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Dougan, Marcelle M., MPH[1], Willett, Walter C., MD, DrPH [1,3,4], Michels, Karin B., ScD, PhD [1,2,3]

Author Affiliations

[1] Department of Epidemiology, Harvard School of Public Health, Boston, MA
[2] Obstetrics and Gynecology Epidemiology Center, Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA
[3]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA
[4]Department of Nutrition, Harvard School of Public Health, Boston, MA

Corresponding Author: Karin B. Michels, Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Avenue, Boston, MA 02115. E-mail: kmichels@research.bwh.harvard.edu

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Abstract

Background/Objectives: In animal studies, exposure to multi-vitamins may be associated with obesity in the offspring; however, data in humans is sparse. We therefore examined the association between prenatal vitamin intake during pregnancy and offspring obesity.

Subjects/Methods: We investigated the association between prenatal vitamin intake and obesity among 29 160 mother-daughter dyads in the Nurses' Health Study II. Mothers of participants provided information on prenatal vitamin use during pregnancy with the nurse daughter. Information on body fatness at ages 5 and 10, body mass index (BMI) at age 18, weight in 1989 and 2009, waist circumference, and height was obtained from the daughter. Polytomous logistic regression was used to predict BMI in early adulthood and adulthood, and body fatness in childhood. Linear regression was used to predict waist circumference in adulthood.

Results: *In utero* exposure to prenatal vitamins was not associated with body fatness, either in childhood or adulthood. Women whose mothers took prenatal vitamins during pregnancy had a covariate-adjusted odds ratio of being obese in adulthood of 0.99 (95% CI 0.92 – 1.05, *P*-value = 0.68) compared to women whose mothers did not take prenatal vitamins. Women whose mothers took prenatal vitamins during pregnancy had a covariate-adjusted odds ratio of having the largest body shape at age 5 of 1.02 (95% CI 0.90 – 1.15, *P*-value = 0.78). In additional analyses, *in utero* exposure to prenatal vitamins was also unrelated to adult abdominal adiposity.

Conclusions: Exposure to prenatal vitamins was not associated with body fatness either in childhood or in adulthood.

KEYWORDS: prenatal vitamins body mass index childhood obesity

1. Introduction

Over the past 30 years, the prevalence of obesity has increased dramatically across the United States and elsewhere. Although recent data suggest that the rise in the prevalence of obesity in adults and children appears to be slowing down and may even be leveling off, currently, 35.7% of adults and 18.4% of adolescents are obese (1), compared to 14.5% of adults (2) and 6.1% of adolescents (3) in 1971-1974. The increase in obesity is concerning, as it is well documented that obesity has serious consequences, including premature mortality, and elevated risks for diabetes, cardiovascular disease(4), some cancers (5-7), sub-fertility(8),(9), and depression(10). The economic burden associated with obesity is also quite significant: in one study, investigators reported that obese 45-year olds had a significantly reduced chance of surviving to age 65, and survivors incurred an approximately 40% higher lifetime Medicare costs, compared to normal weight 45-year olds (11).

In recent years, with growing acceptance that the intrauterine environment provides an important basis for future health outcomes(12), considerable progress has been made in examining this environment as a predictor of obesity later on in life. Ravelli *et al* (13) reported that men exposed to maternal starvation *in utero* during the first half of pregnancy had a significantly increased risk of being obese. In another study, exposure to maternal diabetes *in utero* and larger size for gestational age predicted obesity during childhood (14). In other studies, maternal obesity and gestational weight gain predicted childhood (15-16),(17) and later obesity(16).

Prenatal vitamin intake may increase obesity by increasing the amount of adipose tissue cells in the developing fetus. In animal studies, multivitamin supplementation was found to increase the

risk of obesity among the offspring of Wistar rats who were fed an obesogenic diet (18). However, to the best of our knowledge, the role of prenatal vitamin supplementation during pregnancy in adult obesity in humans has not been examined.

We therefore examined the association between prenatal vitamin intake during pregnancy and obesity throughout life course among 29 160 participants of the Nurses' Health Study II (NHS II) whose mothers provided information on prenatal vitamin intake during pregnancy.

Materials/Subjects and Methods

Study subjects

Participants of this study are mother-daughter dyads from the Nurses' Health Study II (NHS II) and the Nurses' Mothers' Cohort Study. The NHS II was started in 1989 with the recruitment of 116 478 female registered nurses living in one of 15 US states, who were aged between 25 and 42 years. Participants were mailed a questionnaire about health and lifestyle factors in 1989 (baseline) and every 2 years thereafter. In 2001, participants of the NHS II who were alive and free of cancer were asked if their mothers could participate in the Nurses' Mothers' Cohort Study, details of which have been previously published (19).

Assessment of Prenatal Vitamin Intake

Participants in the Nurses' Mothers' Cohort Study were asked whether they had taken prenatal vitamins during their pregnancy with the nurse daughter, and if so, whether they took the vitamins regularly. A total of 20 672 reported to have taken prenatal vitamins during pregnancy, of which 1 026 said they did not take the vitamins regularly. Because of the relatively low

number of women who reported taking vitamins during pregnancy on an irregular basis, these were excluded from the analyses.

Assessment of Body Fatness

NHS II participants were asked at study enrollment to report their current height, current weight, and their weight at age 18. Current weight was updated on each biennial questionnaire. Body mass index (BMI) was calculated as weight in kg divided by the square of height in m^2. The validity of self-reported weight at age 18 and self-reported current height among 118 participants of this cohort was assessed in a validation study from records that were obtained from physical examinations conducted at college/nursing school entrance (20). Troy *et al* reported that the correlation between recalled and measured past weight was 0.87, although there was a slight under-reporting in weight at age 18. The correlation between self-reported height and measured height at age 18 was 0.94. Thus, the validity of recalled weight and self-reported height appears high in this cohort.

Childhood body fatness was determined by asking NHS II participants to identify their body size at age 5 and age 10, using a nine-level drawing which was developed by Stunkard (21) (Figure 1). The validity of long-term recall of childhood body fatness was examined during a follow up of the Third Harvard Growth Study, a longitudinal study of physical and mental growth which took place from 1922-1935 (22). More than 65 years later, using the same diagram described above, subjects who were then aged 71-76 years were asked to identify the level that best described their body size during childhood and adolescence. Among females, Pearson crude correlations between recalled body fatness and BMI at approximately the same ages were 0.60 for age 5, and 0.75 for age 10, which slightly attenuated, after adjusting for current BMI. Similar

results have been observed in other studies (23-25), demonstrating that this type of recalled measure can provide fairly reliable information on early life body fatness.

In the 2005 questionnaire, participants of NHS II were also asked to provide measurements of their waist circumference. A total of 23 741 participants (81%) provided this information. The validity of measured waist circumference was assessed by Rimm *et al* (26) in a sample of 140 participants from a parallel cohort of older women. Self-reported data were compared with the average of measurements taken by two technicians, and the Pearson correlation between these two measures was 0.89, and the mean difference was 0.05 inches. Thus, although self-reported waist circumference may be underestimated, it is a reliable measure.

Assessment of Covariates

Information on possible risk factors for obesity was obtained from both the Nurses' Mothers' questionnaire and the NHS II questionnaire. Information on maternal age at birth of the daughter, birth order of the nurse, maternal education at time of birth, maternal diet during pregnancy, maternal physical activity level, maternal smoking during pregnancy, maternal domestic status, home ownership at time of birth, father's education at time of birth, father's profession at time of birth, preeclampsia, gestational diabetes, gestational weight gain, mother's BMI, utilization of prenatal care, and breastfeeding, was obtained from the Nurses' Mothers' Questionnaire. Age at menarche, age at first birth, smoking history, parity, alcohol consumption, menopausal status, husband's education, household income, and use of oral contraceptives were obtained from the NHS II questionnaire.

Exclusions

A total of 35,830 mothers of participants in the NHS II completed and returned Nurses' Mothers' Questionnaire. Nurses who were adopted or whose adoption status was unknown (n = 1 895), twin births (n = 587), missing information on age 5 body size (n = 583), age 10 body size (n = 47), BMI at age 18 (n = 269), body mass index in 2009 (n = 1 042), or whose mothers were missing information on prenatal vitamin intake (n = 1 221) or whose mothers took prenatal vitamins but not regularly (n = 1 026) were excluded from the analysis. Missing indicators were used for participants missing information on covariates. The final study population comprised 29 160 mother-daughter dyads.

Statistical Analysis

Follow-up for these analyses began in 1989 at NHS II study baseline, and ended in 2009, the most recent year for which complete information on the participants is available. Body mass index (BMI) in 2009 was categorized as < 18, 23- < 25 (reference), 25 - < 28, 28 - < 30, 30 - < 34, and ≥ 34 kg/m^2. Missing BMI in 2009 was substituted with BMI reported in 2007 for 1779 participants. BMI at age 18 was categorized as <18, 18-<20, 20-<22 (reference), 22-<23, 23-<25, ≥25 kg/m^2. We used polytomous logistic regression to estimate odds ratios of having being exposed to prenatal vitamins *in utero*, for each category of BMI relative to the reference group. We also modeled BMI in 2009 as a three-level categorical variable: <25, 25-<30, ≥ 30 kg/m^2. In additional analyses, BMI in 2009 and BMI at age 18 were modeled as continuous variables. Prenatal vitamin intake was coded as a dichotomous variable. Statistical models included potential predictors of obesity during childhood and adulthood: age of nurse at questionnaire

return (continuous), maternal age at birth of nurse (< 20, 20 to < 25, 25 to < 30, 30 to < 35, 35 to < 40, ≥ 40 years), birth order of nurse (1, 2, 3, ≥4), mother's education (< 8 years, 8 years, 1 – 3 years high school, 4 years high school, 1 – 3 years college, ≥ 4 years college), maternal BMI (quintiles), consumption of dark leafy green vegetables during pregnancy (never, less than once a week, 1 – 6 times a week, once a day, twice or more a day), total activity level during pregnancy (highly active, active, mostly inactive/inactive), maternal smoking (non-smoker, quit during first trimester, quit after first trimester, smoked 1 – 15 cigarettes per day, smoked ≥ 15 cigarettes a day), living with nurse's father at time of birth (yes, no), owned a home at time of birth (yes, no), father's education (less than high school, high school, some college, college graduate), father a professional (yes, no), preeclampsia (yes, no), gestational diabetes (yes, no), gestational weight gain (< 10, 10 – 14, 15 – 19, 20 – 29, 30 – 39, ≥40, lbs), utilization of prenatal care during pregnancy (yes, no), and ever breastfed (yes, no). Covariates pertaining to the nurse were age at menarche (< 11, 11, 12, 13, 14, ≥15 years), parity and age at first birth (nulliparous, 1-2 & age at first birth < 25, 1-2 & age at first birth 25-29, 1-2 and age at first birth 30+, 3-4 & age at first birth < 25, 3-4 & age at first birth 25-29, 3-4 & age at first birth 30+, ≥ 5 & age at first birth <25, ≥5 & age at first birth 25-29, and ≥5 children & age at first birth ≥ 30 years), alcohol consumption (non-drinkers, > 0 – 4.9, 5.0 – 9.9, 10.0 – 19.9, ≥ 20 g/day), smoking status (never, past, current), menopausal status (premenopausal, postmenopausal), husband's education (< high school, high school, 2 years college, 4 years college, graduate school), income in 2001, which is the most recent year for which income information was available (< $30 000, 30 000 – 49 000, 50 000 – 74 000, 75 000 – 99 000, 100 000 – 149 000, ≥ 150 000), use of oral contraceptives (never, past, current), and physical activity level (< 3, 3 to < 9, 9 to < 18, 18 to < 27, 27 to < 42, ≥42, metabolic equivalents (METS) per week).

The association between body fatness during childhood (age 5 and age 10) was also analyzed using polytomous logistic regression. Because of sparse sample sizes at larger body types, we combined body size categories from level 5 – 9 into a single category.

Results

Among 29,160 mother-daughter dyads, 67% of the nurse mothers took prenatal vitamins during pregnancy with their nurse daughter whereas 33% did not. In 2009, the mean BMI of the adult nurse daughters was 27.3 kg/m^2, the median was 25.8 and the 5^{th} and 95^{th} percentiles were 19.9 and 39.5 respectively. At age 18, the mean BMI was 21.1 kg/m^2, the median was 20.6, and the 5^{th} and 95^{th} percentiles were 17.5 and 26.8 respectively. A total of 6434 participants reported being a Level 1 and 1843 reported being a Level 5 or higher body size at age 5.

Women whose mothers regularly took prenatal vitamins during pregnancy were slightly younger at baseline than women whose mothers did not take prenatal vitamins during pregnancy. Their mothers were also slightly younger at the time of the nurse's birth (Table 1).

The BMI in 2009 and at age 18, of nurses whose mothers took prenatal vitamins were almost the same as those whose mothers did not take prenatal vitamins. The proportion of participants reporting each level of body size was also similar in each group.

Compared to nurse mothers who did not take vitamins, nurse mothers who took prenatal vitamins during pregnancy were slightly younger. They were also more likely to consume green leafy vegetables during pregnancy and more likely to report a higher level of education (Table 1).

In the age-adjusted analysis, *in utero* exposure to prenatal vitamins was significantly associated with BMI in 2009 only for those with a BMI of 34 kg/m^2 or higher compared to the reference group of 23- < 25 kg/m^2. The age-adjusted odds ratio (95% confidence interval, CI) for having a BMI of 34 or greater was 0.90 (95% CI 0.82-0.98) compared to those with a BMI of 23 - < 25 kg/m^2. After adjusting for other covariates related to the nurse mother this association was no longer significant (Table 2).

We also evaluated a separate model considering additional covariates related to the nurse, including age at menarche, age at first birth, smoking status, parity, and income (Table 2). Exposure to prenatal vitamins was not associated with BMI in 2009 after adjusting for these additional covariates.

Since birth weight may be in the causal pathway between prenatal vitamin intake and body size later in life, we assessed whether it may mediate the association. Associations remained unchanged when birth weight was added to the model.

Prenatal vitamin intake was also unrelated to BMI in 2009 when BMI was modeled as a three-level categorical variable. The age-adjusted OR for being overweight compared to normal weight was 1.00(95% CI 0.94-1.07), and for being obese compared to normal weight was 0.99(95% CI 0.92 –1.05). After adjusting for covariates related to the nurse mother, the OR for being overweight compared to normal weight was 0.99(95% CI 0.93-1.06), and the OR for being obese compared to normal weight was 0.99(95% CI 0.93-1.07).

In utero exposure to prenatal vitamins was significantly associated with BMI at age 18 in the age-adjusted analysis, only for those with a BMI of 25 kg/m^2 or higher. The age-adjusted OR was 0.85(95% CI 0.77-0.93) comparing those with a BMI of 25 kg/m^2 to the reference group of

20 - < 22 kg/m^2. After adjusting for additional covariates, this association was marginally significant (Table 2).

Body fatness at age 5 and age 10, comparing the highest (Type 5+) to the lowest (Type 1), was not significantly associated with exposure to prenatal vitamins before or after adjusting for covariates (Table 3).

In additional analyses, we also assessed the relation between pre-natal vitamin intake and BMI at age 18 and in 2009, modeling BMI as a continuous outcome. Prenatal vitamin intake was not associated with BMI, either at age 18 or in 2009. The average BMI at age 18 of women whose mothers took prenatal vitamins during pregnancy was approximately 0.07 kg/m^2 less than those whose mothers did not take prenatal vitamins during pregnancy (p-value 0.09), and the average BMI in 2009 of women whose mothers took prenatal vitamins during pregnancy was 0.03 kg/m^2 less than those whose mothers did not take prenatal vitamins during pregnancy (p-value 0.73).

Finally, we examined the association between prenatal vitamin intake and adult waist circumference in 2005. Prenatal vitamin intake was associated with waist circumference in the age-adjusted analysis: the mean waist circumference for women whose mothers took prenatal vitamins during pregnancy was 0.31 inches less than that of women whose mothers did not take prenatal vitamins during pregnancy (p-value < 0.01); however, after adjusting for covariates related to the mother and the nurse, the mean difference in waist circumference was 0.11 inches, and the association no longer persisted (p-value 0.16).

Discussion

In the Nurses' Health Study II, exposure to prenatal vitamins *in utero* was not associated with body mass index either at age 18 or in adulthood. Further, body size during childhood and waist circumference during adulthood was also not affected by prenatal vitamin intake.

To our knowledge, the literature on the association between *in utero* exposure to multivitamins and offspring obesity is limited. In animal models, multivitamin supplementation in Wistar rats fed an obesogenic diet was found to lead to an acceleration of obesity (18). Lewis *et al* (27) reported that maternal folate intake during pregnancy did not influence childhood body composition, consistent with our findings for body size at age 5 and age 10.

In utero exposure to prenatal vitamins may influence body fatness in the offspring via different mechanisms. For example, maternal malnutrition is believed to trigger excessive appetite in the offspring (28-29). In addition, fetal exposure to inadequate nutrition may increase the capacity of adipocytes to store lipid(30). These results suggest that the association between maternal nutrition and offspring obesity may depend on the nutritional status of the mother. Since our study was conducted in a relatively well-nourished population (United States, 1947-1964), the null association we found may be a consequence of this.

Our study has some limitations. More detailed information on prenatal vitamin intake may have enhanced our ability to detect differences in offspring body fatness. Furthermore, prenatal vitamin exposure was recalled by the mothers from several decades earlier, introducing the potential for recall bias, since mother were aware of their daughters' body size. However, since an association between vitamin use during pregnancy and offspring overweight was not suspected, we do not expect that the recall would be differential by with respect to the body size in the daughter, and therefore expect any bias to be directed toward the null. Early case-control

studies of peri-conceptional multi-vitamin use and the risk of neural tube defects (31-35) relied on recalled data for estimating maternal intake of prenatal vitamins up to 16 years prior to the study. In most of these studies, a significant protective effect of prenatal vitamin use was reported. These findings were later confirmed in subsequent randomized controlled trials (36-37), indicating that recalled vitamin intake can be a reliable way of assessing exposure.

A second limitation is that the timing of prenatal vitamin intake is unknown. It has been suggested in several studies of *in utero* exposures that the timing of the exposure may be a more important determinant of the outcome than the exposure itself. For example, Ravelli *et al* (13) found that the risk of obesity was significant in the offspring of women exposed to starvation in early pregnancy but not those exposed in the third trimester. In a study of folic acid and neural tube defects, Milunsky *et al* (38) reported that the critical exposure period during which folic acid was protective was between weeks 1 and 6 of conception. Folic acid after that period did not confer any protection. Therefore, more detailed information on when prenatal vitamins were actually taken may have been helpful in resolving this question.

Despite these limitations, our study has several strengths. We have a large study population with a high prevalence of prenatal vitamin supplement use. Furthermore, our measures of body fatness in adulthood, specifically weight and waist circumference have good validity (26).

In conclusion, we did not find any statistically significant association between exposure to prenatal vitamins *in utero*, and overweight or obesity either during childhood or during adulthood in this prospective study. Further studies on this subject should assess the timing and dose of prenatal vitamin intake. Although obesity continues to be an important public health problem in the US population, it is unlikely to be influenced by exposure to prenatal vitamins.

Changes to current clinical recommendations of routine vitamin supplementation in pregnant women are not warranted based on these results.

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Figure 1. Assessment of Childhood Body Fatness