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Maternal healthy lifestyle during early pregnancy and offspring birthweight: differences by offspring sex

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Abstract

Purpose: Individual maternal lifestyle factors during pregnancy have been associated with offspring birthweight; however, associations of combined lifestyle factors with birthweight and potential differences by offspring sex have not been examined.

Materials and methods: Participants (N=2,924) were identified from a pregnancy cohort in Washington State. Lifestyle factors during early pregnancy were dichotomized based on Alternate Healthy Eating Index score ≥62, leisure time physical activity (LTPA) ≥150 minutes/ week, not smoking during pregnancy, and Perceived Stress Scale score ≤3, then combined into a lifestyle score (0–4). Regression models were run overall and stratified by offspring sex, pre-pregnancy overweight/obese (BMI≥25kg/m^2), and pre-pregnancy LTPA.

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Disclosure of interest
The authors report no conflicts of interest.

Results: Overall, 20% of participants had healthy diet, 95% were non-smokers, 55% had low stress levels, and 66% were physically active. Lifestyle score was not associated with birthweight (β=3.3g; 95% CI: -14.5, 21.0); however, associations differed by offspring sex (P=0.009). For each unit increase in lifestyle score, there was a suggested 22.4g higher birthweight (95% CI: -2.7, 47.6) among males and 14.6g lower birthweight (95% CI: -39.9, 10.7) among females. Pre-pregnancy BMI and LTPA did not modify associations.

Conclusions: Healthy lifestyle score in early pregnancy may be associated with greater birthweight among male offspring, but lower birthweight among female offspring.

Keywords

birthweight; diet; lifestyle; physical activity; physiological stress; pregnancy; smoking

Introduction

Birthweight is an important indicator of fetal growth and newborn health [1]. Low birthweight has been associated with increased perinatal morbidity and mortality [2] as well as increased risk of chronic diseases in adulthood, including cardiovascular disease [3] and type 2 diabetes [4]. On the other extreme of the birthweight spectrum, high birthweight is associated with increased risk of obesity [5] and type 2 diabetes [6].

Several maternal lifestyle behaviors during early pregnancy have been associated with offspring birthweight. Healthy diet, such as adherence to the alternate Healthy Eating Index, not smoking, and low stress have individually been associated with greater offspring birthweight [7–9]. Physical activity during early pregnancy has been associated with lower offspring birthweight [10].

Healthy behaviors promote and reinforce each other [11]. Public health messaging and interventions to promote healthy lifestyle during pregnancy for healthy fetal growth and development may be more successful if multiple maternal behaviors are included. Initiation of prenatal care during early pregnancy provides an opportunity to impact maternal behavior during an important developmental period. However, previous studies have not examined combined maternal healthy behaviors during early pregnancy in relation to offspring birthweight.

Previous research has shown sex-specific differences in offspring birth size in response to maternal characteristics and changes in the intrauterine environment [12]. For instance, we recently reported that associations of maternal physical activity before and during pregnancy with offspring birth size differ by offspring sex [10]. Sex-specific associations of prenatal risk factors with fetal growth may reflect male-female differences in fetal growth patterns, fetal programming, and responses to adverse intrauterine exposure. These may have different implications on long-term health among males and females. However, the role of offspring sex in associations of combined maternal healthy behaviors during pregnancy and offspring birthweight has not been studied. The objective of this study was to investigate the association of a composite measure of maternal healthy lifestyle, including healthy diet,

non-smoking, low stress, and physical activity, during early pregnancy with offspring birthweight and to examine if this association differs by offspring sex.

Materials and methods

Study setting and study population

Data from participants of the Omega study, a prospective pregnancy cohort designed to assess dietary risk factors of pregnancy complications, were used in these analyses. Details about the study design have been published previously [13]. 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, and planned to carry the pregnancy to term and deliver 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 singleton births were included in these analyses (N=4,445). Participants with missing data on birthweight (N=306), implausible values for total caloric intake (<500 or >3500) (N=75) or leisure time physical activity (>35 hours/week) (N=133), or missing information on any component of the healthy lifestyle score (N=1,277) were also excluded. A total of 2,924 study participants remained for analyses after these exclusions.

Data collection

Study participants completed an in-person interviewer-administered structured interview at an average of 15 weeks gestation. Information collected during the interview included sociodemographic characteristics (maternal age, race), reproductive and medical history (parity, height, pre-pregnancy weight), and lifestyle behaviors before and during pregnancy (diet, physical activity, stress, smoking). Participants were followed until delivery, and trained study personnel abstracted maternal medical records for information on course and outcomes of the pregnancy (birthweight, gestational age at delivery, and offspring sex). Pre-pregnancy body mass index 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).

Lifestyle score factors

Diet—Participants were asked to recall diet over the past 3 months using a self-administered semi-quantitative food frequency questionnaire. We used a modified version of the Alternate Health Eating Index-2010 (AHEI-2010) [14] to assess healthy diet during early pregnancy. Ten of the 11 dietary components of the AHEI-2010 (higher intakes of vegetables, fruit, whole grains, nuts, long-chain (n-3) fatty acids, and polyunsaturated fatty acids, and lower intakes of red/processed meat, sugar-sweetened beverages, trans fat, and sodium) were each assigned a score ranging from 0 to 10, with 10 representing optimal dietary behavior, based on AHEI-2010 criteria. Alcohol consumption was not included in our score. Scores for each

component were summed to obtain total AHEI-2010 score for each participant, with a possible range from 0 to 100.

Smoking—Participants reported smoking history and smoking status at the beginning of pregnancy. Participants were categorized as never smoker, quit before pregnancy, or smoked during pregnancy.

Stress—Stress was measured using the four-item version of the Perceived Stress Scale [15], a scale designed to measure the degree to which situations in one's life are appraised as stressful. Participants were asked how often in the past 3 months each of the following statements were true: 1) "How often have you felt confident about your ability to handle personal problems?", 2) "How often have you felt difficulties were piling up so high that you could not overcome them?", 3) "How often have you felt you were unable to control important things in your life?", and 4) "How often have you felt things were going your way?". Response options ranged from 0 to 4 where 0 was 'never' and 4 was 'very often'. Responses were summed to obtain a total Perceived Stress Scale score for each participant, with a possible range from 0 to 16, where greater score indicated higher stress levels.

Leisure time physical activity—Physical activity during the week before the study interview, indicating early pregnancy leisure time physical activity, and the year before the pregnancy, indicating pre-pregnancy leisure time physical activity, was assessed in all participants during the early pregnancy interview, using the following questions: 1) "Which recreational physical activities did you participate in during the last 7 days?" or "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 days?", and 3) "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. Total duration of each leisure time physical activity reported was calculated and summed to obtain total leisure time physical activity duration (minutes/week).

Healthy lifestyle score

Responses to questions about diet, smoking, and stress during early pregnancy were dichotomized into a binary healthy/unhealthy variable (1/0, respectively) for each participant. Healthy diet was considered to be AHEI-2010 score in the upper two-fifths of the distribution (≥62) [16]. Healthy smoking behavior was considered to be never smoking or quitting before pregnancy. Healthy levels of stress were considered to be Perceived Stress Scale scores less than or equal to the median of the distribution (≤3). Healthy leisure time physical activity was considered to be ≥150 minutes per week using the American Congress of Obstetrics and Gynecologists recommendation for physical activity during pregnancy [17]. For each participant, the number of healthy lifestyle behaviors was summed to create a healthy lifestyle score ranging from 0 to 4. Healthy lifestyle score was used in models as a continuous variable and as a categorical variable.

Birthweight

Birthweight (g) was abstracted from newborn medical records. Measurements were made by hospital personnel immediately after birth and rounded to the nearest 1g. Birthweight was categorized as small-for-gestational age (SGA), appropriate-for-gestational age, or large-for-gestational age (LGA) based on birthweight standards [18]. We also categorized birthweight as low birthweight (<2,500g), normal birthweight (2,500–4.000g), and macrosomia (>4,000g).

Statistical analyses

Continuous variables were described using mean and standard deviation. Categorical variables were described using frequency and percentage. Linear regression was used to determine mean differences and 95% confidence intervals (CI) in birthweight for each healthy lifestyle factor individually and for each additional healthy lifestyle factor. Similarly, generalized logistic regression was used to determine odds ratios (OR) and 95% CI for SGA, LGA, low birthweight, or macrosomia. Regression models were adjusted for the following a prior selected confounders: maternal age, race (white/non-white), nulliparity (Y/N), pre-pregnancy BMI category (underweight/normal weight/overweight/obese), gestational age at delivery, and offspring sex. All models did not have high multicollinearity among covariates (variance inflation factor<1.1). Linear regression models all had adjusted R^2=0.4. Goodness of fit measures are not available for generalized logistic regression.

Models were also stratified by offspring sex and within each sex, by pre-pregnancy overweight/obese (BMI≥25 kg/m^2), and healthy pre-pregnancy leisure time physical activity (≥150 minutes per week) to assess effect modification. Multiplicative interaction terms were used to test for statistical significance of interactions. 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

Participants included in these analyses were 33 years old, on average, and the majority were white, had a least a high school education, were married, nulliparous, and normal weight before pregnancy (**Table 1**). Overall, 20% of participants had a healthy diet, 95% were non-smokers, 55% had low stress levels, and 66% were physically active during early pregnancy (**Table 2**). Individually, healthy diet, physical activity, and not smoking during pregnancy were not associated with birthweight (diet: β=-18.8, 95% CI=-56.7, 19.1; physical activity: β=-8.9, 95% CI: -41.0, 23.3; not smoking: β=-20.4, 95% CI: -90.6, 49.9). Low stress levels were associated with a 33.1g increase in birthweight (95% CI: 2.5, 63.8).

Associations of physical activity and non-smoking during pregnancy with offspring birthweight differed significantly by offspring sex (P for interaction=0.05 and 0.04, respectively) (**Table 2**). There were suggested, but not statistically significant, associations of physical activity with greater birthweight among males (β=16.8; 95% CI: -28.8, 62.4) and reduced birthweight among females (β=-35.5; 95% CI: -80.8, 9.8). There were suggested, but not statistically significant, associations of not smoking during pregnancy with increased

birthweight among males (β=49.6; 95% CI: -52.6, 151.9) and reduced birthweight among females (β=-81.2; 95% CI: -177.7, 15.3). Associations of healthy diet and low stress with birthweight were similar among males and females (P=0.50 and 0.41, respectively).

After adjusting for maternal age, race, nulliparity, pre-pregnancy BMI category, gestational age at delivery, and offspring sex, each additional healthy lifestyle factor was not associated with birthweight overall (β=3.3; 95% CI: -14.5, 21.0). Associations between healthy lifestyle score and birthweight differed by offspring sex (P for interaction = 0.009) (**Table 3**). For each additional healthy lifestyle behavior there was a suggested, but not statistically significant, 22.4g greater birthweight (95% CI: -2.7, 47.6) among males and with 14.6 lower birthweight (95% CI: -39.9, 10.7) among females. For male and female offspring, associations between healthy lifestyle score and birthweight were similar among normal weight and overweight/obese women (P for interaction = 0.42 and 0.71, respectively) and among women who met physical activity recommendations pre-pregnancy and those who did not (P for interaction = 0.86 and 0.30, respectively). Additional adjustment for pre-pregnancy comorbidities (pre-pregnancy diabetes, chronic hypertension) did not change estimates meaningfully. We did not adjust for pregnancy complications because they are potentially consequences of healthy lifestyle.

There was a suggested trend of increasing number of healthy lifestyle behaviors with increased birthweight in males, but not females (P for trend=0.08 and 0.26, respectively) (**eTable 1**). Results of analyses of birthweight as a categorical outcome (SGA/LGA and low birthweight/macrosomia) were consistent with those observed for birthweight as a continuous outcome for independent and composite healthy lifestyle behaviors (**eTable 2**, **eTable 3**).

Discussion

Among participants of the Omega study, we observed suggested associations of maternal healthy lifestyle during early pregnancy, consisting of healthy diet, not smoking, low stress, and physical activity, with greater birthweight among male infants and with lower birthweight among female infants. Observed associations were similar among strata defined by pre-pregnancy BMI or physical activity.

To our knowledge, our study is the first observational study of multiple maternal lifestyle behaviors during early pregnancy and offspring birthweight. Randomized controlled trials of lifestyle interventions promoting healthy diet and physical activity during pregnancy have not found associations between lifestyle interventions and offspring birthweight. A meta-analysis of 3 randomized controlled trials of lifestyle interventions during pregnancy among normal weight women did not find an association with offspring birthweight (β=21.6; 95% CI: -98.8, 141.9), macrosomia (RR=2.19; 95% CI: 0.63, 7.60), or low birthweight (RR=1.03; 95% CI: 0.40, 2.63) [19]. In a meta-analysis of 7 randomized controlled trials of lifestyle interventions during pregnancy among overweight and obese women, diet and physical activity interventions were marginally associated with lower offspring birthweight (β=-56.6; 95% CI: -120.2, 6.9) but not LGA (OR=0.91; 95% CI: 0.62, 1.32) [20]. Previous studies of lifestyle interventions during pregnancy were likely not powered to detect

differences in offspring birthweight, as birthweight was not the primary outcome in any of these studies. In addition, lifestyle interventions have not included not smoking or low maternal stress during pregnancy as part of a healthy maternal lifestyle. Previous studies have also not examined potential effect modification by offspring sex.

Maternal lifestyle factors during pregnancy may affect placental development and endocrine regulation of fetal growth. Maternal malnutrition has been associated with altered levels of growth hormones in cord blood at birth, including placental lactogen, prolactin, insulin, and insulin-like growth factor 1 [21]. Smoking during pregnancy results in decreased vascularization of the placenta, reducing fetal oxygen supply and growth [22]. Maternal malnutrition and chronic stress during pregnancy are associated with down-regulation of the 11 β-hydroxysteroid type 2 enzyme in placenta [9, 23], reducing the ability of the placenta to serve as a barrier to fetal glucocorticoid exposure, which is associated with fetal growth restriction [24]. Physical activity during pregnancy is associated with lower levels of insulin-like growth factor 1 and 2 in cord blood at birth [25]. Given the overlap in physiological effects of healthy lifestyle factors on placental growth, it is reasonable to evaluate them in combination.

We observed differences in associations of maternal healthy lifestyle and offspring birthweight by offspring sex. This may reflect differences in how male and female fetuses respond to changes in nutrient availability during development [12]. In a nonhuman primate model of maternal nutrient restriction, genes in pathways related to programmed cell death and cell proliferation were altered in female, but not male, placentas [26]. Our previous work in the Omega study found differences in associations between early pregnancy physical activity and offspring birth size by offspring sex that are consistent with the results of this study [10]. Previous research has reported that female fetuses may be more sensitive to the detrimental effects of smoking during pregnancy [27]. Our unexpected suggested association of maternal non-smoking during pregnancy and reduced birthweight among female offspring may be explained by selection bias due to restriction of our study to live births. If female fetuses are more susceptible to fetal death due to maternal smoking, larger fetuses may be more likely to survive until birth, resulting in the suggested inverse association between not smoking and birthweight among female offspring. Although suggested differences in birthweight associated with maternal lifestyle factors during early pregnancy are small, these differences in birthweight may reflect changes in fetal programming with long-term health consequences.

Several strengths of our study include consideration of multiple aspects of healthy maternal lifestyle during pregnancy, large sample size, prospective design, and assessment of several potential effect modifiers, including offspring sex, maternal pre-pregnancy BMI, and meeting physical activity recommendations before pregnancy. However, recall and self-report of all lifestyle factors in our study may have introduced misclassification of healthy lifestyle factors in our score. Measurement characteristics of instruments used to assess diet, physical activity, and stress were good (food frequency questionnaire Pearson r=0.18–0.63 [28], physical activity questionnaire Spearman r=0.12–0.24 [29], and 4-item Perceived Stress Scale Pearson r=0.62 [30]) among pregnant women, reducing concerns about measurement error. We did not collect information about maternal lifestyle during later

pregnancy and are unable to examine associations of lifestyle and fetal growth during different periods of pregnancy. Our study was likely underpowered to detect associations in subgroups. Thirty six percent of the Omega study population was excluded from our analysis due to missing data, which may have introduced selection bias into our results. However, sociodemographic characteristics were similar between the full Omega cohort, our analytic sample, and excluded observations (eTable 4).

Results of our study suggest that the influence of maternal healthy lifestyle during early pregnancy (characterized by healthy diet, not smoking, low stress, and physical activity) on offspring birthweight may differ between male and female offspring. Additional studies confirming these suggested associations in diverse populations as well as potential mechanisms may contribute to the body of literature guiding public health messages and clinical recommendations for maternal lifestyle during early pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of Omega Participants (N=2,924), Seattle WA, 1996–2008

Characteristic	
Age (years), mean (SD)	33 (4.3)
Pre-pregnancy BMI (kg/m^2), mean (SD)	23 (4.5)
White race, n (%)	2565 (88)
High school education or more, n (%)	2853 (98)
Nulliparous, n (%)	1849 (63)
Married, n (%)	2720 (93)
Pre-pregnancy diabetes, n (%)	34 (1)
Chronic hypertension, n (%)	116 (4)
Gestational diabetes mellitus, n (%)	139 (5)
Preeclampsia, n (%)	70 (2)
Pre-pregnancy BMI category	
Underweight (<18.5 kg/m^2)	55 (2)
Normal weight (18.5–24.9 kg/m^2)	2186 (75)
Overweight (25–29.9 kg/m^2)	462 (16)
Obese (≥30 kg/m^2)	221 (8)
IOM gestational weight gain category, n (%)	
Inadequate	593 (20)
Adequate	1269 (44)
Excessive	1055 (36)
Offspring birthweight (g), mean (SD)	3446 (553)
Offspring sex	
Male	1489 (51)
Female	1435 (49)

Abbreviations: body mass index (BMI), gestational diabetes mellitus (GDM), standard deviation (SD)

Table 2.

Associations of Maternal Healthy Lifestyle Factors in Early Pregnancy and Offspring Birthweight Overall and by Infant Sex Among Omega Participants, Seattle WA, 1996–2008

Lifestyle factor	Criteria for healthy score	N (%) with healthy score	Adjusted Mean Difference in Birthweight[a] (95% CI)
Overall			
Healthy diet	AHEI-2010 diet score ≥62	591 (20)	-18.8 (-56.7, 19.1)
Physically active	≥150 min/week of leisure time physical activity	1927 (66)	-8.9 (-41.0, 23.2)
Non-smoker	Never smoker or quit before pregnancy	2777 (95)	-20.4 (-90.6, 49.9)
Low stress	Perceived Stress Scale score ≤3	1617 (55)	33.1 (2.5, 63.8)
Males			
Healthy diet	AHEI-2010 diet score ≥62	320 (21)	-11.7 (-64.0, 40.7)
Physically active	≥150 min/week of leisure time physical activity	992 (67)	16.8 (-28.8, 62.4)
Non-smoker	Never smoker or quit before pregnancy	1419 (95)	49.6 (-52.6, 151.9)
Low stress	Perceived Stress Scale score ≤3	831 (56)	38.0 (-5.8, 81.9)
Females			
Healthy diet	AHEI-2010 diet score ≥62	271 (19)	-29.2 (-84.0, 25.7)
Physically active	≥150 min/week of leisure time physical activity	935 (65)	-35.5 (-80.8, 9.8)
Non-smoker	Never smoker or quit before pregnancy	1358 (95)	-81.2 (-177.7, 15.3)
Low stress	Perceived Stress Scale score ≤3	786 (55)	23.9 (-19.1, 67.0)

Abbreviations: Alternate Healthy Eating Index (AHEI)

[a]Model is adjusted for maternal age, race (white/other), nulliparity (Y/N), pre-pregnancy BMI category (underweight/normal weight/overweight/obese), gestational age at delivery, offspring sex, and all lifestyle factors listed.

Table 3.

Association of Maternal Healthy Lifestyle Score in Early Pregnancy with Offspring Birthweight Overall and by Offspring Sex, Maternal Pre-pregnancy Overweight/obese Category, and Pre-pregnancy Leisure Time Physical Activity Among Omega Participants, Seattle WA, 1996–2008

	Adjusted Mean Difference in Birthweight[a] (95% CI)			
	N	Male	N	Female
Overall	1489	22.4 (-2.7, 47.6)	1435	-14.6 (-39.9, 10.7)
Interaction P value		0.009		
Normal weight	1104	13.8 (-14.2, 41.8)	1082	-12.0 (-40.6, 16.6)
Overweight/obese	281	44.5 (-19.5, 108.5)	236	-0.8 (-65.1, 63.5)
Interaction P value		0.42		0.71
Pre-pregnancy LTPA≥150 min/week	1120	18.2 (-11.6, 48.0)	1062	-5.6 (-35.3, 24.0)
Pre-pregnancy LTPA<150 min/week	369	6.1 (-45.7, 57.9)	373	-41.6 (-94.4, 11.2)
Interaction P value		0.86		0.30

Abbreviations: leisure time physical activity (LTPA)

[a]Model is adjusted for maternal age, race (white/other), nulliparity (Y/N), pre-pregnancy BMI category (underweight/normal weight/overweight/obese), gestational age at delivery, and offspring sex.