maternal physical activity and change in the children's body mass index, but that we will find an inverse relationship between maternal physical activity and child fat deposition.

BACKGROUND AND SIGNIFICANCE

Birth weight, Body Size, and Blood Pressure in Youth

From the many studies of Barker and colleagues, birth weight has been found to be inversely related to blood pressure (and other CVD risk factors) in adulthood (5,6,42). Further, the association appears to be largely independent of length of gestation, inferring that the relationship is related to reduced fetal growth or intrauterine growth retardation, rather than premature delivery. If the fetal origins hypothesis is correct, then children's blood pressures, which track fairly well into adulthood (40), should also be related to birth weight.

For example, Whincup et al (81) studied over 3,000 children in Great Britain in areas known for either very high, or low cardiovascular disease mortality rates. Students aged 5-7 were sampled from 10 schools stratified by size and geographic location. Birth weights were divided into quintiles, and were compared to the children's blood pressures. Using linear regression, the authors found a significant ($P<0.001$), and inverse relationship between birth weight and systolic blood pressure, but only when current child body size was adjusted for. The difference in blood pressures between the lowest (765-2950 g) and highest (3741-4880 g) birth weight quintiles was <3.0 mm Hg. In addition, this same blood pressure difference existed between the second and third birth quintiles and the highest, even though birth weights were in the normal range (2951-3460 g). Thus, it appears that the relationship between birth weight and blood pressure is not found solely in growth-restricted infants.

In contrast to previous studies in adults, this relationship held when the authors controlled for gestational age.

In a later study, Whincup et al (82) studied children in two English towns (Guildford and Carlisle) using 10 grammar schools from each. Children were surveyed at ages 5-7 and 9-11. Blood pressure values and anthropometric data were gathered and compared to recalled birth weights and placental weights (when available). Final response rate in the analysis was only a small fraction of the total subjects available. The results showed an inverse relationship between birth weight and blood pressure (when controlling for current height, weight, and BMI), which was amplified with age. Specifically, regression analysis showed that the children's blood pressure values at any given birth weight grouping were 1-2 mm Hg greater (CI=0.07-3.35 mm Hg) at age 9-11 compared to when they were age 5-7.

Not all investigations of the relationship between birth weight and blood pressure in youth have supported the fetal origins hypothesis. Seidman et al (73) studied the effect of birth weight and body weight on blood pressure in late adolescence. Subjects were 19,734 men and 12,846 women born between 1964-71 in three hospitals in Israel. The authors examined the correlations between blood pressure at age 17, current weight, and birth weight. Results showed a small, yet *positive* relationship between birth weight and blood pressure in late adolescence. They found that body weight at age 17 (>66 kg in females; >75 kg in males) was a much better predictor of blood pressure than birth weight. A strength of this study was that it included nearly every child born

in Israel from 1964-1971, since complete data were available from the Israeli Defense Forces records.

Matthes et al (49) studied the relationship between birth weight and blood pressure during adolescence using a retrospective design. Subjects were chosen from individuals born in Cardiff in the mid 1970's. The authors divided the subjects into cases (infants born <2500 g, at least 38 weeks gestation) and controls (3000-3800 g, at least 38 weeks gestation). Subjects were matched for sex, delivery hospital, parity, birth date, and gestational length (using last menstrual period). The authors speculated that if the fetal origins hypothesis is valid, real differences in blood pressure would certainly appear based on the groups chosen. However, the results showed no significant difference between systolic blood pressures in case vs control study participants. Barker and Law (7) later criticized this study by stating that adolescence is not the appropriate age for comparison, due to a perturbation of blood pressure tracking during the adolescent period. However, Mathes et al suggested that any perturbation during adolescence would likely be present in both cases and controls, and an effect of birth weight on blood pressure would still be present.

Rabbia et al (67) studied more than 1300 Italian school children and showed mixed support for the fetal origins hypothesis. The authors did not find a significant relationship between birth weight and adolescent blood pressure when the entire sample was analyzed. However, when they examined women

who were exposed to a significant stress of placental hypoperfusion, an inverse relationship was evident.

It appears that not only is small birth weight a risk factor for CVD, but those who become heaviest in childhood have the greatest risk. For example, Barker et al (8) measured body size and fat patterning in 216 adolescent girls from Southampton, UK. Girls who were the smallest at birth, and fattest during adolescence tended to have a greater central/peripheral fat ratio, which is indicative of greater cardiovascular disease risk. We found no studies that examined the influence of maternal physical activity on this relationship.

In a longitudinal study of young adults living in Southern England, Law et al (38) examined the interrelationships between birth weight, weight gain in the first five years of life, and blood pressure at 22 years of age. The investigators were able to obtain complete data on 346 of the 1800+ participants enrolled in the original birth cohort. Major findings were that both birth weight and weight gain between 1-5 years of age were most strongly related to adult blood pressure. When the authors controlled for adult body weight, most of the relationship between weight gain and blood pressure disappeared. This suggests that the early childhood growth effect is mediated somewhat by its prediction of adult body fatness. In addition, the results support the idea proposed by Lucas et al (45) that the relationship between offspring blood pressure and change in weight percentile may be artifactual, since the lower the child's birth weight, the greater the possibility for body weight percentile

increasing during early childhood. It is not known whether the type of weight gain (fat or fat free mass) is related to blood pressure in early childhood.

Adair and Cole (1) found that Filipino adolescents, light at birth and heavy during adolescence, were nearly twice as likely to develop high blood pressure (defined as >90th%tile of the sample) compared to those of average size. This relationship was significant only when the authors controlled for birth length, indicating it is thinness, rather than birth weight per se that is important. Their sample was obtained from a developing country, with 20% of the study participants being small for gestational age. Therefore, it is possible that the growth was more "catch-up" rather than excess, as might be seen in a more developed nation.

Although excess catch-up growth may predispose a very light baby to be a heavy child, this may be the exception, rather than the rule. Brody et al (14) studied birth weight and childhood size in a national sample (NHES data) of more than 4600 children. The authors found that overall, birth weight was positively related to attained height and weight in childhood. Maternal data were not available, nor was birth length. The authors suggest that although growth patterns in preadolescent years are related to birth weight, other factors such as diet and physical activity may be more important to the risk of childhood obesity.

Using a longitudinal approach, Fuentes et al (25) studied more than 200 Scandinavian children for 15 years. They found that birth weight was not a good predictor of early childhood BMI, which tracked well from age 7 through

15. These results infer that environmental influences (e.g., physical activity, diet) learned during childhood may exert a greater influence on growth than fetal programming.

Perhaps one of the major shortcomings of studies that have found relationships between birth weight and offspring blood pressure is the statistical data analysis. There is no question that many investigations have shown inverse associations between the two variables, yet most strongly, and in some cases, only when controlling for current body weight or body mass index (5,6,42). The authors claim that current body weight is a confounder, and therefore, should be controlled. However, it is also possible that it is actually an intervening variable. That is, current body size, rather than birth weight, is the true cause of current blood pressure. As Paneth and Susser (55) point out, "body mass index may well be an intervening variable; to adjust for such a variable is to overcontrol and, usually, to misinterpret".

There are certainly ample data available that indicate body size/fatness is a cause of high blood pressure (40). From a mechanistic prospective, a causal relationship has biologic plausibility. For a given perfusion rate, the pressure gradient must increase in the face of increasing resistance to blood flow; and, in general, there is greater resistance to blood flow in individuals with high BMI values. Therefore, it is possible that body mass may represent a significant portion of the cause (relative to birth weight) of variation in an individual's adult blood pressure.

Unfortunately, statistical manipulation cannot determine whether a variable is intervening or confounding, and the decision must come from rational argument of the scientific logic behind any proposed causal mechanisms. This is currently a strong point of contention with the fetal origins hypothesis (34,53). Whatever the argument, factors that have been shown to be related to blood pressure should be considered appropriately in the experimental design and data analysis. Lucas et al (45) have suggested that researchers investigating the relationship between birth size and CVD risk should construct both individual (using fetal and offspring data) and combined models so that all plausible causal scenarios can be considered.

Environmental Factors Related to Childhood Blood Pressure and Body Size

While birth weight may play a significant role in childhood blood pressure, other environmental factors such as physical activity and fitness may be equally or more important. Based on data obtained from adults (12,13), these variables may exert their influence through body mass and fatness, as well as have an independent relationship with blood pressure.

Using a cross sectional approach, Riberio et al (69) found a significant positive relationship between children's (aged 8-16 yr) BMI and blood pressure. No association was found between BMI and the children's physical activity levels. In contrast, others have found that physical activity is significantly related to young children's BMI, skinfold thicknesses, and overall body fatness (31,79,80).

In a recent review paper, Malina (48) presented longitudinal data indicating that physical training begun during early adolescence can alter the typical fat deposition patterns associated with normal growth and maturation. Less is known about how this may occur during young childhood. Some evidence is provided by Shea et al (74), who studied nearly 200 children at 5 years of age and followed them for nearly two years. The investigators found that children who increased their aerobic fitness and/or showed the smallest increases in BMI during the follow-up had a blunted age-related rise in blood pressure. The same research group also found that aerobic fitness in children was inversely related to the cardiovascular disease biomarker C-reactive protein in children as young as six years of age (36).

Maternal Physical Activity and Offspring Characteristics

There are few data available that have resulted from systematic analyses of the role of physical activity on the characteristics of the offspring. Most of the few relevant examples available come from the work of Clapp and colleagues (15-18).

In 1990, Clapp and Capeless reported the results of a study designed to evaluate the effect of continued maternal exercise throughout pregnancy on fetal growth parameters (16). More than 120 women participated in the study and were divided into those who continued to exercise throughout pregnancy, and those who chose to discontinue their physical activity routines. Children born to the continuing exercisers weighed less (-310 gms), were thinner, and

had lower fetal/placental ratios compared to the offspring of the control women. Crown heel length and head circumference measures were similar in both offspring groups. The authors reported further that most of the difference in birth weights between groups was in the neonatal fat mass. Women who continued to exercise also gained less weight during pregnancy than controls (13.5 kg vs 16.4 kg). Based on their study results, Clapp et al suggested that "the interaction between the physiologic adaptations to exercise and the physiologic adaptations to pregnancy are multifaceted and warrant further study".

A few years later, Clapp (15) studied the morphometric and neurodevelopmental characteristics of a subgroup (n=20) of their 1990 study cohort whose children had now reached five years of age. As stated previously, despite similar head circumference and body lengths measured at birth, the babies born to the exercising mothers weighed less, and had less body fat. At five years of age, these differences persisted. Results of neurodevelopmental tests showed that the offspring of the women who exercised throughout pregnancy scored either similar to (motor and integrative skills, academic readiness), or better than (IQ and oral language skills), the control children. The offspring studied by Clapp et al were similar in birth weight to our proposed study cohort, as was the SES of the women study participants (personal communication, JF Clapp).

In contrast to the cohort in Clapp's 1990 study, Clapp et al later found that healthy, yet previously sedentary women who began an exercise program

early in pregnancy delivered *heavier* babies, and had larger placentas, compared to nonexercising controls (17). Body fatness did not differ between the offspring groups. The authors suggested that the higher birth weights, compared to those found in previous studies, may be due to the very modest volume and intensity of activity performed by the beginning exercisers. Most recently, Clapp et al (18) supported this hypothesis when they randomly assigned women to either a low or high volume exercise group. Although normal fetal growth was seen in all cases, women in the low volume exercise group showed greater fetoplacental growth, and delivered heavier and fatter babies compared to the high volume exercisers.

While the results of Clapp et al's studies are somewhat mixed, overall they provide support for the hypothesis that children who have lower birth weights resulting from maternal physical activity may not be predisposed to the same CVD risk factors as children born to sedentary mothers. Much of this difference in risk may be related to the fact that the lighter babies in the Clapp et al studies (15,16) did not show the same weight and body fat gain in early childhood as shown in previous reports. Clapp et al did not report the blood pressures of the children studied, nor was there any mention of their physical activity and/or cardiorespiratory fitness levels.

Summary

Several researchers have shown that an inverse relationship exists between birth weight and subsequent offspring blood pressure at various ages.

However, not all investigators have found this relationship, and in many cases, statistical analysis may be enhancing the effect found. This is expected, given the multi-association that exists among the various risk factors for CVD, regardless of whether they are programmed in utero or environmental influences that do not appear until after birth. Thus, whenever possible, studies should be performed on cohorts that can provide new ways of investigating the fetal origins hypothesis. Our existing cohort of pregnant women carefully studied for their physical activity behaviors represents such an opportunity. We have clearly shown a significant, inverse relationship between maternal physical activity and birth weight, as well as FGR. What is not known is how this relates to subsequent CVD risk factors such as childhood blood pressure and body size. We also have the opportunity to determine how other known effectors of childhood blood pressure and size, namely aerobic fitness and physical activity, may be related to maternal physical activity levels. Results from this investigation will be unique, and can further our knowledge of the long-term consequences of maternal physical activity, and add key data for larger, longitudinal studies designed to test the fetal origins hypothesis.

PRELIMINARY STUDIES

Previous Experience by the Principal Investigator (J.M. Pivarnik)

James M. Pivarnik, PhD is a Professor in the Departments of Kinesiology and Epidemiology at Michigan State University (MSU), and Director of the recently formed MSU Center for Physical Activity and Health. He has pursued

post-doctoral training at MSU, completing all course work for an MS degree in epidemiology. He has extensive experience in studies involving acute and chronic maternal and fetal responses to physical activity during pregnancy. Dr. Pivarnik was recently asked by a CDC lead epidemiologist (Bill Kohl of the Physical Activity and Health Branch) to organize a research roundtable addressing the role of maternal physical activity and chronic disease risk.

Most relevant to this proposal, Dr. Pivarnik recently completed a detailed evaluation of maternal physical activity throughout pregnancy (66,76). This study was supported by an RO3 grant from NICHD. Study participants were healthy, nonsmokers, and most were college educated. The investigators measured physical activity using three methods: continuous heart rate monitoring via telemetry, motion sensing via accelerometry, and participant recall. This study was undertaken because of the need for evaluation and standardization of physical activity monitoring during pregnancy. Participants were studied during second (20 weeks) and third (32 weeks) trimesters, as well as 12 weeks postpartum. At each study time point, physical activity data were collected continuously for 48 hours in order to obtain precise and accurate measures of all waking energy expenditure. In addition to maternal physical activity, maternal blood pressure, weight gain, resting energy expenditure, and heart rate response to moderate treadmill exercise were measured. Fetal measures were abstracted from medical records. These included birth weight, birth length, Apgar scores, gestational age at delivery (via ultrasound and dates of last menstrual cycle), and mode of delivery.

A key finding from this recent investigation was that the relationship between heart rate and energy expenditure (i.e., oxygen consumption [VO_2]) during exercise is affected by pregnancy (66). Specifically, a woman's true energy expenditure would be overestimated at rest, and underestimated during physical activity, if these physiological changes are not taken into account. In addition, results showed that heart rate monitoring, accelerometry, and physical activity recall can all reliably estimate physical activity during pregnancy (76). However, absolute values obtained from the various techniques should not be compared directly.

Most directly related to this application is a recent abstract describing Pivarnik et al's finding that maternal physical activity levels were inversely related to birth weight and fetal growth ratio ($r=-0.45$; $P<0.001$), even when controlling for gestational weight gain (58, and manuscript in review). This finding is significant for the current proposal because the women were followed very closely throughout pregnancy, and a clear relationship between their activity levels and birth weight was demonstrated. Thus, these carefully collected data and intact cohort provide an excellent opportunity to expand the investigation to the offspring, by evaluating their blood pressures, body size and growth.

Other Exercise and Pregnancy Studies

In the late 1980's, the PI was part of an investigative team that compared noninvasive and invasive measures of maternal and fetal responses to positional change, exercise, and volume loading (19,20). Specifically, the

protocol involved subjects having catheters inserted into their pulmonary and radial arteries. During both cycle and treadmill exercise, the investigators determined that VO_2, cardiac output, and stroke volume responses were greater when exercise was performed at 37 weeks gestation, compared to postpartum (61). However, heart rate responses to cycle exercise were not affected by pregnancy status. Also, despite similar change in maternal pH, $PaCO_2$ was unaffected during exercise at 37 weeks gestation, but decreased at 12 weeks postpartum. Overall, the investigators found no compromise in maternal acid-base status during aerobic exercise in pregnancy (64).

In another study, Pivarnik and colleagues followed 16 women at monthly intervals throughout gestation. The purpose of the investigation was to determine hemodynamic, metabolic, and perceptual responses to exercise as pregnancy progressed (44,62,63). In support of previous investigations, the authors found resting heart rate and VO_2 values increased with advancing gestation. However, while the energy cost of both cycle and treadmill exercise increased as pregnancy progressed, there was no gestational age affect on heart rate response to either activity. Also, the women did not perceive the exercise to be more difficult with advancing gestation, despite the increased energy expenditure. The data suggested that the subjects incurred a mild training effect over the course of their pregnancies. This is plausible in the population studied as subjects were all sedentary women who did not participate in any organized physical activities. These results demonstrate that methods used to measure a woman's energy expenditure during pregnancy

may be affected by gestational age. For instance, if heart rate monitoring is to be used as a criterion measure, heart rate/VO_2 relationships should be determined at various time points during pregnancy to insure validity of the technique.

In a later study, Pivarnik et al investigated the effect of continued exercise performance on maternal hemodynamics in highly motivated, physically active gravidas (60). Women who were chronic exercisers, and continued their activity routines throughout pregnancy, were compared to a control group of healthy, yet sedentary gravidas. Results showed, at a given maternal heart rate (~140 $b \cdot min^{-1}$), fit women demonstrated a greater energy expenditure and higher stroke volume than controls, during recumbent cycle exercise. Also, although the physically active women had higher energy expenditures at a given heart rate, their ratings of perceived exertion during the exercise were the same as those of their sedentary counterparts. These findings demonstrate the relationship between true energy expenditure and a woman's heart rate response and perception of effort during physical activity is moderated by her fitness level and usual exercise patterns. As part of this same study, Pivarnik et al (65) examined whether pregnancy induced blood volume expansion is affected by physical activity status of the gravidas. Results showed that the exercise trained women had higher blood volumes postpartum, and greater blood volume expansion throughout pregnancy, compared to the sedentary controls. However, the exercise trained women did not deliver higher birth weight babies. These unique study results are

significant given the well-known positive relationship between birth weight/fetal viability in sedentary women.

Exercise, and CVD Risk Factors in Children

Dr. Pivarnik also has extensive experience in studies involving physical activity, fitness and other CVD risk factors in children, both in the laboratory and field settings. Dr. Pivarnik spent three years as the first Director of the Wellness Center at Texas Children's Hospital in Houston, TX. In addition to his clinical duties, he initiated and performed many investigations involving maternal exercise during pregnancy, as well as pediatric physical activity and fitness.

Since arriving at MSU in 1994, Dr. Pivarnik has performed studies in several area schools with a multi-ethnic/racial makeup. In a Lansing, MI middle school, he recruited ~70% of the girls enrolled in grades 6-8 for a physical activity/fitness evaluation study in this high-risk group. In addition to cardio-respiratory fitness and blood pressure evaluations, he studied the students' after school physical activity behaviors via Caltrac accelerometry, heart rate monitoring, and physical activity recall (2,3,22).

In addition, Dr. Pivarnik has been involved with two national service opportunities related to children, physical activity and health. First, he is a member of the physical activity working group for the proposed National Children's Study (NCS). The group met in Washington, DC in November 2003, and was charged with developing physical activity measurement recommendations for the NCS, which is designed to study children from in utero through young adulthood. Most recently, Dr. Pivarnik joined an expert panel

that was charged with developing evidence-based guidelines for physical activity in children. The CDC funded this panel's efforts and the recommendations are currently in review for publication.

Previous Experience by the Co-Investigator (N. Paneth)

Nigel Paneth MD, MPH (Co-investigator) is a Professor of Epidemiology and Pediatrics and Human Development. Since 1978, Dr. Paneth has had virtually continuous NIH support for a program of research into the perinatal origins of infant mortality and childhood handicap, including studies of the effects of medical care. This includes principal investigatorship of five RO1 grants and one RO3 grant, and participation as sub-contract principal investigator on five additional NIH grants, all RO1 efforts. The major research studies have been investigations into the effect of medical care on patterns of infant and fetal mortality in NYC (1978-1983); a population study of etiology and prognosis of brain injury in preterm infants, the Neonatal Brain Hemorrhage Study- NBH (1984-present); a multi-center study of etiology of white matter injury in preterm infants, the Developmental Epidemiology Network Study - DEN (1991-1996); an international study of low birth weight outcomes in five countries funded by AHRQ (1996-1999); and a multicenter study of molecular antecedents of white matter injury, the Extremely Low Gestational Age Newborn Study - ELGAN (2002-present). Dr. Paneth led the NBH Study from 1984-1991, and three subsequent rounds of follow-up have been conducted by two of his mentees at Columbia University, Dr. Jennifer Pinto-Martin (studied

age 9) and Dr. Agnes Whitaker (studied ages 6 and 15). He has written on methodological issues in the fetal origins hypothesis (52,53,55) and is currently developing, with statistician Professor Wen Jiang Fu, a computer simulation model of the effect of different adjustment techniques for internally correlated data such as birth weight, adult weight, and blood pressure (54).

RESEARCH DESIGN AND METHODS

Study Participants and Design

Participants will be women studied previously throughout gestation (as discussed in the preliminary studies section of this proposal) and their offspring from that pregnancy. The maternal cohort consisted of 51 gravidas, who were studied from 1997-1999. The women were healthy, nonsmokers, and all of similar SES. They were recruited by word of mouth and with the help of local obstetric clinics affiliated with the MSU Colleges of Human and Osteopathic Medicine.

Of the original cohort, 44 of 51 (86%) have thus far been successfully contacted by the PI and all have agreed to allow their children to participate. We contacted these women with the permission of the Michigan State University IRB, where our original protocol remains active. While we will continue to search for the remaining seven women it is possible that some have moved away from the area. All women contacted were very agreeable and enthused about having their children participate in this follow-up study. All study participants delivered healthy singleton babies, and none have any known

chronic illnesses. The children were born between January, 1998 and November, 1999. Assuming a March 2005 start date, the children's ages will range from 5.5 – 7.5 years at that time. We will time the children's study order so that all will be between 6-8 years of age when they are evaluated.

Maternal and Birth Weight Measures

Maternal physical activity was measured during second (20 weeks) and third (32 weeks) trimesters. We used three techniques to estimate energy expenditure: heart rate monitoring (which we calibrated with oxygen consumption/heart rate regression lines constructed from treadmill testing), motion sensor accelerometry, and physical activity recall. All women wore the monitors and completed the recall instruments over 48 continuous hours at each study time point. Regardless of the measurement technique, maternal energy expenditures were converted to kilocalories expended (above resting levels) during waking hours. Caloric expenditure was converted to average MET (metabolic equivalent units) intensity by dividing by body weight and length of time the women were measured over the two consecutive days.

Maternal weight gain during pregnancy was calculated by subtracting body weight at week 20 from body weight at week 32 of pregnancy. We realize that this measure does not capture the entire maternal weight gain from conception to delivery. However, we are quite confident of the accuracy of this measure (obtained in our laboratory) and it was significantly related to birth weight and FGR ($r=-0.45$; $P<0.001$).

Birth weight, birth length, and gestational age at delivery were abstracted from medical records. For this investigation, fetal growth rates will be estimated by adjusting birth weights by gestational age, race, sex, and parity (84).

Offspring Measures

All measurements will be performed in the Michigan State University Human Energy Research Laboratory, the site of the previous study performed on the mothers during their pregnancies. Children will be brought to the lab on three occasions within a one month period. Although it may not be possible to test all children at the same time of day, each individual child's test times will remain consistent, regardless of the time of day chosen. Table 1 shows the testing schedule. Multiple measures of the child's blood pressure, physical activity, and dietary recall will be done to improve their validity.

Table 1: Study Participant Testing Schedule

Variable	**Visit 1**	**Visit 2**	**Visit 3**
Blood Pressure	X	X	X
Physical Activity	X	X	X
Dietary Recall	X	X	X
Anthropometrics	X		
Body Composition	X		
Aerobic Fitness		X	X

Blood Pressure Measurement

Since the children's blood pressure is our most important outcome variable, great care will be taken when obtaining our measurements. We will follow recommendations from the National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents (50). Guidelines will be followed, paying special attention to arm position, cuff size, and posture. There are pros and cons for both auscultory and automated blood pressure measurement techniques (51). After careful consideration, we decided to use the Dynamap (Critikon, Inc; Tampa, FL) automated blood pressure system for this study. This apparatus has been shown to be valid for use with young children (56) and has been used previously in epidemiological research studies with this age group (74). All manufacturer's instructions for calibration and measurement will be followed. On each test occasion the child will be seated for at least five minutes before measurements begin. Five measures will be taken, at least two minutes apart. The last three measures will be averaged and considered to be resting blood pressure for the day. The average of the three days of measurement will be considered the child's pressure.

Physical Activity

Children's physical activity levels will be measured via the Computer Science and Applications, Inc (CSA; Shalimar, FL) uniaxial accelerometer. This unit has shown excellent reliability and validity with children (24), and the PI has

found that it is sensitive enough to discriminate between light, moderate, and heavy exercise intensities in a field setting (21). It is an excellent method to use with young children that may not have the cognitive ability to recall their recent physical activity behavior patterns (57).

The CSA is a very small device, measuring 6.6x4.3x1.5 cm and weighing 70 g. The CSA is initialized using a Reader Interface Unit attached to a PC. Predetermined time periods (epochs) are set, as well as time and day, prior to beginning data collection. The CSA detects movement through the use of a piezoelectric plate that picks up acceleration signals as it moves. The CSA records activity counts by first filtering and then digitizing acceleration signals. These signals are converted to a numerical value or count, and the counts are summed over each epoch. After the activity count for an epoch is recorded, the device is automatically reset to zero. For this study, epoch intervals will be set for 30 minutes. Information from the CSA will be downloaded to a PC after the data collection is completed.

At each test session, the mother and her child will be given detailed explanation of how the CSA operates, and the procedures to follow for this study. The CSA will be placed on the child's right hip using an adjustable nylon belt, which will be removed the next day, approximately 24-hours later. If the mother cannot return the instrument to our laboratory, we will drive to the participant's residence to pick it up. Even though there are no switches or buttons on the CSA, it will be placed in a locked pouch so the child cannot remove it during the day. The children will wear the CSA at all times except

during, sleeping, bathing and swimming. We will provide a log for the mother to record any times (and reasons) that the CSA is removed before the end of data collection.

Data will be downloaded into our laboratory PC in the form of CSA "counts", which are directly related to volume and intensity of activity performed during the test interval. Total counts for all epochs recorded during the three collection days will be averaged and considered as the child's usual daily activity level.

Dietary Recall

A 24-hour dietary recall will be used to determine each child's nutrient intake on each of the three visits. This has been shown to be a valid instrument in young children (77,78), particularly if the child's parent or caretaker is present to help with the responses (38,75). The Food Processor SQL software system (ESHA Research; Salem OR) will be used to estimate the total caloric intake for the 24-hour period, as well as macronutrient subgroups. The ESHA system is used extensively for evaluation of dietary recalls, and its database compares favorably with the one used in NHANES investigations (10).

Anthropometrics and Body Composition

Each child's standing height and weight will be assessed using a calibrated stadiometer and beam balance, respectively. Standing height and weight measures will be used to calculate each participant's body mass index

(BMI; $kg \cdot m^{-2}$). Since we have birth weight and length measures, we will also calculate BMI at birth. Although ponderal index (wt divided by $length^3$) is frequently calculated in infants, we will be analyzing the data for change in weight per height over the child's first six years, and BMI is thought to be a better predictor of CVD risk factors (26).

Body fatness will be assessed via bioelectric impedance analysis (BIA: RJL Quantum II analyzer; Clinton Township, MI). BIA induces a small current through the body, providing resistance and reactance values (both measured in Ohms) from body tissues. This current measures total body water, which is indicative of fat free mass (4,33). Individuals of a given height and weight will offer different resistance to the current, based on the fat content of their bodies (46). Percent body fat will be calculated by subtracting fat free mass from body weight, then dividing by body weight. We will use the BIA equation developed by Kushner et al (39), which is appropriate, and has been validated for, young children (28). Body composition procedures will be performed based on methods described by Heyward and Stolarczyk (32) in a setting of ambient temperature (~23-25 degrees). The study participant will lay supine on a portable mattress, with the arms abducted 45 degrees from the legs (which are less abducted than the arms). All measurements will be performed on the right side of the body.

In addition to BIA, body composition will be evaluated using skinfolds (abdominal, axillary, calf, chest, subscapular, suprailiac, thigh, triceps) that will be measured in triplicate according to standard procedures (32). These sites

will provide an index of overall body fatness, as well as a trunk/extremity fat ratio.

Aerobic Fitness

Each child's aerobic fitness will be estimated using a physical work capacity test in which the child will walk on a treadmill until his/her heart rate achieves 170 $b \cdot min^{-1}$ (PWC-170). This protocol has been used extensively in studies with young children (72,74) and has the advantage of not requiring the child to perform a maximal effort. Although the test is extremely reliable, it will be performed on visits 2 and 3. Each child will be given time to acclimate to the treadmill during the first, as well as second visits (when aerobic fitness will be measured) if necessary.

When the test begins, speed will be set at 4 $km \cdot hr^{-1}$ at 0% grade for two minutes. Speed will remain constant, but grade will increase 5% each subsequent two minutes. This will continue until the child's heart rate exceeds 170 $b \cdot min^{-1}$, or s/he can no longer continue. At this time, the treadmill elevation will return to 0%, and the child will walk for a cool-down period. Each child's aerobic fitness will be estimated by developing a regression line (heart rate vs treadmill elevation) and estimating the grade coincident with 170 $b \cdot min^{-1}$ (72).

Statistical Analysis

Analytic strategies:

The children's blood pressures, body mass indices, change in body mass indices, and body fatness will all be measured on a continuous scale and will then be modeled as continuous outcomes. Each child will have exactly one measurement value for each outcome. Although the child's blood pressure will be measured at several occasions, only an average measurement will be considered. Therefore, linear regression models (ANCOVA) with both continuous and categorical independent variables will be used to model the four primary outcomes (68). These models describe how the mean outcome, for example the blood pressure, depends linearly on the physical activity and other confounding independent variables. The strategy will consist of modeling each of the four main outcomes in relation to each of the confounding variables. Only the confounding variables which are statistically important (at 5% significance level for a two-sided test) will be retained and included in the model containing the main exposure of interest, the physical activity during pregnancy. We will also assess the interaction effects of the physical activity during pregnancy with important confounders on the main outcomes of interest. We will check model fits for individual and systematic departures of the observed and fitted values using informal (e.g., inspection of residuals) and formal methods (based on F- or t-tests). When certain assumptions are not met (e.g., relationships are not linear) we may need to draw upon more recently developed statistical methods such as generalized additive models (GAMs). GAMs are non-parametric

models that use a smoother to provide a graphical depiction of the relationship between an outcome and continuous covariates (30). This approach minimizes the possible bias resulting from misspecification of a parametric model using continuous predictors (for example, linear or polynomial terms). We will also employ descriptive statistics such as means and standard deviations to describe the distributions of the four main outcomes.

Power analysis:

With N=44, we will have a power (1-B) of 0.78 to find a significant ($P<0.05$) correlation of 0.36 between birth weight and child blood pressure. This size correlation is considered moderate, and is likely at the low end of clinical significance. A lower correlation would indicate that the relationship did not exist, because the maternal physical activity is the true cause of the birth weight reduction, not a negative stress such as has been found in some previous studies.

PROTECTION OF HUMAN SUBJECTS

1. Risks to the Subjects

Human Subjects Involvement and Characteristics

Subjects for this project include the offspring of a cohort of women studied previously during their pregnancies. Children's ages will range from 4-6 years. According to conversations with the mothers, the children are all healthy at this time. We are studying these children because our intent is to determine the effect, if any, of their mothers' physical activity levels during pregnancy on their current blood pressures and body size.

Sources of Materials

We will measure resting blood pressure, height, weight, body composition, and current physical activity levels of the child study participants. In addition, we will archive data collected previously including maternal physical activity, birth weight, and gestational length at delivery.

Potential Risks

The potential risks to the child study participants are virtually nonexistent. Blood pressure and anthropometric measures are done routinely in physicians' offices. The maternal data will be archived.

2. Adequacy of Protection Against Risks

Recruitment and Informed Consent

Study participants will be the children born to women who we studied 5-7 years ago in another project. The original cohort have been called to discern their interest. We were able to make contact with 44 of our original 51 maternal

study participants, and all agreed verbally to allow their children to participate. We will obtain permission from the Michigan State University Institutional Review Board (known as the University Committee for Research Involving Human Subjects) before initiating the project. Written informed consent will be obtained from the mothers of our study participant children.

Protection Against Risk

The risks involved with this study are very remote. The study coordinator and PI are trained in the measurements being obtained, so they will be done correctly, with little chance of discomfort to the study participants. Files of the data collected will be kept confidential, in a locked cabinet, and the study participants will not be identified individually.

Potential Benefits

The mothers of the study participants will obtain growth information on their children, as well as current blood pressure measurements. In addition, each mother will be paid $100 for participation and to defray the cost of transportation and parking. There may be no additional benefit to an individual study participant.

Importance of the Knowledge to be Gained

Research over the past two decades has shown clearly that maternal physical activity is rarely acutely harmful to the mother or fetus. However, less is known about the long term effect on the offspring. Results from this study will add significantly to the body of knowledge regarding the role of maternal

physical activity on the growth, development, and potential cardiovascular disease risk to the children.

INCLUSION OF WOMEN

All 44 of our adult study participants will be women. Women will be included in our study due to the nature of our investigation. That is, part of our study design involves evaluating the physical activity level of women during pregnancy.

INCLUSION OF MINORITIES

Due to the fact that we are archiving data collected on a cohort of women who we measured during a previous pregnancy, the extent of our ability to include minority participants is limited to the minorities that enrolled in our original sample (see attached sheet).

INCLUSION OF CHILDREN

Children will be included in our study due to the nature of our investigation. That is, we are studying the offspring of women who we studied previously during their pregnancies. Thus, we will study 44 children of the 44 women (the number contacted at this time) enrolled in our original cohort. The PI and study coordinator are experienced in obtaining all the measures that we will make on the children.

VERTEBRATE ANIMALS

none

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APPENDIX A

Introduction to Revised Application

We thank the obstetrics and maternal-fetal biology subcommittee for their careful evaluation of our proposal. In this introductory section we will address the concerns of each reviewer. Location of significant additions to the proposal will be specified in this introduction, and new passages in the body of the application will be typed in `14 pt Courier Font`.

Responses to Critique 1

Major concerns of reviewer one center around a) incomplete presentation of birth weight data and superficial evaluation of mothers during pregnancy, b) cursory measures proposed to evaluate the children, and c) not studying growth restricted infants and/or children who are hypertensive. We have addressed these specific concerns below.

Incomplete presentation of birth weight data and superficial evaluation of mothers during pregnancy

We agree that we could have done a better job of presenting our birth weight data, and indicating the importance of our finding a significant inverse relationship between maternal physical activity and birth weight. We have now provided our raw birth weight data in the introduction and specific aims section, and have calculated fetal growth ratios (FGR) for each child. We developed FGRs by calculating the ratio our birth weights to the 50%tile for similar gender,

parity, and length of gestation (84). For example, an FGR value of 1.10 indicates that birth weight was 10% greater than the 50th %tile value, after adjusting for gender, parity, and length of gestation. We present these data graphically in our figure. The relationship between FGR and maternal physical activity is significant (and nearly identical to the one calculated using raw birth weights). The correlation was R=-0.45, indicating that maternal physical activity accounts for 20 % of the birth weight variance in this cohort (58). We know of no other exposure variable (i.e., smoking, SES, race, etc) that shows such a strong relationship to birth weight, particularly in such a homogeneous sample and adjusting for gestational age. As the reviewer points out, the fact that physical activity is modifiable may be extremely important when considering maternal behaviors during the antenatal period. Moreover, we found the relationship between FGR and maternal physical activity existed even when just considering the exercise performed at 20 weeks gestation prior to most of the maternal weight gain (58). This finding highlights not only the strength of the relationship, but also the great care we took in performing our original study in the late 1990's. We are very familiar with the physical activity literature, and are confident that these are the most carefully studied women in terms of their physical activity behaviors during pregnancy.

Cursory measures proposed to evaluate the children

There is concern that our proposed measures will not be adequate to address the proposed research aims. While a longer, more longitudinal

approach would result in greater data collection, we do not believe that it would add significantly to the specific aims of this pilot project. Our main outcome measure is blood pressure, with secondary measures of body size, which we will estimate with weight, body mass index, and body fatness (% fat). In addition, we plan to evaluate the children's physical activity and aerobic fitness levels. Body size, physical activity and aerobic fitness are primary exposure variables that have been shown to be related to children's blood pressure levels. Recent guidelines from the American Heart Association discuss the importance of these measures for primary prevention of atherosclerotic cardiovascular disease (37). Thus, we felt it important to measure them in this study, both for their own importance, and also to determine their potential role as confounders or mediators of the relationships among maternal physical activity, birth weight and current child blood pressure. The techniques we are using to obtain these measures are the most valid and reliable available, particularly when considering the age of our sample.

Physical activity will be measured via an accelerometer. It is similar to the one we used so successfully in our previous maternal exercise study, but is an updated version with no buttons to distract the child who is wearing it. The PI is a member of the physical activity working group for the National Children's Study (NCS), and this is the primary measurement mode that we are suggesting to the national advisory group of NCS (personal communication). Any type of physical activity recall instrument to be implemented by the parents is less valid and would likely add to the measurement error. The body

composition technique (bioelectrical impedance) has been shown to be very reliable and valid on young children (28). Treadmill testing the children to a heart rate of 170 beats·min-^{1}, is not a maximal test, but will provide us a valid estimate of their aerobic fitness (72). However, personal experience of investigators who study children's fitness (including the PI) shows that it is very difficult, and perhaps even unethical to perform a maximal test on a healthy young child under the age of 8 years. The PWC 170 is the test of choice in many large-scale children's exercise intervention trials (72,74). Finally, our dietary recall data will provide information regarding the potential role of sodium and/or other nutrient intakes that have been shown to influence childhood blood pressure.

Concern that the sample was not growth restricted, nor will they likely be hypertensive

We agree that very few of our sample children will likely have blood pressures that exceed the 95th %tile for their age and gender. However, we expect there to be a range of blood pressures, some of which will be on the high or low end of normal. Since blood pressure in childhood tends to track into adulthood, children with higher blood pressures are more likely to become hypertensive as adults, and have increased risk for heart disease (11,35,40,47). The same issue is true for body weight and fatness. Children's body size tends to track into adulthood, predisposes them to obesity later in life, which in turn is a significant risk factor for heart disease (11). Our aim is to determine the

interaction of maternal physical activity, which we have shown to be clearly related to birth weight and FGR, with childhood risk factors such as higher than average blood pressure and body size.

Studies showing a relationship between birth weight and blood pressure later in life have not been limited to severely growth restricted infants or children/adults with hypertension. For example, Eriksson et al (23) studied a cohort of over 7000 Finlanders, and found a significant trend for hypertension in adulthood in individuals who weighed between 3000-4000+ grams at birth. Barker et al (8) found significantly higher blood pressures in 10 year-old British children when he compared the lowest tertile birth weights (~3000 g), to the highest (~3700 g). Adair and Cole (1) studied Filipino adolescents and found that, all else being equal, the predicted probability of high blood pressure by mid-adolescence was twice as great if the child was of average (~3000 g) compared to higher (~4000 g) birth weight. All these significant findings were obtained from children and adults whose birth weights were similar to our range of 2753-4943 g. These and other results discussed in the background and significance section support the hypothesis that an inverse relationship can exist between birth weight and blood pressure later in life, even throughout the normal ranges of both measures.

Responses to Critique 2

Major concerns of reviewer two include a) question about how the accelerometer data will be evaluated b) expected changes in blood pressure

and c) limited sample size which may lead to negative findings. We have addressed these specific concerns below.

Accelerometer data analysis

The accelerometer epochs will be set to 30 minutes. In addition, we will record the beginning and ending times the accelerometer is worn, as well as any time it is removed for any reason. Epochs are internal settings that allow the computer to calculate total activity, as well as separate it by time increments; 30 minute increments in this study. Thirty minutes is the time interval most often used in exercise measurement studies, particularly when children are asked to recall their activities throughout the day. By knowing the start and stop time the accelerometer is worn, we can partial the activity into before, during, or after school periods. Thus, we will have significant flexibility in our ability to analyze the children's physical activity behaviors throughout the day. As was stated in the response to reviewer one, the accelerometer is being recommended for use in the National Children's Study because of its measurement validity and flexibility.

Expected differences in blood pressure and limited statistical power

The reviewer raises an important question regarding the differences in blood pressure we would expect to see between lighter vs heavier birth weight children. According to the Second Task Force on blood Pressure Control in Children (71), systolic blood pressures should average ~96±10 mm Hg, and

diastolic pressures will average ~59±11 mm Hg in our sample. Thus, it appears that we will see a fairly normally distributed range of pressures among our study participants. Rather than splitting our sample in half, or tertiles, we plan to evaluate the data on a continuum, using a correlation approach comparing across the range of birth weights vs blood pressures. Then, maternal physical activity will be entered into the model to determine if it modifies the relationship between birth weight and blood pressure. The normal distribution of our data will allow us to use this analytical approach.

Limited sample size and negative findings

Given this analytical approach discussed above, and with a sample size of N=44, we will have a power (1-B) of 0.78 to find a significant (at an alpha level of $P<0.05$) correlation of 0.36 between birth weight and child blood pressure. Although a correlation of this magnitude is considered moderate, it is likely to have meaningful clinical implications, given the many variables that may contribute to birth weight.

We would not interpret a very low or nonexistent relationship between birth weight and blood pressure in offspring as a "negative" finding in the usual sense. This could just as likely indicate that the mothers' physical activity levels dampened this oft-reported relationship. Lack of the expected relationship could indicate that lower birth weight due to maternal physical activity represents a physiologic adaptation, rather than a significant stress affecting development of the child's cardiovascular system. Therefore, whether we find a

relationship between birth weight and blood pressure, or it is removed/dampened due to the influence of maternal physical activity, our results will provide novel and valuable pilot data for future study of the fetal origins hypothesis.

Responses to Critique 3

Major concerns of reviewer three include a) an inability to distinguish between physiology and pathology and b) the study may be underpowered. We have addressed these specific concerns below.

Inability to distinguish between physiology and pathology

We have acknowledged that the sample is not SGA, and there may not be many children with blood pressures above the 95th%tile. However, as discussed above, previous investigators have shown an inverse relationship between birth weight and blood pressure even when both variables are within normal ranges, and that blood pressure in childhood tracks into adulthood. Thus, understanding variables that might relate to blood pressure early in life may help prevent hypertension and subsequent coronary heart disease.

The study may be underpowered

We acknowledge that it would be our desire to have a larger sample size, but this is not likely possible. We may be able to contact and enroll a few more of our 51 previous study participants, but some have moved out of the

country and are not available. However, we would like to stress that this is a pilot project, incorporating a carefully studied cohort in which a significant relationship between maternal physical activity and birth weight has been established. We believe the importance of the study topic offsets our less than optimal sample size.

Overall Response to Reviewers

We hope we have responded adequately to the reviewers' concerns. While we are confident that our measurement techniques are appropriate to address our specific aims, we appreciate the reviewers' concern of small sample size. However, we feel strongly that this meticulously studied cohort of women presents an important opportunity to provide meaningful pilot data in the study of the role of maternal physical activity on the fetal origins hypothesis. Based on the results of this study, our next project will be a more longitudinal approach, using larger sample. However, in order to design an effective longitudinal study, we must first learn what we can from this cohort where we have clearly shown a significant relationship between maternal physical activity and birth weight.


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