Published in final edited form as:

Obesity (Silver Spring). 2019 January ; 27(1): 137–144. doi:10.1002/oby.22326.

Association of Maternal Pre-Pregnancy Weight with Offspring Adiposity Throughout Adulthood over 37 years of Follow-up

Isabelle Schoppa^{1,2}, Asya Lyass^{1,3}, Nancy Heard-Costa^{1,4}, Sarah de Ferranti⁵, Caroline Fox^{1,2,†}, Matthew W. Gillman^{6,#}, Sr Ralph D'Agostino^{1,3}, Daniel Levy^{1,2}, and Michael Mendelson^{1,2,5}

¹Framingham Heart Study, Framingham, MA

²Population Studies Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Framingham, MA

³Department of Mathematics and Statistics, Boston University, Boston, Massachusetts

⁴Boston University School of Medicine, Boston University, Boston, Massachusetts

⁵Department of Cardiology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts

⁶Department of Population Medicine at Harvard Medical School and Harvard Pilgrim Health Care Institute

Abstract

Objective: To determine the relation of maternal pre-pregnancy weight with offspring body mass index across adulthood from almost 40 years of follow-up.

Methods: Body mass index (BMI) was measured in Framingham Heart Study Offspring cohort participants between 1971 and 2008. We tested the association of maternal pre-pregnancy weight category (ascertained via direct measure and questionnaire) with serial offspring BMI, overweight, obesity, and change in BMI over time, adjusted for age, sex, and a BMI genetic risk score; secondary models additionally adjusted for physical activity, dietary factors, smoking, education, and familial relatedness.

Results: Among 863 participants at initial assessment (83 exposed and 780 controls), mean (SD) age was 33 (10) years, 53% were female, and mean BMI was 24.5 (4.1) kg/m². Exposed offspring

[†]Current affiliation: Merck Research Laboratories, Merck & Co., Boston, MA

[#]Current affiliation: Office of the Director, National Institutes of Health, Bethesda, Maryland

CORRESPONDING AUTHOR: Michael Mendelson, Department of Cardiology, Boston Children's Hospital, 300 Longwood Ave, Boston, MA, 02115. Phone: 617-355-600. Michael.mendelson@cardio.chboston.org

Author Contributions

Conceptualization of this project was by IS, AL, RD, DL, and MM. Data collection was assisted by CF, DL and MM. Formal analyses were conducted by AL and RD. Additional methodology were contributed by NHC, SDF, CF, and MG. Interpretation and further analytic planning were by IS, NHC, SDF, CF, DL, MG, and MM. The first draft of the manuscript was written by IS. All authors made critical edits to the manuscript and gave final approval in its current form.

Competing Interests

No conflicts of interest to declare. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services. CF is now an employee of Merck, but she was not an employee when the work was conducted.

BMI was higher at every examination cycle; ranging from 1.5 (0.5) to 3.0 (0.5) kg/m² ($p<0.001$), with larger differences at later assessments. The rate of increase in offspring BMI over time was higher in exposed offspring before the age of 50 years (β [SE]=0.07 [0.02] kg/m² per year, $p=0.004$), but not after the age of 50 years (-0.05 [0.04] kg/m² per year, $p=0.2$).

Conclusions: Maternal pre-pregnancy weight is associated with greater offspring body mass index throughout adulthood, with more rapid weight acceleration in early and mid-adulthood.

Keywords

Maternal Obesity; Epidemiology; Epigenetics; Body Mass Index; Obesity

INTRODUCTION

Obesity is a well-established risk factor for numerous non-communicable diseases, such as cancer, diabetes, hypertension, and cardiovascular disease (CVD).^{1,2} Accumulating evidence suggests that the roots of obesity may begin *in utero* through fetal exposure to maternal overweight and obesity.³ Unfortunately, maternal pre-pregnancy overweight (body mass index [BMI] 25–29.9 kg/m²) and obesity (BMI ≥ 30 kg/m²) is common. The prevalence of obesity during pregnancy doubled in the United States between 1976 and 2004,⁴ and the US Centers for Disease Control recently reported that the prevalence of overweight and obesity among women before pregnancy in 2014 was over 50%.⁵

Extending the Barker hypothesis that fetal programming due to maternal undernutrition contributes to offspring obesity and CVD,⁶ maternal obesity leads to fetal overnutrition, which may also contribute to deleterious cardiometabolic outcomes in the offspring.³ Fetal programming and epigenetic inheritance are potential mechanisms.^{7–11} Although many studies have demonstrated a robust association between maternal and offspring obesity,^{12–22} little is known about how this association persists beyond young adulthood or changes over an offspring's lifetime in excess of genetic variation and learned lifestyle behaviors.^{23,24}

The Framingham Heart Study (FHS) provides a unique opportunity to leverage a multi-generational structure, extensive genotypes and phenotypes, and long-term follow-up to examine the association of maternal pre-pregnancy weight with offspring body mass index across the adult lifespan. Our study, using data from eight examinations obtained during almost forty years of prospective follow-up, provides insight into the lasting role that maternal pre-pregnancy overweight and obesity plays in offspring body mass index throughout the life course.

Methods

Study Design

This study examined prospectively collected clinical data from participants in the Offspring cohort of the FHS.²⁵ Our objective was to examine the associations between maternal pre-pregnancy overweight and obesity and the prevalence and progression of overweight and obesity throughout the life of adult offspring beyond inherited genetic and lifestyle factors.

An analytic plan including the primary, secondary, and longitudinal models was determined *a priori*, and the sensitivity models were conducted *post-hoc*.

Ethics

The FHS protocols and participant consent forms were approved by the institutional review board of Boston University School of Medicine according to the Declaration of Helsinki. Written informed consent was obtained from all FHS cohort participants.

Study Sample

The present study included FHS Offspring cohort participants for whom maternal weight status was known (either via direct measure from a mother in the Original cohort or via questionnaire). The details of the FHS Original and Offspring cohorts have been previously described.^{25,26} Briefly, the study began in 1948 with 5209 participants enrolled in the Original cohort. In 1971, 5124 spouses and children of participants from the Original cohort were enrolled in the Offspring cohort. We excluded Offspring cohort participants for whom maternal weight status was not known and those who were less than 18 years of age at any examination cycle. Figure 1 illustrates study sample inclusion and exclusion. Since only 117 Offspring cohort participants had directly-measured paternal BMI data and there was no available questionnaire on paternal weight status, we did not examine paternal pre-pregnancy weight category as an exposure.

Maternal pre-pregnancy weight status exposure

We ascertained maternal pre-pregnancy weight status using a combined measure of directly-measured data and questionnaire data. Directly measured maternal pre-pregnancy BMI was obtained from study examinations of participants in the Original cohort that occurred before the birth of the Offspring cohort child (Original cohort examination cycles 1 or 2 [1948–1953 and 1950–1955, respectively]). Questionnaire data was obtained from Offspring cohort participants at examination cycle 6 (1995–1998), where they were asked to select yes or no in response to “Did your mother have any of the following conditions while she was pregnant with you? c) Overweight (before the pregnancy).” Directly measured BMI was categorized as either normal weight (BMI <25kg/m²) or overweight/obese (≥ 25kg/m²) to correspond to the questionnaire response, and then combined with questionnaire reported values. The questionnaire did not ascertain maternal pre-pregnancy underweight and no directly-measured mothers were underweight (BMI < 18.5 kg/m²) pre-pregnancy in our study sample.

To assess the reliability of the self-reported maternal weight status measure, we examined the subset with both directly measured maternal pre-pregnancy BMI and self-reported maternal weight category (n=48). We found that the self-reported measure had a positive predictive value of 100% (95% CI 69, 100) and a negative predictive value of 95% (95% CI 82, 99) (Table S1).

Offspring BMI and weight status outcomes

All participants underwent standard clinical examinations. Examination details and protocols can be found at <http://www.framinghamheartstudy.org/researchers/>. Briefly, height

and weight were taken during a routine physical examination. Height was measured with a vertical stadiometer while the participant stood without shoes facing straight ahead with heels together. Weight was measured with a scale positioned at zero while the participant stood with weight evenly distributed on both feet. Height was rounded to the nearest quarter inch and weight was rounded to the nearest pound. Height and weight measurements were converted to International System (SI) of units. BMI was calculated as weight (kg) divided by height (m) squared. Overweight was defined as BMI 25–29.9 kg/m² and obesity was defined as BMI ≥ 30 kg/m².

Covariates

Figure S1 shows the hypothesized causal pathways considered in selecting covariates, based on available data, for adjustment to detect an association between maternal pre-pregnancy weight category and offspring BMI in excess of inherited genotype and lifestyle factors. Ascertainment of lifestyle factors and creation of a BMI genetic risk score is described in the supplementary methods. Briefly, dietary intake and physical activity index (PAI) was assessed using questionnaires and genotype by microarray. The BMI genetic risk score was comprised of 32 single-nucleotide polymorphisms (Table S2).

Statistical Analysis

We produced summary statistics with means, standard deviations, counts, and frequencies of clinical and demographic characteristics of the sample. Details of the statistical analysis are presented in the Supplemental Methods. For our primary analysis, we tested the association of maternal weight category (specified as the independent variable of interest) with offspring BMI (specified as the dependent variable) at each of the eight examination cycles in separated linear regression models adjusted for offspring age and sex (model 1) and offspring age, sex, and BMI genetic risk score (model 2). A secondary model tested the association of maternal weight category and offspring BMI at examination 8 (2005–2008) including covariates from model 2 plus additional lifestyle factors known to contribute to BMI; specifically PAI (METs), total fat intake (g/day), total carbohydrate intake (g/day), total energy intake (kcal/day), smoking (current/former/never), and education (years completed). The secondary model with lifestyle factors was conducted only at examination 8 because PAI and dietary data were not available in earlier examinations.

To test the association of maternal weight with offspring overweight and obesity categories, we repeated the same successive adjustments, as described above, in multivariable-adjusted logistic regression models at each of the eight examination cycles with offspring weight category (obese vs normal weight [reference] and overweight vs normal weight [reference]) as the dependent variable and maternal weight category as the independent variable of interest.

Details of the longitudinal analyses are presented in the Supplemental Methods. For sensitivity analyses, we accounted for family structure by conducting a generalized linear model using generalized estimating equations to account for family structure (clustered by siblings) in the association of maternal weight category with offspring BMI at examination 1 adjusted for offspring age, sex, and BMI GRS. Second, we conducted an additional

sensitivity model adjusted for maternal age at birth. Maternal age at birth was not included in primary models as we only had this information in the subset of individuals where the mother participated in the first generation and was not available for the entire study sample. Third, to determine if the relationship between maternal pre-pregnancy weight and offspring BMI differed by either offspring sex or genetic risk for higher BMI we also included an interaction term for offspring sex and BMI GRS (separately in different models). Fourth, we examined the association of maternal pre-pregnancy weight category and offspring BMI in the subset of participants with directly-measured maternal BMI (n=130). Finally, we also compared the GRS weighted by GWAS effect estimates to a non-weighted GRS (sum of risk alleles per individual) and found very similar results (not presented), therefore only models with the weighted GRS are presented.

RESULTS

Study Sample Characteristics

The eligible study sample included 863 participants (83 exposed and 780 unexposed), 53% female, who at baseline (examination 1; 1971–1975) were of mean (SD) age 33 (10) years and mean BMI 24.5 (4.1) kg/m², and at the end of follow-up (examination 8; 2005–2008) were 66 (9) years old and mean BMI of 28.1 (5.4) kg/m². Examination dates and age distributions for all examination cycles are presented in Table S3. We did not include 4170 participants of the Offspring Cohort for whom no assessment of maternal pre-pregnancy weight category was available and a further 91 participants were excluded who were < 18 years of age at examination 1. We had both direct measurements and self-report, only direct measures, and only self-report measures of maternal pre-pregnancy weight category for 6% (48), 10% (82), and 85% (733) of eligible participants, respectively (Figure 1). At examination 1, the participants exposed to maternal pre-pregnancy overweight and obesity were younger than the unexposed offspring, with mean (SD) ages 30 (11) and 33 (9) years, respectively (Table 1). The mean BMI GRS was similar in exposed and unexposed offspring, with mean (SD) values of 4.1 (0.5) and 4.0 (0.5) weighted risk alleles, respectively. Cardiometabolic risk factors, such as hypertension, diabetes, and hypercholesterolemia, were infrequent at examination 1 and were of similar prevalence in exposed and unexposed offspring. In the subset of participants with directly-measured maternal BMI (n=130), the mean (SD) maternal pre-pregnancy BMI was 27.1 (1.7) and 21.8 (2.1) kg/m², in the maternal overweight/obese group and maternal normal weight group, respectively.

Association of maternal pre-pregnancy overweight/obesity with adult offspring BMI

The unadjusted BMI at each examination cycle in the exposed and unexposed groups is shown in panel A of Figure 2. Maternal overweight/obesity was associated with offspring BMI at every examination cycle (p<0.001) in the age and sex adjusted linear models (Table 2). Adult offspring with a history of maternal pre-pregnancy overweight and obesity had a BMI 1.4 – 3.0 kg/m² higher as compared to unexposed offspring. After additional adjustment for the inheritance of BMI-related genetic variants using the offspring BMI GRS, we found that the effect estimates were slightly strengthened and that the BMI GRS accounted for an additional 1–3% of inter-individual variation (partial R²) in offspring BMI across adulthood beyond age, sex, and maternal weight category. The genetic contribution is

of similar magnitude to the proportion of inter-individual variation in offspring BMI accounted for by the maternal weight category (partial R^2 0.7–3%) in the multivariable adjusted model. Pairwise comparisons demonstrated that the association between maternal weight category and adult offspring BMI at examinations 2 through 7 persisted after adjustment for adult offspring BMI at examination 1 ($p < 0.05$ for all pairwise models).

Association of maternal pre-pregnancy overweight/obesity with risk of adult offspring obesity

The prevalence of overweight and obesity among the offspring at each examination cycle in the exposed and unexposed groups is shown in panel B of Figure 2. The odds of obesity at every examination cycle was elevated among offspring exposed to maternal overweight/obesity compared to unexposed offspring (Table 3). At examination 1, exposed offspring had a 2.6 (95% CI 1.2, 5.7) fold higher odds of obesity compared to the unexposed offspring. The dichotomous outcome of offspring overweight versus normal weight [reference] in age and sex adjusted models yielded elevated but smaller odds ratios (OR) at every examination cycle (Table S3). Additional adjustment for the offspring BMI GRS (model 2) did not substantially change the effect estimates for obesity and overweight in offspring exposed to maternal overweight/obesity compared to unexposed offspring (Table 3 and Table S4).

Adjustment for measured lifestyle factors

Distribution of lifestyle factors were similar in the exposed and unexposed groups at examination 8 (Table S5). The association between maternal weight category and offspring BMI at examination 8 remained robust after additionally adjusting the linear model for the physical activity measure (PAI), dietary factors (total fat, total carbohydrates, and total energy intake), smoking status, and education (β [SE]= 2.5 [0.7] kg/m^2 higher BMI in exposed as compared to unexposed offspring, $p=0.0009$). Additional adjustment for the offspring BMI GRS slightly attenuated the association (β [SE]= 1.9 [0.8] kg/m^2 higher BMI in exposed as compared to unexposed offspring, $p=0.01$). In combination, measured lifestyle factors accounted for an additional ~0.8% of inter-individual variation (partial R^2) in offspring BMI at examination 8 after accounting for age, sex, offspring BMI GRS, and maternal weight category. In total, the combined model with age, sex, lifestyle factors, offspring BMI GRS, and maternal weight category, explained 11% (adjusted R^2) of the variation in adult offspring BMI at examination 8.

Similarly, the OR for obesity and the OR for overweight remained higher in exposed offspring compared to unexposed after additional adjustment for lifestyle factors at examination 8 (OR [95% CI]= 4.5 [1.7, 11.4], $p=0.002$). Additional adjustment for the offspring BMI GRS attenuated the association (OR [95% CI]= 3.5 [1.3, 9.9], $p=0.01$).

Change in BMI over time in adulthood in relation to maternal pre-pregnancy overweight/obesity

Modelling the change in adult offspring BMI over time using mixed effects models and linear splines, we observed a difference in slope of BMI change at 50 years of age ($p < 0.05$). In separate models stratified at the age of 50 years, the increase in BMI per year of age in exposed offspring younger than 50 years old was 0.20 (0.02) kg/m^2 per year ($p < 0.0001$) as

compared to 0.13 (0.01) kg/m² per year ($p < 0.0001$) in unexposed offspring. The excess increase in BMI per year among the exposed compared to unexposed between 18 and 50 years of age was 0.06 (0.02) kg/m² per year, $p = 0.003$, and 0.07 (0.02) kg/m² per year, $p = 0.004$, in model 1 and model 2 (additionally BMI GRS adjusted), respectively. The difference in BMI change over time among exposed as compared to unexposed after 50 years of age was not significantly different (-0.07 [0.04] kg/m² per year, $p = 0.07$ and -0.05 [0.04] kg/m² per year, $p = 0.2$, in models 1 and 2, respectively).

Effect Modification

The interaction term for maternal weight category by offspring sex was not significant ($p = 0.3$), indicating that the relationship between maternal weight category and offspring BMI was similar in female and male offspring. Additionally, we did not detect effect modification with a BMI GRS interaction term ($p = 0.4$), suggested that the relationship between maternal weight category and offspring BMI was consistent regardless of the burden of BMI-related genetic risk in the offspring.

Sensitivity Analyses

There were 542 mothers for the 863 participants. Accounting for family structure minimally affected the association between maternal weight category and offspring BMI at examination 1 (β [SE] = 1.2 [0.4] kg/m², $p = 0.01$). When we adjusted for maternal age at pregnancy, the association of maternal weight category with offspring BMI at examination 1 mirrored the effect estimate we observed in the primary model (β [SE] = 1.4 [0.4] kg/m², $p = 0.001$), suggesting that the relationship between maternal weight and offspring BMI is not affected by maternal age at birth. Finally, the association of maternal weight category with offspring BMI from examination 1 to 8 in the subset of participants with directly-measured maternal BMI supported our findings in the larger study sample that included questionnaire data (Table S6).

DISCUSSION

In a large, well-phenotyped, prospective study, we identified an association between maternal pre-pregnancy overweight and obesity with offspring body mass index throughout the adult life course. The association persisted after adjusting for an inherited genetic predisposition to obesity (BMI GRS) and measured lifestyle factors (physical activity, diet, smoking, and education). Overall, adult offspring exposed to maternal pre-pregnancy overweight or obesity had higher BMI (0.8 – 3.1 kg/m²) and odds of obesity (OR 2.6 – 4.9) compared to unexposed offspring. Furthermore, we described for the first time that the rate in increase of BMI over time was higher among offspring 18 to 50 years of age who were exposed to maternal pre-pregnancy overweight compared to those with normal weight mothers. For an average height adult (5 foot 7 inches; 1.7 meters), this would equate to a 12.3-pound (5.6kg) excess weight gain from 18 to 50 years of age.

Our results support the findings of previous studies demonstrating an association between maternal obesity and offspring adiposity in childhood and young adulthood.^{12–15,27} Maternal pre-pregnancy overweight and obesity was found to be associated with higher

BMI, waist circumference, and fat percentage as compared to controls among 891 participants at a mean of 24 years of age in two birth cohorts.²⁸ Our findings show that the difference in offspring BMI among exposed as compared to controls continues to widen past early adulthood. This is supported by previous reports in the Helsinki Birth Cohort demonstrating an association of maternal BMI with higher adult offspring BMI and a less favorable body composition as compared to controls among over 2000 participants at a mean age of 62 years.²⁴ Additionally, we demonstrate that higher BMI among adult offspring exposed to maternal pre-pregnancy overweight and obesity persists after adjustment for genetic variants and learned lifestyle behaviors related to BMI. In previous studies, accounting for a BMI genetic risk score in early adulthood, maternal pre-pregnancy BMI was shown to be associated with longitudinal changes in BMI from 17 to 32 years among 1400 participants of the Jerusalem Perinatal Study.²³

Causal evidence for a connection between maternal weight and offspring body mass index has been demonstrated in Mendelian randomization studies of increased maternal genetic risk of obesity with increased offspring birthweight by analyzing data on 30,487 women from 18 studies.²⁹ Our results suggest that eliminating maternal overweight and obesity has the potential to reduce adult BMI in the subsequent generation a substantial degree, by up to 3 kg/m². Since previous studies have demonstrated that an increase of 5 kg/m² in BMI is associated with at least 30% higher mortality in adults,³⁰ our findings indicate that reducing overweight and obesity in women of child-bearing age could have considerable public health benefits. Further interventional research is needed in this area to confirm the observational findings as recent Mendelian randomization studies have not supported a causal role for maternal BMI on childhood BMI.³¹ However, this study in the Avon Longitudinal Study of Parents and Children and Generation R only included 6000 participants, which may not have sufficient power for Mendelian randomization for an effect of this magnitude and the difference may not be large enough in childhood. In contrast, a Mendelian randomization study of over 237,000 participants of the UK biobank demonstrated a causal association of higher birthweight on higher BMI and body fat.³²

The association between maternal pre-pregnancy overweight and obesity with offspring BMI, which persists after adjustment for genetic and lifestyle factors, supports previous research describing intergenerational inheritance of metabolic outcomes beyond the inheritance of genetic sequence variants and learned behavior. Although the mechanism underlying fetal programming of obesity is not fully understood, both animal and human models examining the fetal over-nutrition hypothesis support a possible epigenetic link between maternal and offspring adiposity.^{7–11,33–40} Numerous genomic regulatory mechanisms have been implicated in the intergenerational epigenetic inheritance of metabolic disease, including nuclear and ribosomal DNA methylation, histone modifications, and non-coding micro-RNAs (miRNAs). In murine models, maternal obesity is associated with differential methylation of genes involved in fatty acid, cholesterol, and glycogen metabolism.^{33,34} In mammalian fetal models, miRNAs previously linked to CVD and insulin signaling are differentially expressed among animals exposed to maternal obesity compared to normal weight mothers.^{36,37} Human studies have demonstrated associations between maternal BMI and offspring methylation levels.¹⁰ Global methylation levels are also higher in the placentas of women with obesity,³⁸ and are lower in the offspring of

women exposed to famine.^{9,39} In a quasi-experimental human model, offspring exposed to maternal obesity have higher levels of methylation in glucoregulatory, inflammatory, and vascular disease genes compared to their siblings born after maternal gastric bypass surgery without exposure to maternal obesity.⁸ Further research is warranted in understanding the epigenetic mechanisms linking maternal exposures to offspring adiposity.

Our study has limitations. First, residual confounding due to unmeasured lifestyle and genetic factors may have contributed to our results. Although we accounted for some lifestyle factors and a BMI genetic risk score in our models, our measured variables do not account for all lifestyle and genetic contribution to offspring adiposity. Second, we used a combination of directly measured maternal pre-pregnancy BMI data and offspring-reported maternal pre-pregnancy weight category to maximize our sample size. It is possible that there was recall bias present in the offspring-reported data. An overlap analysis suggested that offspring tended to underreport maternal obesity; this would result in bias to the null and would attenuate the effect we observed. The results were similar in the directly measured subset, which also supports the validity of the combined exposure measure. Third, we were not able to adjust models for other maternal factors such as socioeconomic status (SES), smoking, blood pressure, and cholesterol level, although these maternal factors are known to be associated with offspring cardiometabolic traits. For example, lower SES is strongly linked with obesity, and SES can be intergenerationally ‘inherited’, which we do not account for in our analyses. Fourth, we were not able to adjust for perinatal factors. We lacked information about whether offspring were breastfed, so we could not adjust for breastfeeding, which is a protective factor against offspring obesity.⁴¹ Birth complications, small or large birth weight, and preterm birth, were also not included in our models, although these factors are associated with maternal obesity and offspring CVD outcomes.^{6,29,42–44} Our results were robust in all sensitivity models based on available data. Fifth, we did not account for rare genetic variants in the genetic risk score, instead choosing to use a risk score based on 32 common variants. However, research suggests that rare variants account for little additional variation in genetic contribution to BMI at the population level,⁴⁵ so this likely did not substantially affect our results. Sixth, we had an insufficient sample size to include paternal BMI associations with offspring BMI. Therefore, we could not indirectly infer the contribution from intrauterine exposure to higher maternal adiposity by contrasting maternal and paternal pre-pregnancy BMI. Seventh, BMI is not a perfect measure of fat mass and adiposity. Eighth, our study sample is enriched for younger participants for whom their mothers were enrolled in the study prior to their pregnancies. Therefore, our study sample is younger and generally healthier than the overall FHS Offspring cohort.²⁵ Lastly, our study population was of European descent. The results of our study may not be generalizable to populations of other ethnicities.

In conclusion, our results suggest that adult children of mothers with overweight or obesity prior to pregnancy have higher BMI and odds of obesity throughout adulthood compared to adult children of mothers with normal weight. The association was of a clinically-relevant magnitude and was not accounted for by the inheritance of common BMI-related genetic variants and measured lifestyle factors. In addition, we observed greater weight acceleration in early and mid-adulthood. Our results support the hypothesis that *in utero* exposure to maternal overweight and obesity imposes greater risk of developing obesity across the

lifecourse beyond genetic variants and inherited lifestyle factors. The large non-genetic contributions to the intergenerational transmission of obesity, as shown in this study, demonstrates that genes do not completely dictate destiny of inherited obesity risk.

To address the needs of this at-risk population, it may be appropriate to begin lifestyle interventions in women of child-bearing age to prevent and treat overweight and obesity. In addition, obesity prevention efforts should not stop after childhood as we demonstrate that weight acceleration continues well into mid-adulthood. Interventions in young adults would have a potential dual benefit of halting accelerated weight gain in themselves and additional potential obesity reduction among their offspring in adulthood. Further refining prevention efforts has the potential to substantially reduce the financial and social burden of obesity worldwide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Data on the association of genetic variants with body mass index have been contributed by GIANT investigators and have been downloaded from <https://www.broadinstitute.org/collaboration/giant/index.php/>.

Funding

The Framingham Heart Study is funded by National Institutes of Health contract N01-HC-25195 and HHSN268201500001I. MM is supported by the NHLBI (K99 HL136875) and The Tommy Kaplan Fund, Department of Cardiology, Boston Children's Hospital. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

REFERENCES

1. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Archives of internal medicine* 2002; 162(16): 1867–72. [PubMed: 12196085]
2. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003; 348(17): 1625–38. [PubMed: 12711737]
3. Dabelea D, Crume T. Maternal environment and the transgenerational cycle of obesity and diabetes. *Diabetes* 2011; 60(7): 1849–55. [PubMed: 21709280]
4. Institute of Medicine (US) and National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines; Rasmussen KM Y A, editors. *Weight Gain During Pregnancy: Reexamining the Guidelines*. Washington (DC): National Academies Press (US); 2009 2009.
5. Branum AM, Kirmeyer SE, Gregory ECW. *Prepregnancy Body Mass Index by Maternal Characteristics and State: Data From the Birth Certificate, 2014*. Hyattsville, Maryland: National Center for Health Statistics, 2016.
6. Barker DJ. Obesity and early life. *Obes Rev* 2007; 8 Suppl 1: 45–9. [PubMed: 17316301]
7. Attig L, Vige A, Gabory A, et al. Dietary alleviation of maternal obesity and diabetes: increased resistance to diet-induced obesity transcriptional and epigenetic signatures. *PloS one* 2013; 8(6): e66816. [PubMed: 23826145]
8. Guenard F, Deshaies Y, Cianflone K, Kral JG, Marceau P, Vohl MC. Differential methylation in glucoregulatory genes of offspring born before vs. after maternal gastrointestinal bypass surgery. *Proc Natl Acad Sci U S A* 2013; 110(28): 11439–44. [PubMed: 23716672]

9. Heijmans BT, Tobi EW, Stein AD, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci U S A* 2008; 105(44): 17046–9. [PubMed: 18955703]
10. Herbstman JB, Wang S, Perera FP, et al. Predictors and consequences of global DNA methylation in cord blood and at three years. *PloS one* 2013; 8(9): e72824. [PubMed: 24023780]
11. Liu X, Chen Q, Tsai HJ, et al. Maternal preconception body mass index and offspring cord blood DNA methylation: exploration of early life origins of disease. *Environmental and molecular mutagenesis* 2014; 55(3): 223–30. [PubMed: 24243566]
12. Daraki V, Georgiou V, Papavasiliou S, et al. Metabolic profile in early pregnancy is associated with offspring adiposity at 4 years of age: the Rhea pregnancy cohort Crete, Greece. *PloS one* 2015; 10(5): e0126327. [PubMed: 25970502]
13. Davey Smith G, Steer C, Leary S, Ness A. Is there an intrauterine influence on obesity? Evidence from parent child associations in the Avon Longitudinal Study of Parents and Children (ALSPAC). *Arch Dis Child* 2007; 92(10): 876–80. [PubMed: 17595200]
14. Fleten C, Nystad W, Stigum H, et al. Parent-offspring body mass index associations in the Norwegian Mother and Child Cohort Study: a family-based approach to studying the role of the intrauterine environment in childhood adiposity. *Am J Epidemiol* 2012; 176(2): 83–92. [PubMed: 22771730]
15. Hochner H, Friedlander Y, Calderon-Margalit R, et al. Associations of maternal prepregnancy body mass index and gestational weight gain with adult offspring cardiometabolic risk factors: the Jerusalem Perinatal Family Follow-up Study. *Circulation* 2012; 125(11): 1381–9. [PubMed: 22344037]
16. Lawlor DA, Smith GD, O'Callaghan M, et al. Epidemiologic evidence for the fetal overnutrition hypothesis: findings from the mater-university study of pregnancy and its outcomes. *Am J Epidemiol* 2007; 165(4): 418–24. [PubMed: 17158475]
17. Linabery AM, Nahhas RW, Johnson W, et al. Stronger influence of maternal than paternal obesity on infant and early childhood body mass index: the Fels Longitudinal Study. *Pediatr Obes* 2013; 8(3): 159–69. [PubMed: 23042783]
18. Murrin CM, Kelly GE, Tremblay RE, Kelleher CC. Body mass index and height over three generations: evidence from the Lifeways cross-generational cohort study. *BMC Public Health* 2012; 12: 81. [PubMed: 22276639]
19. Reynolds RM, Allan KM, Raja EA, et al. Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1 323 275 person years. *BMJ* 2013; 347: f4539. [PubMed: 23943697]
20. Stamnes Kopp UM, Dahl-Jorgensen K, Stigum H, Frost Andersen L, Naess O, Nystad W. The associations between maternal pre-pregnancy body mass index or gestational weight change during pregnancy and body mass index of the child at 3 years of age. *International journal of obesity* 2012; 36(10): 1325–31. [PubMed: 22929211]
21. Whitaker KL, Jarvis MJ, Beeken RJ, Boniface D, Wardle J. Comparing maternal and paternal intergenerational transmission of obesity risk in a large population-based sample. *Am J Clin Nutr* 2010; 91(6): 1560–7. [PubMed: 20375189]
22. Yu Z, Han S, Zhu J, Sun X, Ji C, Guo X. Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis. *PloS one* 2013; 8(4): e61627. [PubMed: 23613888]
23. Lawrence GM, Shulman S, Friedlander Y, et al. Associations of maternal pre-pregnancy and gestational body size with offspring longitudinal change in BMI. *Obesity (Silver Spring)* 2014; 22(4): 1165–71. [PubMed: 24124160]
24. Eriksson JG, Sandboge S, Salonen M, Kajantie E, Osmond C. Maternal weight in pregnancy and offspring body composition in late adulthood: findings from the Helsinki Birth Cohort Study (HBCS). *Ann Med* 2015; 47(2): 94–9. [PubMed: 25797690]
25. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham offspring study. *Am J Epidemiol* 1979; 110(3): 281–90. [PubMed: 474565]

26. Dawber TR, Kannel WB. An epidemiologic study of heart disease: the Framingham study. *Nutr Rev* 1958; 16(1): 1–4. [PubMed: 13493903]
27. Lawlor DA, Timpson NJ, Harbord RM, et al. Exploring the developmental overnutrition hypothesis using parental-offspring associations and FTO as an instrumental variable. *PLoS Med* 2008; 5(3): e33. [PubMed: 18336062]
28. Kaseva N, Vaarasmaki M, Matinolli HM, et al. Pre-pregnancy overweight or obesity and gestational diabetes as predictors of body composition in offspring twenty years later: evidence from two birth cohort studies. *Int J Obes (Lond)* 2018; 42(4): 872–9. [PubMed: 29146992]
29. Tyrrell J, Richmond RC, Palmer TM, et al. Genetic Evidence for Causal Relationships Between Maternal Obesity-Related Traits and Birth Weight. *JAMA* 2016; 315(11): 1129–40. [PubMed: 26978208]
30. Global BMIMC. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet* 2016.
31. Richmond RC, Timpson NJ, Felix JF, et al. Using Genetic Variation to Explore the Causal Effect of Maternal Pregnancy Adiposity on Future Offspring Adiposity: A Mendelian Randomisation Study. *PLoS Med* 2017; 14(1): e1002221. [PubMed: 28118352]
32. Zanetti D, Tikkanen E, Gustafsson S, Priest JR, Burgess S, Ingelsson E. Birthweight, Type 2 Diabetes Mellitus, and Cardiovascular Disease: Addressing the Barker Hypothesis With Mendelian Randomization. *Circ Genom Precis Med* 2018; 11(6): e002054. [PubMed: 29875125]
33. Wu Q, Suzuki M. Parental obesity and overweight affect the body-fat accumulation in the offspring: the possible effect of a high-fat diet through epigenetic inheritance. *Obes Rev* 2006; 7(2): 201–8. [PubMed: 16629875]
34. Yu HL, Miao HT, Gao LF, et al. Adaptive responses by mouse fetus to a maternal high lipid and high energy diet by down-regulating SREBP1: a microarray- and bio-analytic-based study. *J Lipid Res* 2013.
35. Handy DE, Castro R, Loscalzo J. Epigenetic modifications: basic mechanisms and role in cardiovascular disease. *Circulation* 2011; 123(19): 2145–56. [PubMed: 21576679]
36. Maloyan A, Muralimanoharan S, Huffman S, et al. Identification and Comparative Analyses of Myocardial miRNAs Involved in the Fetal Response to Maternal Obesity. *Physiol Genomics* 2013.
37. Nicholas LM, Rattanatrak L, Maclaughlin SM, et al. Differential effects of maternal obesity and weight loss in the periconceptional period on the epigenetic regulation of hepatic insulin-signaling pathways in the offspring. *FASEB J* 2013; 27(9): 3786–96. [PubMed: 23729590]
38. Nomura Y, Lambertini L, Rialdi A, et al. Global Methylation in the Placenta and Umbilical Cord Blood From Pregnancies With Maternal Gestational Diabetes, Preeclampsia, and Obesity. *Reprod Sci* 2013.
39. Tobi EW, Slagboom PE, van Dongen J, et al. Prenatal famine and genetic variation are independently and additively associated with DNA methylation at regulatory loci within IGF2/H19. *PloS one* 2012; 7(5): e37933. [PubMed: 22666415]
40. Liang X, Yang Q, Fu X, et al. Maternal obesity epigenetically alters visceral fat progenitor cell properties in male offspring mice. *J Physiol* 2016.
41. Kelishadi R, Farajian S. The protective effects of breastfeeding on chronic non-communicable diseases in adulthood: A review of evidence. *Adv Biomed Res* 2014; 3: 3. [PubMed: 24600594]
42. de Jongh BE, Paul DA, Hoffman M, Locke R. Effects of Pre-pregnancy Obesity, Race/Ethnicity and Prematurity. *Matern Child Health J* 2013.
43. Magnussen EB, Vatten LJ, Mykkestad K, Salvesen KA, Romundstad PR. Cardiovascular risk factors prior to conception and the length of pregnancy: population-based cohort study. *Am J Obstet Gynecol* 2011; 204(6): 526 e1–8. [PubMed: 21457914]
44. Ryckman KK, Borowski KS, Parikh NI, Saftlas AF. Pregnancy Complications and the Risk of Metabolic Syndrome for the Offspring. *Curr Cardiovasc Risk Rep* 2013; 7(3): 217–23. [PubMed: 23997844]
45. Grarup N, Sandholt CH, Hansen T, Pedersen O. Genetic susceptibility to type 2 diabetes and obesity: from genome-wide association studies to rare variants and beyond. *Diabetologia* 2014; 57(8): 1528–41. [PubMed: 24859358]

What is already known about this subject?

- Maternal pre-pregnancy overweight and obesity is common.
- There is a robust association between maternal pre-pregnancy weight and offspring obesity in childhood and early adulthood, but little is known about how this association persists beyond young adulthood or changes over a lifecourse.

What does this study add?

- The relation between maternal pre-pregnancy overweight and obesity and higher offspring weight was present across adulthood and persisted after adjustment for inherited genetic sequence variants (SNPs associated with BMI from genome-wide association studies) and measured lifestyle factors (dietary intake, physical activity, smoking, and education)
- The contribution of maternal pre-pregnancy weight explained as much inter-individual variation of adult offspring BMI as did the BMI genetic risk score when included in the same model with lifestyle factors.
- The increase in BMI over time in early adulthood (18 to 50 years of age) was faster among adults with a history of maternal pre-pregnancy overweight and obesity compared to unexposed. For an average height adult, this equates to an excess 5.6 kg (12.3-pound) weight gain between 18 and 50 years of age.

Figure 1.
Study sample inclusion and exclusion at examination 1.

Figure 2: Unadjusted mean BMI (Panel A) and prevalence of obesity (Panel B) among adult offspring exposed to maternal pre-pregnancy overweight/obesity and controls across examination cycles in the Framingham Heart Study Offspring Cohort. Error bars depict standard deviation. BMI = body mass index.

Table 1.

Baseline characteristics of study sample at examination 1

Characteristic	Offspring with obese/overweight mother pre-pregnancy		Offspring with normal weight mother pre-pregnancy	
	Total n	Mean (SD) or n (%)	Total n	Mean (SD) or n (%)
Age (years)	83	30 (11)	780	33 (9)
Female	83	49 (59)	780	406 (52)
BMI (kg/m ²)	83	25.2 (4.1)	780	24.4 (4.1)
Maternal BMI (kg/m ²)	31	27.1 (1.7)	99	21.8 (2.1)
BMI GRS, risk alleles	72	4.1 (0.5)	694	4.0 (0.5)
Hypertension, No. (%)	83	10 (12)	779	137 (17)
Diabetes, No. (%)	82	0 (0)	755	6 (0.8)
Hypercholesterolemia, No. (%)	83	8 (10)	775	90 (12)

BMI = body mass index. GRS = genetic risk score. Maternal BMI available only in the directly measured subset.

Table 2:

Association of maternal pre-pregnancy overweight/obesity with adult offspring BMI at eight Framingham Heart Study examination cycles from separate multivariable-adjusted linear regression models.

Exam	Sample Size	Model 1 (age and sex adjusted)		Model 2 (age, sex, and BMI GRS adjusted)	
	N	β [SE] kg/m ²	p-value	β [SE] kg/m ²	p-value
1	863	1.4 (0.4)	0.0012	1.6 (0.5)	0.0005
2	759	2.0 (0.5)	0.0002	2.2 (0.5)	<0.0001
3	781	3.0 (0.5)	<0.0001	3.1 (0.6)	<0.0001
4	796	2.4 (0.6)	<0.0001	2.6 (0.6)	<0.0001
5	802	2.2 (0.6)	0.0002	2.5 (0.6)	<0.0001
6	822	2.7 (0.6)	<0.0001	3.0 (0.6)	<0.0001
7	783	2.8 (0.6)	<0.0001	3.1 (0.7)	<0.0001
8	701	2.3 (0.7)	0.0010	2.6 (0.7)	0.0004

BMI=body mass index, GRS= genetic risk score.

Table 3:

Association of maternal pre-pregnancy weight category with offspring obesity (BMI $\geq 30\text{kg/m}^2$) at eight Framingham Heart Study examination cycles.

Exam	Sample Size	Model 1 (age and sex adjusted)		Model 2 (age, sex, and BMI GRS adjusted)	
	n	OR (95% CI)	p-value	OR (95% CI)	p-value
1	863	2.5 (1.1, 5.4)	0.02	3.0 (1.3, 6.7)	0.009
2	759	3.0 (1.4, 6.2)	0.003	3.4 (1.6, 7.5)	0.002
3	781	4.9 (2.5, 9.6)	<0.0001	5.3 (2.5, 11.1)	<0.0001
4	796	3.3 (1.6, 6.4)	<0.0001	3.5 (1.7, 7.2)	0.0006
5	802	2.7 (1.4, 5.1)	0.003	3.1 (1.6, 6.3)	0.001
6	822	4.5 (2.2, 9.0)	<0.0001	4.3 (2.1, 8.9)	<0.0001
7	783	4.3 (2.0, 9.0)	0.0002	4.3 (1.9, 9.4)	0.0004
8	701	3.5 (1.7, 7.6)	0.001	4.3 (1.8, 10.4)	0.001

BMI=body mass index, GRS= genetic risk score.