Maternal periconceptional physical activity, sedentary behavior, and offspring growth

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Abstract

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Background: Current guidelines recommend regular moderate/vigorous physical activity before and during pregnancy to reduce pregnancy complications. However, the recommendations do not include light physical activity or address fetal and postnatal growth. While reductions in sedentary behavior, in addition to regular moderate/vigorous physical activity, have been recommended for the general population, little is known about the effect of maternal sedentary behavior before and during pregnancy on offspring in utero or postnatal growth. In addition, consequences of long-term patterns of preconception physical activity during young adulthood, offspring sex-specific differences in associations, as well as potential mechanisms of observed associations have not been adequately investigated.

Objectives: The specific aims of this dissertation project were to investigate associations of 1) maternal pre-pregnancy and early pregnancy light physical activity and sedentary behavior with measures of offspring birth size, 2) maternal early pregnancy moderate/vigorous physical activity and sedentary behavior with offspring growth at 12 months of age, 3) trajectories of maternal preconception moderate/vigorous physical activity and sedentary time during adolescence and young adulthood with offspring birthweight, and 4) maternal pre-pregnancy and early pregnancy moderate/vigorous physical activity and epigenetic regulation in maternal peripheral blood.

Methods: Aim 1 was addressed using data from participants (N=3,687) of the Omega study, a pregnancy cohort study based in Seattle, WA. Aim 2 was addressed using data from participants (N=40,638) of the Danish National Birth Cohort (DNBC). Aim 3 was addressed using data from participants (N=1,408) of the National Longitudinal Study of Adolescent to Adult Health (Add Health). Aim 4 was addressed using data and specimens collected from a subset (N=92) of Omega study participants. I used self-reported leisure time physical activity and sedentary behavior before and during pregnancy, information on offspring birth size and offspring weight at 12 months from medical records (Omega study) or maternal report (DNBC and Add Health), and epigenetic biomarkers (DNA methylation and microRNA expression) in peripheral blood (Aim 4), as well as information on relevant covariates in regression (linear and logistic) models and group-based trajectory analyses (Aim 3) to examine associations. Offspring sex-specific associations were evaluated using interaction terms and stratified analyses.

Results: Leisure time walking in the year before pregnancy and in early pregnancy were positively associated (0.8 kg/m^3 comparing the highest tertile to no walking (95% CI: 0.2, 1.4 and 0.2, 1.3, respectively)) with greater offspring ponderal index at birth (Aim 1). Moderate/vigorous leisure time physical activity in early pregnancy was inversely associated (0.01 kg per hour per week (95% CI: -0.02, -0.001)) with offspring weight at 12 months old among males, but not females (Aim 2). Early pregnancy leisure time sedentary behavior was also inversely associated (0.09 kg comparing 5+ hours per day to 0-1 hours per day (95% CI: -0.17, -0.003)) with offspring weight at 12 months old (Aim 2). I identified sex-specific associations of a pattern of preconception moderate/vigorous physical activity characterized by high physical activity at age 15 years followed by decreasing physical activity by age 22 years compared to a pattern of low then decreasing physical activity from ages 15-22 years with 90g (95% CI: -4, 184) greater birthweight and 1.7 (95% CI: 0.9, 3.1) times greater odds of large-for-gestational age among female offspring, but not male offspring (Aim 3). I did not observe associations of pre-pregnancy or early pregnancy yoga practice with offspring birth size (Aim 1) or associations of maternal pre-pregnancy or early pregnancy sedentary behavior with offspring birth size (Aim 1 and 3). Each additional hour per week of pre-pregnancy and early pregnancy moderate/vigorous physical activity were associated with peripheral blood DNA methylation in C1orf212 and circulating miR-146b expression (Aim 4).

Conclusions: Our results support associations of maternal physical activity with offspring birth size, postnatal growth, and maternal epigenetic regulation. Our results also support associations of maternal sedentary behavior with offspring postnatal growth. Several of these associations were sex-specific. Future research in this area, conducted in diverse populations and using objective measurement to capture accurate measures of time spent in these behaviors across multiple domains, will facilitate adoption of effective interventions to promote physical activity among reproductive age and pregnant women and improve maternal and fetal health outcomes.

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INTRODUCTION

Perinatal physical activity, sedentary behavior, and offspring growth

Leisure time moderate/vigorous intensity physical activity is recommended during the perinatal period for its cardiovascular and metabolic benefits to the mother and its potential protective effect against pregnancy complications (1). Recent research supports beneficial associations of light intensity physical activity, the major determinant of variability in total energy expenditure (more time is spent in light activity than moderate/vigorous physical activity) (2), with risk factors for cardiovascular disease, independent of moderate/vigorous intensity physical activity (3-6). A growing body of literature has identified prolonged sedentary behavior, regardless of moderate/vigorous intensity physical activity, as a risk factor for mortality, cardiovascular disease, and risk factors for cardiovascular disease (7). Recently, the American College of Sports Medicine issued recommendations for reduction of total time spent in sedentary behavior in addition to regular moderate/vigorous intensity physical activity (8). The vascular and metabolic changes associated with maternal physical activity or sedentary behavior not only affect the mother but also placental development, the intrauterine environment, and nutrient transfer to the developing fetus (9). Optimal placental function and fetal nutrition can program offspring metabolic axes for healthy postnatal growth (10). Accumulating evidence, including our previous work, supports associations of maternal moderate/vigorous intensity physical activity in the year before pregnancy and during early pregnancy with measures of birth size, including offspring birthweight (11-15) and decreased risk of small- and large-for-gestational age at birth (16, 17), both indicators of fetal growth and life course risk for health and disease (18-20). However, associations of maternal light intensity physical activity or sedentary behavior with birth size as well as associations of periconceptional moderate/vigorous intensity physical activity with offspring postnatal growth are not clear.

Life course approach to perinatal health

Maternal experiences across the life course, including preconception lifestyle behaviors, influence maternal health and preparation for the metabolic changes associated with pregnancy. Physical activity in adolescence and adulthood is associated with cardiovascular and metabolic health benefits, including lower body mass index and body fat (21-23), increased insulin sensitivity (24-26), decreased blood pressure (27, 28), and decreased inflammation (29), that affect maternal health status and subsequently the course of pregnancy. Therefore, a life course approach to healthy pregnancy and fetal development requires consideration of lifestyle and behavior during adolescence and young adulthood (30). However, most previous research on determinants of healthy pregnancy has focused on maternal behaviors during pregnancy or the short time period before the pregnancy. More specifically, associations between long-term preconception patterns of physical activity and sedentary behavior and offspring growth are not well understood.

Maternal physical activity and epigenetic regulation

Identifying mechanisms linking maternal physical activity and offspring growth is important for clarifying causal relationships and can eventually contribute to identification of biological targets for interventions to prevent adverse offspring health outcomes. Currently, mechanisms of associations of perinatal moderate/vigorous physical activity with fetal growth are not well understood. Epigenetic mechanisms of gene expression, including DNA methylation and microRNA expression, have been proposed as regulators of physiologic responses to physical activity (31-33). DNA methylation and microRNA expression may play important roles in maternal health, maternal and fetal response to physical activity or sedentary behavior during pregnancy, as well as placental development and function with critical implications for the fetus (34, 35). However, the literature on epigenetic mechanisms of gene regulation during pregnancy related to maternal physical activity is sparse.

Sex-specific determinants of offspring growth

Differences in male and female fetal growth trajectories and birth size are well known. In addition, previous research suggests that male and female fetuses respond differently to changes in the intrauterine environment (11, 36-39). In our previous investigations, we have found sex-specific associations of maternal moderate/vigorous physical activity before and during pregnancy with offspring birthweight (present only among female offspring) and head circumference (present only among male offspring) (11). Sex-specific associations of maternal diet (vitamin D (40), seafood intake (41)), environmental exposures (cadmium (42, 43)), and stress (44) with offspring birthweight have also been reported. Very few, if any, previous studies, evaluated offspring sex-specific differences in associations of maternal physical activity or sedentary behavior with offspring growth outcomes.

Overview of the dissertation

The specific aims of this dissertation were to investigate associations of 1) maternal pre-pregnancy and early pregnancy light physical activity and sedentary behavior with measures of offspring birth size (birthweight, head circumference, ponderal index), 2) maternal early pregnancy moderate/vigorous physical activity and sedentary behavior with offspring growth at 12 months of age, 3) trajectories of maternal moderate/vigorous preconception physical activity and sedentary time during adolescence and young adulthood with offspring birthweight, and 4) maternal pre-pregnancy and early pregnancy moderate/vigorous physical activity and epigenetic regulation (DNA methylation and microRNA expression) in early/mid pregnancy maternal peripheral blood. I also examined whether these associations differed by offspring sex. The aims of this dissertation were addressed using data from three prospective cohort studies: the Omega study (Aim 1 and 4), the Danish National Birth Cohort (DNBC) (Aim 2), and the National Longitudinal Study of Adolescent to Adult Health (Add Health) (Aim 3). Details about each of these cohorts, approaches used to address each study aim, study findings, and related discussion are provided as follows: Chapter 1 describes the study on associations of pre-pregnancy and early pregnancy walking and yoga practice with offspring birth size. Chapter 2 describes the study on associations of pre-pregnancy and early pregnancy sedentary behavior with offspring birth size. Chapter 3 describes the study on associations of early pregnancy moderate/vigorous physical activity and sedentary behavior with offspring growth at 12 months. Chapter 4 describes the study on associations of trajectories of maternal preconception moderate/vigorous physical activity and sedentary behavior with offspring birthweight. Chapter 5 describes the study on associations of maternal pre-pregnancy and early pregnancy moderate/vigorous physical activity with candidate DNA methylation and circulating microRNAs in maternal peripheral blood. Finally, I provide a summary of the main findings from Chapter 1-5 and discussion of implications of this work and directions for future research.

Chapter 1:

Associations of maternal leisure time walking and yoga with offspring birth size

ABSTRACT

Background: While perinatal walking and yoga have been associated with decreased risks of pregnancy complications, associations with offspring birth size have been inconsistent. We investigated associations of maternal pre-pregnancy and early pregnancy leisure time walking and yoga practice with birth size.

Methods: Participants (N=3,687) of the Omega study, a pregnancy cohort, reported leisure time physical activity duration (hours/week) in the year before pregnancy and in early pregnancy. Birth size was abstracted from medical records. Regression was used to determine mean differences in birthweight, head circumference, and ponderal index. Interaction terms were used to assess effect modification by offspring sex.

Results: About 1/3 of women reported leisure time walking and about 10% reported yoga practice. Women in the highest tertile for pre-pregnancy (1.4-20 hours/week) or early pregnancy (3.1-24 hours/week) walking had offspring with 0.8 kg/m^3 greater ponderal index (95% CI: 0.2, 1.4 and 0.2, 1.3, respectively) compared to women who reported no walking in the respective time periods. Walking was not associated with birthweight or head circumference. Yoga practice was not associated with birth size. Associations were similar by offspring sex.

Conclusions: Leisure time walking may be associated with offspring ponderal index, a measure of leanness at birth and pattern of fetal growth. Future studies confirming this association in diverse populations and investigating mechanisms are warranted.

INTRODUCTION

Light intensity physical activity is the major determinant of variability in total energy expenditure (2), but light intensity physical activity is poorly measured using self-report (45-47). Recent research suggests beneficial associations of light intensity physical activity with risk factors for cardiovascular disease, independent of moderate/vigorous physical activity (3-5). Few studies of light intensity physical activity during pregnancy and offspring birthweight exist and findings were inconsistent (48-51). Although total light intensity physical activity is poorly measured by self-report, specific light intensity activities, such as walking and yoga, may be measured more accurately (52).

Walking is the most common physical activity among pregnant women, with 41% of pregnant women in the United States reporting walking during pregnancy (53). A high level of walking during pregnancy is associated with decreased risk for gestational diabetes mellitus (54), preeclampsia (55), and inadequate/excessive gestational weight gain (56, 57) compared to a low level of walking during pregnancy.

Yoga has been increasing in popularity in the United States, and pregnant women perceive yoga to be a beneficial exercise during pregnancy (58). About 7% of pregnant women practice yoga in the United States (53). Yoga has been associated with decreased risk for preeclampsia, gestational diabetes, and preterm birth (59, 60).

Although walking and yoga have been associated with decreased risk of pregnancy complications, associations with offspring birth size have been inconsistent (57, 59-63). Since both walking and yoga are considered beneficial types of exercise among pregnant women, it is important to understand the potential influence of these leisure time activities on offspring health. Measures of birth size, including birthweight, head circumference, and ponderal index, are indicators of newborn health and risk of future disease over the life course. Birthweight is associated with perinatal morbidity and mortality (64) and risk of obesity and cardiovascular disease in later life (65, 66). Head circumference is an indicator of brain development and associated with neurological development and intelligence in childhood (67). Ponderal index, a measure of leanness, indicates differential patterns of intrauterine growth (symmetric/asymmetric) (68) and has also been positively associated with obesity in adulthood (66).

Previous research supports offspring sex-specific placental and fetal growth responses to maternal characteristics, behaviors, and exposures (36-38, 69), including offspring sex-specific differences in associations of maternal moderate/vigorous leisure time physical activity with offspring birth size that we recently reported (11). Despite these sex-specific associations and differences in fetal growth patterns between males and females, potential differences in associations of maternal walking or yoga practice with offspring birth size by offspring sex have not been examined.

Hence, the objective of this study was to investigate associations of maternal pre-pregnancy and early pregnancy leisure time walking and yoga practice with offspring birth size and to determine if these associations differ by offspring sex.

METHODS

Study setting and study population

Data from participants of the Omega study, a prospective pregnancy cohort, were used for this analysis. Details about the study design and data collection have been published previously (11). Pregnant women were recruited from clinics associated with Swedish Medical

Center and Tacoma General Hospital in Washington State from 1996 to 2008. Women were eligible to participate in the Omega study if they were at least 18 years old, were able to speak and read English, initiated prenatal care prior to 20 weeks gestation, planned to carry the pregnancy to term, and delivered at one of the two study hospitals. Of 5,063 eligible women who were approached, 4,602 agreed to participate (91%). The Omega study was approved by the Institutional Review Boards of Swedish Medical Center and Tacoma General Hospital. All participants provided written informed consent.

Participants with live, singleton births were included in these analyses (N=4,434). Participants with missing data on birthweight (N=304), physical activity (N=265), or other covariates (N=178 and N=310 for pre-pregnancy or early pregnancy analysis, respectively) were also excluded. The final analytic population included 3,687 study participants for pre-pregnancy walking and yoga analyses and 3,555 for early pregnancy walking and yoga analyses.

Data collection

Study participants completed an in-person structured interview with a trained study interviewer at an average of 15 weeks gestation. Information collected during the interview included sociodemographic characteristics (maternal age, race, marital status), reproductive and medical history (parity, height, pre-pregnancy weight), and behaviors before and during pregnancy (physical activity, smoking and alcohol use). Participants were followed until delivery, and study personnel abstracted medical records for information on course and outcomes of the pregnancy (birth size, gestational age at delivery, offspring sex). Pre-pregnancy body mass index (BMI) was calculated using self-reported height and pre-pregnancy weight and categorized according to standard cutoffs (underweight: <18.5 kg/m^2, normal: 18.5–24.9 kg/m^2, overweight: 25–29.9 kg/m^2, obese: ≥30 kg/m^2).

Walking and yoga

Pre-pregnancy leisure time physical activity (i.e., exercise, sports, and recreational physical activity (70)) was assessed in all participants using the following questions: 1) "Which activities did you participate in on a regular basis during the year before you became pregnant?", and for each activity reported: 2) "How many times per week?", 3) "How many months did you regularly participate in this activity?", and 4) "How much time did you spend at the activity per episode?". Participants were provided examples of leisure time physical activity including walking, swimming, jogging, weightlifting, dance/aerobics, bicycling, hiking, and hatha yoga. Participants who reported walking also reported speed of walking. Based on reported activities, average duration of walking per week and average duration of hatha yoga practice per week in the year before pregnancy were calculated. Average energy expenditure of walking per week was calculated by multiplying each individual walking activity duration by its corresponding MET value (depending on speed reported), a measure of energy expenditure of a physical activity defined as the ratio of metabolic rate during a specific activity to a reference resting metabolic rate of 3.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ (71). Individual walking activity MET-hours were summed to obtain average pre-pregnancy leisure time walking energy expenditure.

Early pregnancy physical activity was assessed using similar questions that referenced the week prior to the study interview. Total durations of walking and yoga practice reported in the week prior to the study interview were calculated. Energy expenditure of each walking activity was calculated as described for pre-pregnancy walking, and individual MET-hours were summed to obtain early pregnancy leisure time walking energy expenditure.

Participants were categorized into groups based on any walking or yoga practice in pre-pregnancy and in early pregnancy. Participants who reported any walking were categorized into tertiles of hours per week and separately into tertiles of MET-hours per week of pre-pregnancy and early pregnancy walking. Participants who reported any yoga practice were categorized into tertiles of pre-pregnancy yoga duration and separately into tertiles of early pregnancy yoga duration. Participants were also categorized based on their joint distributions of pre-pregnancy and early pregnancy walking (no walking in pre- or early pregnancy, walking in pre-pregnancy only, walking in early pregnancy only, or walking in both pre- and early pregnancy) and yoga (no yoga in pre- or early pregnancy, yoga in pre-pregnancy only, yoga in early pregnancy only, or yoga in both pre- and early pregnancy).

Birth size

Birthweight (g), head circumference (cm), and birth length (cm) were abstracted from infant medical records. Measurements were made immediately after birth and recorded to the nearest 0.5 cm and 1g by hospital personnel. Ponderal index (kg/m^3) was calculated using birthweight and birth length ($birthweight/birth\ length^3$).

Statistical analyses

Maternal characteristics, maternal behaviors, and offspring characteristics were summarized for the analytic population, by pre-pregnancy walking, and by pre-pregnancy yoga.

Mean and standard deviation was used to describe continuous variables. Frequency and percentage was used to describe categorical variables.

Linear regression was used to estimate mean differences and 95% confidence intervals (CI) for birthweight, head circumference, and ponderal index for some maternal walking or yoga practice and also for tertiles of walking or yoga practice compared to no walking or yoga practice. Models were run separately for pre-pregnancy and early pregnancy. Walking and yoga tertiles were also modeled as a continuous variable to determine P value for linear trend. Regression models were adjusted for potential confounders and precision variables, including maternal age, race (white/non-white), nulliparity (Y/N), at least high school education (Y/N), married (Y/N), pre-pregnancy BMI category (underweight/normal weight/overweight/obese), smoking during pregnancy (Y/N), alcohol use during pregnancy (Y/N), gestational age at delivery (weeks), offspring sex, and moderate/vigorous non-walking or non-yoga leisure time physical activity (quartiles) in pre-pregnancy or early pregnancy (depending on exposure).

Walking and yoga models were also re-run stratified by offspring sex. Two-way multiplicative interaction terms and corresponding P values were used to assess interactions of pre-pregnancy and early pregnancy walking and yoga practice with offspring sex.

A two-sided alpha level of 0.05 was used for statistical significance in all analyses. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary NC).

RESULTS

On average, women were 33 years old, and the majority were non-Hispanic white, married, normal weight pre-pregnancy, and had at least a high school education (Table 1.1). Thirty-two and thirty-eight percent of participants reported leisure time walking in pre-

pregnancy or early pregnancy, respectively. Thirteen and nine percent of participants reported yoga practice in pre-pregnancy or early pregnancy, respectively. Participants delivered infants with 3,458 g birthweight, 35 cm head circumference, and 27 kg/m^3 ponderal index, on average. Participants who walked in pre-pregnancy or practiced yoga were more likely to be nulliparous and had higher levels of moderate/vigorous leisure time physical activity.

Walking

Pre-pregnancy and early pregnancy leisure time walking were independently associated with greater offspring ponderal index (P for trend for both=0.02) (Table 1.2). Women in the highest tertile for pre-pregnancy (1.4-20 hours per week) or early pregnancy (3.1-24 hours per week) leisure time walking had offspring with 0.8 kg/m^3 greater ponderal index (95% CI: 0.2, 1.4 and 0.2, 1.3, respectively) compared to women who reported no leisure time walking in pre-pregnancy. Women with leisure time walking in both pre- and early pregnancy periods had offspring with 0.6 kg/m^3 greater ponderal index (95% CI: 0.1, 1.1) compared to women with no leisure time walking during either time period (Table 1.3).

Pre-pregnancy or early pregnancy walking was not associated with offspring birthweight or head circumference individually (all P for trend> 0.05). However, leisure time walking in both pre- and early pregnancy periods was associated with 0.3 cm smaller head circumference (95% CI: -0.5, -0.1) compared to no leisure time walking during either time period. Leisure time walking in both pre- and early pregnancy was not associated with birthweight (mean difference: -24 g; 95% CI: -65, 16). Results for pre- and early pregnancy leisure time walking energy expenditure were similar to those for corresponding leisure time walking duration (Supplemental Table 1.1). Results were also similar for male and female offspring (Supplemental Table 1.2).

Yoga

Yoga practice during pre-pregnancy or early pregnancy individually or during both time periods was not associated with birthweight, head circumference, or ponderal index (Table 1.4 and 1.5). Results were similar for male and female offspring (Supplemental Table 1.3).

DISCUSSION

Leisure time walking during pre-pregnancy or early pregnancy was associated with 0.8 kg/m^3 greater offspring ponderal index in our large cohort of pregnant women. Pre-pregnancy or early pregnancy yoga practice was not associated with offspring birth size. Observed associations of walking before and during pregnancy with offspring birth size were similar for male and female offspring.

Previous studies of leisure time walking during pregnancy and offspring birth size have assessed offspring birthweight, but none have examined head circumference or ponderal index as outcomes. In a cohort of pregnant women with singleton, term births in Norway, leisure time walking in early pregnancy was associated with lower risk for large-for-gestational age among nulliparous, but not parous women (61). Nulliparous women in the study by Owe et al (61) were active at higher levels than multiparous women, which may explain differences in associations of leisure time walking with offspring birth size in that study. Randomized controlled trials of walking interventions beginning in early to mid-pregnancy have also suggested associations of leisure time walking during pregnancy with lower risk of macrosomia or large-for-gestational age (57, 62).

In our study, we found associations of leisure time walking before and during pregnancy with greater offspring ponderal index, but not with birthweight. The magnitude of association between walking and offspring ponderal index observed in our study is potentially clinically significant. In a previous study, a 1 unit increase in ponderal index at birth was associated with 11% decreased risk for hypertension in adulthood (72). Our results are consistent with associations of leisure time walking with lower birth length. Previous research has shown associations of maternal physical activity during pregnancy with decreased offspring bone mineral content at birth (73). Associations of maternal physical activity during pregnancy with decreased bone mineral density in adult offspring have also been reported in animal models (74). Comparisons between birthweight and ponderal index are useful in determining patterns of intrauterine growth and timing of growth restriction. Low birthweight and normal ponderal index indicate growth restriction that may have started in early pregnancy and continued throughout gestation, while low birthweight and low ponderal index indicate growth restriction that may have started in late pregnancy, resulting in asymmetrical growth (68). Exercise starting in early pregnancy is associated with greater placental growth (rate and volume) throughout pregnancy and at term delivery (75). Walking during early pregnancy may positively affect placental development, promoting increased symmetrical growth and a greater ponderal index at birth.

Previous studies of yoga interventions during pregnancy with offspring birth size have also been limited to assessing associations with birthweight. Among pregnant women in India, yoga intervention was associated with 45% decreased risk for small-for-gestational age (60) and 39% decreased risk of low birthweight (59). A yoga intervention among nulliparous pregnant women in Thailand was not associated with offspring birthweight (assessed continuously), but this study did not assess categories of birthweight (low birthweight or small/large-for-gestational age) (63). We did not find associations of yoga before or during pregnancy with offspring birthweight in our study. This may be due to the shorter duration per week spent in yoga practice in our study population. Women practiced yoga, on average, for 2 hours per week in early pregnancy, which is less than the 3 and 7 hours per week spent in yoga practice in previous intervention studies. Hatha yoga was the only type of yoga practice assessed in the Omega study. Previous studies that have found associations with birthweight have been conducted in India, where yoga practice includes physical postures, breathing, and meditation (59, 60). Hatha yoga practiced in the United States is likely different and may not include all components of yoga practiced in India.

We conducted sensitivity analyses, stratifying yoga models by high/low total moderate/vigorous leisure time physical activity, in order to address the possibility that benefits of a low intensity activity, like yoga, may only be apparent in women with low levels of moderate/vigorous intensity leisure time physical activity. High moderate/vigorous intensity leisure time physical activity was defined using the median total physical activity per week (4.3 hours for pre-pregnancy, 3.0 hours for early pregnancy). Among women with low moderate/vigorous leisure time physical activity, any yoga practice in pre-pregnancy was associated with 85g lower birthweight (95% CI: -159, -11) (Table 1.6). Pre-pregnancy yoga duration was not associated with birthweight among women with high moderate/vigorous physical activity (mean difference=30 g; 95% CI: -19, 78). A possible reason for this could be that in the absence of a significant amount of moderate/vigorous physical activity, yoga practice may be enough to cause placental changes similar to those associated with early pregnancy moderate/vigorous physical activity (76). There was no evidence for interaction of pre-pregnancy or early pregnancy yoga practice with moderate/vigorous physical activity level on offspring head circumference or ponderal index.

Strengths of our study include its large size and prospective design, consideration of two specific, well-defined maternal light intensity physical activities (walking and yoga), exposure assessment during two time periods (before and during pregnancy), and evaluation of multiple measures of birth size. Although self-reported walking and yoga may be more valid than self-reported overall light intensity physical activity, there is still potential for measurement error in our study. Maternal leisure time physical activity, including walking and yoga, was assessed using a questionnaire not validated in pregnant women. Previously, a similar physical activity questionnaire had moderate to good validity (Spearman correlation coefficient=0.12-0.34) and good reliability (intraclass correlation coefficient=0.56-0.82) for moderate/vigorous leisure time physical activity recall in early pregnancy (77), but validity of walking and yoga was not assessed. We did not systematically collect data on other domains of physical activity. The 17% of participants from the full Omega cohort excluded from this analysis were in general similar to participants included in this analysis, except for being less likely to be nulliparous and more likely to be obese (Supplemental Table 1.4). Therefore, there may be potential selection bias in our results since these characteristics are associated with physical activity and birthweight. The Omega study population is mostly active and of high socioeconomic status. Caution must be taken when generalizing results to less active women and women of lower socioeconomic status.

In summary, in the Omega study population, we found independent associations of leisure time walking during pre-pregnancy and early pregnancy with greater offspring ponderal index. Associations of maternal yoga practice before pregnancy with birthweight were not apparent overall but may differ by level of total moderate/vigorous leisure time physical activity.

Future studies confirming these observed associations in diverse populations as well as studies investigating mechanisms of these associations may contribute to clinical recommendations and public health messaging promoting specific physical activities for reproductive age and pregnant women.

Table 1.1. Maternal and offspring characteristics of Omega study participants (n=3,687), Seattle WA, 1996-2008

	Total (n=3687)	**Participated in leisure time pre-pregnancy walking (n=1177)**	**Did not participate in leisure time pre-pregnancy walking (n=2510)**	**Participated in leisure time pre-pregnancy yoga (n=477)**	**Did not participate in leisure time pre-pregnancy yoga (n=3210)**
Maternal characteristics					
Age (years), *mean (SD)*	33 (4.4)	33 (4.1)	33 (4.6)	33 (4.0)	33 (4.5)
Non-Hispanic white race, *n (%)*	3173 (86)	1045 (89)	2128 (85)	420 (88)	2753 (86)
High school education or more, *n (%)*	3561 (97)	1161 (99)	2400 (96)	472 (99)	3089 (96)
Married, *n (%)*	3381 (92)	1104 (94)	2277 (91)	432 (91)	2949 (92)
Nulliparous, *n (%)*	2310 (63)	823 (70)	1487 (59)	346 (73)	1964 (61)
Pre-pregnancy BMI (kg/m^2), *n (%)*					
Underweight (<18.5)	69 (2)	18 (2)	51 (2)	11 (2)	58 (2)
Normal weight (18.5-24.9)	2687 (73)	879 (75)	1808 (72)	380 (80)	2307 (72)
Overweight (25-29.9)	617 (17)	197 (17)	420 (17)	66 (14)	551 (17)
Obese (≥30)	314 (9)	83 (7)	231 (9)	20 (4)	294 (9)
Total gestational weight gain (kg), *mean (SD)*	14 (4.7)	14 (4.5)	14 (4.8)	14 (4.3)	14 (4.7)
Maternal behaviors					
Smoking during pregnancy, *n (%)*	213 (6)	45 (4)	168 (7)	26 (5)	187 (6)
Alcohol use during pregnancy, *n (%)*	346 (9)	120 (10)	226 (9)	45 (9)	301 (9)
Pre-pregnancy non-walking moderate/vigorous leisure time physical activity (hours per week), *median (IQR)*	3.9 (1.7, 6.9)	4.3 (2.4, 7.4)	3.6 (1.4, 6.7)	-	-
Pre-pregnancy non-yoga moderate/vigorous leisure time physical activity (hours per week), *median (IQR)*	4.1 (1.9, 7.2)	-	-	5.1 (2.8, 7.8)	4.1 (1.8, 7.1)
Early pregnancy non-walking moderate/vigorous leisure time physical activity (hours per week), *median (IQR)*	1.0 (0, 4.8)	1.3 (0-4.5)	1.0 (0, 5.0)	-	-
Early pregnancy non-yoga moderate/vigorous leisure time physical activity (hours per week), *median (IQR)*	3.0 (0.8, 6.0)	-	-	3.0 (1.0, 6.0)	3.0 (0.7, 6.0)

Offspring characteristics					
Birthweight (grams), *mean (SD)*	3458 (536)	3457 (545)	3458 (532)	3441 (503)	3460 (541)
Small-for-gestational age, *n (%)*	102 (3)	31 (3)	71 (3)	11 (2)	91 (3)
Large-for-gestational age, *n (%)*	473 (13)	141 (12)	332 (13)	51 (11)	422 (13)
Head circumference at birth (cm), *mean (SD)*	35 (2.2)	35 (2)	35 (2)	35 (2.4)	35 (2)
Ponderal index (kg/m^3), *mean (SD)*	27 (11)	27 (14)	27 (10)	28 (20)	27 (9)
Gestational age at delivery (weeks), *mean (SD)*	39 (1.8)	39 (1.9)	39 (1.7)	39 (1.7)	39 (1.8)
Male, *n (%)*	1901 (52)	610 (52)	1291 (51)	241 (51)	1660 (52)

Abbreviations: SD, standard deviation; BMI, body mass index; IQR, interquartile range

Table 1.2. Associations of pre-pregnancy and early pregnancy leisure time walking duration with offspring birth size

	N	Mean difference[a] (95% CI)		N	Mean difference[a] (95% CI)
Pre-pregnancy walking duration (hours/week)			**Early pregnancy walking duration (hours/week)**		
Birthweight (g)					
Any vs none	3687	-1.1 (-30, 28)	Any vs none	3671	-27 (-56, 3.5)
0	2510	Reference	0	2285	Reference
Tertile 1 (0.1-0.6)	395	3.9 (-40, 48)	Tertile 1 (0.1-1.5)	484	4.0 (-38, 46)
Tertile 2 (0.7-1.3)	394	-19 (-63, 26)	Tertile 2 (1.6-3.0)	477	**-59 (-91, -6.9)**
Tertile 3 (1.4-20)	388	12 (-33, 57)	Tertile 3 (3.1-24)	425	-21(-65, 23)
P for trend		0.96	P for trend		0.08
Head circumference (cm)					
Any vs none	3601	-0.1 (-0.3, 0.0)	Any vs none	3585	-0.1 (-0.3, 0.0)
0	2449	Reference	0	2215	Reference
Tertile 1 (0.1-0.6)	389	-0.2 (-0.4, 0.0)	Tertile 1 (0.1-1.5)	476	0.0 (-0.2, 0.2)
Tertile 2 (0.7-1.3)	383	-0.2 (-0.4, 0.0)	Tertile 2 (1.6-3.0)	473	-0.3 (-0.5, 0.0)
Tertile 3 (1.4-20)	380	0.0 (-0.2, 0.2)	Tertile 3 (3.1-24)	421	-0.1 (-0.3, 0.1)
P for trend		0.33	P for trend		0.12
Ponderal index (kg/m³)					
Any vs none	3639	0.3 (-0.1, 0.7)	Any vs none	3623	0.4 (0.0, 0.8)
0	2477	Reference	0	2249	Reference
Tertile 1 (0.1-0.6)	391	-0.1 (-0.7, 0.5)	Tertile 1 (0.1-1.5)	480	0.5 (0.0, 1.1)
Tertile 2 (0.7-1.3)	388	0.2 (-0.4, 0.8)	Tertile 2 (1.6-3.0)	474	0.1 (-0.4, 0.7)
Tertile 3 (1.4-20)	383	**0.8 (0.2, 1.4)**	Tertile 3 (3.1-24)	420	**0.8 (0.2, 1.3)**
P for trend		**0.02**	P for trend		**0.02**

Abbreviations: CI, confidence interval

[a]Model is adjusted for maternal age (years), white race, nulliparity, pre-pregnancy BMI category (underweight/normal weight/overweight/obese), high school education or more, marital status (married/single), smoking during pregnancy, alcohol use during pregnancy, gestational age at delivery (weeks), offspring sex, and pre-pregnancy non-walking moderate/vigorous leisure time physical activity duration (quartiles) for pre-pregnancy walking analyses or early pregnancy non-walking moderate/vigorous leisure time physical activity duration (quartiles) for early pregnancy walking analyses.

Table 1.3. Associations of joint distributions of pre-pregnancy and early pregnancy leisure time walking with offspring birth size

	N	Mean difference[a] (95% CI)
Birthweight (g)		
No walking in pre- or early pregnancy	1638	Reference
Pre-pregnancy walking only	531	7.8 (-33, 49)
Early pregnancy walking only	758	-22 (-60, 16)
Walking in pre- and early pregnancy	628	-24 (-65, 16)
Head circumference (cm)		
No walking in pre- or early pregnancy	1594	Reference
Pre-pregnancy walking only	514	0.0 (-0.2, 0.2)
Early pregnancy walking only	749	0.0 (-0.2, 0.2)
Walking in pre- and early pregnancy	621	**-0.3 (-0.5, -0.1)**
Ponderal index (kg/m^3)		
No walking in pre- or early pregnancy	1615	Reference
Pre-pregnancy walking only	522	0.1 (-0.4, 0.6)
Early pregnancy walking only	751	0.3 (-0.2, 0.8)
Walking in pre- and early pregnancy	623	**0.6 (0.1, 1.1)**

Abbreviations: CI, confidence interval

[a]Model is adjusted for maternal age (years), white race, nulliparity, pre-pregnancy BMI category (underweight/normal weight/overweight/obese), high school education or more, marital status (married/single), smoking during pregnancy, alcohol use during pregnancy, gestational age at delivery (weeks), offspring sex, pre-pregnancy non-walking moderate/vigorous leisure time physical activity duration (quartiles), and early pregnancy non-walking moderate/vigorous leisure time physical activity duration (quartiles).

Table 1.4. Associations of pre-pregnancy and early pregnancy yoga with offspring birth size

	N	Mean difference[a] (95% CI)		N	Mean difference[a] (95% CI)
Birthweight (g)					
Pre-pregnancy yoga duration (hours/week)			**Early pregnancy yoga duration (hours/week)**		
Any vs none	3687	-6.9 (-47, 33)	Any vs none	3555	9.0 (-38, 56)
0	3210	Reference	0	3220	Reference
Tertile 1 (0.04-0.60)	159	-23 (-89, 43)	Tertile 1 (0.08-1.0)	113	36 (-42, 114)
Tertile 2 (0.61-1.48)	158	-8.4 (-75, 58)	Tertile 2 (1.1-1.5)	111	11 (-68, 90)
Tertile 3 (1.49-13.8)	160	11 (-56, 77)	Tertile 3 (1.6-10.0)	111	-21 (-100, 58)
P for trend		0.99	P for trend		0.94
Head circumference (cm)					
Pre-pregnancy yoga duration (hours/week)			**Early pregnancy yoga duration (hours/week)**		
Any vs none	3601	0.0 (-0.2, 0.2)	Any vs none	3478	0.1 (-0.1, 0.3)
0	3129	Reference	0	3147	Reference
Tertile 1 (0.04-0.60)	157	0.1 (-0.2, 0.5)	Tertile 1 (0.08-1.0)	110	**0.5 (0.1, 0.9)**
Tertile 2 (0.61-1.48)	157	-0.2 (-0.5, 0.1)	Tertile 2 (1.1-1.5)	111	0.0 (-0.4, 0.4)
Tertile 3 (1.49-13.8)	158	0.1 (-0.2, 0.5)	Tertile 3 (1.6-10.0)	110	-0.2 (-0.6, 0.2)
P for trend		0.86	P for trend		0.72
Ponderal index (kg/m^3)					
Pre-pregnancy yoga duration (hours/week)			**Early pregnancy yoga duration (hours/week)**		
Any vs none	3639	0.3 (-0.3, 0.8)	Any vs none	3511	0.7 (0.0, 1.3)
0	3166	Reference	0	3179	Reference
Tertile 1 (0.04-0.60)	157	0.4 (-0.4, 1.3)	Tertile 1 (0.08-1.0)	110	**1.3 (0.3, 2.4)**
Tertile 2 (0.61-1.48)	157	0.4 (-0.4, 1.3)	Tertile 2 (1.1-1.5)	111	0.4 (-0.7, 1.4)
Tertile 3 (1.49-13.8)	159	-0.03 (-0.9, 0.8)	Tertile 3 (1.6-10.0)	111	0.3 (-0.8, 1.3)
P for trend		0.54	P for trend		0.19

Abbreviations: CI, confidence interval

[a]Model is adjusted for maternal age (years), white race, nulliparity, pre-pregnancy BMI category (underweight/normal weight/overweight/obese), high school education or more, marital status (married/single), smoking during pregnancy, alcohol use during pregnancy, gestational age at delivery (weeks), offspring sex, and pre-pregnancy non-yoga moderate/vigorous leisure time physical activity duration (quartiles) for pre-pregnancy yoga analyses or early pregnancy non-yoga moderate/vigorous leisure time physical activity duration (quartiles) for early pregnancy yoga analyses.

Table 1.5. Associations of joint distributions of pre-pregnancy and early pregnancy yoga practice with offspring birth size

	N	Mean difference[a] (95% CI)
Birthweight (g)		
No yoga in pre- or early pregnancy	3036	Reference
Pre-pregnancy yoga only	312	-7.5 (-57, 42)
Early pregnancy yoga only	174	21 (-43, 86)
Yoga in pre- and early pregnancy	165	-3.8 (-70, 62)
Head circumference (cm)		
No yoga in pre- or early pregnancy	2957	Reference
Pre-pregnancy yoga only	309	0.0 (-0.2, 0.2)
Early pregnancy yoga only	172	0.1 (-0.2, 0.5)
Yoga in pre- and early pregnancy	163	0.0 (-0.3, 0.4)
Ponderal index (kg/m^3)		
No yoga in pre- or early pregnancy	2994	Reference
Pre-pregnancy yoga only	309	0.3 (-0.3, 1.0)
Early pregnancy yoga only	172	**1.1 (0.2, 1.9)**
Yoga in pre- and early pregnancy	164	0.3 (-0.6, 1.1)

Abbreviations: CI, confidence interval

[a]Model is adjusted for maternal age (years), white race, nulliparity, pre-pregnancy BMI category (underweight/normal weight/overweight/obese), high school education or more, marital status (married/single), smoking during pregnancy, alcohol use during pregnancy, gestational age at delivery (weeks), offspring sex, pre-pregnancy non-yoga moderate/vigorous leisure time physical activity duration (quartiles), and early pregnancy non-yoga moderate/vigorous leisure time physical activity duration (quartiles).

Table 1.6. Associations of pre-pregnancy and early pregnancy yoga with offspring birth size by total moderate/vigorous leisure time physical activity

LOW MODERATE/VIGOROUS LTPA			**HIGH MODERATE/VIGOROUS LTPA**		
	N	**Mean difference[a] (95% CI)**		**N**	**Mean difference[a] (95% CI)**
Birthweight (g)					
Pre-pregnancy yoga duration (hours/week)			**Pre-pregnancy yoga duration (hours/week)**		
Any vs none	1843	**-85 (-159, -11)**	Any vs none	1844	30 (-19, 78)
0	1708	Reference	0	1502	Reference
Tertile 1 (0.04-0.60)	64	-58 (-162, 47)	Tertile 1 (0.04-0.60)	95	5.3 (-80, 90)
Tertile 2 (0.61-1.48)	54	**-116 (-230, -1.9)**	Tertile 2 (0.61-1.48)	104	52 (-30, 134)
Tertile 3 (1.49-13.8)	17	-89 (-290, 111)	Tertile 3 (1.49-13.8)	143	30 (-41, 101)
P for trend		**0.02**	P for trend		0.21
P for interaction		0.03 for any vs none, 0.08 for categorical			
Early pregnancy yoga duration (hours/week)			**Early pregnancy yoga duration (hours/week)**		
Any vs none	1681	66 (-19, 151)	Any vs none	1874	-6.8 (-64, 51)
0	1588	Reference	0	1632	Reference
Tertile 1 (0.08-1.0)	49	29 (-86, 145)	Tertile 1 (0.08-1.0)	64	40 (-66, 145)
Tertile 2 (1.1-1.5)	36	**148 (14, 282)**	Tertile 2 (1.1-1.5)	75	-45 (-143, 52)
Tertile 3 (1.6-10.0)	8	-77 (-358, 204)	Tertile 3 (1.6-10.0)	103	-7.5 (-92, 77)
P for trend		0.13	P for trend		0.67
P for interaction		0.10 for any vs none, 0.11 for categorical			
Head circumference (cm)					
Pre-pregnancy yoga duration (hours/week)			**Pre-pregnancy yoga duration (hours/week)**		
Any vs none	1794	-0.3 (-0.6, 0.1)	Any vs none	1807	0.2 (-0.1, 0.4)
0	1660	Reference	0	1469	Reference
Tertile 1 (0.04-0.60)	65	-0.1 (-0.6, 0.4)	Tertile 1 (0.04-0.60)	94	0.3 (-0.2, 0.7)
Tertile 2 (0.61-1.48)	54	-0.3 (-0.9, 0.2)	Tertile 2 (0.61-1.48)	103	-0.1 (-0.5, 0.3)
Tertile 3 (1.49-13.8)	17	-0.8 (-1.7, 0.1)	Tertile 3 (1.49-13.8)	141	0.2 (-0.1, 0.6)
P for trend		0.05	P for trend		0.26
P for interaction		0.10 for any vs none, 0.20 for categorical			
Early pregnancy yoga duration (hours/week)			**Early pregnancy yoga duration (hours/week)**		
Any vs none	1650	0.4 (0.0, 0.9)	Any vs none	1828	0.0 (-0.3, 0.3)

0	1559	Reference	0	1588	Reference
Tertile 1 (0.08-1.0)	47	**0.8 (0.2, 1.4)**	Tertile 1 (0.08-1.0)	63	0.4 (-0.1, 0.9)
Tertile 2 (1.1-1.5)	36	0.3 (-0.4, 1.0)	Tertile 2 (1.1-1.5)	75	-0.1 (-0.6, 0.3)
Tertile 3 (1.6-10.0)	8	-1.2 (-2.6, 0.3)	Tertile 3 (1.6-10.0)	102	-0.1 (-0.5, 0.3)
P for trend		0.44	P for trend		0.65
P for interaction		0.12 for any vs none, 0.34 for categorical			
Ponderal index (kg/m³)					
Pre-pregnancy yoga duration (hours/week)			**Pre-pregnancy yoga duration (hours/week)**		
Any vs none	1818	-0.2 (-1.0, 0.5)	Any vs none	1821	0.5 (-0.3, 1.2)
0	1685	Reference	0	1481	Reference
Tertile 1 (0.04-0.60)	63	0.0 (-1.2, 1.1)	Tertile 1 (0.04-0.60)	94	0.7 (-0.6, 1.9)
Tertile 2 (0.61-1.48)	53	-0.3 (-1.5, 1.0)	Tertile 2 (0.61-1.48)	104	0.8 (-0.4, 2.0)
Tertile 3 (1.49-13.8)	17	-0.9 (-3.0, 1.3)	Tertile 3 (1.49-13.8)	142	0.1 (-1.0, 1.1)
P for trend		0.33	P for trend		0.49
P for interaction		0.25 for any vs none, 0.54 for categorical			
Early pregnancy yoga duration (hours/week)			**Early pregnancy yoga duration (hours/week)**		
Any vs none	1663	0.6 (-0.6, 1.7)	Any vs none	1848	**0.8 (0.1, 1.5)**
0	1572	Reference	0	1607	Reference
Tertile 1 (0.08-1.0)	47	1.5 (-0.1, 3.0)	Tertile 1 (0.08-1.0)	63	1.4 (0.0, 2.7)
Tertile 2 (1.1-1.5)	36	-0.1 (-1.9, 1.7)	Tertile 2 (1.1-1.5)	75	0.7 (-0.6, 1.9)
Tertile 3 (1.6-10.0)	8	-1.6 (-5.3, 2.2)	Tertile 3 (1.6-10.0)	103	0.5 (-0.6, 1.6)
P for trend		0.02	P for trend		0.21
P for interaction		0.86 for any vs none, 0.79 for categorical			

Abbreviations: LTPA, leisure time physical activity; CI, confidence interval

[a]Model is adjusted for maternal age (years), white race, nulliparity, pre-pregnancy BMI category (underweight/normal weight/overweight/obese), high school education or more, marital status (married/single), smoking during pregnancy, alcohol use during pregnancy, and gestational age at delivery (weeks).

Supplemental Table 1.1. Associations of pre-pregnancy and early pregnancy leisure time walking energy expenditure with offspring birth size

	N	Mean difference[a] (95% CI)		N	Mean difference[a] (95% CI)
Pre-pregnancy walking energy expenditure (MET-hours/week)			**Early pregnancy walking energy expenditure (MET-hours/week)**		
Birthweight (g)					
0	2510	Reference	0	2285	Reference
Tertile 1 (0.1-3.0)	394	-4.1 (-48, 40)	Tertile 1 (0.1-5.2)	477	-12 (-55, 30)
Tertile 2 (3.1-6.6)	389	-7.1 (-52, 37)	Tertile 2 (5.3-10.9)	446	-29 (-73, 14)
Tertile 3 (6.7-123)	394	7.9 (-37, 52)	Tertile 3 (11-120)	463	-24 (-67, 18)
P for trend		0.91	P for trend		0.14
Head circumference (cm)					
0	2449	Reference	0	2215	Reference
Tertile 1 (0.1-3.0)	389	-0.2 (-0.4, 0.0)	Tertile 1 (0.1-5.2)	471	0.0 (-0.2, 0.2)
Tertile 2 (3.1-6.6)	377	-0.1 (-0.4, 0.1)	Tertile 2 (5.3-10.9)	440	-0.2 (-0.4, 0.0)
Tertile 3 (6.7-123)	386	0.0 (-0.3, 0.2)	Tertile 3 (11-120)	459	-0.1 (-0.3, 0.1)
P for trend		0.27	P for trend		0.13
Ponderal index (kg/m^3)					
0	2477	Reference	0	2249	Reference
Tertile 1 (0.1-3.0)	389	0.0 (-0.6, 0.6)	Tertile 1 (0.1-5.2)	472	0.5 (-0.1, 1.0)
Tertile 2 (3.1-6.6)	384	0.0 (-0.5, 0.6)	Tertile 2 (5.3-10.9)	444	0.2 (-0.3, 0.8)
Tertile 3 (6.7-123)	389	0.8 (0.3, 1.4)	Tertile 3 (11-120)	458	0.7 (0.2, 1.3)
P for trend		0.02	P for trend		0.02

Abbreviations: CI, confidence interval

[a]Model is adjusted for maternal age (years), white race, nulliparity, pre-pregnancy BMI category (underweight/normal weight/overweight/obese), high school education or more, marital status (married/single), smoking during pregnancy, alcohol use during pregnancy, gestational age at delivery (weeks), offspring sex, and pre-pregnancy non-walking moderate/vigorous leisure time physical activity duration (quartiles) for pre-pregnancy walking analyses or early pregnancy non-walking moderate/vigorous leisure time physical activity duration (quartiles) for early pregnancy walking analyses.

Supplemental Table 1.2. Associations of pre-pregnancy and early pregnancy walking with offspring birth size by offspring sex

	FEMALES			MALES	
	N	**Mean difference[a] (95% CI)**		**N**	**Mean difference[a] (95% CI)**
Birthweight (g)					
Pre-pregnancy walking duration (hours/week)			**Pre-pregnancy walking duration (hours/week)**		
Any vs none	1786	21 (-20, 62)	Any vs none	1901	-22 (-63, 20)
0	1219	Reference	0	1291	Reference
Tertile 1 (0.1-0.6)	192	21 (-41, 83)	Tertile 1 (0.1-0.6)	203	-11 (-74, 52)
Tertile 2 (0.7-1.3)	187	11 (-51, 74)	Tertile 2 (0.7-1.3)	207	-47 (-110, 15)
Tertile 3 (1.4-20)	188	31 (-32, 94)	Tertile 3 (1.4-20)	200	-5.5 (-69, 58)
P for trend		0.32	P for trend		0.39
P for interaction		0.31 for any vs none, 0.72 for categorical			
Pre-pregnancy walking energy expenditure (MET-hours/week)			**Pre-pregnancy walking energy expenditure (MET-hours/week)**		
0	1219	Reference	0	1291	Reference
Tertile 1 (0.1-3.0)	198	14 (-47, 75)	Tertile 1 (0.1-3.0)	196	-22 (-86, 42)
Tertile 2 (3.1-6.6)	175	30 (-34, 94)	Tertile 2 (3.1-6.6)	214	-38 (-100, 24)
Tertile 3 (6.7-123)	194	20 (-42, 82)	Tertile 3 (6.7-123)	200	-3.1 (-67, 61)
P for trend		0.34	P for trend		0.48
P for interaction		0.60 for categorical			
Early pregnancy walking duration (hours/week)			**Early pregnancy walking duration (hours/week)**		
Any vs none	1779	-37 (-79, 5.8)	Any vs none	1892	-20 (-62, 23)
0	1159	Reference	0	1126	Reference
Tertile 1 (0.1-1.5)	222	-8.7 (-69, 51)	Tertile 1 (0.1-1.5)	262	14 (-45, 73)
Tertile 2 (1.6-3.0)	198	-43 (-106, 19)	Tertile 2 (1.6-3.0)	279	-53 (-111, 4.4)
Tertile 3 (3.1-24)	200	-39 (-102, 23)	Tertile 3 (3.1-24)	225	-8.4 (-71, 54)
P for trend		0.11	P for trend		0.31
P for interaction		0.73 for any vs none, 0.87 for categorical			
Early pregnancy walking energy expenditure (MET-hours/week)			**Early pregnancy walking energy expenditure (MET-hours/week)**		
0	1159	Reference	0	1126	Reference
Tertile 1 (0.1-5.2)	214	-15 (-76, 46)	Tertile 1 (0.1-5.2)	263	-11 (-70, 48)
Tertile 2 (5.3-10.9)	190	-25 (-88, 39)	Tertile 2 (5.3-10.9)	256	-33 (-93, 27)
Tertile 3 (11-120)	216	-49 (-109, 12)	Tertile 3 (11-120)	247	-7.7 (-68, 52)

P for trend		0.10	P for trend		0.51
P for interaction		0.76 for categorical			
Head circumference (cm)					
Pre-pregnancy walking duration (hours/week)			**Pre-pregnancy walking duration (hours/week)**		
Any vs none	1737	-0.2 (-0.3, 0.0)	Any vs none	1864	-0.1 (-0.3, 0.1)
0	1187	Reference	0	1262	Reference
Tertile 1 (0.1-0.6)	189	-0.2 (-0.5, 0.1)	Tertile 1 (0.1-0.6)	200	-0.2 (-0.5, 0.1)
Tertile 2 (0.7-1.3)	179	-0.2 (-0.5, 0.1)	Tertile 2 (0.7-1.3)	204	-0.1 (-0.4, 0.2)
Tertile 3 (1.4-20)	182	0.0 (-0.3, 0.3)	Tertile 3 (1.4-20)	198	0.0 (-0.4, 0.3)
P for trend		0.46	P for trend		0.54
P for interaction		0.52 for any vs none, 0.89 for categorical			
Pre-pregnancy walking energy expenditure (MET-hours/week)			**Pre-pregnancy walking energy expenditure (MET-hours/week)**		
0	1187	Reference	0	1262	Reference
Tertile 1 (0.1-3.0)	196	-0.2 (-0.5, 0.1)	Tertile 1 (0.1-3.0)	193	-0.2 (-0.5, 0.1)
Tertile 2 (3.1-6.6)	166	-0.2 (-0.5, 0.1)	Tertile 2 (3.1-6.6)	211	-0.1 (-0.4, 0.2)
Tertile 3 (6.7-123)	188	0.0 (-0.3, 0.3)	Tertile 3 (6.7-123)	198	0.0 (-0.4, 0.3)
P for trend		0.36	P for trend		0.53
P for interaction		0.90 for categorical			
Early pregnancy walking duration (hours/week)			**Early pregnancy walking duration (hours/week)**		
Any vs none	1730	-0.1 (-0.3, 0.1)	Any vs none	1855	-0.1 (-0.3, 0.1)
0	1118	Reference	0	1097	Reference
Tertile 1 (0.1-1.5)	218	-0.1 (-0.4, 0.2)	Tertile 1 (0.1-1.5)	258	0.2 (-0.1, 0.5)
Tertile 2 (1.6-3.0)	196	-0.1 (-0.4, 0.1)	Tertile 2 (1.6-3.0)	277	-0.3 (-0.6, 0.0)
Tertile 3 (3.1-24)	198	-0.1 (-0.4, 0.2)	Tertile 3 (3.1-24)	223	-0.1 (-0.4, 0.2)
P for trend		0.42	P for trend		0.14
P for interaction		0.88 for any vs none, 0.35 for categorical			
Early pregnancy walking energy expenditure (MET-hours/week)			**Early pregnancy walking energy expenditure (MET-hours/week)**		
0	1118	Reference	0	1097	Reference
Tertile 1 (0.1-5.2)	211	-0.1 (-0.4, 0.2)	Tertile 1 (0.1-5.2)	260	0.1 (-0.2, 0.4)
Tertile 2 (5.3-10.9)	187	-0.1 (-0.4, 0.2)	Tertile 2 (5.3-10.9)	253	-0.3 (-0.6, 0.0)
Tertile 3 (11-120)	214	-0.1 (-0.4, 0.2)	Tertile 3 (11-120)	245	-0.1 (-0.4, 0.0)
P for trend		0.37	P for trend		0.17

P for interaction		0.66 for categorical			

Ponderal index (kg/m^3)

Pre-pregnancy walking duration (hours/week)			**Pre-pregnancy walking duration (hours/week)**		
Any vs none	1758	0.7 (-0.9, 2.2)	Any vs none	1881	0.2 (-0.4, 0.7)
0	1202	Reference	0	1275	Reference
Tertile 1 (0.1-0.6)	189	1.9 (-0.4, 4.3)	Tertile 1 (0.1-0.6)	202	-0.4 (-1.3, 0.4)
Tertile 2 (0.7-1.3)	182	-0.4 (-2.8, 2.0)	Tertile 2 (0.7-1.3)	206	0.3 (-0.5, 1.2)
Tertile 3 (1.4-20)	185	0.5 (-1.9, 2.8)	Tertile 3 (1.4-20)	198	0.6 (-0.3, 1.4)
P for trend		0.75	P for trend		0.19
P for interaction		0.49 for any vs none, 0.50 for categorical			
Pre-pregnancy walking energy expenditure (MET-hours/week)			**Pre-pregnancy walking energy expenditure (MET-hours/week)**		
0	1202	Reference	0	1275	Reference
Tertile 1 (0.1-3.0)	195	1.9 (-0.4, 4.2)	Tertile 1 (0.1-3.0)	194	-0.2 (-1.1, 0.6)
Tertile 2 (3.1-6.6)	170	-0.6 (-3.0, 1.9)	Tertile 2 (3.1-6.6)	214	0.1 (-0.7, 1.0)
Tertile 3 (6.7-123)	191	0.5 (-1.8, 2.9)	Tertile 3 (6.7-123)	198	0.6 (-0.3, 1.4)
P for trend		0.74	P for trend		0.25
P for interaction		0.68 for categorical			
Early pregnancy walking duration (hours/week)			**Early pregnancy walking duration (hours/week)**		
Any vs none	1751	1.6 (-0.1, 3.2)	Any vs none	1872	0.6 (0.0, 1.2)
0	1138	Reference	0	1111	Reference
Tertile 1 (0.1-1.5)	220	1.9 (-0.4, 4.2)	Tertile 1 (0.1-1.5)	260	1.1 (0.3, 1.8)
Tertile 2 (1.6-3.0)	196	0.0 (-2.4, 2.4)	Tertile 2 (1.6-3.0)	278	0.2 (-0.5, 1.0)
Tertile 3 (3.1-24)	197	3.1 (0.8, 5.5)	Tertile 3 (3.1-24)	223	0.6 (-0.3, 1.4)
P for trend		0.03	P for trend		0.17
P for interaction		0.68 for any vs none, 0.16 for categorical			
Early pregnancy walking energy expenditure (MET-hours/week)			**Early pregnancy walking energy expenditure (MET-hours/week)**		
0	1138	Reference	0	1111	Reference
Tertile 1 (0.1-5.2)	211	1.9 (-0.4, 4.2)	Tertile 1 (0.1-5.2)	261	1.0 (0.2, 1.8)
Tertile 2 (5.3-10.9)	189	0.0 (-2.3, 2.4)	Tertile 2 (5.3-10.9)	255	0.3 (-0.5, 1.1)
Tertile 3 (11-120)	213	2.9 (0.6, 5.2)	Tertile 3 (11-120)	245	0.5 (-0.3, 1.3)
P for trend		0.03	P for trend		0.18
P for interaction		0.18 for categorical			

Abbreviations: CI, confidence interval

[a]Model is adjusted for maternal age (years), white race, nulliparity, pre-pregnancy BMI category (underweight/normal weight/overweight/obese), high school education or more, marital status (married/single), smoking during pregnancy, alcohol use during pregnancy, gestational age at delivery (weeks), and pre-pregnancy non-walking moderate/vigorous leisure time physical activity duration (quartiles) for pre-pregnancy walking analyses or early pregnancy non-walking moderate/vigorous leisure time physical activity duration (quartiles) for early pregnancy walking analyses.

Supplemental Table 1.3. Associations of pre-pregnancy and early pregnancy yoga with offspring birth size by offspring sex

	FEMALES N	FEMALES Mean difference[a] (95% CI)		MALES N	MALES Mean difference[a] (95% CI)
Birthweight (g)					
Pre-pregnancy yoga duration (hours/week)			**Pre-pregnancy yoga duration (hours/week)**		
Any vs none	1786	-46 (-102, 10)	Any vs none	1901	32 (-26, 90)
0	1550	Reference	0	1660	Reference
Tertile 1 (0.04-0.60)	85	-50 (-139, 39)	Tertile 1 (0.04-0.60)	74	12 (-87, 111)
Tertile 2 (0.61-1.48)	75	-65 (-159, 29)	Tertile 2 (0.61-1.48)	83	43 (-51, 137)
Tertile 3 (1.49-13.8)	76	-21 (-115, 73)	Tertile 3 (1.49-13.8)	84	39 (-54, 133)
P for trend		0.21	P for trend		0.25
P for interaction		0.04 for any vs none, 0.26 for categorical			
Early pregnancy yoga duration (hours/week)			**Early pregnancy yoga duration (hours/week)**		
Any vs none	1716	1.9 (-67, 71)	Any vs none	1839	14 (-51, 79)
0	1566	Reference	0	1654	Reference
Tertile 1 (0.08-1.0)	52	41 (-71, 153)	Tertile 1 (0.08-1.0)	61	31 (-78, 140)
Tertile 2 (1.1-1.5)	48	61 (-56, 177)	Tertile 2 (1.1-1.5)	63	-20 (-128, 87)
Tertile 3 (1.6-10.0)	50	-96 (-211, 19)	Tertile 3 (1.6-10.0)	61	32 (-76, 141)
P for trend		0.52	P for trend		0.70
P for interaction		0.82 for any vs none, 0.24 for categorical			
Head circumference (cm)					
Pre-pregnancy yoga duration (hours/week)			**Pre-pregnancy yoga duration (hours/week)**		
Any vs none	1737	-0.1 (-0.4, 0.1)	Any vs none	1864	0.2 (-0.1, 0.5)
0	1506	Reference	0	1623	Reference
Tertile 1 (0.04-0.60)	83	0.0 (-0.4, 0.5)	Tertile 1 (0.04-0.60)	74	0.3 (-0.2, 0.8)
Tertile 2 (0.61-1.48)	74	-0.4 (-0.8, 0.0)	Tertile 2 (0.61-1.48)	83	0.0 (-0.5, 0.4)
Tertile 3 (1.49-13.8)	74	0.0 (-0.5, 0.4)	Tertile 3 (1.49-13.8)	84	0.3 (-0.2, 0.7)
P for trend		0.35	P for trend		0.33
P for interaction		0.09 for any vs none, 0.37 for categorical			
Early pregnancy yoga duration (hours/week)			**Early pregnancy yoga duration (hours/week)**		
Any vs none	1672	0.0 (-0.3, 0.3)	Any vs none	1806	0.2 (-0.2, 0.5)
0	1525	Reference	0	1622	Reference

Tertile 1 (0.08-1.0)	50	0.3 (-0.2, 0.9)	Tertile 1 (0.08-1.0)	60	0.7 (0.1, 1.3)
Tertile 2 (1.1-1.5)	48	-0.1 (-0.7, 0.4)	Tertile 2 (1.1-1.5)	63	0.1 (-0.5, 0.6)
Tertile 3 (1.6-10.0)	49	-0.3 (-0.8, 0.3)	Tertile 3 (1.6-10.0)	61	-0.2 (-0.8, 0.3)
P for trend		0.53	P for trend		0.92
P for interaction		0.32 for any vs none, 0.68 for categorical			
Ponderal index (kg/m^3)					
Pre-pregnancy yoga duration (hours/week)			**Pre-pregnancy yoga duration (hours/week)**		
Any vs none	1758	-0.2 (-0.9, 0.5)	Any vs none	1881	0.7 (-0.1, 1.4)
0	1526	Reference	0	1640	Reference
Tertile 1 (0.04-0.60)	83	-0.1 (-1.2, 1.1)	Tertile 1 (0.04-0.60)	74	1.0 (-0.3, 2.3)
Tertile 2 (0.61-1.48)	74	0.1 (-1.1, 1.3)	Tertile 2 (0.61-1.48)	83	0.7 (-0.6, 1.9)
Tertile 3 (1.49-13.8)	75	-0.6 (-1.7, 0.6)	Tertile 3 (1.49-13.8)	84	0.4 (-0.8, 1.6)
P for trend		0.50	P for trend		0.19
P for interaction		0.10 for any vs none, 0.38 for categorical			
Early pregnancy yoga duration (hours/week)			**Early pregnancy yoga duration (hours/week)**		
Any vs none	1690	0.8 (-0.1, 1.7)	Any vs none	1821	0.5 (-0.3, 1.4)
0	1542	Reference	0	1637	Reference
Tertile 1 (0.08-1.0)	50	1.1 (-0.3, 2.6)	Tertile 1 (0.08-1.0)	60	1.5 (0.0, 2.9)
Tertile 2 (1.1-1.5)	48	1.0 (-0.5, 2.4)	Tertile 2 (1.1-1.5)	63	0.0 (-1.4, 1.4)
Tertile 3 (1.6-10.0)	50	0.3 (-1.1, 1.7)	Tertile 3 (1.6-10.0)	61	0.1 (-1.3, 1.6)
P for trend		0.19	P for trend		0.56
P for interaction		0.69 for any vs none, 0.83 for categorical			

Abbreviations: CI, confidence interval

[a]Model is adjusted for maternal age (years), white race, nulliparity, pre-pregnancy BMI category (underweight/normal weight/overweight/obese), high school education or more, marital status (married/single), smoking during pregnancy, alcohol use during pregnancy, gestational age at delivery (weeks), and pre-pregnancy non-yoga moderate/vigorous leisure time physical activity duration (quartiles) for pre-pregnancy yoga analyses or early pregnancy non-yoga moderate/vigorous leisure time physical activity duration (quartiles) for early pregnancy yoga analyses.

Supplemental Table 1.4. Comparison of maternal and offspring characteristics of included and excluded participants, Seattle WA, 1996-2008

	Full Cohort[a] (n=4434)		Analytic Sample (n=3687)	Excluded Participants (n=747)	
Maternal characteristics	**N with data**			**N with data**	
Age (years), *mean (SD)*	4382	33 (4.6)	33 (4.4)	695	33 (5.4)
Non-Hispanic white race, *n (%)*	4382	3724 (85)	3173 (86)	695	551 (79)
High school education or more, *n (%)*	4074	3920 (96)	3561 (97)	387	359 (93)
Married, *n (%)*	4385	3970 (91)	3381 (92)	698	589 (84)
Nulliparous, *n (%)*	4382	2643 (60)	2310 (63)	695	333 (48)
Pre-pregnancy BMI (kg/m^2), *n (%)*	4434			747	
Underweight (<18.5)		81 (2)	69 (2)		12 (2)
Normal weight (18.5-24.9)		3140 (71)	2687 (73)		453 (61)
Overweight (25-29.9)		738 (17)	617 (17)		121 (16)
Obese (≥30)		475 (11)	314 (9)		161 (21)
Total gestational weight gain (kg), *mean (SD)*	4302	13 (5.2)	14 (4.7)	621	11 (6.4)
Maternal behaviors					
Smoking during pregnancy, *n (%)*	4054	242 (6)	213 (6)	367	29 (8)
Alcohol use during pregnancy, *n (%)*	4261	398 (9)	346 (9)	574	52 (9)
Pre-pregnancy non-walking moderate/vigorous leisure time physical activity (hours per week), *median (IQR)*	3966	3.9 (1.7, 6.9)	3.9 (1.7, 6.9)	279	3.9 (1.6, 7.6)
Pre-pregnancy non-yoga moderate/vigorous leisure time physical activity (hours per week), *median (IQR)*	3966	4.2 (1.9, 7.2)	4.1 (1.9, 7.2)	279	4.3 (2.0, 7.8)
Early pregnancy non-walking moderate/vigorous leisure time physical activity (hours per week), *median (IQR)*	3879	1.5 (0, 5.0)	1.0 (0, 4.8)	324	2.3 (0, 7.5)
Early pregnancy non-yoga moderate/vigorous leisure time physical activity (hours per week), *median (IQR)*	3879	3.0 (0.8, 6.3)	3.0 (0.8, 6.0)	324	3.5 (0.8, 8.3)
Offspring characteristics					
Birthweight (grams), *mean (SD)*	4130	3448 (558)	3458 (536)	443	3370 (708)
Birthweight-for-gestational age, *n (%)*	4121			439	
Small-for-gestational age,		114 (3)	102 (3)		12 (3)
Large-for-gestational age,		525 (13)	473 (13)		52 (12)
Head circumference at birth (cm), *mean (SD)*	4028	35 (2)	35 (2.2)	427	35 (2.2)
Ponderal index (kg/m^3), *mean (SD)*	4071	27 (17)	27 (11)	430	30 (40)
Gestational age at delivery (weeks), *mean (SD)*	4200	38 (3.8)	39 (1.8)	513	35 (9.0)
Male, *n (%)*	4122	2110 (51)	1901 (52)	435	209 (48)

Abbreviations: SD, standard deviation; BMI, body mass index; IQR, interquartile range
[a]Participants with live, singleton births

Chapter 2:

Maternal sedentary behavior during pre-pregnancy and early pregnancy and offspring birth size: a cohort study

ABSTRACT

Background: Sedentary behavior is associated with adverse health outcomes in the general population. Associations between maternal sedentary behavior during pregnancy and birth size have been inconsistent. While previous research suggests that male and female fetuses respond differently to maternal behaviors, such as physical activity, the role of infant sex in sedentary behavior-birth size associations has not been examined.

Methods: Participants (N=1,535) in the Omega study, a pregnancy cohort in Washington State (1996-2008), reported leisure time sedentary behavior (non-work time spent sitting), light intensity physical activity, and moderate/vigorous leisure time physical activity duration in the year before pregnancy and in early pregnancy (mean 15 weeks). Offspring birth size was abstracted from delivery records. Non-parametric calibration weighting was used to assign adjustment weight (to match the distribution of sociodemographic and medical characteristics of the full cohort) to participants with available sedentary behavior data (N=4,128). Weighted linear regression models were used to estimate mean differences in offspring birthweight, head circumference, and ponderal index (birthweight/length^3) associated with leisure time sedentary behavior. Regression models were run overall and stratified by offspring sex. Isotemporal substitution modeling was used to determine mean differences in birthweight associated with replacing sedentary behavior with light or moderate/vigorous physical activity.

Results: On average, women spent 2.3 and 2.6 hours per day in leisure time sedentary behavior during pre- and early pregnancy, respectively. There were no associations of pre-pregnancy leisure time sedentary behavior with birthweight, head circumference, or ponderal index (β=-12, 95% CI: -28, 4.1; β=0.0, 95% CI: -0.04, 0.1; and β=0.1, 95% CI: -0.2, 0.4, respectively). Early pregnancy sedentary behavior was also not associated with birth size. Associations of sedentary behavior with birth size did not differ by offspring sex. Replacing sedentary time with light or moderate/vigorous physical activity was not associated with birthweight.

Conclusions: We did not observe associations of maternal sedentary behavior during pre- or early pregnancy with offspring birth size. Pre-pregnancy and early pregnancy sedentary behavior may have important adverse effects on maternal health, but our results do not support associations with offspring birth size.

BACKGROUND

A growing body of literature has identified prolonged sedentary behavior, independent of moderate/vigorous leisure time physical activity, as a risk factor for mortality, diabetes mellitus, and cardiovascular disease (7, 78). Recognizing the adverse health impact of sedentary behavior, the American Heart Association recently issued an advisory to "Sit less, move more" (79), and the American College of Sports Medicine issued recommendations for reduction of total time spent in sedentary behavior in addition to recommended levels of regular physical activity (8).

Similar to the general population, pregnant women may spend as much as half of their day being sedentary, if not more (80, 81). Sedentary behavior during pregnancy has been associated with increased risk for gestational diabetes mellitus (82), a strong risk factor for macrosomia (83). The adverse cardiometabolic changes associated with maternal sedentary behavior, including increased blood pressure and triglycerides in addition to changes in glucose metabolism (84), may affect the intrauterine environment and fetal development. An altered intrauterine environment may adversely affect fetal nutrition in the short term, possibly resulting in increased risk for fetal overgrowth, and programming of somatotrophic axes regulating metabolism and postnatal growth in the long term (85). Birthweight and ponderal index are associated with risk of obesity and cardiovascular disease in later life (65, 66). Head circumference is associated with neurological development and intelligence in childhood (67).

Previous reports of associations of maternal sedentary behavior during pregnancy and offspring birth size, an indicator of newborn health and risk of future disease, have been inconsistent. Investigators have found associations of sedentary behavior during pregnancy with lower birthweight (48, 86) or macrosomia (87), while other studies have found no associations (51, 88, 89). All previous studies have considered sedentary behavior independently of other leisure time activities, such as light intensity or moderate/vigorous intensity physical activity, which sedentary behavior may be replacing. Leisure time sedentary behavior, light intensity physical activity, and moderate/vigorous physical activity can be considered together in analyses involving substitution modeling, a more informative approach that addresses the relationships between leisure time behaviors. This approach considers substitution of one type of activity for another, rather than independent associations of each type of activity with outcomes in single activity regression models. Moreover, despite sex-specific fetal growth patterns [15] and sex-specific differences in response to changes in the intrauterine environment [16] and maternal behaviors, such as physical activity [17], the role of infant sex in associations of sedentary behavior and offspring birth size has not been examined.

The objective of this study was to investigate associations of maternal pre-pregnancy and early pregnancy leisure time sedentary behavior with offspring birth size using single activity regression models and substitution modeling, and to examine if associations differ by offspring sex.

METHODS

Study setting and study population

Data from the Omega study, a prospective pregnancy cohort, were used for the current analyses. Details about the study design and data collection have been published previously (90). Briefly, pregnant women were recruited from clinics associated with Swedish Medical Center and Tacoma General Hospital in Washington State from 1996 to 2008. Women were eligible to participate in the Omega study if they were at least 18 years old, were able to speak and read English, initiated prenatal care prior to 20 weeks gestation, planned to carry the pregnancy to term, and delivered at one of the two study hospitals. Of 5,063 eligible women who were approached, 4,602 agreed to participate (91%). The Omega study was approved by the Institutional Review Boards of Swedish Medical Center and Tacoma General Hospital. All participants gave written informed consent.

Participants with live, singleton births were considered for inclusion in the current analyses (N=4,434). Participants with missing data on birthweight (N=304) were excluded. Sedentary behavior data was available for participants who enrolled in the Omega study in 2003-2008, as information on sedentary behavior was collected only during this period of the study (N=1,406 for pre-pregnancy, N=1,568 for early pregnancy). Participants with missing data for smoking (N=11), alcohol use (N=16), or other covariates (N=6) were also excluded. A total of 1,373 study participants remained for pre-pregnancy sedentary behavior analyses and 1,535 remained for early pregnancy sedentary behavior analyses after these exclusions (Table 2.1).

Data collection

Study participants completed an in-person structured interview with a trained study interviewer at an average of 15 weeks gestation. Information collected during the interview included sociodemographic characteristics (maternal age, race, marital status), reproductive and medical history (parity, height, pre-pregnancy weight), and behaviors before and during pregnancy (sedentary behavior, physical activity, smoking and alcohol use). Participants were followed until delivery, and study personnel abstracted medical records for information on course and outcomes of the pregnancy (birth size, gestational age at delivery, offspring sex). Pre-pregnancy body mass index (BMI) was calculated using reported height and pre-pregnancy weight and categorized according to standard cutoffs (underweight: <18.5 kg/m^2, normal: 18.5–24.9 kg/m^2, overweight: 25–29.9 kg/m^2, obese: ≥30 kg/m^2).

Sedentary behavior

Pre-pregnancy leisure time sedentary behavior was assessed using the following questions: 1) "In the year before you became pregnant, how many hours per day did you sit quietly and watch TV?" and 2) "In the year before you became pregnant, how many hours per day did you sit quietly and perform an activity such as reading or knitting?". Early pregnancy leisure time sedentary behavior was assessed using the same questions but for the period of time since becoming pregnant. Total leisure time sedentary behavior per day was calculated by summing responses for these two questions, separately for pre-pregnancy and early pregnancy periods. Participants were also categorized into groups based on quartiles of pre-pregnancy sedentary behavior as well as quartiles of early pregnancy sedentary behavior.

Birth size

Birthweight (g), head circumference (cm), and birth length (cm) were abstracted from infant medical records. Measurements were made immediately after birth and recorded to the nearest 0.5 cm and 1 g by hospital personnel. Ponderal index (kg/m^3) was calculated using birthweight and birth length (birthweight/birth $length^3$).

Statistical analysis

Maternal characteristics, maternal behaviors, and offspring characteristics were summarized for the full Omega cohort and the analytic populations. Continuous variables were described using mean and standard deviation. Categorical variables were described using frequency and percentage.

Participants with available data on pre-pregnancy or early pregnancy sedentary behavior were assigned adjustment weights (to match the distribution of age, race, parity, pre-pregnancy

BMI, and marital status of the full Omega study cohort) using non-parametric calibration weighting (91). This missing data approach increases the precision of estimates over a complete case analysis because it uses information from the full study cohort (92). Weighted linear regression was used to estimate mean differences and 95% confidence intervals (CI) for birthweight, head circumference, and ponderal index for maternal sedentary behavior as a continuous and categorical (quartiles) exposure. Models were run separately for pre-pregnancy and early pregnancy. Sedentary behavior quartiles were also modeled as a continuous variable to determine P values for linear trend. Regression models were adjusted for maternal age, race (white/non-white), nulliparity (Y/N), at least high school education (Y/N), being married (Y/N), pre-pregnancy BMI category (underweight/normal weight/overweight/obese), smoking during pregnancy (Y/N), alcohol use during pregnancy (Y/N), moderate/vigorous leisure time physical activity (quartiles) in pre-pregnancy or early pregnancy (depending on exposure), gestational age at delivery (weeks), and offspring sex. Models were also run stratified by offspring sex. Two-way multiplicative interaction terms and corresponding P values were used to assess statistical significance of interactions by offspring sex.

We also conducted isotemporal substitution modeling analyses (93) to determine mean differences in offspring birthweight associated with replacing leisure time sedentary behavior with light physical activity or moderate/vigorous physical activity. For these analyses, light physical activity duration was calculated from reported activities with a MET value <3 (94). The regression models contain terms for total leisure time duration (calculated as the sum of average leisure time moderate/vigorous physical activity, light physical activity, and sedentary behavior), moderate/vigorous leisure time physical activity duration, light leisure time physical activity duration, and adjustment covariates listed above. Models were run separately for pre-pregnancy and early pregnancy. Results from this model are interpreted as the mean change in birthweight of increasing one parameter (hours per week of light or moderate/vigorous physical activity) at the expense of time spent in sedentary behavior (the component of total leisure time not included as a variable in the model), while keeping the other variables constant. Isotemporal substitution models were also stratified by low/high sedentary time. High sedentary time was defined using the median sedentary time (14 hours/week in pre-pregnancy, 17 hours/week in early pregnancy). Two-way multiplicative interaction terms and corresponding P values were used to assess interaction by low/high sedentary time.

A two-sided alpha level of 0.05 was used for statistical significance in all analyses. Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary NC) and R 3.0.2 (95).

RESULTS

Omega participants were 33 years old, on average. The majority were non-Hispanic white, married, and 97% had more than a high school education (Table 2.1). Women spent about 2 hours per day in sedentary time pre-pregnancy and about 3 hours in sedentary time during early pregnancy. Pre-pregnancy and early pregnancy sedentary time were strongly correlated (ρ=0.6). Characteristics were similar for participants included in pre-pregnancy or early pregnancy analyses and participants in the full Omega study.

Although offspring birthweight was lower by 12 g (95% CI: -28, 4.1) for each additional hour spent in pre-pregnancy sedentary behavior, there were no statistically significant associations between pre-pregnancy leisure time sedentary behavior or early pregnancy leisure time sedentary behavior and offspring birthweight (Table 2.2). There were no associations of pre-pregnancy or early pregnancy leisure time sedentary behavior with head circumference or ponderal index. Associations of pre-pregnancy or early pregnancy sedentary behavior with birth size were similar in male and female offspring (Table 2.3).

Similarly, there were no statistically significant associations when replacing leisure time sedentary behavior with light physical activity or moderate/vigorous physical activity (all $P>0.05$) (Table 2.4). Estimates for differences in birthweight associated with replacing leisure time sedentary behavior with light physical activity or moderate/vigorous physical activity were similar in women with low or high levels of sedentary time.

DISCUSSION

In our study, we did not observe associations between pre-pregnancy or early pregnancy leisure time sedentary behavior and offspring birth size. Replacing sedentary behavior with light or moderate/vigorous physical activity did not change results. In addition, we did not observe effect modification of associations by offspring sex.

Our findings are similar to several (51, 88, 89), but not all (48, 86, 87), reports. Prospective cohort studies of singleton births in the United Kingdom (51), the Netherlands (88), and India (89), with either objectively measured or self-reported sedentary behavior in early, mid, and late pregnancy did not find associations of duration of sedentary time or percent of total time spent in sedentary behavior with birthweight. These studies were small, with study sizes ranging from 111 to 546 participants, and may not have been adequately powered to detect smaller, but still clinically important differences in birthweight. A larger prospective cohort study of singleton births (N=11,759) in the United Kingdom by Hayes et al found that a sedentary lifestyle in early and mid-pregnancy was associated with 21 g (95% CI: -3.5, -40) and 22 g (95% CI: -3.7, -40) lower offspring birthweight, respectively, compared to an active lifestyle (86). In the study by Hayes et al, sedentary behavior was characterized by self-report of 'mostly sitting' during the day and duration of sedentary behavior was not quantified. A case-control study in Brazil reported 30% higher risk for intrauterine growth restriction (OR=1.30; 95% CI: 1.27, 1.31) associated with sedentary behavior (watching TV) ≥4 hours per day compared to <1.5 hours per day during mid-pregnancy (48), but the higher risk observed may be an overestimate due to absence of control for potential confounding variables. A cross-sectional study in Ireland reported that women who delivered macrosomic infants spent 2.0 more hours per day (95% CI: 0.3, 3.7) in sedentary time during late pregnancy compared to women who delivered normal weight infants (87). In that study, sedentary behavior included sleep, which has also been associated with offspring birth size (96), and this may explain the observed association between sedentary behavior and macrosomia. Our study addressed limitations of previous studies by controlling for several potential confounders and quantifying leisure time sedentary behavior duration. Additionally, we evaluated the effect of replacing leisure time sedentary behavior with light physical activity or moderate/vigorous physical activity in a substitution model.

Strengths of our study include its prospective design, multiple measures of birth size, and use of non-parametric calibration weighting to address missing data and increase the power of our study. Despite this approach to missing data, our study may not have been adequately powered to detect small differences in birthweight that have been reported in previous studies. Omega study participants were generally healthy, with high participation in physical activity, low smoking rates, and other healthy behaviors. Our population may be less sedentary than other populations as the average sedentary time in our population was much lower than in the general population. Sedentary behavior was also recalled and self-reported, and we only assessed a limited number of sedentary behaviors (watching TV and quiet activities such as reading and knitting), which may have introduced measurement error into our study. However, self-reported time spent watching television has been shown to be a good indicator of sedentary behavior compared to accelerometer and activity diary data on time spent watching television (r=0.83) in non-pregnant women, though self-report generally underestimated time spent watching television compared to accelerometer and activity diary data (97). Validity of self-reported time spent watching television as a measure of sedentary behavior may be different during pregnancy. Finally, the majority of participants in the Omega study were of high socioeconomic status, and results may not be generalizable to more socioeconomically diverse populations. Future studies of sedentary behavior during pregnancy, conducted among diverse populations, should assess a range of sedentary behaviors across leisure time, occupational, and transportational domains using objective measurement to more accurately capture sedentary behavior in this population.

CONCLUSIONS

In summary, we did not find associations of pre-pregnancy or early pregnancy sedentary time and offspring birth size. Pre-pregnancy and early pregnancy sedentary behavior may have important adverse effects on maternal health, but our results do not support associations of maternal sedentary behavior before or during pregnancy with offspring birth size.

Table 2.1. Maternal and offspring characteristics of the full Omega cohort, participants included in the current pre-pregnancy and early pregnancy analyses, and participants missing pre- or early pregnancy sedentary behavior data

	Full Omega cohort (n=4,128)	**Pre-pregnancy analysis[a] (n=1,373)**	**Early pregnancy analysis[a] (n=1,535)**	**Missing pre- or early pregnancy sedentary behavior data**
Maternal characteristics				
Age (years), *mean (SD)*	33 (5)	33 (4)	33 (4)	32 (5) (n=2,756)
Non-Hispanic white race, *n (%)*	3504 (85)	1196 (87)	1329 (87)	447 (16) (n=2,756)
High school education or more, *n (%)*	3733 (96)	1337 (97)	1496 (97)	2397 (96) (n=2,498)
Married, *n (%)*	3746 (91)	1263 (92)	1417 (92)	2484 (90) (n=2,756)
Nulliparous, *n (%)*	2510 (61)	803 (58)	894 (58)	1708 (62) (n=2,756)
Pre-pregnancy BMI, *n (%)*				(n=2,756)
Underweight (<18.5 kg/m^2)	76 (2)	28 (2)	31 (2)	1965 (71)
Normal weight (18.5-24.9 kg/m^2)	2961 (72)	997 (73)	1121 (73)	48 (20
Overweight (25-29.9 kg/m^2)	700 (17)	250 (18)	273 (18)	450 (16)
Obese (≥30 kg/m^2)	391 (9)	98 (7)	110 (7)	293 (11)
Total gestational weight gain (kg), *mean (SD)*	14 (5)	14 (4)	14 (5)	14 (5) (n=2,744)
Maternal behaviors				
Smoking during pregnancy, *n (%)*	225 (6)	71 (5)	80 (5)	154 (6) (n=2,479)
Alcohol use during pregnancy, *n (%)*	375 (9)	167 (12)	172 (11)	209 (8) (n=2,694)
Pre-pregnancy sedentary time (hours per day)[a], *mean (SD)*	2.3 (1.4)	2.3 (1.3)	2.3 (1.3)	2.1 (1.5) (n=34)
Early pregnancy sedentary time (hours per day)[a], *mean (SD)*	2.6 (1.6)	2.7 (1.6)	2.6 (1.5)	2.6 (1.5) (n=196)
Pre-pregnancy moderate/vigorous leisure time physical activity (hours per week), *median (IQR)*	4.3 (5.4)	4.5 (4.7)	4.4 (4.6)	4.2 (5.9) (n=2,396)
Early pregnancy moderate/vigorous leisure time physical activity (hours per week), *median (IQR)*	3.0 (5.7)	2.3 (3.6)	2.3 (3.8)	4.0 (7.7) (n=2,322)
Offspring characteristics				
Birthweight (grams), *mean (SD)*	3449 (555)	3447 (524)	3440 (534)	3451 (570) (n=2,756)
Gestational age at delivery (weeks), *mean (SD)*	39 (2)	39 (2)	39 (2)	39 (2) (n=2,752)
Male, *n (%)*	2110 (51)	738 (54)	830 (54)	1373 (50) (n=2,747)

[a]Sedentary behavior data was collected in 2003-2008 only.

Table 2.2. Associations of pre-pregnancy and early pregnancy sedentary time with offspring birth size

	N	Mean difference[a] (95% CI)		N	Mean difference[a] (95% CI)
Birthweight (g)					
Pre-pregnancy sedentary time (hours/day)			**Early pregnancy sedentary time (hours/day)**		
Continuous (hours)	1373	-12 (-28, 4.1)	Continuous (hours)	1535	-0.8 (-15, 13)
Quartile 1 (0.0-1.4)	327	Reference	Quartile 1 (0.0-1.5)	418	Reference
Quartile 2 (1.5-2.0)	409	-29 (-90, 31)	Quartile 2 (1.6-2.4)	340	11 (-48, 69)
Quartile 3 (2.1-2.9)	220	-46 (-119, 26)	Quartile 3 (2.5-3.1)	395	16 (-42, 75)
Quartile 4 (3.0-13)	417	-51 (-114, 11)	Quartile 4 (3.2-13)	382	-18 (-80, 44)
P for trend		0.11	P for trend		0.64
Head circumference (cm)					
Pre-pregnancy sedentary time (hours/day)			**Early pregnancy sedentary time (hours/day)**		
Continuous (hours)	1362	0.0 (-0.04, 0.1)	Continuous (hours)	1524	0.1 (-0.03, 0.2)
Quartile 1 (0.0-1.4)	323	Reference	Quartile 1 (0.0-1.5)	413	Reference
Quartile 2 (1.5-2.0)	405	0.2 (-0.1, 0.6)	Quartile 2 (1.6-2.4)	338	-0.2 (-0.5, 0.1)
Quartile 3 (2.1-2.9)	220	**0.6 (0.2, 0.9)**	Quartile 3 (2.5-3.1)	393	0.1 (-0.2, 0.4)
Quartile 4 (3.0-13)	414	0.1 (-0.2, 0.4)	Quartile 4 (3.2-13)	380	0.1 (-0.3, 0.5)
P for trend		0.45	P for trend		0.40
Ponderal index (kg/m^3)[b]					
Pre-pregnancy sedentary time (hours/day)			**Early pregnancy sedentary time (hours/day)**		
Continuous (hours)	1364	0.1 (-0.2, 0.4)	Continuous (hours)	1525	0.0 (-0.3, 0.4)
Quartile 1 (0.0-1.4)	324	Reference	Quartile 1 (0.0-1.5)	414	Reference
Quartile 2 (1.5-2.0)	406	0.6 (-0.5, 1.6)	Quartile 2 (1.6-2.4)	339	-1.5 (-3.1, 0.2)
Quartile 3 (2.1-2.9)	219	0.5 (-0.7, 1.7)	Quartile 3 (2.5-3.1)	392	-0.8 (-2.5, 0.8)
Quartile 4 (3.0-13)	415	0.6 (-0.2, 1.5)	Quartile 4 (3.2-13)	380	-0.7 (-2.5, 1.0)
P for trend		0.25	P for trend		0.53

[a]Weighted model is adjusted for maternal age (years), white race, nulliparity, pre-pregnancy BMI category (underweight/normal weight/overweight/obese), high school education or more, marital status (married/single), smoking during pregnancy, alcohol use during pregnancy, gestational age at delivery (weeks), offspring sex, and pre-pregnancy moderate/vigorous leisure time physical activity duration (quartiles) for pre-pregnancy sedentary time analyses or early pregnancy moderate/vigorous leisure time physical activity duration (quartiles) for early pregnancy sedentary time analyses.
[b]Results are excluding outliers (n=10) for ponderal index (>400 kg/m^3).

Table 2.3. Associations of pre-pregnancy and early pregnancy sedentary time with offspring birth size by offspring sex

	FEMALES			**MALES**	
	N	**Mean difference[a] (95% CI)**		**N**	**Mean difference[a] (95% CI)**
Birthweight (g)					
Pre-pregnancy sedentary time (hours/day)			**Pre-pregnancy sedentary time (hours/day)**		
Continuous (hours)	635	-9.9 (-29, 9.6)	Continuous (hours)	738	-14 (-41, 13)
Quartile 1 (0.0-1.4)	139	Reference	Quartile 1 (0.0-1.4)	188	Reference
Quartile 2 (1.5-2.0)	186	-6.8 (-96, 84)	Quartile 2 (1.5-2.0)	223	-39 (-120, 43)
Quartile 3 (2.1-2.9)	105	-68 (-175, 39)	Quartile 3 (2.1-2.9)	115	-14 (-110, 83)
Quartile 4 (3.0-13)	205	-54 (-145, 37)	Quartile 4 (3.0-13)	212	-38 (-124, 48)
P for trend		0.15	P for trend		0.52
P for interaction		continuous=0.37, quartiles=0.70			
Early pregnancy sedentary time (hours/day)			**Early pregnancy sedentary time (hours/day)**		
Continuous (hours)	705	1.8 (-17, 21)	Continuous (hours)	830	-1.1 (-22, 20)
Quartile 1 (0.0-1.5)	190	Reference	Quartile 1 (0.0-1.5)	228	Reference
Quartile 2 (1.6-2.4)	145	44 (-46, 135)	Quartile 2 (1.6-2.4)	195	-14 (-88, 61)
Quartile 3 (2.5-3.1)	195	44 (-44, 132)	Quartile 3 (2.5-3.1)	200	5.7 (-70, 81)
Quartile 4 (3.2-13)	175	-4.4 (-96, 88)	Quartile 4 (3.2-13)	207	-17 (-102, 68)
P for trend		0.97	P for trend		0.81
P for interaction		continuous=0.45, quartiles=0.71			
Head circumference (cm)					
Pre-pregnancy sedentary time (hours/day)			**Pre-pregnancy sedentary time (hours/day)**		
Continuous (hours)	631	0.0 (-0.04, 0.1)	Continuous (hours)	731	0.1 (-0.1, 0.2)
Quartile 1 (0.0-1.4)	138	Reference	Quartile 1 (0.0-1.4)	185	Reference
Quartile 2 (1.5-2.0)	184	**0.5 (0.02, 0.9)**	Quartile 2 (1.5-2.0)	221	0.1 (-0.4, 0.5)
Quartile 3 (2.1-2.9)	105	**0.7 (0.3, 1.2)**	Quartile 3 (2.1-2.9)	115	0.5 (-0.1, 1.1)
Quartile 4 (3.0-13)	204	0.1 (-0.3, 0.4)	Quartile 4 (3.0-13)	210	0.2 (-0.3, 0.7)
P for trend		0.99	P for trend		0.29
P for interaction		continuous=0.84, quartiles=0.51			
Early pregnancy sedentary time (hours/day)			**Early pregnancy sedentary time (hours/day)**		
Continuous (hours)	701	0.1 (-0.1, 0.2)	Continuous (hours)	823	0.0 (-0.1, 0.2)
Quartile 1 (0.0-1.5)	189	Reference	Quartile 1 (0.0-1.5)	224	Reference

Quartile 2 (1.6-2.4)	145	0.1 (-0.3, 0.5)	Quartile 2 (1.6-2.4)	193	-0.4 (-0.9, 0.1)
Quartile 3 (2.5-3.1)	193	0.3 (-0.1, 0.6)	Quartile 3 (2.5-3.1)	200	0.0 (-0.5, 0.5)
Quartile 4 (3.2-13)	174	0.1 (-0.3, 0.6)	Quartile 4 (3.2-13)	206	0.0 (-0.6, 0.6)
P for trend		0.45	P for trend		0.62
P for interaction		continuous=0.48, quartiles=0.34			
Ponderal index (kg/m^3)[b]					
Pre-pregnancy sedentary time (hours/day)			**Pre-pregnancy sedentary time (hours/day)**		
Continuous (hours)	691	0.2 (-0.2, 0.6)	Continuous (hours)	733	0.0 (-0.3, 0.3)
Quartile 1 (0.0-1.4)	139	Reference	Quartile 1 (0.0-1.4)	185	Reference
Quartile 2 (1.5-2.0)	184	0.8 (-0.6, 2.3)	Quartile 2 (1.5-2.0)	222	0.4 (-1.0, 1.8)
Quartile 3 (2.1-2.9)	104	0.3 (-0.8, 1.4)	Quartile 3 (2.1-2.9)	115	0.7 (-1.2, 2.7)
Quartile 4 (3.0-13)	204	1.0 (-0.03, 2.1)	Quartile 4 (3.0-13)	211	0.3 (-1.0, 1.6)
P for trend		0.17	P for trend		0.64
P for interaction		continuous=0.45, quartiles=0.70			
Early pregnancy sedentary time (hours/day)			**Early pregnancy sedentary time (hours/day)**		
Continuous (hours)	700	0.2 (-0.2, 0.6)	Continuous (hours)	825	-0.1 (-0.6, 0.4)
Quartile 1 (0.0-1.5)	190	Reference	Quartile 1 (0.0-1.5)	224	Reference
Quartile 2 (1.6-2.4)	144	-0.2 (-1.3, 0.9)	Quartile 2 (1.6-2.4)	195	-2.5 (-5.3, 0.4)
Quartile 3 (2.5-3.1)	192	0.2 (-0.9, 1.3)	Quartile 3 (2.5-3.1)	200	-1.5 (-4.5, 1.4)
Quartile 4 (3.2-13)	174	0.2 (-1.4, 1.8)	Quartile 4 (3.2-13)	206	-1.5 (-4.3, 1.3)
P for trend		0.74	P for trend		0.38
P for interaction		continuous=0.35, quartiles=0.55			

[a]Weighted model is adjusted for maternal age (years), white race, nulliparity, pre-pregnancy BMI category (underweight/normal weight/overweight/obese), high school education or more, marital status (married/single), smoking during pregnancy, alcohol use during pregnancy, gestational age at delivery (weeks), and pre-pregnancy moderate/vigorous leisure time physical activity duration (quartiles) for pre-pregnancy sedentary time analyses or early pregnancy moderate/vigorous leisure time physical activity duration (quartiles) for early pregnancy sedentary time analyses.

[b]Results are excluding outliers (n=10) for ponderal index (>400 kg/m^3).

Table 2.4. Substitution of light or moderate/vigorous leisure time physical activity for sedentary behavior and associations with offspring birthweight (g)

	OVERALL	LOW SEDENTARY TIME	HIGH SEDENTARY TIME
		Mean difference[a] (95% CI)	
Pre-pregnancy (n=1373)			
Light physical activity (hours/week)	-48 (-116, 21)	-54 (-147, 39)	-57 (-154, 41)
Moderate/vigorous physical activity (hours/week)	0.4 (-5.2, 6.0)	-2.7 (-13, 7.8)	4.5 (-4.0, 13)
P for interaction=0.96 for light physical activity, 0.28 for moderate/vigorous physical activity			
Early pregnancy (n=1535)			
Light physical activity (hours/week)	-1.2 (-19, 17)	11 (-5.5, 27)	-8.3 (-44, 27)
Moderate/vigorous physical activity (hours/week)	-4.7 (-12, 2.0)	-10 (-22, 1.8)	-1.9 (-12, 8.3)
P for interaction=0.18 for light physical activity, 0.67 for moderate/vigorous physical activity			

[a]Model is adjusted for pre-pregnancy or early pregnancy sedentary time (hours/week), total pre-pregnancy or early pregnancy leisure time (hours/week), maternal age (years), white race, nulliparity, pre-pregnancy BMI category (underweight/normal weight/overweight/obese), high school education or more, marital status (married/single), smoking during pregnancy, alcohol use during pregnancy, gestational age at delivery (weeks), and offspring sex.

Chapter 3:

Associations of early pregnancy physical activity and sedentary behavior with offspring size at 12 months

ABSTRACT

Background: Growth in infancy has been associated with future risk of disease over the life course. Maternal leisure time physical activity and sedentary behavior during pregnancy may influence offspring programming of postnatal growth. However, associations of maternal leisure time physical activity and sedentary behavior during pregnancy with offspring postnatal growth have not been well studied. Further, previous studies have reported sex-specific associations of maternal leisure time physical activity during pregnancy with offspring birth size, but the role of associations of maternal physical activity and sedentary behavior with offspring postnatal growth is not known.

Methods: This study was conducted among participants of the Danish National Birth Cohort. Study participants (N=40,638) reported moderate/vigorous leisure time physical activity (hours/week) and time spent watching television or videos (hours/day) during a study interview in early pregnancy (16 weeks gestation, on average). Offspring weight and length at 12 months of age, measured during routine early childhood care, was reported by participants during a postpartum interview at 18 months, on average. Exposures were early pregnancy leisure time physical activity or sedentary behavior. Regression models, adjusted for offspring length, demographic characteristics, and pregnancy characteristics, were used to estimate mean differences, odds ratios, and 95% confidence intervals (CI). Regression models were also run stratified by offspring sex. Multiplicative interaction terms were used to assess interaction by offspring sex.

Results: During early pregnancy, 37% of participants reported some leisure time physical activity, and 16% reported ≥3 hours of leisure time sedentary behavior per day. Leisure time physical activity was not associated with offspring weight at 12 months overall (mean difference=-0.006 kg per hour/week; 95% CI: -0.01, 0.001); however associations differed by offspring sex. Among male offspring, each additional hour of early pregnancy leisure time physical activity was associated with 0.01 kg lower weight at 12 months (95% CI: -0.02, -0.001). Physical activity was not associated with weight at 12 months in female offspring (mean difference=0.001 kg per hour/week; 95% CI: -0.008, 0.01). Leisure time sedentary behavior was associated with lower offspring weight at 12 months overall (P for trend=0.001). Early pregnancy sedentary behavior ≥5 hours/day was associated with 0.09 kg lower weight at 12 months (95% CI: -0.17, -0.003) compared to 0-1 hours/day. Associations of leisure time sedentary behavior with weight at 12 months were similar in male and female offspring (P for interaction=0.79). Associations of maternal sedentary behavior with offspring underweight and obesity differed by offspring sex (P for interaction=0.12 and 0.04, respectively). Among female offspring, 4-5 hours per day of maternal sedentary behavior was associated with 2.48 times greater odds of underweight status compared to 0-1 hours per day (95% CI: 1.27, 4.83). Among male offspring, there was a suggested inverse association of maternal sedentary behavior with offspring obesity (P for trend=0.09).

Conclusions: Maternal early pregnancy leisure time physical activity may be associated with lower weight at 12 months in male, but not female offspring. Maternal early pregnancy leisure time sedentary behavior may be associated with lower weight at 12 months in male and female offspring, greater odds of underweight in female offspring, and lower odds of obesity in male offspring. Our results provide support for potential programming of infant growth by maternal early pregnancy leisure time physical activity and sedentary behavior.

INTRODUCTION

Growth in infancy has been associated with future risk of cardiovascular and metabolic disease, including coronary heart disease (98) and glucose intolerance (99) over the life course. Factors that determine growth in infancy, including those related to maternal perinatal characteristics, however, have not been fully described. Maternal factors and offspring growth in early life have potential long-term effects on offspring childhood and adult health through processes that involve fetal programming (100, 101). Therefore, maternal physical activity and sedentary behavior, which have been related to pregnancy complications (54, 55, 102) and fetal growth (11, 17), may affect offspring postnatal growth and health. However, these associations have not been well investigated.

Previous studies of maternal physical activity during pregnancy with offspring growth have focused on growth during childhood (5-8 years old) (103, 104). Results from these studies suggest maternal physical activity during pregnancy is associated with a decrease in offspring weight and weight-for-length. Infancy is another critical period of growth that needs consideration, but previous studies have not investigated associations of maternal physical activity or sedentary behavior with offspring growth in the first year of life.

Patterns and determinants of fetal and infant growth differ by sex (38). We have previously reported that associations of maternal physical activity with offspring birth size differ between male and female offspring (11). The objective of this study was to investigate associations of maternal physical activity and sedentary time during early pregnancy with offspring growth during infancy and whether these associations differ by offspring sex.

METHODS

Study setting and study population

This study was conducted using data collected from 1996-2002 as part of the Danish National Birth Cohort (105), a prospective pregnancy cohort study designed to study early life risk factors of pregnancy complications and offspring diseases. Pregnant women in Denmark were recruited for this study by general practitioners and midwives at their initial visit to confirm pregnancy. General practitioners and midwives provide prenatal care to more than 99% of pregnant women at no cost through the public health system. All pregnant women in Denmark who sought prenatal care between 6 and 12 weeks, were able to speak Danish well enough to participate in telephone interviews, and planned to carry the pregnancy to term were eligible to participate in the Danish National Birth Cohort study. A total of 100,418 women (~35% of the eligible population) participated in the study. All participants gave written informed consent. This study was approved by the Danish Data Protection Agency.

Participants with live, singleton births (N=92,667) were eligible for the current analyses. Participants who had offspring with conditions affecting growth (chromosomal abnormalities (n=53) and congenital malformations (N=2,433)) were excluded. Participants missing data on infant growth at 12 months (N=38,348), maternal perinatal physical activity (N=1,860) (or physical activity >35 hours per week (N=3)), smoking (N=8,423), pre-pregnancy BMI (N=626), or other covariates (N=283) were also excluded. Selected characteristics of eligible participants, participants included in the current analyses, and participants excluded from the current analyses were evaluated and found to be similar (Supplemental Table 3.1), minimizing concerns of selection bias.

Data collection

Study participants completed four computerized telephone interviews: two during pregnancy at an average of 16 (range 11-25 weeks) and 31 (range 27-37 weeks) weeks gestation and two after delivery, when the child was 6 and 18 months old. Information collected during interviews included sociodemographic characteristics, reproductive and medical history, physical activity and sedentary behavior during pregnancy, breastfeeding, and infant growth at 5 and 12 months of age.

Maternal pre-pregnancy BMI, calculated using self-reported height and weight, was categorized using standard cut points: underweight: <18.5 kg/m^2, normal: 18.5–24.9 kg/m^2, overweight: 25–29.9 kg/m^2, obese: ≥ 30 kg/m^2. Parental socio-occupational status was determined using reported employment information for mothers and their partners obtained at the early pregnancy interview. Mothers or fathers in management positions or jobs requiring higher education were classified as 'high'. Mothers or fathers who were office workers, service workers, skilled manual workers, or in the armed forces were classified as 'middle', and mothers or fathers who were unskilled workers, unemployed, or outside the work force were classified as 'low'. The highest category for either the participant or her partner was used to adjust for socio-occupational status. These categorizations have been employed previously in studies that used data from the Danish National Birth Cohort (106).

Physical activity

During the early pregnancy interview, participants were asked to report any moderate/vigorous physical activity during early pregnancy (aerobics/gymnastics, dancing, cycling, fast walking, jogging, ball games, swimming, fitness classes, badminton, tennis, horseback riding, or other activities) and for each activity reported, the average frequency per week and average duration of each episode of physical activity. Average physical activity duration per week during early pregnancy was calculated by summing duration per week of reported physical activities.

Sedentary behavior

During the early pregnancy interview, participants were asked to report the average number of hours spent watching TV per day. Response options ranged from <1 hour to 5 or more hours per day in ½ hour increments (1, 1 ½, 2, 2 ½, 3, 3 ½, 4, 4 ½ hours). Response categories were collapsed to <1 hour, 1-2 hours, 2-3 hours, 3-4 hours, and >4 hours.

Infant growth

During the 18 month postpartum interview, mothers reported weight (kg) and length (cm) of their children at 12 months, as measured by a general practitioner or public health nurse during routine early childhood care. Weight-for-length at 12 months was categorized as underweight (<3rd percentile), normal weight (3rd-97th percentile), or overweight (>97th percentile) using sex-specific international standards for weight-for-length (107).

Statistical analyses

Mean and standard deviation were used to describe continuous variables. Frequency and percentage were used to describe categorical variables.

Linear regression was used to determine mean differences and corresponding 95% confidence intervals (CI) in weight at 12 months associated with each additional hour of early pregnancy physical activity and each category of early pregnancy sedentary behavior. Physical activity was also categorized into tertiles among women who reported any early pregnancy physical activity. Generalized logistic regression models (baseline-category logit models (108)) were used to calculate odds ratios and 95% CIs for underweight, overweight, or obese compared to normal weight at 12 months. The baseline-category logit model is a polytomous logit model that simultaneously describes log odds for each response category compared to a baseline category (normal weight in our models). Physical activity and sedentary behavior categories were also modeled as a continuous variables to determine P value for linear trend. We fit several models as follows. Model I was adjusted for maternal age (years), pre-pregnancy BMI category (underweight/normal weight/overweight/obese), nulliparity (Y/N), smoking during pregnancy (Y/N), spouse/partner (Y/N), parental socio-occupational status (low/middle/high), and offspring sex. Model II was additionally adjusted for offspring birthweight (g) and gestational age at delivery (weeks), which are potential mediators of the associations between maternal physical activity, sedentary behavior, and offspring growth at 12 months. For sedentary behavior, models were additionally adjusted for early pregnancy moderate/vigorous physical activity duration.

Two-way multiplicative interaction terms and corresponding P values were used to assess interactions of early pregnancy physical activity and early pregnancy sedentary behavior with offspring sex. For outcomes with evidence of interaction, models were re-run stratified by offspring sex.

A two-sided alpha level of 0.05 was used for statistical significance in all analyses. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary NC).

RESULTS

Thirty-seven percent of participants reported some moderate/vigorous leisure time physical activity in early pregnancy, while the majority of participants spent 1-3 hours per day in sedentary behavior (Table 3.1). About two-thirds of participants were normal weight, and about half were of high socio-occupational status and nulliparous. Offspring weighted 10.2 kg at 12 months old, on average.

Overall, early pregnancy physical activity was not associated with continuous weight at 12 months (mean difference=-0.006 kg per hour/week; 95% CI: -0.01, 0.001) (Table 3.2). However, associations of maternal physical activity with offspring weight at 12 months differed by offspring sex (P for interaction=0.25 for Model I, 0.03 for Model II). Among males, each additional hour of maternal early pregnancy physical activity duration was associated with 0.01 kg lower weight (95% CI: -0.02, -0.001) at 12 months (Table 3.3). Maternal physical activity was not associated with weight at 12 months among female offspring (mean difference=-0.001 kg per hour/week; 95% CI: -0.01, 0.01). Maternal early pregnancy physical activity was inversely associated with offspring overweight at 12 months (OR=0.98 per hour/week; 95% CI: 0.96, 0.99; P for trend=0.04). We did not find differences with offspring sex in these associations (P for interaction=0.14 for Model I, 0.13 for Model II).

Maternal sedentary behavior during early pregnancy was inversely associated with offspring weight at 12 months of age (P for trend=0.001, Table 3.4). Compared to women with early pregnancy sedentary time of 0-1 hours per day, women in categories of early pregnancy sedentary time of 2 or more hours per day had offspring with 0.04-0.08 kg lower offspring weight at 12 months. We did not find significant interactions with offspring sex in these associations (P for interaction=0.79 for Model I, 0.92 for Model II).

Compared to women with early pregnancy sedentary time of 0-1 hours per day, women in categories of sedentary time of 2 or more hours per day had offspring with 36-46% greater odds of offspring underweight at 12 months (P for trend=0.02). Although the P value for interaction was not statistically significant (P=0.12 for Model I, 0.10 for Model II), associations of maternal sedentary behavior with offspring underweight status at 12 months differed by offspring sex. Among female offspring, 3-4 hours per day of maternal sedentary behavior was associated with 72% greater odds of underweight status (95% CI: 1.03, 2.86) compared to 0-1 hours per day of sedentary behavior (Table 3.5). Similarly, among female offspring, 4-5 hours per day of maternal sedentary behavior was associated with 2.48 times greater odds of underweight status compared to 0-1 hours per day (95% CI: 1.27, 4.83). Sedentary behavior was not associated with offspring underweight status among male offspring (P for trend=0.33). Associations of maternal sedentary behavior with offspring obesity status at 12 months differed by offspring sex as well (P for interaction=0.04). There was a suggested inverse association of maternal sedentary behavior with odds of offspring obesity among male offspring, but not female offspring (P for trend=0.09 and 0.75, respectively).

In general, results were similar after additional adjustment for offspring birthweight and gestational age at delivery (Model II).

DISCUSSION

In this study, we observed inverse associations of maternal early pregnancy physical activity with offspring overweight status at 12 months of age overall and with offspring weight at 12 months of age in male, but not female offspring. We also observed inverse associations of maternal early pregnancy sedentary behavior with offspring weight at 12 months of age overall, positive associations of early pregnancy sedentary behavior with underweight status among female offspring, and suggested inverse associations of early pregnancy sedentary behavior with obesity status among male offspring.

Only one previous study, to our knowledge, has examined the association of physical activity during pregnancy with offspring size in infancy (109). Mattran et al recruited 23 women from prenatal clinics in Michigan and measured infant height, weight, and body fat percentage at 18 to 24 months old. At the same follow up study visit, mothers were asked to recall leisure time physical activity during each trimester of pregnancy. Mattran et al reported that third trimester leisure time physical activity was negatively correlated with infant weight (unadjusted Spearman r=-0.39; P=0.06) and weight-for-height Z score (unadjusted Spearman r=-0.40, P=0.06) at 18-24 months of age. Physical activity during the first or second trimester was not associated with offspring size in that study. Although women in the Mattran et al study were recruited during pregnancy, physical activity was not assessed until 18-24 months after delivery. Participants were asked to recall trimester-specific physical activity 2 or more years in the past, and measurement error may have reduced the study power and accounted for null findings. We did not include late pregnancy physical activity in the current analysis. We are not aware of any previous study that examined associations of sedentary time during pregnancy with offspring size in infancy.

Other studies have examined associations of maternal physical activity during pregnancy with offspring growth later in childhood, between 5-8 years of age (103, 104, 110). In a retrospective cohort study using nationally representative data on Greek school children, Mourtakos et al reported that offspring of women who performed any moderate physical activity during pregnancy had 23% lower odds of overweight/obesity at 8 years old than offspring of women who were not physically active during pregnancy (95% CI: 0.65, 0.91) (104). Clapp et al also reported that offspring of women who performed regular moderate/vigorous leisure time physical activity before pregnancy (runners and aerobic dancers) and remained active throughout pregnancy weighed 0.24 kg less and had 4.6% lower body fat at 5 years old than offspring of women who were active before pregnancy but stopped regular leisure time physical activity during pregnancy (P=0.01 for both) (103). However, in a previous study using the Danish National Birth Cohort, Schou Andersen et al did not observe associations between early or late pregnancy moderate/vigorous leisure time physical activity with offspring BMI z-score or overweight status at 7 years old (110). Measurement error in assessment of offspring height and weight may explain null associations of maternal physical activity during pregnancy with offspring growth. Mothers reported their child's height and weight at 7 years old in the Danish National Birth Cohort, whereas offspring height and weight were measured by study staff or physicians in the other two studies. These studies suggest that maternal physical activity during pregnancy may continue to affect offspring growth beyond the first 12 months of life.

Adjustment for birthweight and gestational age at delivery did not change our results, suggesting that associations of maternal physical activity and sedentary behavior during early pregnancy with infant size at 12 months are independent of offspring birthweight. Our results suggest that maternal physical activity and sedentary behavior during early pregnancy may affect fetal programming of infant growth that is not acting through changes in birthweight.

Differences in infant weight observed in our study were small. Despite their size, however, they may indicate differences in fetal programming with meaningful health effects later in life. Maternal physical activity during pregnancy has been associated with growth in childhood, as previously discussed, as well as lower offspring resting systolic blood pressure at 8-10 years old (111), lower offspring HDL cholesterol, and higher diastolic blood pressure at 20 years old (112). Additionally, animal studies (in mice and rats) of physical activity during pregnancy have reported sex-specific associations with offspring glucose and insulin tolerance in adulthood (113). Infant growth may be a mediator in the observed relationships between maternal physical activity during pregnancy and metabolic health in adulthood.

The observed sex-specific associations of maternal physical activity and sedentary behavior with offspring size at 12 months we observed in the current study extend our previous report of sex-specific associations of maternal physical activity before and during pregnancy with offspring birth size (11). In a previous study in rodents, investigators also observed sex-specific associations of maternal physical activity during pregnancy with body composition (114). Carter et al reported associations of physical activity during pregnancy with increased lean mass and decreased fat mass in male offspring only (114). We also observed associations of maternal physical activity with lower weight in male offspring only. Therefore, lower male offspring weight associated with maternal physical activity may be due to decreased fat mass. Sedentary behavior during pregnancy affects glucose metabolism (82), and glycemic sensitivity may differ in male and female offspring (115). The observed sex-specific associations of maternal sedentary behavior with offspring size at 12 months in the current study may be a result of sex-specific adaptations to growth in response to sedentary behavior-related changes in maternal glucose metabolism.

Strengths of this study include its large size and prospective data collection. However, several limitations must also be considered. Physical activity and sedentary behavior were self-reported in this study, which may have introduced measurement error. Because data collection was prospective, measurement error is likely non-differential, biasing our results toward the null. Infant height and weight at 12 months was reported by mothers based on measurements made by health care professionals at the child's routine 12 month check up for increased accuracy of measurements. Maternal depression may play a role in the observed associations of sedentary behavior with offspring size at 12 months, as high amounts of time spent in sedentary behavior may be a marker for depression, but we did not consider maternal depression in the current study. A large portion of participants were missing covariate and infant size data. However, demographic and pregnancy characteristics of all eligible participants, participants included in this analysis, and participants excluded in this analysis were similar (Supplemental Table 3.1). Participants in the Danish National Birth Cohort were of Danish descent and of middle to high socio-occupational status. Results may not be generalizable to more racially and socioeconomically diverse populations.

In conclusion, we observed sex-specific associations of maternal physical activity and sedentary behavior during early pregnancy with offspring size at 12 months old. Associations were independent of birthweight, suggesting potential fetal programming of infant growth that is independent of birthweight. Our results contribute to the literature on sex-specific fetal programming associated with maternal behaviors during pregnancy. Future studies should investigate mechanisms of observed associations as well as associations of infant growth with later childhood and adult growth and health. Infancy, in addition to pregnancy, may be an opportune period for clinical and public health interventions to prevent future disease.

Table 3.1. Maternal and offspring characteristics, Danish National Birth Cohort

Maternal characteristics		
	N	**Mean (SD)**
Age (years)	40638	30 (4.2)
Early pregnancy leisure time physical activity (hours/week)	40638	0.8 (1.6)
	N	**%**
Any early pregnancy leisure time physical activity	14869	37
Early pregnancy sedentary behavior (hours/day)		
0-1	5783	14
1-2	14684	36
2-3	13461	33
3-4	4477	11
4-5	1362	3
5+	835	2
Pre-pregnancy BMI category		
Underweight (<18.5 kg/m^2)	1661	4
Normal weight (18.5-24.9 kg/m^2)	27394	67
Overweight (25-29.9 kg/m^2)	8147	20
Obese (≥30 kg/m^2)	3436	8
Spouse/partner	40143	99
Socio-occupational status		
High	21611	53
Middle	15691	39
Low	3336	8
Nulliparous	18508	46
Smoking during pregnancy		
No	30935	76
Yes	9703	24
Gestational diabetes	358	1
Preeclampsia	879	2
Offspring characteristics		
	N	**Mean (SD)**
Birthweight (g)	40638	3607 (547)
Gestational age at delivery (weeks)	40638	39 (1.7)
Weight at 12 months (kg)	40638	10.2 (1.2)
	N	**%**
Male	20429	50
Weight-for-length category at 12 months		
Underweight (<5th percentile)	949	2
Normal weight (5th-84th percentile)	27988	69
Overweight (85th-94th percentile)	6420	16
Obese (≥95th percentile)	5200	13

Table 3.2. Associations of early pregnancy physical activity (hours/week) with offspring size at 12 months

	N	Model I[a]	Model II[b]
	N	Mean Difference (95% CI)	
Weight (kg) adjusted for length (cm)			
Continuous (hours/week)	40638	-0.006 (-0.01, 0.001)	-0.004 (-0.01, 0.002)
No physical activity	25769	Reference	Reference
Tertile 1 (0.01-1.0 hrs/wk)	5730	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.01)
Tertile 2 (1.01-2.09 hrs/wk)	4181	**-0.04 (-0.07, -0.002)**	**-0.04 (-0.07, -0.008)**
Tertile 3 (2.10-35 hrs/wk)	4958	-0.002 (-0.03, 0.03)	0.003 (-0.03, 0.03)
P for trend		0.30	0.35
	N	Odds Ratio (95% CI)[c]	
Underweight (<5th percentile)			
Continuous (hours/week)	949	1.00 (0.96, 1.04)	1.00 (0.96, 1.04)
No physical activity	596	Reference	Reference
Tertile 1 (0.01-1.0 hrs/wk)	140	1.05 (0.87, 1.27)	1.05 (0.87, 1.27)
Tertile 2 (1.01-2.09 hrs/wk)	93	0.93 (0.74, 1.16)	0.95 (0.76, 1.19)
Tertile 3 (2.10-35 hrs/wk)	120	1.04 (0.85, 1.27)	1.03 (0.84, 1.26)
P for trend		0.95	0.91
Overweight (85-95th percentile)			
Continuous (hours/week)	6420	**0.98 (0.96, 0.99)**	0.98 (0.97, 1.00)
No physical activity	4116	Reference	Reference
Tertile 1 (0.01-1.0 hrs/wk)	935	1.02 (0.94, 1.10)	1.02 (0.94, 1.10)
Tertile 2 (1.01-2.09 hrs/wk)	616	**0.89 (0.81, 0.98)**	**0.88 (0.80, 0.97)**
Tertile 3 (2.10-35 hrs/wk)	753	0.94 (0.87, 1.03)	0.95 (0.87, 1.04)
P for trend		**0.04**	**0.048**
Obese (>95th percentile)			
Continuous (hours/week)	5200	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
No physical activity	3371	Reference	Reference
Tertile 1 (0.01-1.0 hrs/wk)	698	0.93 (0.85, 1.02)	0.93 (0.85, 1.02)
Tertile 2 (1.01-2.09 hrs/wk)	494	**0.88 (0.79, 0.97)**	**0.87 (0.78, 0.96)**
Tertile 3 (2.10-35 hrs/wk)	637	0.98 (0.90, 1.08)	0.99 (0.90, 1.09)
P for trend		0.14	0.18

P for interaction with offspring sex: continuous LTPA: weight Model I P=0.25, Model II P= 0.03; weight categories Model I P=0.14, Model II P=0.13; LTPA tertiles: weight Model I P=0.86, Model II P=0.71; weight categories Model I P=0.64, Model II P=0.73

[a]Model I is adjusted for maternal age (years), pre-pregnancy BMI category (underweight/normal weight/overweight/obese), nulliparity (Y/N), smoking during pregnancy (Y/N/quit at some point during pregnancy), spouse/partner (Y/N), socio-occupational status (high/middle/low), and offspring sex.

[b]Model II is adjusted for all covariates in Model I, offspring birthweight (grams), and gestational age at delivery (weeks).

[c]Model is a generalized logistic regression model with normal weight as the reference group.

Table 3.3. Associations of early leisure time physical activity (hours/week) with offspring size at 12 months by sex

	Males			Females		
		Model I[a]	**Model II[b]**		**Model I[a]**	**Model II[b]**
	N	**Mean Difference (95% CI)**		**N**	**Mean Difference (95% CI)**	
Weight (kg) adjusted for length (cm)	20429	**-0.01 (-0.02, -0.001)**	-0.01 (-0.02, 0.001)	20209	-0.001 (-0.01, 0.01)	-0.0004 (-0.01, 0.01)
	N	**Odds Ratio (95% CI)[c]**		**N**	**Odds Ratio (95% CI)[c]**	
Underweight	392	1.03 (0.98, 1.09)	1.03 (0.98, 1.09)	273	0.96 (0.88, 1.05)	0.96 (0.88, 1.04)
Overweight	2427	**0.97 (0.94, 0.99)**	**0.97 (0.94, 0.99)**	2214	0.99 (0.96, 1.02)	1.00 (0.97, 1.03)
Obese	2052	0.98 (0.95, 1.01)	0.98 (0.95, 1.01)	1689	1.01 (0.98, 1.04)	1.01 (0.98, 1.04)

P for interaction with offspring sex: weight Model I P=0.25, Model II P= 0.03; weight categories Model I P=0.14, Model II P=0.13

[a]Model I is adjusted for maternal age (years), pre-pregnancy BMI category (underweight/normal weight/overweight/obese), nulliparity (Y/N), smoking during pregnancy (Y/N/quit at some point during pregnancy), spouse/partner (Y/N), and socio-occupational status (high/middle/low).

[b]Model II is adjusted for all covariates in Model I, offspring birthweight (grams), and gestational age at delivery (weeks).

[c]Model is a generalized logistic regression model with normal weight as the reference group.

Table 3.4. Associations of early pregnancy sedentary behavior with offspring size at 12 months

	N	Model I[a]	Model II[b]
	N	Mean Difference (95% CI)	
Weight adjusted for length			
0-1 hours/day	5783	Reference	Reference
1-2 hours/day	14684	-0.009 (-0.04, 0.03)	-0.002 (-0.03, 0.03)
2-3 hours/day	13461	**-0.04 (-0.07, -0.001)**	-0.03 (-0.06, 0.002)
3-4 hours/day	4477	**-0.06 (-0.10, -0.01)**	-0.04 (-0.07, 0.003)
4-5 hours/day	1362	-0.04 (-0.11, 0.03)	-0.03 (-0.09, 0.03)
5+ hours/day	835	**-0.09 (-0.17, -0.003)**	-0.04 (-0.12, 0.02)
P for trend		**0.001**	0.15
	N	Odds Ratio (95% CI)[c]	
Underweight			
0-1 hours/day	119	Reference	Reference
1-2 hours/day	330	1.19 (0.92, 1.54)	1.12 (0.90, 1.39)
2-3 hours/day	333	**1.36 (1.05, 1.76)**	**1.26 (1.01, 1.56)**
3-4 hours/day	111	**1.42 (1.03, 1.96)**	1.24 (0.95, 1.62)
4-5 hours/day	333	1.34 (0.83, 2.16)	1.18 (0.79, 1.76)
5+ hours/day	23	1.46 (0.84, 2.55)	1.39 (0.88, 2.22)
P for trend		**0.02**	**0.04**
Overweight			
0-1 hours/day	902	Reference	Reference
1-2 hours/day	2376	1.05 (0.95, 1.16)	1.04 (0.95, 1.13)
2-3 hours/day	2116	0.98 (0.89, 1.09)	0.98 (0.90, 1.07)
3-4 hours/day	696	0.96 (0.84, 1.09)	0.96 (0.86, 1.08)
4-5 hours/day	197	0.92 (0.75, 1.12)	0.88 (0.74, 1.04)
5+ hours/day	127	0.95 (0.75, 1.20)	0.94 (0.76, 1.16)
P for trend		0.12	**0.046**
Obese			
0-1 hours/day	709	Reference	Reference
1-2 hours/day	1879	1.03 (0.92, 1.15)	1.04 (0.94, 1.14)
2-3 hours/day	1717	0.96 (0.86, 1.08)	0.99 (0.90, 1.10)
3-4 hours/day	587	0.98 (0.85, 1.12)	1.01 (0.90, 1.15)
4-5 hours/day	183	0.94 (0.76, 1.17)	1.00 (0.84, 1.21)
5+ hours/day	119	1.00 (0.77, 1.28)	1.08 (0.86, 1.34)
P for trend		0.33	0.96

P for interaction with offspring sex: categorical sedentary behavior: weight Model I P=0.79, Model II P=0.92; weight categories Model I P=0.12, Model II P=0.13; P for trend: weight Model I P=0.64, Model II P=0.93; underweight Model I P=0.12, Model II P=0.10; overweight Model I P=0.75, Model II: P=0.64; obese Model I P=0.04, Model II P=0.07

[a]Model I is adjusted for maternal age (years), pre-pregnancy BMI category (underweight/normal weight/overweight/obese), nulliparity (Y/N), smoking during pregnancy (Y/N/quit at some point during pregnancy), spouse/partner (Y/N), socio-occupational status (high/middle/low), offspring sex, and maternal early pregnancy LTPA (hours/week).

[b]Model II is adjusted for all covariates in Model I, offspring birthweight (grams), and gestational age at delivery (weeks).
[c]Model is a generalized logistic regression model with normal weight as the reference group.

Table 3.5. Associations of early pregnancy sedentary behavior (hours/day) with weight-for-length categories at 12 months by sex

	N	**Males** Odds Ratio (95% CI)[a]		N	**Females** Odds Ratio (95% CI)[a]	
		Model I[b]	**Model II[c]**		**Model I[b]**	**Model II[c]**
Underweight						
0-1 hours/day	77	Reference	Reference	42	Reference	Reference
1-2 hours/day	196	1.06 (0.77, 1.47)	1.05 (0.76, 1.46)	134	1.42 (0.93, 2.18)	1.46 (0.95, 2.23)
2-3 hours/day	199	1.28 (0.92, 1.77)	1.27 (0.91, 1.76)	134	1.51 (0.98, 2.33)	1.52 (0.99, 2.35)
3-4 hours/day	67	1.26 (0.83, 1.90)	1.22 (0.81, 1.85)	44	**1.72 (1.03, 2.86)**	**1.74 (1.04, 2.90)**
4-5 hours/day	15	0.76 (0.37, 1.57)	0.73 (0.35, 1.52)	18	**2.48 (1.27, 4.83)**	**2.44 (1.25, 4.77)**
5+ hours/day	14	1.30 (0.63, 2.72)	1.22 (0.58, 2.54)	9	1.74 (0.74, 4.10)	1.80 (0.76, 4.25)
P for trend		0.33	0.43		**0.01**	**0.01**
Overweight						
0-1 hours/day	462	Reference	Reference	440	Reference	Reference
1-2 hours/day	1239	1.07 (0.93, 1.23)	1.08 (0.94, 1.25)	1137	1.02 (0.89, 1.18)	1.02 (0.88, 1.17)
2-3 hours/day	1116	1.08 (0.94, 1.25)	1.09 (0.94, 1.26)	1000	0.89 (0.77, 1.03)	0.88 (0.76, 1.02)
3-4 hours/day	350	0.97 (0.80, 1.17)	0.99 (0.82, 1.19)	346	0.95 (0.79, 1.14)	0.95 (0.79, 1.14)
4-5 hours/day	104	0.96 (0.73, 1.26)	0.98 (0.74, 1.29)	93	0.88 (0.65, 1.18)	0.88 (0.65, 1.18)
5+ hours/day	60	0.92 (0.66, 1.29)	0.96 (0.68, 1.34)	67	0.98 (0.70, 1.36)	0.97 (0.69, 1.35)
P for trend		0.48	0.61		0.13	0.12
Obese						
0-1 hours/day	423	Reference	Reference	286	Reference	Reference
1-2 hours/day	1049	0.94 (0.81, 1.09)	0.96 (0.83, 1.11)	830	1.16 (0.98, 1.37)	1.14 (0.97, 1.36)
2-3 hours/day	908	0.87 (0.75, 1.01)	0.87 (0.75, 1.01)	809	1.10 (0.93, 1.31)	1.09 (0.92, 1.29)
3-4 hours/day	318	0.89 (0.73, 1.08)	0.91 (0.75, 1.11)	269	1.10 (0.89, 1.36)	1.09 (0.88, 1.36)
4-5 hours/day	94	0.78 (0.58, 1.05)	0.79 (0.59, 1.07)	89	1.18 (0.86, 1.61)	1.17 (0.86, 1.61)
5+ hours/day	68	0.98 (0.70, 1.37)	1.05 (0.74, 1.47)	51	1.02 (0.69, 1.49)	0.99 (0.67, 1.46)
P for trend		0.09	0.16		0.75	0.82

P for interaction with offspring sex: categorical sedentary behavior: weight Model I P=0.79, Model II P=0.92; weight categories Model I P=0.12, Model II P=0.13; P for trend: weight Model I P=0.64, Model II P=0.93;

underweight Model I P=0.12, Model II P=0.10; overweight Model I P=0.75, Model II: P=0.64; obese Model I P=0.04, Model II P=0.07

[a]Model is a generalized logistic regression model with normal weight as the reference group.

[b]Model I is adjusted for maternal age (years), pre-pregnancy BMI category (underweight/normal weight/overweight/obese), nulliparity (Y/N), smoking during pregnancy (Y/N/quit at some point during pregnancy), spouse/partner (Y/N), socio-occupational status (high/middle/low), and maternal early pregnancy LTPA (hours/week).

[c]Model II is adjusted for all covariates in Model I, offspring birthweight (grams), and gestational age at delivery (weeks).

Supplemental Table 3.1. Maternal and offspring characteristics of analytic cohort, excluded participants, and full cohort, Danish National Birth Cohort

	Analytic Cohort (n=40,638)	Excluded Participants		All Eligible Participants	
	Mean (SD)	**N with data**	**Mean (SD)**	**N with data**	**Mean (SD)**
Age (years)	30 (4.2)	49543	30 (4.4)	90181	30 (4.3)
	%	**N**	**%**	**N**	**%**
Pre-pregnancy BMI category					
Underweight (<18.5 kg/m^2)	4	2097	5	3758	5
Normal weight (18.5-24.9 kg/m^2)	67	28988	68	56382	68
Overweight (25-29.9 kg/m^2)	20	7973	19	16120	19
Obese (≥30 kg/m^2)	8	3358	8	6794	8
Spouse/partner	99	43726	97	84364	98
Socio-occupational status					
High	53	22659	52	44270	53
Middle	39	16128	37	31819	38
Low	8	4661	11	7997	10
Nulliparous	46	24567	50	90181	48
Smoking during pregnancy					
No	76	17490	71	48425	74
Yes	11	3175	13	7603	12
Quit at any point during pregnancy	13	3842	16	9117	14
Gestational diabetes	1	408	1	89928	1
Preeclampsia	2	1124	2	90181	2
Offspring male sex	50	25476	52	90084	51
	Mean (SD)	**N with data**	**Mean (SD)**	**N with data**	**Mean (SD)**
Offspring birthweight (g)	3607 (547)	49035	3565 (581)	89673	3584 (566)
Gestational age at delivery (weeks)	39 (1.7)	49534	39 (1.9)	90172	39 (1.8)
Offspring weight at 12 months (kg)	10.2 (1.2)	11663	10.3 (1.3)	52301	10.2 (1.2)

Chapter 4:

Maternal preconception physical activity and sedentary behavior from adolescence to young adulthood and offspring birthweight

ABSTRACT

Purpose: To examine associations of maternal long-term, preconception patterns of physical activity (PA) and sedentary behavior (SB) with offspring birthweight (BW).

Methods: Participants (N=1,408) were identified from the National Longitudinal Study of Adolescent to Adult Health. Group-based trajectory modeling was used to characterize PA trajectories (frequency/week) and SB trajectories (hours/week) between age 15-22. Weighted regression and Wald tests were used to estimate and test mean differences and odds ratios (ORs) for BW, small-, and large-for-gestational age (SGA, LGA). Offspring sex and pre-pregnancy overweight/obesity-specific differences in associations were evaluated using stratified analyses and interaction terms.

Results: Three trajectories were identified for PA and five for SB. Among female offspring, high followed by decreasing PA was associated with delivering offspring with 90 g greater BW (95% CI: -4, 184) and 72% greater risk of LGA (95% CI: 0.94-3.14), compared to low PA. Among male offspring, PA patterns were not associated with BW or LGA (P for interaction=0.10 and 0.008, respectively). A pattern of high then decreasing PA among normal weight, but not overweight/obese women, was associated with 2.03 times greater risk of LGA (95% CI: 1.06, 3.88). SB trajectories were not associated with BW.

Conclusion: Associations of preconception patterns of PA with offspring BW may differ by offspring sex and pre-pregnancy BMI.

INTRODUCTION

Maternal preconception lifestyle behaviors influence maternal health and can affect pregnancy outcomes including offspring birthweight (11, 30). Leisure time physical activity (LTPA) in adolescence and adulthood is associated with maternal cardiovascular and metabolic health benefits, including lower body mass index (BMI) and body fat (21-23), greater insulin sensitivity (24-26), lower blood pressure (27, 28), and lower inflammation (29). Prolonged sedentary behavior, independent of LTPA, is associated with increased risk of overweight status (23), higher glucose and insulin levels, greater waist circumference, systolic blood pressure, and triglycerides (84, 116).

Birthweight is an important measure of fetal growth and development (117). Extremes of the birthweight distribution have been associated with adverse short- and long-term health outcomes. Low birthweight and small-for-gestational age are associated with perinatal morbidity and mortality (64), as well as risk of chronic diseases in adulthood (65, 118-121). Macrosomia and large-for-gestational age are associated with development of obesity and type 2 diabetes in later life (66, 122).

A life course approach to healthy pregnancy and fetal development requires consideration of preconception lifestyle and behavior (30). However, most previous research on determinants of healthy pregnancy has focused on behaviors during pregnancy or the short time period before the pregnancy. To our knowledge, the only previous study of patterns of maternal LTPA during adolescence and adulthood reported associations of long-term preconception LTPA with reduced risk of preterm birth but not low birthweight (123). This study did not consider macrosomia or preconception leisure time sedentary behavior (LTSB). Further, despite potential differences in response to maternal health status, behavior, and exposure between male and female fetuses (11, 38, 124) and between fetuses born to women who are of normal weight and women who are obese (125, 126), roles of offspring sex and maternal pre-pregnancy BMI in these associations have not been studied.

The objective of this study was to determine the extent to which trajectories of maternal preconception LTPA or LTSB during adolescence and young adulthood were associated with offspring birthweight, and to test if these associations differed by offspring sex or maternal pre-pregnancy overweight/obese status.

METHODS

Study setting and study population

This study was conducted using data collected from 1994-2008 as part of the National Longitudinal Study of Adolescent to Adult Health (Add Health), a prospective cohort study designed to identify social, behavioral, and biological determinants of health across the life course (127). Add Health participants were identified from 132 “feeder” schools (schools that send graduates to a specific high school) of a stratified, random sample of high schools in the United States based on region, rural/urban setting, school size/type, and racial composition of the student body. At each school, a stratified, random sample of students based on grade and sex were selected for participation in the study. A total of 20,745 adolescents in grades 7-12 (age 11-21 years) participated in Wave I (1994-1995). Follow up of participants occurred in 1996 (Wave II), 2001-2002 (Wave III), and 2007-2009 (Wave IV) when participants were 12-22 years old, 18-26 years old, and 24-32 years old, respectively. Between 71% and 76% of the baseline cohort completed study interviews at each follow-up assessment. Among 2,983 participants with at least one live birth after Wave III, 78%, 100%, and 99.9% of participants completed study interviews at Wave II, III, and IV, respectively. Add Health was approved by the Institutional Review Board of the University of North Carolina at Chapel Hill. This secondary analysis was conducted using deidentified data obtained under an Add Health Restricted-Use Data Contract at the University of Washington.

Participants with ≥1 live, singleton birth between Wave III and IV were included in this study (N=2,983). For participants who reported ≥1 live, singleton birth between Wave III and IV, only the first birth after Wave III study interview was included in this study. Participants with missing data for survey weight (N=182), birthweight (N=23), LTPA or LTSB trajectory (N=649), parental income and pre-pregnancy BMI (N=711), or other covariates (N=10) were excluded. A total of 1,408 participants with follow-up, on average, over 7 years between age 15-22, remained for analyses. Sociodemographic and pregnancy characteristics were similar between all eligible participants, participants included in this study, and participants excluded due to missing data (Supplemental Table 4.1).

Data collection

During in-person study interviews, data on sociodemographic characteristics (age, race, income of participant's parents), pregnancy history and outcomes (live births, smoking and alcohol use during pregnancies), anthropometric measurements (height and weight), LTPA and LTSB were collected. Pre-pregnancy BMI was calculated using reported height and weight at Wave III and categorized according to standard cutoffs (underweight: <18.5 kg/m^2, normal: 18.5–24.9 kg/m^2, overweight: 25–29.9 kg/m^2, obese: ≥30 kg/m^2).

Physical activity

In Waves I and II, participants reported frequency of the following LTPAs in the past week: jogging, walking, karate, jumping rope, gymnastics, dancing, roller-blading, roller-skating, skate-boarding, bicycling, baseball, softball, basketball, soccer, swimming, and football. At Wave III, participants reported frequency of the following LTPAs in the past week: bicycling, skate-boarding, dancing, hiking, hunting, yard work, gymnastics, weight lifting, strength training, running, wrestling, swimming, cross-country skiing, cycle racing, martial arts, football, soccer, basketball, lacrosse, rugby, field hockey, ice hockey, gold, fishing, bowling, softball, baseball, roller-blading, roller-skating, downhill skiing, snowboarding, racquet sports, aerobics, and walking. Because more LTPAs were assessed at Wave III (34 activities) than at Wave I or II (16 activities), total reported frequency of LTPA at Wave III was scaled by (16/34) to avoid overestimating LTPA at Wave III, as has previously been done in Add Health (128).

Sedentary behavior

Participants reported frequency and duration (hours) of the following LTSBs in the past week at each study visit: watching a movie, playing video or computer games, and using a computer for something other than school work.

Birthweight

At Wave IV, participants reported current pregnancy status and pregnancy history, including birth date, birthweight, sex, and gestational age of live births. Offspring birthweight was categorized as small-for-gestational age (SGA, $<10^{th}$ percentile) or large-for-gestational age (LGA, $>90^{th}$ percentile) using INTERGROWTH-21st birthweight standards, which are considered to be valid for multiethnic populations (129).

Statistical analyses

Maternal and offspring characteristics were summarized for the analytic population. Weighted mean and standard deviation using survey weights was used to describe continuous variables. Frequency and weighted percentage was used to describe categorical variables.

Group-based trajectory analysis using a censored normal model for continuous measures, implemented through the TRAJ procedure in SAS, was used to identify trajectories of LTPA and LTSB from Wave I to Wave III (130, 131). This approach assumes the population is composed of a mixture of distinct groups defined by their trajectories. Sets of probability distributions for the specified number of LTPA and LTSB trajectory groups were calculated using maximum likelihood with age as the time scale. The optimal number and form (shape of the pattern of change) of trajectories were identified by comparing Bayesian Information Criteria (BIC) for models with different numbers of trajectory groups. Model comparisons with logged Bayes factor ($2*\Delta BIC$)>10 were considered strong evidence for the better model (131). Additionally, even if logged Bayes factor comparison suggested a model with <20 participants in one trajectory group was a better model, this model was not considered better because of the challenges of using such small numbers in adjusted regression models (132). First, models with different numbers of trajectory groups with all groups of quadratic form were compared. After the optimal numbers of trajectory groups were determined, the form of all trajectory groups was changed to cubic form and the model was compared to one with all groups in quadratic form to identify the optimal form of each trajectory group. For the final models with the optimal number of trajectory groups and optimal form for each group, the probability of group membership in each of the identified trajectory groups was calculated for each participant. Each participant was assigned to the trajectory group for which she had the highest posterior predictive probability on an age time scale. Trajectory groups were identified in the total analytic study population and in groups defined by pre-pregnancy BMI category (normal weight or overweight/obese). Final forms for trajectory groups are presented in Supplemental Table 4.2. Final models had good discrimination for LTPA (average posterior predictive probability=0.67) and LTSB (average posterior predictive probability=0.77).

Weighted linear regression using survey weights was used to estimate mean differences and 95% confidence intervals (CI) in offspring birthweight associated with LTPA and LTSB trajectories. Weighted logistic regression was used to estimate odds ratios and 95% CIs for SGA and LGA associated with trajectories. Wald tests were used to test joint significance of all LTPA or LTSB trajectories. Model I was adjusted for maternal age at delivery (years), race (non-Hispanic white/non-Hispanic black/Hispanic/other), parental income category (<$20K/$20-60K/>$60K), nulliparity (Y/N), smoking during pregnancy (Y/N), alcohol use during pregnancy (Y/N), gestational age at delivery (weeks), and offspring sex. Model II was additionally adjusted for pre-pregnancy BMI category (underweight/normal weight/overweight/obese).

Regression models were also fit stratified by offspring sex and by pre-pregnancy overweight/obese status. Two-way multiplicative interaction terms and corresponding P values were used to assess interactions of LTPA or LTSB trajectories with offspring sex. Because trajectories were different for normal weight and overweight/obese women, there was no test of interaction for these groups. We used another longitudinal data approach, generalized estimating equations (133) with repeated exposure and exchangeable correlation structure, which is robust to the type of correlation present in the data, to conduct sensitivity analyses that do not take pattern of exposure into account.

A two-sided alpha level of 0.05 was used for statistical significance in all analyses. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary NC) or Stata 12.1 (StataCorp, College Station TX).

RESULTS

Participants were 24 years old at delivery and delivered newborns that weighted 3,281g, on average (Table 4.1). Sixty-seven percent of women were white, 14% were black, and 11% were Hispanic. About half of the participants were nulliparous and normal weight. Twenty-four percent smoked during pregnancy. We identified three LTPA trajectories in adolescence and early adulthood among all participants, four LTPA trajectories among women with normal pre-pregnancy BMI, and three LTPA trajectories among women with overweight/obese pre-pregnancy BMI (Figure 4.1, Supplemental Table 4.3). We identified five LTSB trajectories among all participants, two LTSB trajectories among women with a normal pre-pregnancy BMI, and three LTSB trajectories among women with overweight/obese pre-pregnancy BMI (Figure 4.2, Supplemental Table 4.4). Maternal and offspring characteristics by LTPA and LTSB trajectory groups are shown in Supplemental Table 4.5 and Supplemental Table 4.6.

LTPA trajectories were not associated with offspring birthweight in the overall population or among groups defined by pre-pregnancy BMI categories (Supplemental Table 4.7). However, there was suggestive evidence that associations differed by offspring sex (P value for interaction=0.10) (Table 4.2). Among participants who delivered female offspring, participants with high LTPA at 15 years old followed by decreasing LTPA at 22 years old delivered offspring with 90 g greater birthweight (95% CI: -4, 184; P=0.06) compared to participants with low then decreasing LTPA. Among participants delivering male offspring, the same trajectory was not associated with birthweight (mean difference=-22; 95% CI: -110, 67; P=0.63). Results were similar after adjusting for pre-pregnancy BMI category.

LTPA trajectories were not associated with SGA or LGA in the overall population (Supplemental Table 4.8), but associations with LGA differed by offspring sex (P value for interaction=0.008) (Table 4.3). Among participants who delivered female offspring, participants with high LTPA at 15 years old followed by decreasing LTPA at 22 years old delivered offspring with 72% greater odds of LGA (95% CI: 0.94, 3.14; P=0.08) than participants with low then decreasing LTPA. Among male offspring, LTPA trajectories were not associated with LGA (P=0.15). LTPA trajectories were associated with LGA among normal weight women, but not overweight/obese women. Among normal weight women, participants with high LTPA at 15 years old followed by decreasing LTPA at 22 years old delivered offspring with 2.03-fold greater odds of LGA (95% CI: 1.06, 3.88) than participants with consistently moderate LTPA (Table 4.3). There were no associations of LTPA trajectories with SGA in female offspring, male offspring, normal weight women, or overweight/obese women. Results were similar after adjusting for pre-pregnancy BMI category.

LTSB trajectories were not associated with offspring birthweight (continuous or categorical) in the overall population and among groups defined by offspring sex or pre-pregnancy BMI categories. Results were similar with additional adjustment for pre-pregnancy BMI category. Preconception LTPA or LTSB was not associated with offspring birthweight in sensitivity analyses using generalized estimating equations (Supplemental Table 4.7).

DISCUSSION

Associations of maternal preconception (adolescence and young adulthood) LTPA and LTSB trajectories with offspring birthweight differed by offspring sex and pre-pregnancy BMI. Among participants who delivered female offspring, participants with high LTPA in adolescence followed by decreasing LTPA in early adulthood delivered offspring with 90g greater birthweight and 72% greater odds for LGA than participants with low then decreasing LTPA. This association was not observed among participants who delivered male offspring. Among women with normal pre-pregnancy BMI, participants with high LTPA in adolescence (15-16 years) followed by decreasing LTPA in early adulthood (22 years) had 2.0-fold greater odds for having LGA offspring compared with participants with consistently moderate LTPA throughout adolescence and young adulthood. This association was not observed among overweight/obese women.

A previous study of patterns of maternal preconception LTPA and pregnancy outcomes using Add Health data by Vamos et al found that maintaining high LTPA (≥5 times per week, based on meeting physical activity recommendations through 30 min of physical activity 5 days per week) in adolescence and adulthood was not associated with low birthweight (OR=0.79; 95% CI: 0.45, 1.39) (123). Vamos et al identified patterns of LTPA a priori, which may not capture observed patterns in the data. In order to better capture observed LTPA patterns, we used a data-driven approach to identify trajectories in our analyses. We did not find associations of any identified LTPA trajectory with SGA. Vamos et al did not examine LTSB or LGA in their analyses or stratify by offspring sex or maternal pre-pregnancy BMI. No other study, to our knowledge, has examined these associations.

The sex-specific and pre-pregnancy BMI-specific findings we report are consistent with sex-specific and pre-pregnancy BMI-specific associations of LTPA in the year before pregnancy with offspring birthweight we reported previously (11). In a cohort based in western Washington State, we found that pre-pregnancy LTPA was associated with lower offspring birthweight among female offspring and among offspring of women with normal pre-pregnancy BMI. LTPA in adolescence and young adulthood is correlated with LTPA later in adulthood, which influences adult health (134). Participants with high LTPA in adolescence followed by decreasing LTPA in early adulthood likely continued to have a low LTPA level in adulthood, including during the time period immediately preceding the pregnancy. Low levels of LTPA in the year before pregnancy and during early pregnancy may have sex-specific direct effects on early placental development (75), resulting in greater offspring birthweight among females, but not males, as we observed previously. Female fetuses may respond to changes in the intrauterine environment by changing growth rate, while male fetuses may respond by adapting placental function to continue normal growth (38). Additionally, low LTPA in adolescence and adulthood is associated with greater risk of abnormal glucose metabolism (24-26), which is a strong pre-pregnancy risk factor for gestational diabetes and large offspring birth size (135). Decreasing LTPA across adolescence to adulthood may be a stronger risk factor for abnormal glucose metabolism before pregnancy in normal weight women than in overweight/obese women, which may contribute to the observed increased risk of large-for-gestational age in normal weight women.

The data driven approach we used in our study identified, in general, similar distributions of longitudinal LTPA and LTSB patterns as a previous study among the female Add Health population using a priori specified patterns (128). However, we did not identify a pattern of consistently high LTPA, as reported previously (123, 128). We also identified an additional LTSB trajectory with consistently moderate LTSB. There were no associations of LTPA or

LTSB with offspring birthweight in sensitivity analyses using GEE models (Supplemental Table 4.9). GEE models do not take pattern of exposure into account, suggesting that pattern of preconception LTPA is important to consider.

Strengths of our study include characterization of long-term, longitudinal patterns of preconception LTPA and LTSB, use of continuous and categorical measures of birthweight to better characterize associations with birth size, and generalizability of results to the United States female population, as this was a nationally representative sample. However, results should be interpreted with several limitations in mind. LTPA and LTSB were recalled and self-reported, and LTPA duration was not collected, which may have introduced measurement error. Similar LTPA recalls among adolescents have good validity (r=0.44) compared to heart rate monitors and fair to good reliability (r=0.25-0.41 depending on intensity of the activity) among female respondents (136). LTSB self-report among adolescent girls tends to underestimate sedentary behavior by about 3 hours per week compared to accelerometry (137) and has good reliability (κ=0.42-0.55) (138). Measurement error is likely non-differential as LTPA and LTSB data were assessed before participants became pregnant. This may have biased our results toward the null. Offspring birthweight and gestational age at delivery were also recalled and self-reported. Maternal recall of birthweight has excellent validity (r=0.90) compared to birthweight in the medical record (139). Maternal recall of gestational age is also good (ICC=0.68) compared with medical records (140). A large portion of eligible participants were excluded due to missing data; however, sociodemographic and pregnancy characteristics were similar between eligible participants, participants included in this analysis, and participants excluded due to missing data, reducing concerns about selection bias. Low P values for associations of LTSB trajectories with LGA in males and females were driven by one trajectory (with no cases of LGA) and estimates may not be reliable (Supplemental Table 4.10). Three time points is the minimum number of time points necessary in order to apply trajectory modeling, which may have affected the estimation of trajectories.

In conclusion, we found potential associations of a pattern of high LTPA in adolescence followed by decreasing LTPA in young adulthood with larger offspring birth size among female offspring and participants with normal pre-pregnancy BMI. Our results contribute to a growing body of literature on sex-specific determinants of fetal growth and development. Our results and future studies in this area may have important public health significance to help identify women at risk for LGA offspring at the beginning of pregnancy based on history of long-term LTPA prior to conception.

Figure 4.1. Physical activity trajectory groups for study participants overall (N=1,408) and by pre-pregnancy overweight/obesity status (N=662 for normal weight, N=695 for overweight/obese)

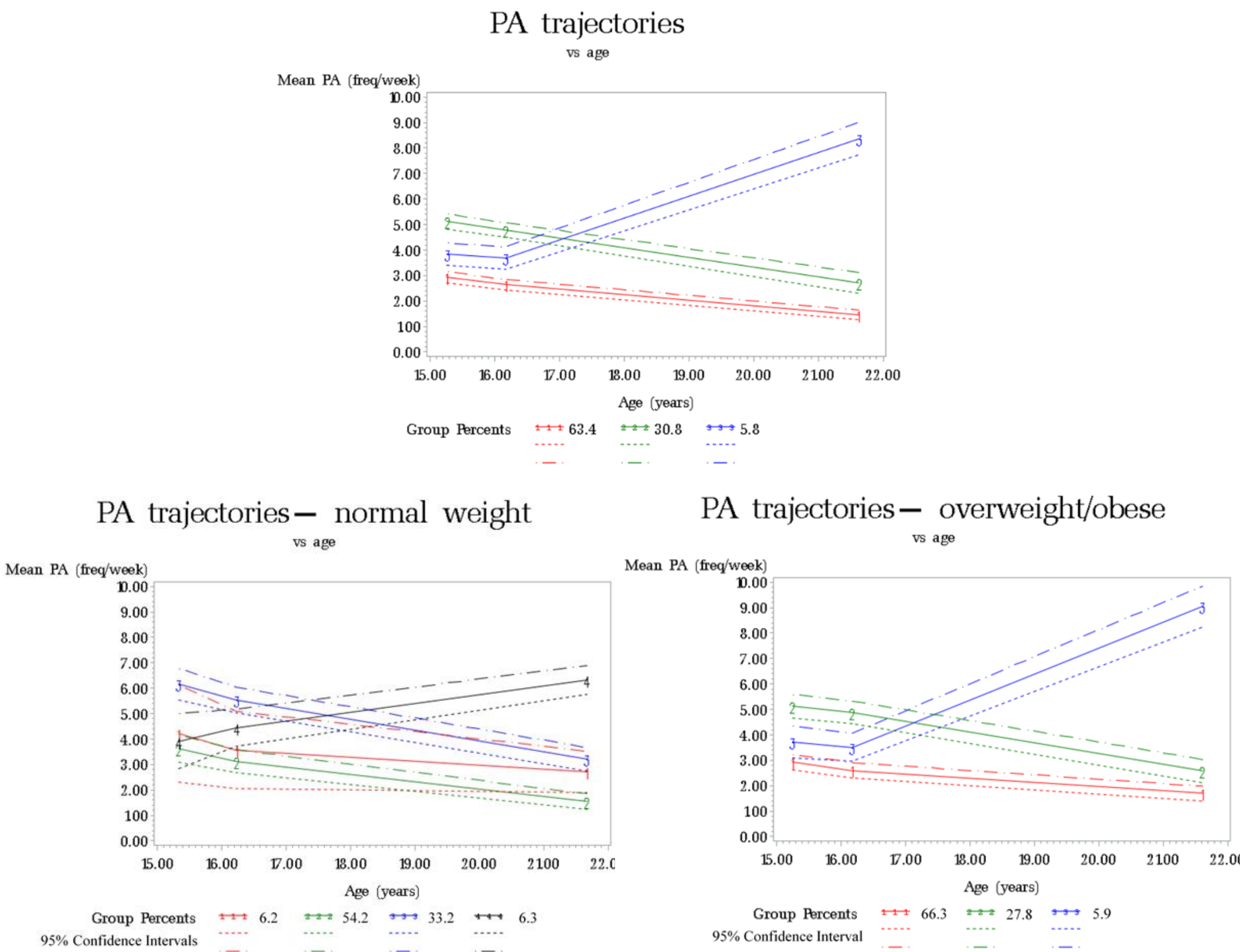

Figure 4.2. Sedentary behavior trajectory groups for study participants (N=1,408) and by pre-pregnancy overweight/obesity status (N=662 for normal weight, N=695 for overweight/obese)

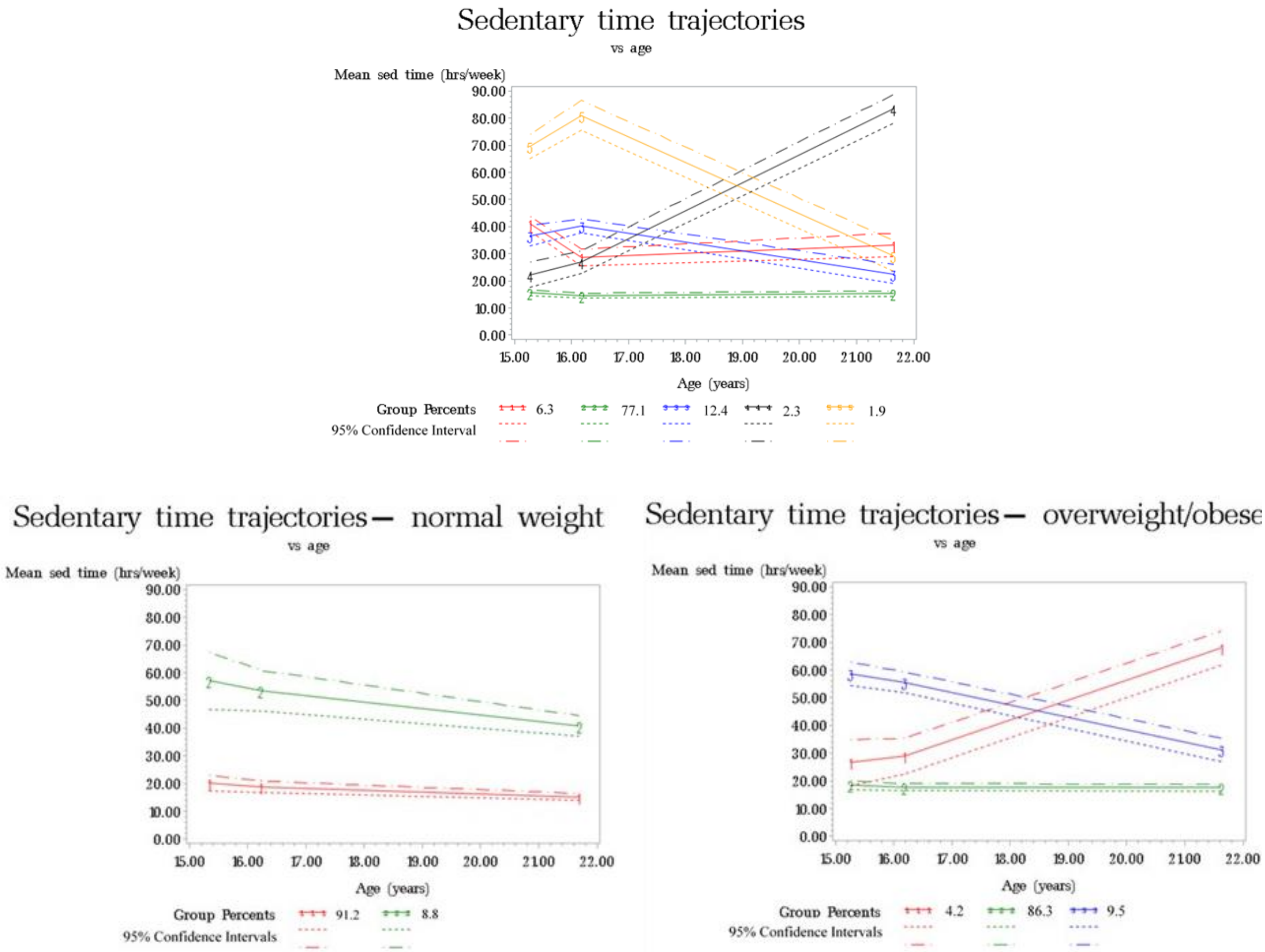

Table 4.1. Maternal and offspring characteristics of Add Health study participants, 1994-2008

	Total (n=1,408)
Maternal characteristics	
Age at delivery (years), weighted mean (SE)	24 (0.2)
Race, n (weighted %)	
Non-Hispanic white	813 (67)
Non-Hispanic black	274 (14)
Hispanic	213 (11)
Other	108 (7)
Married at time of pregnancy, (n, weighted %)	770 (81)[a]
Parental income[b] ($K), weighted mean (SE)	40 (1.4)
Parental income[b] category (n, weighted %)	
<$20,000	335 (25)
$20,000-60,000	776 (55)
>$60,000	297 (20)
Nulliparous, n (weighted %)	813 (56)
Pre-pregnancy BMI (kg/m^2), weighted mean (SE)	26 (0.3)
Pre-pregnancy BMI category, n (weighted %)	
Underweight	51 (4)
Normal weight	662 (47)
Overweight	336 (24)
Obese	359 (25)
Smoking during pregnancy, n (weighted %)	284 (24)
Alcohol use during pregnancy, n (weighted %)	86 (7)
Offspring characteristics	
Birthweight (grams), weighted mean (SE)	3281 (23.0)
Low birthweight (<2,500g), n (weighted %)	113 (8)
SGA, n (weighted %)	110 (8)
LGA, n (weighted %)	216 (15)
Gestational age at delivery (weeks), weighted mean (SE)	39 (0.1)
Male, n (weighted %)	717 (52)

[a]n=937

[b]Income of participant's parents at age 11-21 years.

Table 4.2. Associations of physical activity trajectory groups with birthweight

	N	Mean birthweight (g)	Mean difference (95% CI) Model I[a]	Model II[b]
Physical activity trajectory				
OVERALL	1408			
1 (decreasing from low activity)	940	3293	Reference	Reference
2 (decreasing from high activity)	391	3273	26 (-44, 96)	25 (-44, 94)
3 (increasing activity)	77	3171	-35 (-191, 120)	-48 (-202, 106)
FEMALES	691			
1 (decreasing from low activity)	468	3208	Reference	Reference
2 (decreasing from high activity)	181	3178	90 (-4, 184)	92 (-1, 186)
3 (increasing activity)	42	3067	-73 (-258, 112)	-70 (-261, 121)
MALES	717			
1 (decreasing from low activity)	472	3375	Reference	Reference
2 (decreasing from high activity)	210	3341	-22 (-110, 67)	-27 (-113, 59)
3 (increasing activity)	35	3307	15 (-217, 246)	-10 (-230, 209)

P value for interaction of PA trajectories with offspring sex= Model I: 0.10, Model II: 0.08

[a]Model is adjusted for maternal age at delivery (years), race (non-Hispanic white/non-Hispanic black/Hispanic/other), parental income category (<$20K/$20-60K/>$60K), nulliparity (Y/N), smoking during pregnancy (Y/N), alcohol use during pregnancy (Y/N), gestational age at delivery (weeks), and offspring sex.

[b]Model II is adjusted for all covariates in Model I and pre-pregnancy BMI category (underweight/normal weight/overweight/obese).

Table 4.3. Associations of physical activity trajectory groups with categorical birthweight

	SGA			LGA		
	N	**Odds Ratio (95% CI)**		**N**	**Odds Ratio (95% CI)**	
		Model I[a]	**Model II[b]**		**Model I[a]**	**Model II[b]**
Physical activity trajectory						
OVERALL						
1 (decreasing from low activity)	76/922	Reference	Reference	139/922	Reference	Reference
2 (decreasing from high activity)	24/376	0.85 (0.39, 1.87)	0.86 (0.39, 1.89)	64/376	1.07 (0.98, 1.69)	1.08 (0.69, 1.70)
3 (increasing activity)	10/74	1.71 (0.70, 4.20)	1.89 (0.74, 4.84)	13/74	1.07 (0.46, 2.46)	1.03 (0.46, 2.33)
FEMALES						
1 (decreasing from low activity)	37/462	Reference	Reference	64/462	Reference	Reference
2 (decreasing from high activity)	9/172	0.81 (0.26, 2.52)	0.75 (0.23, 2.41)	33/172	1.72 (0.94, 3.14)	1.83 (0.98, 3.41)
3 (increasing activity)	6/41	1.28 (0.35, 4.70)	1.54 (0.35, 6.86)	5/41	0.38 (0.11, 1.33)	0.40 (0.12, 1.33)
MALES						
1 (decreasing from low activity)	39/460	Reference	Reference	75/460	Reference	Reference
2 (decreasing from high activity)	15/204	0.75 (0.32, 1.78)	0.74 (0.31, 1.77)	31/204	0.69 (0.40, 1.21)	0.68 (0.39, 1.18)
3 (increasing activity)	4/33	2.51 (0.61, 10.3)	2.49 (0.62, 10.0)	8/33	1.84 (0.74, 4.62)	1.66 (0.65, 4.21)
NORMAL WEIGHT						
1 (consistently moderate activity)	3/40	1.10 (0.18, 6.76)	Reference	8/40	2.33 (0.71, 7.67)	Reference
2 (decreasing from low activity)	33/355	Reference	-	44/355	Reference	-
3 (decreasing from high activity)	17/218	1.11 (0.51, 2.42)	-	35/218	**2.03 (1.06, 3.88)**	-
4 (increasing from high activity)[c]	-	-	-	6/41	0.52 (0.15, 1.87)	-
OVERWEIGHT/OBESE						
1 (consistently low activity)	35/450	Reference	Reference	76/450	Reference	Reference
2 (decreasing activity)	8/179	0.54 (0.21, 1.37)	-	37/179	1.11 (0.58, 2.14)	-
3 (increasing activity)	6/39	2.23 (0.42, 11.9)	-	8/39	1.51 (0.62, 3.68)	-

P value for interaction with of PA trajectory with offspring sex: SGA Model I=0.89, SGA Model II=0.84; LGA Model I=0.008, LGA Model II=0.007

[a]Model I is adjusted for maternal age at delivery (years), race (non-Hispanic white/non-Hispanic black/Hispanic/other), parental income category (<$20K/$20-60K/>$60K), nulliparity (Y/N), smoking during pregnancy (Y/N), alcohol use during pregnancy (Y/N), gestational age at delivery (weeks), and offspring sex.
[b]Model II is adjusted for all covariates in Model I and pre-pregnancy BMI category (underweight/normal weight/overweight/obese).
[c]Number of SGA in this category is too small (<3) to be shown, in order to comply with Add Health guidelines for statistics.

Supplemental Table 4.1. Characteristics of eligible participants and analytic sample

	All Eligible (n=2801)		**Analytic Sample (n=1408)**	**Excluded (n=1393)**	
Maternal characteristics	**N**			**N**	
Age (years), weighted mean (SE)	2800	25 (0.1)	24 (0.2)	1391	25 (0.2)
Race, n (weighted %)	2793			1384	
Non-Hispanic white	1505	65	813 (67)	692	63
Non-Hispanic black	604	16	274 (14)	330	18
Hispanic	438	11	213 (11)	224	11
Other	246	7	108 (7)	138	7
Married at time of pregnancy, (n, weighted %)	1846	1545 (84)	770 (81)[a]	909	775 (88)
Nulliparous, n (weighted %)	2801	1572 (56)	813 (56)	1392	759 (56)
Smoking during pregnancy, n (weighted %)	2796	512 (21)	284 (24)	1387	227 (19)
Alcohol use during pregnancy, n (weighted %)	2798	146 (6)	86 (7)	1389	60 (4)
Offspring characteristics					
Birthweight (grams), weighted mean (SE)	2778	3288 (17.6)	3281 (23.0)	1369	3295 (23.9)
Gestational age at delivery (weeks), weighted mean (SE)	2783	39 (0.1)	39 (0.1)	1374	39 (0.1)
Male, n (weighted %)	2801	1459 (52)	717 (52)	1392	741 (52)

[a]n=937

Supplemental Table 4.2. Finals forms for trajectory groups

Trajectory groups	**Form of trajectories**
Physical activity	
Overall	All cubic
Normal weight	All quadratic
Overweight/obese	All cubic
Sedentary behavior	
Overall	All cubic
Normal weight	All quadratic
Overweight/obese	All quadratic

Supplemental Table 4.3. Mean physical activity at each study visit by trajectory groups

Trajectory group		**Mean physical activity (frequency/week)**		
Overall	**N**	**Wave I**[a]	**Wave II**[b]	**Wave III**[c]
1 (decreasing from low activity)	940	2.5	2.3	1.4
2 (decreasing from high activity)	391	4.8	4.8	3.1
3 (increasing activity)	77	4.3	4.2	8.7
Female offspring				
1 (decreasing from low activity)	468	2.5	2.4	1.5
2 (decreasing from high activity)	181	4.7	4.7	3.0
3 (increasing activity)	42	4.5	4.2	8.8
Male offspring				
1 (decreasing from low activity)	472	2.5	2.2	1.4
2 (decreasing from high activity)	210	4.8	4.8	3.2
3 (increasing activity)	35	3.9	4.1	8.5
Normal Weight				
1 (consistently moderate activity)	41	2.2	2.4	6.0
2 (decreasing from low activity)	359	2.1	2.1	1.1
3 (decreasing from high activity)	220	4.7	4.4	2.4
4 (increasing from high activity)	42	5.0	5.5	7.1
Overweight/obese				
1 (consistently low activity)	461	2.5	2.3	1.6
2 (decreasing activity)	193	4.9	4.9	2.9
3 (increasing activity)	41	4.1	4.0	9.4

[a]Wave I data collection occurred 1994-1995 when participants were in grade 7-12 (age 11-21 years).
[b]Wave II data collection occurred in 1996 when participants were age 12-22 years.
[c]Wave III data collection occurred 2001-2002 when participants were age 18-26 years.

Supplemental Table 4.4. Mean sedentary time at each study visit by trajectory groups

		Mean sedentary behavior (hours/week)		
Overall	**N**	**Wave I**	**Wave II**	**Wave III**
1 (consistently moderate SB)	88	41.2	24.4	41.6
2 (consistently low SB)	1085	14.6	12.9	15.3
3 (decreasing from moderate SB)	175	39.1	40.2	23.6
4 (increasing SB)	33	28.7	31.2	80.4
5 (decreasing from high SB)	27	74.1	73.2	37.1
Female offspring				
1 (consistently moderate SB)	42	38.8	24.3	41.5
2 (consistently low SB)	525	14.5	12.8	15.8
3 (decreasing from moderate SB)	90	41.1	39.4	23.5
4 (increasing SB)	16	21.9	34.2	73.9
5 (decreasing from high SB)	13	77.1	72.7	36.4
Male offspring				
1 (consistently moderate SB)	46	43.5	24.4	41.8
2 (consistently low SB)	556	14.8	12.9	14.9
3 (decreasing from moderate SB)	84	37.0	41.1	23.7
4 (increasing SB)	16	35.4	28.3	87.2
5 (decreasing from high SB)	11	70.6	73.7	37.8
Normal Weight				
1 (consistently low SB)	604	15.8	14.3	15.9
2 (decreasing SB)	58	51.6	41.9	39.6
Overweight/obese				
1 (increasing SB)	29	33.4	30.3	78.6
2 (consistently low SB)	600	18.0	16.0	18.6
3 (decreasing SB)	66	60.2	56.1	26.2

Abbreviations: sedentary behavior, SB

[a]Wave I data collection occurred 1994-1995 when participants were in grade 7-12 (age 11-21 years).

[b]Wave II data collection occurred in 1996 when participants were age 12-22 years.

[c]Wave III data collection occurred 2001-2002 when participants were age 18-26 years.

Supplemental Table 4.5. Maternal and offspring characteristics of Add Health study participants by physical activity trajectory group, 1994-2008

	Decreasing from low activity (n=940)	**Decreasing from high activity (n=391)**	**Increasing activity (n=77)**
Maternal characteristics			
Age at delivery (years), weighted mean (SE)	24 (0.2)	25 (0.2)	24 (0.4)
Race, n (weighted %)			
Non-Hispanic white	523 (66)	250 (73)	40 (61)
Non-Hispanic black	198 (16)	63 (11)	13 (17)
Hispanic	142 (12)	54 (9)	17 (18)
Other	77 (7)	24 (6)	7 (4)
Married at time of pregnancy, (n, weighted %)	506 (80)	222 (83)	42 (86)
Parental income[a] ($K), weighted mean (SE)	39 (1.5)	41 (2.2)	39 (5.4)
Parental income[a] category (n, weighted %)			
<$20,000	222 (25)	94 (23)	19 (29)
$20,000-60,000	525 (55)	209 (54)	42 (52)
>$60,000	193 (20)	88 (23)	16 (18)
Nulliparous, n (weighted %)	528 (55)	235 (59)	50 (63)
Pre-pregnancy BMI (kg/m^2), weighted mean (SE)	26 (0.3)	26 (0.5)	27 (1.0)
Pre-pregnancy BMI category, n (weighted %)			
Underweight	38 (4)	11 (4)	33 (38)[b]
Normal weight	449 (48)	182 (49)	
Overweight	211 (23)	100 (24)	25 (33)
Obese	242 (25)	98 (23)	19 (29)
Smoking during pregnancy, n (weighted %)	198 (23)	73 (25)	13 (21)
Alcohol use during pregnancy, n (weighted %)	46 (6)	34 (10)	6 (8)
Offspring characteristics			
Birthweight (grams), weighted mean (SE)	3293 (28.2)	3273 (35.8)	3171 (105)
Low birthweight (<2,500g), n (weighted %)	71 (7)	32 (8)	10 (10)
SGA, n (weighted %)	76 (8)	24 (7)	10 (13)
LGA, n (weighted %)	139 (15)	64 (17)	13 (15)

Gestational age at delivery (weeks), weighted mean (SE)	39 (0.1)	38 (0.2)	38 (0.4)
Male, n (weighted %)	472 (51)	210 (58)	35 (43)

[a]Income of participant's parents at age 11-21 years.

[b]Includes underweight and normal weight in order to comply with Add Health guidelines for statistics.

Supplemental Table 4.6. Maternal and offspring characteristics of Add Health study participants by sedentary behavior trajectory group, 1994-2008

	Consistently moderate (n=88)	Consistently low (n=1085)	Decreasing from moderate (n=175)	Increasing (n=33)	Decreasing from high (n=27)
Maternal characteristics					
Age at delivery (years), weighted mean (SE)	24 (0.3)	25 (0.1)	25 (0.3)	23 (0.4)	24 (0.7)
Race, n (weighted %)					
Non-Hispanic white	40 (51)	675 (72)	68 (52)	22 (71)	8 (36)
Non-Hispanic black	29 (28)	159 (10)	62 (30)	8 (20)	16 (58)
Hispanic	11 (10)	170 (12)	31 (13)	0 (0)	3 (6)[b]
Other	8 (11)	81 (7)	14 (5)	3 (9)	
Married at time of pregnancy, (n, weighted %)	37 (67)	644 (84)	74 (78)	10 (57)	5 (25)
Parental income[a] ($K), weighted mean (SE)	30 (2.5)	42 (1.6)	33 (2.6)	31 (5.3)	26 (5.6)
Parental income[a] category (n, weighted %)					
<$20,000	31 (37)	226 (21)	54 (35)	14 (36)	10 (51)
$20,000-60,000	46 (50)	613 (57)	92 (49)	15 (45)	10 (35)
>$60,000	11 (13)	246 (22)	29 (17)	4 (19)	7 (14)
Nulliparous, n (weighted %)	48 (49)	661 (61)	82 (36)	15 (56)	7 (24)
Pre-pregnancy BMI (kg/m^2), weighted mean (SE)	28 (1.2)	26 (0.3)	28 (0.6)	26 (1.5)	32 (1.6)
Pre-pregnancy BMI category, n (weighted %)					
Underweight	5 (8)	40 (4)	5 (2)	15 (57)[c]	7 (12)[c]
Normal weight	31 (31)	545 (52)	65 (33)		
Overweight	22 (24)	250 (23)	49 (32)	6 (17)	9 (33)
Obese	30 (37)	250 (22)	56 (34)	12 (26)	11 (55)
Smoking during pregnancy, n (weighted %)	24 (32)	205 (22)	38 (31)	10 (30)	7 (28)
Alcohol use during pregnancy, n (weighted %)	-[d]	76 (8)	6 (4)	-[d]	1 (0.2)
Offspring characteristics					
Birthweight (grams), weighted mean (SE)	3218 (76.8)	3288 (23.6)	3237 (58.7)	3261 (93.6)	3500 (212)
Low birthweight (<2,500g), n (weighted %)	9 (10)	79 (7)	21 (9)	-[d]	3 (11)
SGA, n (weighted %)	8 (6)	82 (8)	13 (8)	3 (11)	4 (17)
LGA, n (weighted %)	8 (8)	176 (16)	24 (13)	4 (10)	4 (21)

Gestational age at delivery (weeks), weighted mean (SE)	38 (0.3)	38 (0.1)	38 (0.2)	39 (0.5)	39 (0.3)
Male, n (weighted %)	46 (56)	558 (53)	84 (47)	16 (42)	13 (57)

[a]Income of participant's parents at age 11-21 years.
[b]Includes Hispanic and other in order to comply with Add Health guidelines for statistics.
[c]Includes underweight and normal weight in order to comply with Add Health guidelines for statistics.
[d]Frequency is <3 and cannot be shown in order to comply with Add Health guidelines for statistics.

Supplemental Table 4.7. Associations of physical activity and sedentary behavior trajectory groups with birthweight

	Wald test P value[a]				
		Offspring Sex		**Pre-pregnancy BMI**	
	Total Population	**Females**	**Males**	**Normal Weight**	**Overweight/ obese**
			Model I[b]		
Physical activity trajectories	0.66	0.12	0.86	0.41	0.38
Sedentary behavior trajectories	0.85	0.92	0.47	0.88	0.91
			Model II[c]		
Physical activity trajectories	0.60	0.11	0.82	-	-
Sedentary behavior trajectories	0.93	0.88	0.58	-	-

[a]Wald test P-value for joint significance of all physical activity or sedentary behavior trajectories (testing if any coefficient is not equal to 0).
[b]Model I is adjusted for maternal age at delivery (years), race (non-Hispanic white/non-Hispanic black/Hispanic/other), parental income category (<$20K/$20-60K/>$60K), nulliparity (Y/N), smoking during pregnancy (Y/N), alcohol use during pregnancy (Y/N), gestational age at delivery (weeks), and offspring sex.
[c]Model II is adjusted for all covariates in Model I and pre-pregnancy BMI category (underweight/normal weight/overweight/obese).

Supplemental Table 4.8. Associations of physical activity and sedentary behavior trajectory groups with categories of birthweight

	Total		Offspring Sex: Females		Offspring Sex: Males		Pre-pregnancy BMI: Normal Weight		Pre-pregnancy BMI: Overweight/obese	
	N	**P value[a]**	**N**	**P value[a]**	**N**	**P value[a]**	**N**	**P value[a]**	**N**	**P value[a]**
Model I[b]										
Physical activity trajectories										
Small-for-gestational age	110/1372	0.43	52/675	0.87	58/697	0.31	55/654	0.82	49/668	0.22
Large-for-gestational age	216/1372	0.95	102/675	0.07	111/697	0.15	93/654	0.02	121/668	0.66
Sedentary behavior trajectories										
Small-for-gestational age	110/1372	0.47	52/675	0.77	58/697	0.55	55/654	0.52	49/668	0.97
Large-for-gestational age	216/1372	0.61	102/675	<0.001	111/697	<0.001	93/654	0.48	121/668	0.30
Model II[c]										
Physical activity trajectories										
Small-for-gestational age	110/1372	0.34	52/675	0.73	58/697	0.27	55/654	-	49/668	-
Large-for-gestational age	216/1372	0.95	102/675	0.05	111/697	0.18	93/654	-	121/668	-
Sedentary behavior trajectories										
Small-for-gestational age	110/1372	0.43	52/675	0.51	58/697	0.62	55/654	-	49/668	-
Large-for-gestational age	216/1372	0.64	102/675	<0.001	111/697	<0.001	93/654	-	121/668	-

[a]Wald Test P-value for joint significance of all physical activity or sedentary behavior trajectories (testing if any coefficient is not equal to 0).
[b]Model I is adjusted for maternal age at delivery (years), race (non-Hispanic white/non-Hispanic black/Hispanic/other), parental income category (<$20K/$20-60K/>$60K), nulliparity (Y/N), smoking during pregnancy (Y/N), alcohol use during pregnancy (Y/N), gestational age at delivery (weeks), and offspring sex.
[c]Model II is adjusted for all covariates in Model I and pre-pregnancy BMI category (underweight/normal weight/overweight/obese).

Supplemental Table 4.9. GEE sensitivity analysis for associations of physical activity and sedentary behavior with birthweight

	Regression coefficient P value[a]				
		Offspring Sex		Pre-pregnancy BMI	
	Total	**Females**	**Males**	**Normal Weight**	**Overweight/ obese**
Birthweight (g)					
Physical activity	0.34	0.50	Not estimable	Not estimable	0.40
Sedentary behavior	0.32	0.16	0.79	0.65	0.39
Small-for-gestational age					
Physical activity	Not estimable	0.70	Not estimable	Not estimable	Not estimable
Sedentary behavior	0.87	Not estimable	0.50	Not estimable	0.78
Large-for-gestational age					
Physical activity	0.16	0.66	0.22	0.80	0.09
Sedentary behavior	0.99	0.57	0.71	0.59	0.44

[a]Model is adjusted for maternal age at delivery (years), race (non-Hispanic white/non-Hispanic black/Hispanic/other), parental income category (<$20K/$20-60K/>$60K), nulliparity (Y/N), smoking during pregnancy (Y/N), alcohol use during pregnancy (Y/N), gestational age at delivery (weeks), and offspring sex.

Supplemental Table 4.10. Associations of sedentary behavior trajectory groups with categorical birthweight

	SGA			LGA		
	N	Odds Ratio (95% CI)		N	Odds Ratio (95% CI)	
		Model I[a]	**Model II[b]**		**Model I[a]**	**Model II[b]**
Sedentary behavior trajectory						
OVERALL						
1 (consistently moderate SB)	8/85	0.56 (0.17, 1.84)	0.54 (0.18, 1.64)	8/85	0.59 (0.19, 1.87)	0.61 (0.18, 2.00)
2 (consistently low SB)	82/1056	1.21 (0.53, 2.76)	1.11 (0.48, 2.56)	176/1056	1.23 (0.64, 2.39)	1.33 (0.68, 2.59)
3 (decreasing from moderate SB)	13/171	Reference	Reference	24/171	Reference	Reference
4 (increasing SB)	3/33	1.56 (0.39, 6.29)	1.40 (0.35, 5.60)	4/33	0.75 (0.20, 2.81)	0.87 (0.25, 3.06)
5 (decreasing from high SB)	4/27	2.55 (0.50, 12.9)	2.63 (0.51, 13.4)	4/27	2.19 (0.47, 10.3)	1.94 (0.43, 8.77)
FEMALES						
1 (consistently moderate SB)	3/41	0.74 (0.13, 4.09)	0.47 (0.10, 2.13)	4/41	1.12 (0.32, 3.86)	1.07 (0.27, 4.18)
2 (consistently low SB)	41/512	1.42 (0.48, 4.18)	1.04 90.34, 3.15)	83/512	1.96 (0.68, 5.66)	2.17 (0.72, 6.53)
3 (decreasing from moderate SB)	6/91	Reference	Reference	11/91	Reference	Reference
4 (increasing SB)[c]	-	-	1.66 (0.15, 17.9)	4/17	2.99 (0.75, 11.9)	3.47 (0.90, 13.4)
5 (decreasing from high SB)[c]	-	-	3.07 (0.24, 40.0)	0/14	0.00 (not estimated)	0.00 (not estimated)
MALES						
1 (consistently moderate SB)	5/44	0.41 (0.09, 2.00)	0.43 (0.09, 2.07)	4/44	0.42 (0.09, 2.00)	0.46 (0.10, 2.13)
2 (consistently low SB)	41/544	0.99 (0.35, 2.76)	1.03 (0.36, 2.93)	93/544	0.91 (0.46, 1.83)	0.96 (0.48, 1.92)
3 (decreasing from moderate SB)	7/80	Reference	Reference	13/80	Reference	Reference
4 (increasing SB)[c]	-	-	1.53 (0.28, 8.31)	0/16	0.00 (not estimated)	0.00 (not estimated)
5 (decreasing from high SB)	3/13	2.20 (0.30, 16.4)	1.96 (0.26, 14.7)	4/13	4.53 (0.72, 28.7)	3.90 (0.65, 23.3)

P value for interaction= Model does not converge

[a]Model I is adjusted for maternal age at delivery (years), race (non-Hispanic white/non-Hispanic black/Hispanic/other), parental income category (<$20K/$20-60K/>$60K), nulliparity (Y/N), smoking during pregnancy (Y/N), alcohol use during pregnancy (Y/N), gestational age at delivery (weeks), and offspring sex.

[b]Model II is adjusted for all covariates in Model I and pre-pregnancy BMI category (underweight/normal weight/overweight/obese).

[c]Number of SGA in this category is too small (<3), so cannot show estimate according to Add Health rules.

Chapter 5:

Physical activity and epigenetic biomarkers in maternal blood during pregnancy

ABSTRACT

While epigenetic mechanisms potentially play key roles in associations between leisure time physical activity (LTPA) before and during pregnancy and pregnancy complications and fetal outcomes, few studies have investigated maternal epigenetic biomarkers in relation to LTPA. We investigated associations of maternal moderate/vigorous LTPA with early-mid pregnancy candidate gene DNA methylation (NSMAF, NXN, MSGN1, C1orf212, NOS2A, H19, HSD11B2, F2) and circulating microRNAs (miRNA) (miR-126-3p, 146b-5p, miR-155-5p, miR-21-3p, miR-210-3p, miR-222-3p, miR-223-3p, miR-517-5p, miR-518a-3p, miR-29a-3p) among a random sample of uncomplicated pregnancies in a pregnancy cohort study (N=92). Participants self-reported pre-pregnancy and early pregnancy LTPA duration (hours/week) and energy expenditure (MET-hours/week). DNA methylation and miRNA levels were measured in peripheral blood collected shortly after study interview (average 15 weeks gestation) using PCR experiments. Linear regression adjusted for maternal age and gestational age at blood draw was used to determine effect size estimates and their 95% confidence intervals (CI). Each additional hour of pre-pregnancy LTPA was associated with hypermethylation of a site in C1orf212 (β=0.137, 95% CI=0.004, 0.270, P=0.05), higher circulating levels of miR-146b-5p (β=0.084, 95% CI=0.017, 0.151, P=0.02), and marginally associated with higher circulating levels of miR-222-3p (β=0.074, 95% CI=-0.002, 0.150, P=0.07). Results were similar for pre-pregnancy LTPA energy expenditure. Early pregnancy LTPA was not associated with DNA methylation or circulating miRNAs. Our findings suggest that pre-pregnancy LTPA may influence maternal epigenetic biomarkers related to pathways that have been linked to pregnancy complications. Similar, larger studies can enhance understanding of mechanisms underlying associations of maternal LTPA with pregnancy complications and fetal growth.

INTRODUCTION

Physical activity is recommended across the lifespan for its cardiovascular and metabolic benefits (94). Physical activity before and during pregnancy has been associated with lower risk of pregnancy complications, such as gestational diabetes mellitus (54, 102), preeclampsia (55), excessive gestational weight gain (141-143), and improved fetal growth (11, 17). Effects of physical activity on inflammation, blood pressure control, lipid metabolism, and glucose metabolism contribute to observed cardiovascular and metabolic benefits in the general population (144, 145) and among pregnant women (146-148), however specific mechanisms are not well understood.

Previous studies have reported changes in epigenetic regulation of gene expression by DNA methylation and microRNA (miRNA) expression after physical activity (31-33). Regions in genes involved in systemic/local inflammation (149, 150) and glucose metabolism (149, 151) were differentially methylated in blood and skeletal muscle in response to an acute bout of aerobic physical activity (one cycling session) (149) and long-term (6 months) aerobic physical activity interventions (walking, spinning, aerobics) (150, 151) in adults. Changes in levels of circulating miRNAs involved in inflammatory pathways and angiogenesis have also been observed after a long-term physical activity intervention (cycling and rowing) among healthy, physically active men (152-154). Physical activity-related epigenetic changes during the perinatal period, a period of major physiologic changes in the mother, have not been well studied. Recently, McCullough et al published the first, and to our knowledge the only, study of maternal physical activity during pregnancy and epigenetic regulation of imprinted genes in newborn cord blood at birth (155). In their study, physical activity during pregnancy was associated with lower methylation in an imprinted region of *PLAGL1*. To our knowledge, previous studies have not examined associations of maternal physical activity before or during pregnancy with DNA methylation or circulating miRNAs in maternal blood.

Epigenetic regulatory mechanisms such as DNA methylation and miRNA expression may play important roles in systemic physiological functioning and placental development and function, with critical implications for pregnancy complications (e.g. gestational diabetes and preeclampsia (156, 157)) and fetal growth (34, 35, 157-159). Circulating epigenetic biomarkers have previously been used to characterize pathophysiology of pregnancy complications and in early pregnancy, to identify women at higher risk for pregnancy complications (160-163) and adverse outcomes (e.g., macrosomia (164-166)). Physical activity-associated epigenetic changes may also be useful biomarkers for identifying high risk women during pregnancy.

The objective of this study was to examine associations of candidate epigenetic biomarkers (DNA methylation and miRNA expression) in maternal peripheral blood with pre-pregnancy and early pregnancy physical activity.

RESULTS

Eighty-six percent of participants reported some pre-pregnancy leisure time physical activity and 73% reported some early pregnancy leisure time physical activity (Table 1). Women who reported some pre-pregnancy leisure time physical activity and women who reported some early pregnancy leisure time physical activity were more likely to have at least a high school education, be married, and have a lower pre-pregnancy BMI.

Each additional hour (duration) or MET-hour (energy expenditure) of pre-pregnancy moderate/vigorous leisure time physical activity duration or energy expenditure was associated with hypermethylation of a site in C1orf212 (β=0.137, 95% CI=0.004, 0.270, P=0.05 and β=0.030, 95% CI=0.001, 0.059, P=0.05, respectively) (Table 2). Early pregnancy leisure time physical activity was not associated with levels of DNA methylation in candidate genes.

Each additional hour (duration) or MET-hour (energy expenditure) of pre-pregnancy moderate/vigorous leisure time physical activity was associated with higher circulating levels of miR-146b-5p (β=0.084, 95% CI=0.017, 0.151, P=0.02 and β=0.017, 95% CI=0.001, 0.033, P=0.03, respectively) (Table 3). Pre-pregnancy physical activity duration and energy expenditure were also marginally associated with higher circulating levels of miR-222-3p (β=0.074, 95% CI=-0.002, 0.150, P=0.07 and β=0.017, 95% CI=0.001, 0.033, P=0.06, respectively). Early pregnancy leisure time physical activity was not associated with levels of circulating miRNAs.

Results were similar after adjustment for pre-pregnancy BMI. Pre-pregnancy or early pregnancy physical activity, categorized according to recommendations for physical activity issued by the American Congress of Obstetricians and Gynecologists, was not associated with candidate miRNA or DNA methylation levels (Supplemental Table 1 and 2).

DISCUSSION

In the current study, pre-pregnancy leisure time physical activity was associated with hypermethylation at sites in C1orf212, and higher circulating levels of miR-146b-5p. We also observed potential associations of pre-pregnancy physical activity with higher circulating levels of miR-222-3p.

A previous study of maternal physical activity during pregnancy and epigenetic regulation in newborn cord blood found associations between maternal total physical activity and methylation of an imprinted gene (*PLAG1)* (155). The study was nested within the Newborn Epigenetic Study, based in Durham County, North Carolina. Newborns of women in the highest quartile for total self-reported physical activity during pregnancy had 1.5% (absolute) lower methylation of *PLAGL1*, an imprinted differentially methylated region associated with fetal growth, compared with newborns of women in the lowest quartile (P for trend=0.0136).We did not assess methylation in newborn cord blood or methylation in *PLAGL1*. We did not find associations of early pregnancy moderate/vigorous physical activity with candidate DNA methylation or miRNA levels in maternal blood. However, maternal blood was drawn shortly after the early pregnancy interview. Early pregnancy physical activity may influence epigenetic regulation in maternal blood later in pregnancy.

Reports from previous studies in non-pregnant populations have indicated changes in levels of circulating miR-146 and miR-222 in response to physical activity. In male athletes, acute and sustained aerobic physical activity was associated with upregulation of miR-146a and miR-222 (154). In another study of male athletes, Wardle et al reported that endurance athletes (engaged in long-term aerobic physical activity) had higher levels of circulating miR-222 than non-exercising controls, whereas strength trained athletes had lower levels of miR-222 than non-exercising controls (167). Wardle et al did not observe differences in circulating miR-146a between endurance athletes, strength trained athletes, and non-exercising controls. Our results suggest that previously reported changes in circulating miR-146 and miR-222 in male athletes in response to long-term aerobic physical activity may also be present in pregnant women in relation to leisure time physical activity. To our knowledge, DNA methylation in C1orf212 has not been previously associated with physical activity.

Targets of miR-146b include genes associated with inflammation (*NFKB1*, *TRAF6*), cell cycle regulation (*CDKN1A*), apoptosis (*TRAF6*), and extracellular matrix degradation (*MMP16*) (168). Targets of miR-222 also include genes associated with cell cycle regulation (*CDKN1B*, *CDKN1C*), apoptosis (*STAT5A, FOXO3*), and extracellular matrix degradation (*MMP1*) (168). These pathways play important roles in the normal progression of pregnancy. Both miRNAs have also been related to pregnancy complications (miR-222 with severe preeclampsia (169)) and risk factors (miR-146a with maternal smoking (170)). To our knowledge, no prior studies have evaluated associations between C1orf212 and pregnancy-related conditions.

Circulating miRNAs and methylated DNA in maternal blood, which is easily accessible and routinely collected during prenatal care, may be non-invasive biomarkers for early detection of systemic (tissue non-specific) or local (tissue-specific, such as placental) pathophysiologic processes and identification of women at high risk for pregnancy complications. For instance, previous studies have identified placenta-specific epigenetic biomarkers in maternal blood (171-174), suggesting that epigenetic biomarkers from the placenta may be released or leak into maternal circulation during pregnancy.

Strengths of our study include assessment of perinatal physical activity in two independent time periods, before and during pregnancy, and consideration of multiple types of epigenetic mechanisms of gene regulation (DNA methylation and miRNA expression). On the other hand, the candidate approach we used for selecting DNA methylation sites and circulating miRNAs of interest did not allow us to identify novel DNA methylation sites or circulating miRNAs that have not been previously characterized. Due to the small size of our study, we were unable to control for other potential confounders (besides maternal age and gestational age at blood draw) of associations of perinatal physical activity, DNA methylation, and miRNA expression, such as socioeconomic status, parity, and smoking during pregnancy. We also had low power to detect associations across categories of LTPA according to recommendations. Results were similar after adjustment for pre-pregnancy BMI and smoking in sensitivity analyses, suggesting pre-pregnancy BMI and smoking was not confounding observed associations. Self-report of LTPA may have introduced misclassification into our study. A similar interviewer-administered physical activity questionnaire had moderate to good validity (Spearman correlation coefficient = 0.12-0.24) and good reliability (intraclass correlation coefficient = 0.82) for moderate to vigorous physical activity recall in early pregnancy for all domains of physical activity compared to accelerometer data (77). The majority of our study population was composed of active, educated, white women, and results of our study may not be generalizable to less active, more racially diverse populations.

In summary, we observed associations of maternal pre-pregnancy physical activity with methylation in C1orf212 and circulating levels of miR-146b-5p, and potential associations of pre-pregnancy physical activity with circulating levels of miR-222-3p. Our findings suggest pre-pregnancy physical activity may influence epigenetic regulation of genes involved in pathways that have been linked to pregnancy complications. Larger studies of physical activity-related epigenetic regulation in the perinatal period are warranted. Findings from such studies will enhance understanding of mechanisms underlying associations of maternal physical activity with pregnancy complications and fetal growth.

MATERIALS AND METHODS

Study Setting and Study Population

Data used in this study were collected as part of the Omega study, a prospective pregnancy cohort designed to assess risk factors of pregnancy complications. Details about the study design have been published previously (90). Briefly, pregnant women initiating prenatal care at clinics associated with Swedish Medical Center and Tacoma General Hospital in

Washington State were recruited from 1996 to 2008. Women were eligible to participate in the Omega study if they were at least 18 years old, were able to speak and read English, initiated prenatal care prior to 20 weeks gestation, and planned to carry the pregnancy to term and deliver at one of the two study hospitals.

The current study sampled from among randomly selected Omega study participants included in a study investigating traffic-related air pollution and pregnancy complications. We included 100 randomly selected controls with healthy pregnancies (without gestational diabetes, preeclampsia, preterm birth, or low birthweight) from this study in the current analysis. Participants with missing pre-pregnancy or early pregnancy leisure time physical activity (N=6), implausible values for pre-pregnancy or early pregnancy leisure time physical activity duration (>35 hours per week) (N=1 for pre-pregnancy, N=3 for early pregnancy), or missing covariates (N=1 missing gestational age at blood draw) were excluded. The Omega study was approved by the Institutional Review Boards of Swedish Medical Center and Tacoma General Hospital. All participants gave written informed consent.

Data Collection

Participants completed an in-person interview in early pregnancy (average 15 weeks gestation). Trained study interviewers collected sociodemographic characteristics, reproductive and medical history, and physical activity before and during early pregnancy. Maternal peripheral blood was collected shortly after enrollment in the study. Participants were followed until delivery, and trained study personnel abstracted maternal medical records for information on pregnancy outcomes. Pre-pregnancy BMI was calculated using reported height and pre-pregnancy weight.

Leisure Time Physical Activity

Pre-pregnancy physical activity was assessed in all participants using the following questions: 1) “Which activities did you participate in on a regular basis during the year before you became pregnant?”, and for each activity reported: 2) “How many times per week?”, 3) “How many months did you regularly participate in this activity?”, and 4) “How much time did you spend at the activity per episode?”. Participants were provided examples of leisure time physical activity including walking, swimming, jogging, weightlifting, dance/aerobics, bicycling, hiking, and yoga. Each activity reported was matched to its MET value (71), a measure of energy expenditure of a physical activity defined as the ratio of metabolic rate during a specific activity to a reference resting metabolic rate of 3.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$. Total duration of each leisure time physical activity reported was calculated and summed to obtain total leisure time physical activity duration per week. Energy expenditure of each leisure time physical activity was calculated by multiplying each individual activity duration by its corresponding MET value. Individual MET-hours were summed to obtain average pre-pregnancy leisure time physical activity energy expenditure per week.

Early pregnancy physical activity was similarly assessed. Total duration of each leisure time physical activity reported in the week prior to the study interview was calculated and summed to obtain total early pregnancy leisure time physical activity duration. Energy expenditure of each leisure time physical activity was calculated, and individual MET-hours were summed to obtain early pregnancy leisure time physical activity energy expenditure per week. Participants were categorized according to recommendations for physical activity before and during pregnancy (not active, active<150 minutes/week, active≥150 minutes/week) (1).

Sample Collection, Pre-processing, DNA and RNA Extraction

Maternal peripheral blood samples were collected at 16 weeks gestation, on average (interquartile range=15-17 weeks). After collection, samples were stored at 4°C until processing. Maternal peripheral blood buffy coat specimens were prepared from whole blood collected in early pregnancy. DNA, for methylation profiling, was extracted from maternal buffy coat samples using the Gentra PureGene Cell kit for DNA preparations (Qiagen, Valencia, California). Approximately 200µL of plasma was used for extracting small RNAs using the ExiqonmiRCURY™ RNA Biofluids Isolation Kit (Exiqon, Woburn, MA). Integrity, purity, and quantity of purified miRNA was assessed using spectrophotometry and an Agilent 2100 Bioanalyzer capillary electrophoresis system (Agilent Technologies Inc, Palo Alto, CA).

Candidate DNA Methylation Site and miRNA Selection and Profiling, Data Processing, and Normalization

Selected candidate DNA methylation sites are presented in Supplemental Table 3. Genomic DNA (250-300ng) was bisulfide treated, using EpiTect Fast DNA Bisulfite Kit (Qiagen, Valencia, CA). Following clean-up of the converted product, DNA was brought up to a concentration of 10ng/µl and 20ng of converted DNA was run in the Pyromark PCR reaction as per manufacturer's protocol (Qiagen). Each 25µl PCR reaction consisted of 12.5µl 2x PyroMark PCR Master Mix (Qiagen), 5 pmol forward primer, 5 pmol reverse primer, 20ng of bisulfite-treated DNA, and water. Thermocycling conditions were 15 min at 95°C followed by 45 cycles of 30 seconds at 94°C, 30 seconds at 56°C, and 30 seconds at 72°C, with a final extension of 10 minutes at 72°C. After visual determination of a single band on an agarose gel, 8µl of the PCR product was used in a Qiagen Q24 Pyrosequencing Assay using the manufacturer's protocol. Briefly, the biotin-labeled amplicon was bound to streptavidin-coated sepharose beads. The product was then denatured to remove un-bound DNA and washed via a vacuum workstation. The resulting bound single-stranded DNA was mixed with sequencing primer, heated at 80°C for 2 minutes and allowed to slowly cool. DNA methylation status was determined on this final product using a Pyromark Q24 instrument. By detecting the intensity of light generated during each nucleotide dispensation, the sequence information was collected. Final results were analyzed using Pyromark Q24 software.

MiRNAs that have previously been associated with pregnancy complications and mechanisms related to pregnancy complications were identified from the literature (175-181): miR-126-3p, -155-5p, -21-3p, -146b-5p, -210-3p, -222-3p, -223-3p, -517-5p, -518a-3p, and -29a-3p. We constructed a custom targeted panel of the candidate miRNAs and two control miRNA assays using ExiqonLNA™ primers. An exogenous miRNA cel-miR-39 was added as a positive control for technical factors including RNA extraction, complementary DNA synthesis, and PCR amplification (182), and an endogenous "housekeeping" miRNA, miR-423-3p, was chosen for normalization, based on previous recommendations (183). qPCR was conducted in duplicate using 96-well qPCR plates. Reactions were run on an ABI PRISM 7000 Real Time PCR machine (Applied Biosystems, Foster City, CA), using default cycling conditions. We recorded threshold cycle (CT) values on two measurements per sample. Original plasma samples were split, completely independent RNA preps were done, an independent RT reaction was performed for each replicate, and each replicate was run on a different qPCR 96-well plate. CT values of duplicates differing by greater than 0.2 times the standard deviation were re-tested, and replicates were averaged for analyses. Lab personnel was blinded to physical activity. Data from miRNA qRT-PCR arrays were imported into SDS Enterprise Software (V2.2.2, Applied Biosystems) and CT values were calculated using a consistent thresholding value for each assay across all plates. Raw CT values were scaled to values for cel-miR-39-3p. Then, ΔΔCT values were expressed relative to values of miR-423-3p and used in subsequent analyses.

Statistical analyses

Means and standard deviations were used to describe distributions of continuous variables. Frequencies and percentages were used to describe distributions of categorical variables. Sociodemographic and pregnancy characteristics were summarized overall, by pre-pregnancy physical activity, and by early pregnancy physical activity. MiRNA CT values were log-transformed to achieve normal distribution. DNA methylation levels were normally distributed.

Linear regression was used to examine associations of leisure time physical activity (continuous and according to recommendations) with levels of each candidate DNA methylation site and each candidate circulating miRNA, adjusting for maternal age and gestational age at blood draw. Models were run separately for pre-pregnancy and early pregnancy physical activity. We also conducted sensitivity analyses with additional adjustment for pre-pregnancy BMI and smoking. A two-sided alpha level of 0.05 was used for statistical significance in all analyses. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary NC).

Table 5.1. Characteristics of Omega participants overall, by pre-pregnancy activity status, and by early pregnancy activity status

	Total (n=92)	Any pre-pregnancy LTPA (n=80)	No pre-pregnancy LTPA (n=12)	Any early pregnancy LTPA (n=69)	No early pregnancy LTPA (n=21)
Maternal age (years), *mean (SD)*	33 (4)	33 (4	33 (5)	33 (4)	33 (5)
Non-Hispanic white race, *n (%)*	77 (84)	67 (84)	10 (83)	58 (84)	17 (81)
At least high school education, *n (%)*	89 (97)	79 (99)	10 (83)	68 (99)	19 (90)
Married, *n (%)*	83 (90)	73 (91)	10 (83)	64 (93)	17 (81)
Pre-pregnancy BMI (kg/m^2) , *mean (SD)*	23 (4)	22 (4)	26 (6)	22 (4)	24 (5)
Nulliparous, *n (%)*	50 (54)	45 (56)	5 (42)	36 (52)	13 (62)
Gestational age at blood draw (weeks) , *mean (SD)*	16 (3)	16 (3)	16 (2)	16 (3)	17 (2)
Smoked during pregnancy, *n (%)*	7 (8)	7 (9)	0 (0)	4 (6)	3 (15)
Infant birthweight, *mean (SD)*	3427 (508)	3384 (503)	3699 (467)	3421 (540)	3467 (363)

Abbreviations: LTPA (leisure time physical activity)

Table 5.2. Associations of pre- and early pregnancy physical activity duration with DNA methylation

	Pre-pregnancy								Early pregnancy							
DNA methylation	Duration (hours per week)				Energy Expenditure (MET-hours per week)				Duration (hours per week)				Energy Expenditure (MET-hours per week)			
site	N	Est[a]	95% CI	P value	N	Est[a]	95% CI	P value	N	Est[a]	95% CI	P value	N	Est[a]	95% CI	P value
NSMAF	92	-0.020	-0.055, 0.015	0.28	92	-0.004	-0.012, 0.004	0.27	90	-0.004	-0.057, 0.049	0.89	90	0.060	-0.03, 0.15	0.20
NXN	90	-0.057	-0.165, 0.051	0.30	90	-0.009	-0.033, 0.015	0.46	88	0.097	-0.058, 0.252	0.22	88	0.125	-0.144, 0.394	0.37
MSGN1	90	-0.009	-0.105, 0.087	0.85	90	-0.002	-0.024, 0.020	0.84	88	-0.041	-0.168, 0.086	0.52	88	-0.081	-0.302, 0.14	0.48
C1orf212	92	**0.137**	**0.004, 0.270**	**0.05**	92	**0.030**	**0.001, 0.059**	**0.05**	90	-0.149	-0.343, 0.045	0.13	90	-0.109	-0.448, 0.23	0.53
NOS2A	92	-0.047	-0.118, 0.024	0.20	92	-0.010	-0.026, 0.006	0.23	90	0.003	-0.097, 0.103	0.96	90	0.078	-0.096, 0.252	0.38
H19	92	0.053	-0.055, 0.161	0.34	92	0.016	-0.008, 0.040	0.20	90	-0.010	-0.165, 0.145	0.90	90	-0.035	-0.304, 0.234	0.80
HSD11B2	92	-0.036	-0.110, 0.038	0.34	92	-0.007	-0.023, 0.009	0.43	90	0.012	-0.094, 0.118	0.82	90	0.048	-0.136, 0.232	0.61
F2	92	-0.006	-0.069, 0.057	0.84	92	-0.004	-0.018, 0.010	0.61	90	-0.075	-0.165, 0.015	0.11	90	-0.065	-0.224, 0.094	0.42

[a]Outcome is percent methylation. Model is adjusted for maternal age (years) and gestational age at blood draw (weeks).
Results were similar after additional adjustment for pre-pregnancy BMI and smoking.

Table 5.3. Associations of pre- and early pregnancy physical activity duration (hours/week) and candidate microRNAs

	Pre-pregnancy								Early pregnancy							
	Duration (hours per week)				Energy Expenditure (MET-hours per week)				Duration (hours per week)				Energy Expenditure (MET-hours per week)			
microRNA	N	Est[a]	95% CI	P value	N	Est[a]	95% CI	P value	N	Est[a]	95% CI	P value	N	Est[a]	95% CI	P value
miR-146b-5p	75	**0.084**	**0.017, 0.151**	**0.02**	75	**0.017**	**0.001, 0.033**	**0.03**	74	0.017	-0.110, 0.144	0.80	74	-0.041	-0.213, 0.131	0.65
miR-126-3p	75	0.070	-0.01, 0.150	0.09	75	0.012	-0.006, 0.030	0.19	74	-0.015	-0.162, 0.132	0.84	74	0.019	-0.181, 0.219	0.85
miR-155-5p	75	0.050	-0.032, 0.132	0.24	75	0.008	-0.012, 0.028	0.39	74	0.027	-0.124, 0.178	0.72	74	0.005	-0.199, 0.209	0.96
miR-210-3p	74	0.066	-0.024, 0.156	0.15	74	0.016	-0.004, 0.036	0.12	73	0.018	-0.145, 0.181	0.83	73	-0.043	-0.264, 0.178	0.70
miR-21-3p	75	0.071	-0.021, 0.163	0.14	75	0.013	-0.009, 0.035	0.22	74	0.053	-0.116, 0.222	0.54	74	0.098	-0.131, 0.327	0.40
miR-222-3p	75	0.074	-0.002, 0.150	0.07	75	0.017	-0.001, 0.035	0.06	74	0.003	-0.140, 0.146	0.97	74	-0.020	-0.214, 0.174	0.84
miR-223-3p	75	0.079	-0.001, 0.159	0.06	75	0.014	-0.004, 0.032	0.14	74	-0.001	-0.148, 0.146	0.99	74	0.037	-0.163, 0.237	0.71
miR-29a-3p	75	0.055	-0.031, 0.141	0.22	75	0.013	-0.007, 0.033	0.20	74	0.023	-0.134, 0.180	0.78	74	0.009	-0.205, 0.223	0.93
miR-517-5p	73	0.060	-0.032, 0.152	0.20	73	0.013	-0.009, 0.035	0.22	72	0.021	-0.148, 0.19	0.81	72	-0.156	-0.379, 0.067	0.17
miR-518a-3p	74	0.073	-0.045, 0.191	0.23	74	0.016	-0.011, 0.043	0.25	73	0.052	-0.169, 0.273	0.65	73	-0.004	-0.306, 0.298	0.98

[a]Model is adjusted for maternal age (years) and gestational age at blood draw (weeks). Outcome is log transformed.
Results were similar after adjustment for pre-pregnancy BMI and smoking.

Supplemental Table 5.1. Associations of pre-pregnancy and early pregnancy physical activity according to ACOG recommendations with DNA methylation

microRNA	Not active		Active below recommendations				Active at or above recommendations			
	N	β	N	β[a]	SE	P	N	β[a]	SE	P
Pre-pregnancy										
NSMAF	12	Ref	16	-0.018	0.360	0.96	64	-0.224	0.293	0.45
NXN	12	Ref	16	-0.062	1.075	0.95	62	0.327	0.875	0.71
MSGN1	12	Ref	15	-0.429	0.981	0.66	63	-0.111	0.784	0.89
C1orf212	12	Ref	16	0.437	1.343	0.75	64	1.526	1.09	0.17
NOS2A	12	Ref	16	-0.120	0.713	0.87	64	-0.177	0.579	0.76
H19	12	Ref	16	0.487	1.061	0.65	64	1.436	0.862	0.10
HSD11B2	12	Ref	16	-0.698	0.739	0.35	64	-0.401	0.600	0.51
F2	12	Ref	16	0.067	0.635	0.92	64	0.014	0.515	0.98
Early pregnancy										
NSMAF	21	Ref	20	0.526	0.292	0.07	49	0.139	0.242	0.57
NXN	21	Ref	19	0.065	0.873	0.94	48	1.148	0.718	0.11
MSGN1	21	Ref	20	0.380	0.720	0.60	47	0.140	0.602	0.82
C1orf212	21	Ref	20	0.722	1.109	0.52	49	-0.082	0.919	0.93
NOS2A	21	Ref	20	0.224	0.572	0.70	49	0.286	0.474	0.55
H19	21	Ref	20	-0.445	0.867	0.61	49	0.657	0.718	0.36
HSD11B2	21	Ref	20	0.013	0.604	0.98	49	0.286	0.501	0.57
F2	21	Ref	20	0.256	0.513	0.62	49	-0.444	0.425	0.30

Abbreviations: β (estimate), SE (standard error), P (P value)

[a]Model is adjusted for maternal age (years) and gestational age at delivery (weeks).

Supplemental Table 5.2. Associations of pre-pregnancy and early pregnancy physical activity according to ACOG recommendations and microRNAs

microRNA	Not active		Active below recommendations				Active at or above recommendations			
	N	β	N	β[a]	SE	P	N	β[a]	SE	P
Pre-pregnancy										
miR-146b-5p	10	Ref	13	-0.261	0.716	0.72	52	0.363	0.586	0.54
miR-126-3p	10	Ref	13	-0.456	0.834	0.59	52	0.235	0.683	0.73
miR-155-5p	10	Ref	13	-0.778	0.857	0.37	52	-0.283	0.702	0.69
miR-210-3p	10	Ref	12	0.423	0.954	0.66	52	0.421	0.767	0.58
miR-21-3p	10	Ref	13	-0.699	0.956	0.47	52	0.244	0.783	0.76
miR-222-3p	10	Ref	13	0.200	0.813	0.81	52	0.457	0.666	0.49
miR-223-3p	10	Ref	13	-0.680	0.830	0.42	52	0.282	0.680	0.68
miR-29a-3p	10	Ref	13	0.276	0.910	0.76	52	0.574	0.732	0.44
miR-517-5p	9	Ref	13	-1.377	0.960	0.16	51	-0.797	0.797	0.32
miR-518a-3p	9	Ref	13	0.142	1.260	0.91	52	0.660	1.047	0.53
Early pregnancy										
miR-146b-5p	20	Ref	16	-0.572	0.570	0.32	38	0.035	0.464	0.94
miR-126-3p	20	Ref	16	0.104	0.664	0.88	38	0.177	0.540	0.74
miR-155-5p	20	Ref	16	-0.107	0.675	0.87	38	0.192	0.549	0.73
miR-210-3p	19	Ref	16	-0.145	0.728	0.84	38	-0.039	0.600	0.95
miR-21-3p	20	Ref	16	0.279	0.760	0.71	38	0.508	0.619	0.41
miR-222-3p	20	Ref	16	0.156	0.644	0.81	38	0.084	0.524	0.87
miR-223-3p	20	Ref	16	0.239	0.662	0.72	38	0.351	0.538	0.52
miR-29a-3p	20	Ref	16	0.064	0.703	0.93	38	0.148	0.580	0.80
miR-517-5p	20	Ref	16	**-1.436**	**0.725**	**0.05**	36	-0.137	0.594	0.82
miR-518a-3p	19	Ref	16	-0.695	0.998	0.49	38	0.028	0.813	0.97

Abbreviations: β (estimate), SE (standard error), P (P value)

[a]Model is adjusted for maternal age (years) and gestational age at delivery (weeks). Outcome is log transformed.

Supplemental Table 5.3. Sequence information for candidate DNA methylation sites

Gene Name	Sequence[a]
NSMAF	GAGT**Y**GGTA
NXN	T**Y**GGAAGGTG T
MSGN1	AGAGGGT**Y**GT GT
C1orf212	TTGT**Y**GGGTT TA
NOS2A	G**Y**G**Y**GG**Y**GTG **Y**GAGGT**Y**GT**Y** G
H19	TT**Y**GGATGTT AAAGGAGGGG TG**Y**GGGGAGG T**Y**GTTTTT
HSD11B2	T**Y**GGGAG**Y**GG T**Y**GTTTTGTT TTTT**Y**GTTA
F2	ACTC**R**CC**R**AA CCC**R**CTAAAA

[a]Methylation sites are in bold.

DISCUSSION

Summary of Results

In this dissertation, I investigated associations of maternal preconception and perinatal physical activity and sedentary behavior with offspring birth size, offspring growth in infancy, and epigenetic gene regulation. Data from three prospective cohort studies (the Omega study, the DNBC, and Add Health) were used to address the aims of this dissertation. Omega study participants were active, with 90% of participants reporting some leisure time physical activity. Only 37% of DNBC participants reported some leisure time physical activity, and 66% of Add Health participants had low physical activity in young adulthood. I observed associations of leisure time walking in the year before pregnancy and in early pregnancy with greater offspring ponderal index at birth in the Omega study. I observed associations of moderate/vigorous leisure time physical activity in early pregnancy with lower offspring weight at 12 months old among males, but not females, in the DNBC. I also observed inverse associations of early pregnancy leisure time sedentary behavior with offspring weight at 12 months old overall, positive associations of early pregnancy sedentary behavior with offspring underweight status among female offspring, and suggested inverse associations of early pregnancy sedentary behavior with offspring obesity status among male offspring in the DNBC. I identified sex-specific and pre-pregnancy BMI-specific associations of a pattern of preconception physical activity characterized by high physical activity at age 15 years followed by decreasing physical activity by age 22 years with offspring birthweight in Add Health. This decreasing pattern of preconception physical activity was associated with greater birthweight and greater odds of LGA among female offspring and women with normal pre-pregnancy BMI. I did not observe associations of pre-pregnancy or early pregnancy yoga practice with offspring birth size in the Omega study. I also did not observe associations of maternal long-term (adolescence to young adulthood) or short-term (year before pregnancy) pre-pregnancy or early pregnancy sedentary behavior with offspring birth size in Add Health and the Omega study. Finally, in the mechanistic study, I observed associations of pre-pregnancy and early pregnancy physical activity with candidate DNA methylation and circulating microRNA expression in a subset of the Omega study. In summary, I observed associations of long-term maternal preconception physical activity, short-term pre-pregnancy physical activity, and physical activity during pregnancy with offspring birth size, weight at 12 months, and epigenetic regulation. I also observed associations of maternal sedentary behavior during pregnancy with offspring weight at 12 months old. These results suggest that the influence of maternal periconceptional physical activity and sedentary behavior on offspring size at birth and at 12 months old may be sex-specific.

Strengths and Limitations

There are several strengths of this dissertation. First, I used multiple large, well-characterized cohorts to address research questions related to maternal physical activity, sedentary behavior, and offspring growth. Cohorts used in this dissertation were local (Omega study), national (Add Health), and international (DNBC), allowing investigation of associations among various populations. This dissertation also included comprehensive assessment of exposures across the physical activity spectrum (sedentary behavior, light physical activity, and moderate/vigorous physical activity) and during multiple time periods (adolescence and young adulthood, the year before pregnancy, and early pregnancy). This dissertation used novel statistical methods to address limitations in available data (non-parametric calibration weighting, isotemporal substitution modeling, and group-based trajectory analysis). The studies included in this dissertation were the first to assess offspring sex-specific associations of maternal physical activity, sedentary behavior, and offspring growth. Investigations of sex-specific associations in this dissertation project are in line with initiatives at the National Institutes of Health for consideration of the role of sex in all studies of health outcomes (184). A better understanding of sex-specific associations of maternal behaviors during the perinatal period and offspring health may eventually lead to sex-specific personalized prenatal care. Finally, this dissertation project included exploration of potential epigenetic mechanisms linking maternal physical activity with pregnancy and offspring health outcomes to strengthen evidence for causal associations and identify potential preventive targets for interventions or personalized medicine.

Several limitations should also be considered when interpreting results of these studies. Physical activity and sedentary behavior were assessed using maternal self-report in all of the cohorts included in this dissertation. Accurate self-report of physical activity and sedentary behavior is challenging, and use of self-reported measures of these exposures introduces measurement error into the results. Validity of self-reported overall moderate/vigorous leisure time physical activity, leisure time walking, and time spent watching television is fair to good (52, 77, 97), while validity of self-reported overall light intensity physical activity is poor (45, 46). As all studies were prospective, measurement error in physical activity and sedentary behavior is likely non-differential, biasing results toward the null. Additionally, we only considered leisure time physical activity and used leisure time spent watching television to assess sedentary behavior in our studies. However, a large portion of light activity and sedentary behavior occurs in occupational and transportational domains (185). Additionally, I did not capture all forms of leisure time sedentary behavior, such as time spent in front of a computer. The outcomes in this dissertation project (birth size and offspring growth at 12 months old) were used as markers of adverse fetal and offspring growth, but these outcomes may not fully capture the effects of maternal physical activity and sedentary behavior on offspring health. Observed differences in birth size associated with periconceptional patterns of leisure time physical activity, walking in the year before pregnancy, and walking during early pregnancy were small. Therefore, their significance may not be apparent unless we follow the offspring into adulthood when they start presenting with cardiovascular or metabolic diseases (186-188). In addition, this project did not consider the role of additional risk factors for offspring health outcomes, such as diet, environmental exposures, or genetics. Finally, while we controlled for important measured confounding variables, unmeasured confounding may explain observed associations.

Recommendations

Future studies of periconceptional leisure time physical activity and sedentary behavior should:

1) Use objective measures, such as accelerometry, to capture accurate measures of time spent in sedentary behavior, light and moderate/vigorous physical activity across multiple domains (leisure time, occupational, transportational). Accelerometry has been established as a more accurate instrument for measuring activity (189) than self-report.
2) Investigate associations of maternal sedentary behavior and physical activity with offspring outcomes that may better capture effects on offspring health, such as cardiovascular and metabolic disease risk in adulthood and biomarkers of disease processes (epigenetics, glucose, blood pressure, lipids).

3) Assess the role of additional factors associated with pregnancy complications and offspring health, including diet (vitamin D, fiber, calcium), environmental exposures (air pollution), and genetics (fetal growth genes, type 2 diabetes genes, vascular function genes).
4) Use randomized controlled trials of physical activity-promoting and sedentary behavior-reducing interventions to address unmeasured confounding in observational studies of maternal physical activity and sedentary behavior with offspring health. Causal inference methods, such as instrumental variables and inverse probability weighting, can also be used to address unmeasured confounding.
5) Consider sex as a potential effect modifier in all studies of health outcomes, from fetal growth to adult risk of disease. Identifying and understanding differences in physiology and disease etiology between males and females will inform diagnosis and intervention strategies for adverse health outcomes across the life span.
6) Continue to assess epigenetic mechanisms associated with maternal physical activity and sedentary behavior for identification of mechanisms linking maternal physical activity and sedentary behavior with offspring growth and health outcomes. Assessment of associations of maternal physical activity and sedentary behavior with epigenome-wide epigenetic regulation may be warranted to identify novel regulatory mechanisms.
7) Develop and test effective interventions to promote physical activity among reproductive age and pregnant women. Despite the benefits of perinatal physical activity I observed in this dissertation and a large body of literature supporting beneficial associations of perinatal physical activity with decreased risk of pregnancy complications (54, 55), from 1999-2006 only 57% of pregnant women engaged in any form of moderate/vigorous

physical activity in the United States and only 23% met the physical activity recommendation (53). Developing effective interventions requires an understanding of motivators and barriers to physical activity, use of behavioral change theory, and learning from previous successful public health strategies in perinatal health.

In summary, our results support associations of maternal physical activity with offspring birth size, postnatal growth, and epigenetic regulation. Our results also support associations of maternal sedentary behavior with offspring postnatal growth. Future research in this area should continue to investigate sex-specific associations, use objective measures, such as accelerometry, to capture accurate measures of time spent in these behaviors across multiple domains, and be conducted in large and diverse study populations. A stronger evidence base will facilitate adoption of effective interventions to promote physical activity among reproductive age and pregnant women and improve maternal and fetal health outcomes.

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