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ARTICLE

Pediatrics

Lifestyle of women before pregnancy and the risk of offspring obesity during childhood through early adulthood

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Abstract

Background In women, adhering to an overall healthy lifestyle is associated with a dramatically reduced risk of cardiometabolic disorders. Whether such a healthy lifestyle exerts an intergenerational effects on child health deserves examination.

Methods We included 5701 children (9–14 years old at baseline) of the Growing Up Today Study 2, and their mothers, who are participants in the Nurses' Health Study II. Pre-pregnancy healthy lifestyle was defined as a normal body mass index, no smoking, physical activity ≥150 min/week, and diet in the top 40% of the Alternative Healthy Eating Index-2010. Obesity during childhood and adolescence was defined using the International Obesity Task Force age- and sex-specific cutoffs. Multivariable log-binominal regression models with generalized estimating equations were used to evaluate the association of pre-pregnancy healthy lifestyle and offspring obesity.

Results We identified 520 (9.1%) offspring who became obese during follow-up. A healthy body weight of mothers and no smoking before pregnancy was significantly associated with a lower risk of obesity among offspring: the relative risks [RRs; 95% confidence intervals (CIs)] were 0.37 (0.31–0.43) and 0.64 (0.49–0.84), respectively. Eating a healthy diet and regular moderate-to-vigorous physical activities were inversely related to offspring obesity risk, but these relations were not statistically significant. Compared to children of mothers who did not meet any low-risk lifestyle factors, offspring of women who adhered to all four healthy lifestyle factors had 75% lower risk of obesity (RR: 0.25, 95% CI: 0.14–0.43).

Conclusion Adherence to an overall healthy lifestyle before pregnancy is strongly associated with a low risk of offspring obesity in childhood, adolescence, and early adulthood. These findings highlight the importance of an overall healthy lifestyle before pregnancy as a potential strategy to prevent obesity in future generations.

Introduction

Obesity during childhood has become a major public health challenge in the United States [1–3]. Childhood obesity increases the risk of several health conditions, including high blood pressure, dyslipidemia, and insulin resistance [4–6]. In addition, childhood obesity increases the likelihood of entering adulthood with obesity [7],

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which in turn contributes significantly to the development of chronic diseases, such as type 2 diabetes, cardiovascular disease, and certain types of cancer [8–10]. Effective strategies for preventing childhood obesity are critically needed to halt the rising rates of chronic health conditions in adulthood.

A growing body of evidence suggests that maternal lifestyle before or during pregnancy contributes to the risk of obesity in offspring [11–19]. Among modifiable lifestyle factors, maternal obesity and smoking are known to have adverse effects on pregnancy outcomes [20, 21] and long-term consequences among offspring through increasing the risk of obesity during childhood [11–14]. In addition, studies focusing on offspring obesity have also suggested that unhealthy dietary pattern and physical inactivity during pregnancy are associated with an increased BMI in offspring [15–19]. However, no studies have determined the effects of adopting an overall healthy lifestyle before pregnancy that consists of multiple healthy lifestyle and dietary practices, such as having a healthy body weight, no smoking, regular physical activity, and consumption of a healthful diet, that could jointly produce greater health benefits than any individual factors [22]. In women, adhering to such an overall healthy lifestyle was associated with a dramatically reduced risk of developing cardio-metabolic conditions [23–25]. Whether such a healthy lifestyle exerts any intergenerational effects on child health deserves examination.

Evaluation of an overall lifestyle before pregnancy in relation to offspring obesity risk is biologically meaningful. Accumulating evidence shows that lifestyle factors (e.g., smoking) have long-lasting effects on DNA methylation, which in turn might lead to changes in gene expression and ultimately to the development of diseases later in life [26, 27]. Since epigenetic modifications remain relatively intact even after the interruption of environmental exposures (i.e., smoking cessation) [26] and epigenetic traits can be passed from mothers to their offspring [28], a process named intergenerational epigenetic inheritance [29], it is likely that mothers' lifestyle before pregnancy may have lasting effects on children's health. Of note, a survey showed that women were willing to change their behaviors to adopt a healthier lifestyle during pregnancy [30], although an overall long-term pre-pregnancy lifestyle may also play a critical role in children's health.

To address this novel research question, we prospectively examined the association of an overall maternal lifestyle before pregnancy with risk of obesity in their children using data from mother–child pairs enrolled in the Nurses' Health Study II (NHSII) and Growing Up Today Study 2 (GUTS2), respectively.

Subjects and methods

Study population

The study was conducted among NHSII participants [31] and their children who participated in the GUTS2 cohort (http://www.gutsweb.org). NHSII is an ongoing prospective cohort study established in 1989 with the recruitment of 116,430 female registered nurses aged 25–42 years. A baseline questionnaire was administered to collect detailed information on medical history, lifestyle characteristics, and medications. In 2004, participants of NHSII who had children aged 8–15 years received an invitation letter for enrolling their children to participate in GUTS2. Invitation letters and questionnaires were mailed to 17,280 children and a total of 10,918 returned completed questionnaires. Follow-up questionnaires of GUTS2 were sent in 2006, 2008, 2011, and 2013. The study was approved by the Human Subjects Committees of the Harvard T. H. Chan School of Public Health and Brigham and Women's Hospital. In NHSII and GUTS2 return of the questionnaire was considered as informed consent.

Children in the GUTS2 cohort were born between January 1989 and December 1995. Their mothers reported lifestyle factors on the NHSII questionnaires in 1989, 1991, 1993, and 1995 (Supplementary Figure 1). Using the return date of the NHSII questionnaire, we selected the questionnaire proceeding to the birthday of each child. For women who were pregnant when filling out the questionnaire, we used data assessed in the previous questionnaire cycle if available, or otherwise excluded such women from the analyses. Of 7820 mothers of 10,918 children of GUTS2, 5421 returned a questionnaire before pregnancy corresponding to 6623 children. Of those, we excluded women who reported chronic diseases (diabetes, cardiovascular disease, or cancer; 63 mothers and their 78 children) or had no information in lifestyle factors (625 mothers and their 794 children). Among offspring we excluded those who did not report any measure of body weight throughout follow-up (50 children and their 35 mothers). After these exclusions, 5701 children born to 4698 mothers were included in the final analysis.

The first diet survey was conducted in 1991 and was updated every 4 years. For all births before 1991, we computed cumulative averages between 1991 and 1995 to better assess mothers' long-term diet quality [32]. We examined changes in diet before and after pregnancy in 2831 mothers who were pregnant between 1991 and 1995, and found no significant difference ($p = 0.51$) in overall diet quality (Supplementary Figure 2).

Assessment of lifestyle factors in mothers

Dietary information was obtained through validated Food Frequency Questionnaires (FFQs), which use a structured

list of over 130 food items and are designed to measure diet over the past year [33, 34]. We calculated an Alternate Healthy Eating Index-2010 (AHEI) score to assess the overall dietary quality [35]. The AHEI diet score summarizes information of the following dietary factors: higher intakes of vegetables, fruits, nuts, whole grains, polyunsaturated fatty acids, and long chain omega-3 fatty acids and lower intakes of red and processed meats, sugar-sweetened beverages, *trans*-fats, and sodium. Alcohol was not considered in the AHEI score because of the adverse effects of alcohol on fetal outcomes. Physical activity was assessed with a validated questionnaire [36], which inquired about the average time per week participants spent in moderate/vigorous activities during the preceding year. Participants reported height and weight and whether they were current, past, or never smokers on each biennial questionnaire. We computed participants' body mass index (BMI) by dividing weight in kilograms by the square of height in meters (kg/m^2).

Definition of low-risk group

Based on the abundant evidence for health benefits of lifestyle factors in the prevention of chronic diseases among women [23–25], we considered four low risk lifestyle practices including eating a healthy diet (top 40% of distribution), having a health body weight (BMI 18.5–25.0), engaging in regular moderate/vigorous physical activity (>150 min/week), and no cigarette smoking.

Outcome assessment

BMI in offspring was calculated by using self-reported weight and height. Previous studies found that self-reported weight and height are reasonably accurate in children and adolescents, although there is a potential underestimation of weight in children less than 14 years of age [37, 38]. To define obesity in childhood and adolescence, we used the age- and sex-specific cutoffs of BMI from the International Obesity Task Force [39], and for offspring aged 18 years and older we defined obesity by using World Health Organization cutoff points (i.e., BMI ≥30) [40]. Our main outcome is being obese at least once during the follow-up in GUTS2 (2004–2013) [41]. Our secondary outcome is persistent obesity, which we defined as being obese in at least two consecutive self-reports during follow-up.

Assessment of the covariates and risk factors of offspring obesity

Information on covariates and other risk factors for offspring obesity were collected through the GUTS2 baseline questionnaire in 2004, biennial questionnaires of NHSII, and NHSII pregnancy questionnaire in 2009 [42]. The GUTS2 baseline questionnaire inquired about the date of birth, gender, duration of breastfeeding, and other characteristics for each child. Maternal race/ethnicity, pre-pregnancy alcohol intake, parity, educational attainment of spouse/partner, and other information were recorded in NHSII questionnaires. Maternal age at delivery was calculated as the difference between children's and mothers' date of birth. The NHSII pregnancy questionnaire administered in 2009 assessed lifetime pregnancy information for each child on the type of delivery, hypertensive disorders during pregnancy, pre-eclampsia, gestational diabetes, offspring birth weight, and gestational age at delivery.

Statistical analysis

We assessed associations with risk of offspring obesity for each maternal lifestyle factor independently, as well as for the overall maternal lifestyle before pregnancy, by calculating the relative risks (RRs) and 95% confidence intervals (CIs) using multivariable log-binominal regression models with generalized estimating equations (GEE) and specifying an exchangeable correlation structure. Correlations of outcomes between siblings born to the same mother were accounted for using the GEE model. Covariates in multivariable models included maternal factors such as age at delivery, mom's race/ethnicity, parity, and pre-pregnancy alcohol intake; and educational attainment of spouse/partner; and offspring gender. We generated a missing category for covariates, including parity (0.8%) and educational attainment of spouse/partner (4.8%). Given the small proportion of missing in parity, we assumed parity of 1 to avoid unstable estimates caused by sparse missing parity.

We calculated the population attributable risk (PAR) percentages and 95% CIs to estimate the proportion of offspring obesity that would be potentially avoided if all women were in low-risk group [43]. We used multivariable log-binominal GEE models to calculate RRs comparing participants in the low-risk category with the rest of the GUTS2 participants when calculating the PARs.

We performed secondary analyses to assess the robustness of our findings. We evaluated effect modification by risk factors for offspring obesity including pre-pregnancy BMI, pregnancy complications, gestational age, birth weight, breastfeeding, and parity. *P* values for interaction were assessed by testing the significance of multiplicative interaction term in the multivariable regression model. Moreover, we conducted the analysis separately in boys and girls to explore potential gender differences. Given that maternal BMI may mediate the effects of maternal lifestyle and diet on offspring health, we performed a secondary analysis by including the other three low-risk lifestyle factors to define the overall healthy lifestyle and adjusted for

BMI to evaluate whether maternal BMI accounted for the association for other low-risk lifestyle factors. Finally, to analyze time-varying data we used GEE to take into consideration of all available information in obesity status through follow-up, allowing obesity measures missing at random.

All statistical tests were two-sided and were considered statistically significant at $p < 0.05$. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Baseline characteristics of the 5701 offspring and their 4698 mothers are presented in Table 1. Women were on average 33 years old at the delivery, had a healthy body weight (mean BMI 23.0), and did not smoke (92.6%) before pregnancy. The offspring population included more girls (53.1%) than boys.

We identified 520 (9.1%) offspring who were ever obese during follow-up. Table 2 shows the associations between individual maternal lifestyle factors and risk of offspring obesity during childhood through early adulthood. In multivariable analysis, offspring born to women with obesity (BMI ≥30) had an RR of 4.15 (95% CI: 3.36–5.13) of developing obesity, compared to children born to mothers with a BMI of 18.5–25. Offspring of women who smoked before pregnancy were also at a higher risk (RR: 1.64, 95% CI: 1.25–2.15) of having obesity than children of mothers who never smoked. Pre-pregnancy AHEI diet score and moderate-vigorous physical activity were not associated with the risk of offspring obesity.

Table 3 presents the association between low-risk lifestyle factors in women and risk of obesity in offspring. The risk of offspring obesity was 63% (RR: 0.37, 95% CI: 0.31–0.43) lower in children of women with a healthy weight compared to the rest. Compared to offspring of women who smoked before pregnancy, children of non-smoking mothers had 36% (RR: 0.64, 95% CI: 0.49–0.84) lower risk of obesity. Adherence to a healthy diet and regular physical activity were not significantly associated with offspring obesity risk; the RRs (95% CIs) were 0.98 (0.82, 1.17) and 0.90 (0.76, 1.08), respectively.

When we grouped women based on the number of low-risk factors, a higher number of low-risk factors was significantly associated with a lower risk of offspring obesity (Fig. 1 and Supplementary Table 1). Offspring born to women who adhered to all four low-risk factors had 75% lower risk (RR: 0.25, 95% CI: 0.14–0.43) of obesity, compared to children born to mothers who did not adhere to any low-risk factor. The corresponding PAR was 55.1% (95% CI: 41.9–63.2%). These associations did not change materially when analyses were stratified by gender

Table 1 Characteristics of the cohort study of mothers and their offspring

Maternal characteristics	
No of mothers	4698
Age at delivery, year, mean (SD)	32.8 (3.6)
White race/ethnicity, %	97.1
Lifestyle factors	
Alternative healthy eating index, mean (SD)	43.7 (9.8)
Body mass index, kg/m^2, mean (SD)	23.0 (4.0)
Moderate to vigorous intensity exercise, minutes/week, median (IQR)	77 (18; 222)
Alcohol intake in g/day, median (IQR)	1.0 (0; 3.4)
Smoking status, %	
Never smoker	72.5
Former smoker	20.1
Current smoker	7.4
Pregnancy complications, %	
Gestational diabetes	5.0
Pre-eclampsia	3.3
Pregnancy-induced hypertension	4.5
Cesarean delivery	21.0
Parity before pregnancy with current offspring, %	
Nulliparous	35.9
One previous pregnancy	36.5
Two previous pregnancies	19.7
Three previous pregnancies	5.4
Four or more previous pregnancies	1.7
Missing	0.8
Highest level of education competed by spouse/partner, %	
High school or less	14.1
College	48.8
Graduate school	32.3
Missing	4.8
Offspring characteristics	
No. of children	5701
Sex, %	
Girl	53.1
Boy	46.9
Age at baseline, year, mean (SD)	11.8 (1.3)
Birth weight group, kg, %	
<2.30	2.5
2.30–3.19	17.9
3.20–3.0	42.3
3.90–4.49	21.7
≥4.50	2.4
Missing	13.2
Gestational age at delivery, week, %	
<37	7.4
37–39	25.4

Table 1 (continued)

Maternal characteristics	
40–42	50.9
≥43	3.8
Missing	12.5
Breastfeeding duration, month, %	
Never	11.2
≤6	30.8
>6	40.4
Missing	17.6

Values are means (SD), median (IRQ) or percentages of the study population

SD standard deviation, *IQR* interquartile range (25th to 75th percentile)

(Supplementary Figure 3 and Supplementary Table 2) and were strengthened when we evaluated the low-risk factors in relation to persistent obesity in offspring (Supplementary Table 3). The risk of persistent obesity in offspring of mothers who adhered to four low-risk factors was 84% (RR: 0.16, 95% CI: 0.04–0.59) lower than in offspring of women who did not adhere to any low-risk factor. Adherence to three low-risk factors (healthy diet, ≥150 min/week of moderate/vigorous exercise, and non-smoking) was marginally associated with offspring obesity risk (RR: 0.64, 95% CI: 0.41–1.00), in comparison with offspring of women with no low-risk factors. Adjusting for BMI led to attenuated risk reduction of 12% (RR: 0.76, 95% CI: 0.49–1.16) and the mediation analysis showed that 47.9% of this association was explained by BMI (Supplementary Table 4).

We did not observe effect modification by established childhood obesity risk factors (all $p > 0.05$ for interaction) (Table 4). Compared with offspring born to women who did not adhere to any low-risk factor, the effect estimates of obesity risk in offspring of women who adhered to all low-risk factors did not materially change by strata of gestational age, pregnancy complications, and pre-pregnancy BMI.

The time-varying analysis showed that compared to children born from women with any low-risk factor, offspring of women with four low-risk factors had 80% (RR: 0.20, 95% CI: 0.09–0.42) lower risk of obesity (Supplementary Table 5).

Discussion

In this prospective investigation among US women and their children, we observed that a pre-defined overall healthy lifestyle before pregnancy characterized by maintenance of a healthy body weight, avoidance of cigarette smoking, moderate/vigorous exercise, and consumption of a healthful diet, was strongly associated with a lower risk of obesity in offspring. Offspring born to women who adhered to all four healthy lifestyle factors had 75% lower risk of developing obesity in childhood through early adulthood, in comparison with children born to mothers without any low-risk factors. We found that maternal lifestyle factors could explain 55% of offspring obesity during childhood through early adulthood. The majority of this relationship was explained by maternal pre-pregnancy BMI alone. These findings demonstrate the potentially important role of maternal lifestyle, especially weight control, before entering pregnancy in the development of obesity in offspring.

Several studies have been conducted to evaluate the role of lifestyle factors during pregnancy or the period proximal to pregnancy on the risk of offspring obesity. A meta-analysis evaluating the association of pre-pregnancy BMI with offspring obesity showed that children born to mothers who were obese had three times higher risk of obesity during childhood [11]. Findings from another meta-analysis including 236,687 children revealed that offspring of mothers who smoked during pregnancy had 55% greater risk of becoming obese during childhood than children of mothers who did not smoke [13]. In contrast, the evidence is limited regarding the role of maternal physical activity and dietary patterns in relation to offspring obesity, and such evidence is primarily generated from investigations that focused on these lifestyle practices during pregnancy [15–19]. In 5125 Greek mother-offspring pairs, higher physical activity levels during pregnancy were associated with a lower risk of offspring obesity at age 8 years [19]. Regarding maternal diet, findings from a Danish study showed that maternal "western diet" consisted of high intakes of red and processed meat and high-fat dairy products was associated with higher risk of lower birth weight, which is a risk factor of childhood obesity [44]. In a US study, a higher AHEI score of maternal diet during pregnancy was not significantly associated with birth weight [45]. Lastly, a prospective study of Dutch mother-offspring pairs failed to demonstrate significant associations between either a healthy diet pattern or an unhealthy diet pattern consumed during pregnancy and body composition in children at age six after adjustment for other childhood obesity risk factors [15]. Apparently, more evidence is needed to elucidate whether long-term physical activity levels and healthy diet practiced before pregnancy is beneficial for children's metabolic health.

The data collected in the NHSII and GUTS2 allowed us to evaluate the joint effects of major lifestyle factors in women before pregnancy in relation to the risk of offspring obesity. We confirmed the findings of previous studies that maternal obesity is one of the most influential risk factors for obesity in offspring. Likewise, in line with previous

Table 2 Individual pre-pregnancy risk factors and risk of obesity in offspring

	No. (%) of women	No. (%) of offspring	No. (%) of obese offspring	Relative risk (95% CI)[a]	Relative risk (95% CI)[b]
Alternate healthy eating index-2010 diet score in quintiles					
Q1	955 (20.3)	1182 (20.7)	125 (10.6)	1.00 (reference)	1.00 (reference)
Q2	948 (20.2)	1160 (20.4)	104 (9.0)	0.88 (0.69, 1.13)	0.90 (0.70, 1.14)
Q3	927 (19.7)	1123 (19.7)	103 (9.2)	0.91 (0.71, 1.16)	0.95 (0.74, 1.20)
Q4	917 (19.5)	1100 (19.3)	90 (8.2)	0.87 (0.67, 1.12)	0.91 (0.70, 1.17)
Q5	951 (20.3)	1136 (19.9)	98 (8.6)	0.95 (0.73, 1.23)	1.02 (0.79, 1.32)
Body mass index (kg/m^2)					
<18.5	213 (4.5)	245 (4.3)	4 (1.6)	0.27 (0.10, 0.70)	0.26 (0.10, 0.68)
18.5–24.9	3490 (74.3)	4175 (73.3)	253 (6.1)	1.00 (reference)	1.00 (reference)
25–29.9	688 (14.7)	897 (15.7)	159 (17.7)	2.87 (2.37, 3.48)	2.83 (2.35, 3.42)
≥30	307 (6.5)	384 (6.7)	104 (27.1)	4.23 (3.42, 5.23)	4.15 (3.36, 5.13)
Moderate to vigorous intensity exercise, min/week					
0	806 (17.2)	961 (16.9)	111 (11.6)	1.00 (reference)	1.00 (reference)
1–149	2000 (42.5)	2454 (43.1)	230 (9.4)	0.89 (0.72, 1.09)	0.87 (0.71, 1.08)
150–299	938 (20.0)	1133 (19.9)	89 (7.9)	0.81 (0.63, 1.06)	0.82 (0.63, 1.07)
≥300	954 (20.3)	1153 (20.1)	90 (7.8)	0.90 (0.69, 1.16)	0.89 (0.69, 1.16)
Smoking status					
Never smoker	3408 (72.5)	4188 (73.5)	355 (8.5)	1.00 (reference)	1.00 (reference)
Former smoker	942 (20.1)	1127 (19.7)	115 (10.2)	1.14 (0.93, 1.40)	1.23 (1.00, 1.51)
Current smoker	348 (7.4)	386 (6.8)	50 (13.0)	1.48 (1.14, 1.94)	1.64 (1.25, 2.15)

[a]Adjusted by variables included in the table and gender of the offspring (girl, boy)

[b]Additionally adjusted for mother's age at birth (years), mom's race/ethnicity (white, others), parity (null-parity, 1, 2, 3, ≥4 previous pregnancies), and pre-pregnancy alcohol intake (0, 0–5, 5–15, ≥15g/day); and educational attainment of spouse/partner (high school/college, graduate school)

reports, we found that pre-pregnancy smoking was independently associated with the risk of offspring obesity. The lack of significant association for physical activity and diet are unexpected, although lack of long-term repeated assessments of these factors before pregnancy may play a role in these null associations. Moreover, the adjustment of maternal BMI may account for partially the beneficial effects of eating a healthy diet and being physically active because maternal body weight control may likely operate in the causal pathways linking diet and physical activities with offspring health. Nonetheless, our results further suggest that the benefits of adhering to an overall healthy lifestyle exceed those of any single lifestyle factors.

A healthy lifestyle and diet may share many health effects in common which in combination contribute to a dramatic decrease in the risk of chronic diseases [23–25]. A consumption of healthy diet, maintaining a healthy body weight, regular physical activity, and avoidance of smoking could induce favorable metabolic and molecular alterations, resulting in improved insulin sensitivity, reduced systemic inflammation, and alleviated oxidative stress which in turn will delay the organ damage and consequently decrease the risk of chronic diseases [46, 47]. In women, lifestyle factors could influence the development and programming of fetus through their effects on the intrauterine environment [14]. When the intrauterine environment is exposed to metabolic stresses induced by hyperinsulinemia, inflammation, and other metabolic changes, the developmental programming and metabolic adaptation of fetus may be altered through epigenetic changes or the disturbance of the homeostatic control mechanisms, leading to an elevated risk of childhood obesity [48]. Indeed, findings from an offspring epigenome-wide human study identified 28 CpG sites that are differentially methylated in the offspring of mothers with obesity [49]. Other potential mechanisms could be ascribed to the development and function of adipose tissue, pancreas, liver, and brain of the fetus. Studies conducted in rodents showed that maternal obesity could promote morphology alteration of adipocytes in the fetus that is related to the development of offspring obesity [50]. Similarly, a maternal diet rich in calories during pregnancy is associated with adverse programming of the hypothalamus in the fetus, which may lead to hyperphagia and obesity [51]. Furthermore, research has shown that epigenetic modifications following environmental exposures could persist for several years even after the exposures stopped [26]. For example,

Table 3 Pre-pregnancy low-risk lifestyle factors and risk of obesity in offspring

	Low-risk group			Relative risk (95% CI)
	No (%) of women	No (%) of offspring	No (%) of obese offspring	
Healthy diet[a]	1868 (39.8)	2236 (39.2)	188 (8.4)	0.98 (0.82, 1.17)
BMI 18.5–25	3490 (74.3)	4175 (73.2)	253 (6.1)	0.37 (0.31, 0.43)
Moderate/vigorous exercise ≥150 min/week	1892 (40.3)	2286 (40.1)	179 (7.8)	0.90 (0.76, 1.08)
Current non-smoker	4350 (92.6)	5315 (93.2)	470 (8.8)	0.64 (0.49, 0.84)

Adjusted for mother's age at birth (years), mom's race/ethnicity (white, others), other variables included in table, parity (null-parity, 1, 2, 3, ≥4 previous pregnancies), pre-pregnancy alcohol intake (0, 0–5, 5–15, ≥15 g/day), educational attainment of spouse/partner (high school/college, graduate school), and gender of the offspring (girl, boy)

Reference group for relative risk calculation includes all other women not in low-risk factor category as defined in table

[a]Alternate Healthy Eating Index-2010 diet score in upper two quintiles. Alcohol intake is not included the calculation of the diet score

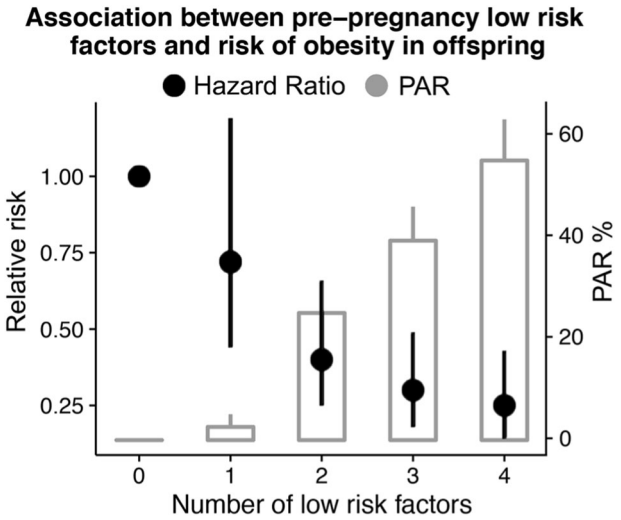

Fig. 1 Association between pre-pregnancy low-risk factors and risk of obesity in offspring. PAR population-attributed risk. Adjusted for mother's age at birth (years), mom's race/ethnicity (white, others), parity (null-parity, 1, 2, 3, ≥4 previous pregnancies), pre-pregnancy alcohol intake (0, 0–5, 5–15, ≥15 g/day), educational attainment of spouse/partner (high school/college, graduate school), and gender of the offspring (boy, girl). Reference group for relative risk calculation is all other women with no low-risk factor. Table 1 in supplement shows the numeric estimates of relative risk and population-attributed risk

an epigenome-wide study of cigarette smoking showed that methylation levels of 36 CpGs (among 2568 CpGs that were differentially methylated in a meta-analysis [26] comparing former versus never smokers) annotated to 19 genes (e.g., TIAM2, PRRT1, and AHRR) in former smokers did not recover to never-smoker levels even after 30 years of smoking cessation [26]. In a review of the dynamics of epigenetic phenomena across generations, Burggren [28] has hypothesized that epigenetic traits could be transmitted from one generation to the next. These mechanisms may pertain to our novel findings that linked pre-pregnancy lifestyle with childhood obesity.

Strengths of our study include a large sample size, prospective study design with long follow-up, detailed pre-pregnancy information acquired by using validated questionnaires, and information on pregnancy which allowed us to conduct comprehensive analyses. Although our goal is to examine long-term lifestyle and dietary practices of mothers before they enter pregnancy in relation to their offspring's health, we mainly used single assessment of lifestyle practices in this analysis to maintain a prospective temporality of the associations of interest. This may introduce misclassification of long-term lifestyle behaviors, although the impact of such a misclassification is likely to nullify the associations because of the prospective study design. Given the prospective study design, the possibility of recall bias is unlikely. Another limitation of our study is the lack of genetic information of mothers and offspring. The potential interactions between genetic predisposition and lifestyle or diet may also play a critical role in the development of obesity later in life [48, 52]. NHSII participants are predominantly white, reflecting the race/ethnic composition of the nursing profession at the time of study enrollment. Therefore our results may not apply to other race/ethnic groups. In addition, the prevalence of specific chronic disease risk factors, such as obesity, is lower in our population compared to the general US population. More studies are warranted to extend this research to more general populations. Another limitation is that we used self-reported weight and height to estimate the obesity status among children, thus introducing measurement errors in outcome ascertainments. Nevertheless, it is unlikely that misclassification of obesity status was associated with maternal lifestyle before pregnancy, and therefore the measurement errors may likely attenuate true associations. In the current analysis, we focused on pre-pregnancy lifestyle practices and did not explicitly assess lifestyle during pregnancy and therefore could not separate the roles of lifestyle before and during pregnancy in the risk of

Table 4 Pre-pregnancy low-risk lifestyle factors[a] and risk of offspring obesity by risk factors of offspring obesity

	No (%) of women	No (%) of offspring	No (%) of obese offspring	Relative risk (95% CI)
Pre-pregnancy BMI, kg/m^2				
<25	3703 (78.8)	4420 (77.5)	257 (5.8)	0.73 (0.38, 1.40)
≥25	995 (21.2)	1281 (22.5)	263 (20.5)	0.75 (0.41, 1.35)
Pregnancy complications[b]				
No	3390 (72.2)	4145 (72.7)	335 (8.1)	0.27 (0.12, 0.60)
Yes	1308 (27.8)	1556 (27.3)	185 (11.9)	0.27 (0.12, 0.61)
Birth weight, kg				
3.20–3.89	2002 (49.1)	2411 (48.7)	209 (8.7)	0.48 (0.13, 1.84)
<3.20 or >3.90	2074 (50.9)	2539 (51.3)	244 (9.6)	0.20 (0.10, 0.41)
Gestational age, week				
<39	1682 (40.9)	2086 (58.2)	188 (9.1)	0.26 (0.11, 0.63)
40–42	2429 (59.1)	2901 (41.8)	270 (9.3)	0.30 (0.14, 0.64)
Breastfeeding				
No	537 (13.7)	636 (86.5)	66 (10.4)	0.06 (0.01, 0.37)
Yes	3374 (86.3)	4059 (13.5)	342 (8.4)	0.57 (0.15, 2.15)
Parity				
Nulliparous	1689 (35.9)	1841 (32.3)	158 (8.5)	0.33 (0.15, 0.75)
Parous	3009 (64.1)	3860 (67.7)	362 (9.4)	0.18 (0.09, 0.38)

[a] Having all four factors in low-risk category (healthy diet, BMI 18.5–25, moderate/vigorous physical activity >150 min/week, and not smoking), except for analysis in women with pre-pregnancy BMI in which other three factors except BMI were included. Reference group for relative risk is women without any low-risk factor. Adjusted for mother's age at birth (years), mom's race/ethnicity (white, others), pre-pregnancy alcohol intake (0, 0–5, 5–15, ≥15 g/day), educational attainment of spouse/partner (high school/college, graduate school), and gender of the offspring (boy, girl)

[b] Pregnancy complications include gestational diabetes, pre-eclampsia, pregnancy-induced hypertension, or C-section delivery

childhood obesity. This remains a question for future studies. Lastly, as in any observational studies, we cannot exclude the possibility of uncontrolled confounding such as offspring physical activity and diet quality, or residual confounding.

Conclusion

In conclusion, we found that children of mothers who adhered to an overall healthful lifestyle before pregnancy had a substantially lower risk of obesity during childhood through early adulthood. Moreover, we observed a monotonic dose–response relationship of this association in that healthier lifestyle practices predicted greater reduction in childhood obesity risk, although clearly, maintaining a healthy body weight and non-smoking of the mom were the two single most critical maternal factors to predict offspring BMI. These findings underscore the importance of adopting an overall healthy lifestyle, particularly in women who plan a pregnancy, to prevent obesity and metabolic consequences later in life of their children.

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Author contributions KD and QS conceptualized the analysis, performed data analysis, interpreted the data, drafted the initial manuscript, and revised the manuscript; ES and AEF designed the study, obtained funding and critically reviewed and revised the manuscript; GZ and CY performed statistical analysis and critically reviewed and revised the manuscript; CZ, XW, FBH, and JEC critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval The study was approved by the Human Subjects Committees of the Harvard T. H. Chan School of Public Health and Brigham and Women's Hospital. In NHSII and GUTS2 return of the questionnaire was considered as informed consent.

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