Associations of Maternal Pre-pregnancy and Gestational Body Size with Offspring Longitudinal Change in BMI

Gabriella M. Lawrence1, Shani Shulman1, Yechiel Friedlander1, Colleen M. Sitlani2,3,4, Ayala Burger1, Bella Savitsky1, Einat Granot-Hershkovitz1, Thomas Lumley5,6, Pui-Yan Kwok7, Stephanie Hesselson7, Daniel Enquobahrie2,4, Pandora L. Wander2,4, Orly Manor1, David S. Siscovick2,3,4 and Hagit Hochner1

Objectives: Studies demonstrate associations between changes in obesity-related phenotypes and cardiovascular risk. Although maternal pre-pregnancy BMI (mppBMI) and gestational weight gain (GWG) may be associated with adult offspring adiposity, no study has examined associations with obesity changes. Associations of mppBMI and GWG with longitudinal change in offspring’s BMI (ΔBMI) were examined, and whether associations are explained by offspring genetics was assessed.

Methods: A birth cohort of 1400 adults, with data at birth, age 17 and 32 years was used. After genotyping offspring, genetic scores, predictive of exposures and outcome were created, and linear regression models with and without scores were fit to examine the associations of mppBMI and GWG with ΔBMI.

Results: A one SD change in mppBMI and GWG was associated with a 0.83 and a 0.75 kg/m² increase in ΔBMI, respectively. The association between mppBMI and offspring ΔBMI was slightly attenuated (12%) with the addition of genetic scores. In the GWG model, a significant substantial 28.2% decrease in the coefficient was observed.

Conclusions: This study points to an association between maternal excess weight in pregnancy and offspring BMI change from adolescence to adulthood. Genetic factors may account, in part, for GWG/ΔBMI association. These findings broaden observations that maternal obesity-related phenotypes have long-term consequences for offspring health.

Introduction

A large body of literature has established a clear link between excess weight and obesity with adverse health outcomes, including diabetes mellitus, coronary heart disease, stroke, heart failure, and increased overall mortality (1,2). More recent literature has indicated that the long-term impact of obesity on adult health begins early in life. For example, a cohort of 37,674 Israeli men, who were followed through the Staff Periodic Examination Center of the Israeli Army Medical Corps from age 17 years well into adulthood, showed that an elevated BMI in adolescence is a major risk factor for coronary heart disease later in life (3). The majority of studies to date, however, have looked at BMI at single points in time, focusing little attention on changes in adiposity over time. There is growing evidence that variability in body weight, that is, weight gain and even weight loss, independent of obesity, is associated with increased cardiovascular risk (4), coronary heart disease (1.5-7), and overall mortality (5). Thus, based on the previously mentioned studies, change in obesity, in and of itself, can be considered a risk factor for negative health outcomes.

As research begins to shed light on the associations between BMI changes with morbidity and mortality, understanding the environmental and/or genetic factors that may explain these associations is of extreme importance. Current research indicates that fetal and early-life characteristics (e.g., birth weight) play an important role in determining disease risk—even decades later. Maternal overnutrition, reflected in part by greater maternal pre-pregnancy body mass index (mppBMI) and gestational weight gain (GWG), has been consistently linked with offspring adiposity throughout life, from infancy, through adolescence, to adulthood (8-11). Yet, the association of these maternal attributes with changes in offspring BMI has yet to be explored. In addition, genetic factors are increasingly recognized as having an important role in the determination of longitudinal changes in obesity.

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and other coronary heart disease (CHD)-risk factors (12,13). Thus, these factors may explain, to some extent, the relationship between the intrauterine environment and longitudinal change in offspring body size, and may have major implications for understanding the interventions needed to reduce offspring health risks. The aim of this study was to examine the associations between mppBMI and GWG with the change in offspring BMI over time, and whether genetic factors may account, at least in part, for these associations.

**Methods**

The Jerusalem Perinatal Study (JPS) population-based cohort includes a subcohort of all 17,003 births to residents of Jerusalem, between the years 1974 and 1976 (14,15). Data consist of demographic and socioeconomic information, medical conditions of the mother during current and previous pregnancies, and offspring birth weight, abstracted from either birth certificates or maternity ward logbooks. Additional information on lifestyle and maternal medical conditions, including gestational age, mother’s smoking status, height and pre-pregnancy weight, end of pregnancy weight and gynecological history, was collected by interviews of mothers on the first- or second-day postpartum. Detailed information on data collection has been previously described (11,14,15). Through data linkage with the Israeli military draft records, information from medical examinations at age 17 years, including BMI, was obtained for approximately 70% of the JPS cohort (16).

The JPS Family Follow-Up Study includes a sample of 1400 offspring from the original 1974-1976 birth cohort, who were interviewed and examined between 2007 and 2009. Sampling frame included singletons and term (gestational age ≥ 36 weeks) births without congenital malformations. We obtained a stratified sample of eligible individuals, where the strata were defined by mppBMI and birth weight. Both low (≤2500 g) and high (≥4000 g) birth weight as well as overweight and obese mothers (BMI ≥ 27) were oversampled. Standard procedures and training protocols were used to measure standing height (without shoes; Seca portable stadiometer), body weight (with indoor light clothes; Seca portable automated scale), and waist circumference (at the midpoint between the lower ribs and iliac crest in the midaxillary line; Seca measurement tape). Additional information on demographics, lifestyle, and medical history was obtained by interview of offspring during follow-up.

Blood samples at fasting (at least 8 hours of fasting) were taken using standard procedures. Samples were immediately spun and biochemical measurements were assayed in plasma. Genomic DNA was extracted at Hebrew University using the salting-out method, and high-throughput genotyping was performed at University of California, San Francisco, using an Illumina, Inc., BeadArray™. The Illumina panel includes 1380 SNPs from 168 genes selected based on molecular pathways associated with cardio-metabolic risk (CMR), such as insulin and insulin-like growth factor (IGF)-signaling related genes, adipocyte homeostasis and energy metabolism-related genes, angiogenesis, vascular- and inflammation-related genes, hypothalamic–adrenal–pituitary axis-related genes, appetite regulatory neural network-related genes and nuclear receptors and transcription factors. For the current investigation genotyping of offspring was utilized.

This study was approved by the Institutional Review Board of the Hadassah-Hebrew University Medical Center. All participants provided informed consent. Analyses were carried out using the IBM SPSS version 19.0 statistical package (SPSS, Inc., Chicago, IL) and Stata 12.0 (StataCorp, College Station, TX).

**Study variables**

The primary outcome examined was offspring longitudinal change in body mass index (ΔBMI, simple difference between BMI at age 32 and 17 years). ΔBMI was treated as a continuous variable.

The following explanatory variables were examined: mppBMI (calculated as weight in kilogram divided by squared height in meter square, continuous variable) and GWG (simple difference between end of pregnancy weight and prepregnancy weight in kilogram, continuous variable).

All models were adjusted for offspring sex and ethnicity. Following an approach suggested by Thomas and Witte (17), ethnicity of offspring was classified based on country of origin of all four grandparents, using nine major ethnicity strata (Israel, Morocco, Other North Africa, Iran, Iraq, Kurdistan, Yemen, Other Asia, and the Balkans and Ashkenazi). Rather than allocating offspring to a single ethnicity, we constructed a covariate for each stratum representing the proportion of grandparents derived from each of the nine ethnic groups (ranging from 0 to 1, reflecting none or all four grandparents originating from the specific ethnic group, respectively) and then included these covariates as adjustment variables in a multiple regression (excluding one stratum (Ashkenazi) to eliminate complete multicollinearity).

We addressed potential confounders at three time points in offspring life, at birth, at age 17 and age 32 years, reflecting the early environment (i.e., pre- and perinatal periods) and the environment at young adulthood. Potential confounders at time of birth were (1) maternal smoking during pregnancy (grouped into four categories: current smoker, stopped during this pregnancy, stopped before this pregnancy, and never smoked); (2) socioeconomic status (SES) based on father’s occupation (grouped into six categories: lower class, lower-middle class, middle class 1, middle class 2, upper-middle class, and upper class); (3) mother’s years of education (continuous); (4) birth weight (continuous); and (5) gestational age (weeks from last menstrual period, continuous). Potential confounders at age 32 years were (1) smoking status (grouped into two categories: current smoker versus never smoked or smoked in the past); (2) years of education (continuous); (3) type of education (grouped into two categories: religious and secular); (4) current physical activity (composite score based on intensity, frequency, and duration of physical activity per week, continuous); and (5) caloric intake (average daily, continuous).

We also examined whether the association between GWG and mppBMI with ΔBMI is independent of BMI at age 17 years.

**Genetic scores**

Genetic scores were created based on established methodology used to create composite scores to study the influence of the additive effect of genetic variations on given relationships (18-20). Using a subset of 388 SNPs from 53 adiposity-related genes among offspring, we created genetic scores that were predictive of the exposures and outcome, and fit linear regression models both with and
without genetic scores to examine the change in the associations of mppBMI and GWG with offspring ΔBMI. Three separate genetic scores were created for ΔBMI, GWG, and mppBMI by fitting linear regression models individually for each of the 388 SNPs with ΔBMI, GWG, and mppBMI as separate outcomes. The final scores were calculated as the mean predicted value of these outcomes calculated across all relevant SNPs for each individual. A second set of scores was created using all 1380 SNPs from 168 genes originally genotyped.

Statistical analyses
Linear regression models were used to investigate the associations of mppBMI and GWG, independent of each other, with ΔBMI, after controlling for potential confounders. Two sets of models were constructed. Model 1 included both mppBMI and GWG, adjusted for ethnicity and sex, as well as for maternal and offspring characteristics at time of birth (i.e., maternal smoking during pregnancy, SES, mother’s years of education, birth weight, and gestational age) and offspring characteristics at ages 17 and 32 years (i.e., BMI at age 17; smoking status, and years and type of education at age 32 years). In model 2, we reexamined the associations of mppBMI and GWG with ΔBMI in a linear model that included two genetic scores: one for the maternal characteristics and one for the offspring outcome, in addition to other covariates included in model 1. This enabled us to assess whether genetics explain, at least in part, the associations of mppBMI and GWG with ΔBMI. In other words, if the apparent association between a maternal characteristic and offspring ΔBMI was attenuated toward its null value under multivariate model 2, genetic effects are likely to explain, at least in part, this association.

We calculated percentage change in model coefficients comparing the models that did and did not adjust for genetic scores, and generated bootstrap confidence intervals for the estimates of percent change. Coefficients presented in the table indicate ΔBMI per one unit increase in mppBMI (kg/m²) or GWG (kg).

Secondary analyses explored possible interactions. Sex interactions with mppBMI and GWG on ΔBMI were assessed by introducing both multiplicative terms (i.e., mppBMI*sex and GWG*sex) into the linear regression models. Additionally, to test whether there is evidence for an interaction between mppBMI and GWG on ΔBMI, an mppBMI*GWG multiplicative term was introduced into the models.

To further illustrate effect sizes and clinical importance, mppBMI and GWG were also examined as categorical variables grouped by quartiles of distribution (mppBMI Q1, <20.8 kg/m²; Q2, 20.8-23.4 kg/m²; Q3, >23.4-26.2 kg/m²; and Q4, >26.2 kg/m²; GWG Q1, <9 kg; Q2, 9-11 kg; Q3, >11-14 kg; and Q4, >14 kg). We used estimates for these categorical variables from linear regressions adjusted for confounders described previously to determine adjusted means and SEs for offspring ΔBMI for all subjects within the same quartile. All models used inverse probability weighting to account for the stratified sampling.

For those missing data from the Israeli military draft records, ΔBMI was calculated based on self-report weight at age 17 years (via interview at age 32 years) and height measured at age 32 years. Use of self-reported weight at age 17 years for those missing military data was done after a relatively high Pearson’s correlation (r = 0.764) was observed for those who had both military data and a reported weight of age 17 years from the age 32 years interview data. Linear regression models were repeated with and without self-reported data and yielded similar regression coefficients and standard errors to those obtained by excluding missing values. The following analyses are therefore based on 939 subjects with complete data.

Results
Maternal and offspring characteristics obtained at birth and offspring characteristics at ages 17 and 32 years (including ΔBMI) are listed in Table 1. Among mothers, mean mppBMI was 23.8 kg/m². Mothers gained on average 11.4 kg during pregnancy. Among both male and female offsprings, mean BMI at age 17 years was 21.8 kg/m². The increase in BMI from age 17 to 32 years, though, was greater among males than females. Offspring BMI increased from age 17 to 32 years by 4.3 kg/m² on average. While among females, BMI increased by 3.7 kg/m², among males an increase of 4.8 kg/m² was seen.

Table 2 presents results of linear regression models examining the association of mppBMI and GWG with ΔBMI, with the coefficient indicating the average change in ΔBMI with one unit increase in mppBMI or GWG. There was an increase of 0.83 kg/m² in ΔBMI over time per increase of one SD in mppBMI (P < 0.001) (0.22 kg/m² increase in ΔBMI per one unit increase in mppBMI). This association was independent of GWG and characteristics at birth and at age 32 years, including current physical activity and caloric intake. GWG, adjusted for mppBMI and characteristics at birth, age 17 and 32 years, was also positively associated with ΔBMI. A one SD change in GWG was associated with a 0.77 kg/m² average increase in ΔBMI (P = 0.001) (0.17 kg/m² increase in ΔBMI per one unit increase in GWG), independent of mppBMI and confounders. The associations between mppBMI/GWG and ΔBMI were independent of BMI at age 17 years.

We further investigated whether the associations mentioned above were confounded by genetics by adding genetic propensity scores into the models (Table 2). The association between mppBMI and ΔBMI was slightly attenuated (though not significantly) with the addition of genetic scores in the model, decreasing by 12% from 0.22 to 0.19 (95% CI: −37.8%, 18.5%). In the GWG model, when adjusted for the genetic scores, a substantial decrease of 36% (95% CI: −58.0%, −1.4%) in the coefficient for GWG was observed, from 0.17 to 0.11. The same results were found when using genetic scores created from the 53 adiposity-related genes or the 168 CMR-related genes.

To further illustrate the effect sizes presented in Table 2, we compared adjusted means of offspring ΔBMI between quartiles of mppBMI and GWG (Figure 1). This assessment revealed that the increase in BMI from age 17 to 32 years among offspring of mothers in the upper quartile of mppBMI (mppBMI > 26.2 kg/m²) was nearly 2 kg/m² higher compared with that of the offspring of mothers in the lower quartile (mppBMI < 20.8 kg/m²), a difference corresponding to 0.52 SD of ΔBMI. When genetic scores were added to the model, this difference was only slightly smaller; 1.75 kg/m² higher ΔBMI among the offspring of mothers in the upper quartile compared with the lower quartile (0.46 SD of ΔBMI). The differences in ΔBMI among offspring of mothers in the upper (GWG > 14
kg) and lower (GWG < 9 kg) quartiles of GWG was 1.45 kg/m² (0.39 SD of ΔBMI) without genetic score and only 0.7 kg/m² (0.19 SD of ΔBMI) when genetic scores were added to the model. This analysis shows that both maternal early characteristics are strongly associated with ΔBMI. For GWG, the decrease in slope when genetic scores are added to the model (Figure 1) illustrates that genetic factors account, in part, for the association between GWG and ΔBMI.

We additionally explored whether there was evidence for sex differences or differences according to BMI at age 17 years in the

| TABLE 1 Study characteristics at birth, age 17 and 32 years |
|---------------------------------------------------------------|
| Women (n=380) | Men (n=559) | Total (n=939) |
| Mean (SD) | Mean (SD) | Mean (SD) |
|---------------------------------------------------------------|
| **Characteristics obtained at birth**<sup>a</sup> | | |
| Maternal pre-pregnancy BMI | 23.91 (4.04) | 23.68 (3.60) | 23.77 (3.79) |
| Gestational weight gain (kg) | 11.26 (4.53) | 11.49 (4.66) | 11.39 (4.60) |
| Ethnic origin (%) | | | |
| Israel | 11.05 | 13.59 | 12.57 |
| Middle east | 32.11 | 24.69 | 27.69 |
| North Africa | 24.21 | 24.51 | 24.39 |
| Ashkenazi | 32.63 | 37.21 | 35.35 |
| Maternal smoking (%) | | | |
| Never smoked | 76.05 | 80.86 | 78.91 |
| Stopped before this pregnancy | 6.31 | 4.47 | 5.22 |
| Stopped during this pregnancy | 2.11 | 0.72 | 1.28 |
| Current smoker | 15.53 | 13.95 | 14.59 |
| Birth weight (kg) | 3.30 (0.60) | 3.54 (0.60) | 3.44 (0.61) |
| Maternal years of education | 11.52 (3.90) | 11.80 (3.78) | 11.69 (3.83) |
| SES (based on father’s occupation) (%) | | | |
| Upper class | 18.42 | 20.57 | 19.70 |
| Upper-middle class | 8.95 | 22.18 | 16.83 |
| Middle class 1 | 25.79 | 17.00 | 20.55 |
| Middle class 2 | 24.47 | 16.64 | 19.81 |
| Lower-middle class | 14.74 | 12.70 | 13.53 |
| Lower class | 7.63 | 10.91 | 9.58 |
| Gestational age (weeks) | 39.96 (1.57) | 39.99 (1.53) | 39.98 (1.55) |
| **Characteristics obtained at age 17 years**<sup>a</sup> | | |
| Offspring BMI at age 17 years | 21.85 (3.36) | 21.76 (3.44) | 21.80 (3.41) |
| **Characteristics obtained at age 32 years**<sup>a</sup> | | |
| Longitudinal change in BMI | 3.66 (4.24) | 4.80 (3.30) | 4.34 (3.75) |
| Smokers (%) | | | |
| Never smoked | 57.89 | 47.76 | 51.86 |
| Past smoker | 17.37 | 16.10 | 16.62 |
| Current smoker | 24.74 | 36.14 | 31.52 |
| Years of education | 15.26 (2.67) | 16.00 (4.24) | 15.70 (3.70) |
| Education type (%) | | | |
| Secular | 99.21 | 83.26 | 90.31 |
| Religious | 0.79 | 15.74 | 9.69 |
| Caloric intake | 1833.35 (766.67) | 1991.62 (848.89) | 1928.19 (820.10) |
| Intense physical activity (%) | | | |
| At least one time per week | 26.32 | 39.44 | 34.18 |
| Less than once a week | 73.68 | 60.56 | 65.82 |
| Mild physical activity (%) | | | |
| At least one time per week | 36.36 | 29.58 | 32.32 |
| Less than once a week | 63.64 | 70.42 | 67.68 |

<sup>a</sup>Values are expressed as mean (SD) or percent.
associations between mppBMI and GWG with offspring ΔBMI. There was little evidence to suggest interactions of sex or BMI at age 17 years with either mppBMI or GWG on ΔBMI (data not shown).

Finally, we investigated whether the association of mppBMI with ΔBMI was modified by GWG. However, we found no support for such interaction (data not shown).

Discussion

Summary of findings

This study investigated the association between mppBMI and weight gain during pregnancy with offspring changes in BMI during early adulthood, from age 17 to 32 years. This study adds to the increasing evidence that maternal characteristics during pregnancy are associated with offspring health. We demonstrated that both mppBMI and GWG were positively associated with ΔBMI. The association between mppBMI and ΔBMI was slightly attenuated with the addition of genetic scores in the model. In the GWG model, when adjusted for the genetic scores a substantial decrease in the coefficient for GWG was observed.

Although multiple studies point to the strong relationship between mppBMI and GWG with offspring adiposity (8-11), we are unaware of other studies examining these associations with changes in BMI.

Importance of change/variability versus levels

The importance of this study was established based on several research investigations indicating that the change over time in adiposity measures is associated with cardiovascular risk above and beyond the risk associated with adiposity measured at a single point in time (1,4-7,21,22). To illustrate, Rosengren et al. (7) found that BMI was a significant predictor of death from coronary disease, but only at a BMI above 27.5 kg/m². However, even a moderate increase (≥35%) in weight (from age 20 years) was associated with increased risk of death from coronary disease (2.6-fold increase in risk compared with subjects with weight increase <35%). Willett et al. (6) further pointed out that according to the US weight guide-

**TABLE 2 Associations between maternal pre-pregnancy BMI and gestational weight gain with offspring longitudinal change in BMI with and without genetic score contribution**

| Model 1a | Model 2a | Change in coefficient (%) | (95% CI) |
|----------|----------|---------------------------|---------|
| **Coefficient** | **(95% CI)** | **P** | **Coefficient** | **(95% CI)** | **P** | **(95% CI)** |
| Exposure: maternal pre-pregnancy BMI | | | | | | |
| 0.218 | (0.099, 0.337) | <0.001 | 0.191 | (0.087, 0.294) | <0.001 | -12.39 | (-0.378, 0.185) |
| Exposure: gestational weight gain | | | | | | |
| 0.168 | (0.067, 0.240) | 0.001 | 0.108 | (0.019, 0.196) | 0.017 | -35.71 | (-0.580, -0.014) |

Linear regression models; coefficient indicates offspring longitudinal BMI change per one unit increase in mppBMI (kg/m²) or GWG (kg).

*Model 1: includes both maternal pre-pregnancy BMI and gestational weight gain, adjusted for ethnicity and sex, characteristics at time of birth (i.e., maternal years of education and smoking, SES based on father’s occupation, birth weight, and gestational age), offspring characteristics at age 17 years (i.e., BMI at age 17 years), and offspring characteristics at age 32 years (i.e., smoking, physical activity, caloric intake, education type, and years of education).

*Model 2: same as model 1 plus additional adjustment for genetic scores.*

Mechanisms underlying the observed association

There are several potential pathways that may underlie the association of mppBMI and GWG with ΔBMI. First, in line with other studies (11,23), we questioned whether the relationship between mppBMI and GWG with ΔBMI was simply a reflection of offspring BMI level during adolescence. However, our analyses found that the association of mppBMI and GWG with ΔBMI remained significant with further adjustment for offspring BMI at age 17 years. This is contrary to other adverse health outcomes, such as elevated blood pressure, insulin, and lipids, in which the associations with mppBMI and GWG are mediated by offspring BMI (11,23). Along the same lines, the associations seen in our study may stem from the strong relationship between mppBMI and GWG with birth weight and the tracking of body size throughout life. Consistent with other studies (9,11,24), adjustment for birth weight did not alter the observed associations.

In addition, the relationship between mppBMI and GWG with ΔBMI may stem from the shared culture and lifestyles of mothers and children sharing a similar ethnic background. Studies have shown that, despite the overarching “Western” culture in Israel, ethnicity, particularly in Israel, is associated with various adiposity-related measures among mothers and offspring both during the prenatal period and in adulthood (25-28).
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between mppBMI and GWG with posity and weight gain may also account for the relationship
Mother–offspring shared genetic factors that are related to both adi-
Genetic factors
were adjusted for caloric intake and physical activity. In addi-
tagion to further account for potential shared environmental factors
as well as the basic drivers of changes in adiposity measures, we
addition was within 9 months of delivery (38). Importantly, evaluation of the
association between GWG and weight gain was based on recall rather than on measure-
ment. GWG Q1, <9 kg; Q2, 9-11 kg; Q3, >11-14 kg; and Q4, >14 kg. Estimates for the categorical vari-
able variables from linear regression models (models 1 and 2) were used to determine adjusted means and SEs for offspring change in BMI for all sub-
jects within the same quartile. Error bars represent SEs. [Color figure can be viewed in the online issue, which is available at

FIGURE 1 Adjusted means of offspring change in BMI by quartiles of maternal pre-pregnancy body mass index (mppBMI) and gestational weight gain (GWG). mppBMI and GWG were grouped by quartiles (Q) of distribution: mppBMI Q1, <20.8 kg/m²; Q2, 20.8-23.4 kg/m²; Q3, >23.4-26.2 kg/m², and Q4, >26.2 kg/m²; GWG Q1, <9 kg; Q2, 9-11 kg; Q3, >11-14 kg; and Q4, >14 kg. Estimates for the categorical vari-
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It is possible that the environment shared by mother and offspring
that is related to adiposity and weight gain may explain the observed associations. However, in order to account for various shared char-
acteristics, we adjusted for ethnicity, SES, maternal smoking and
education, offsppring level of education, and offspring smoking. In addi-
tion to further account for potential shared environmental factors
as well as the basic drivers of changes in adiposity measures, we
adjusted for caloric intake and physical activity.

Genetic factors
Mother–offspring shared genetic factors that are related to both adi-
posity and weight gain may also account for the relationship
between mppBMI and GWG with ΔBMI. Research has indicated that

genetics play a key role in changes in adiposity-related pheno-
types (29). In our study, the association between GWG and ΔBMI
was attenuated upon the inclusion of genetic scores in the model,
raising the possibility that common genetic variation may contribute
to this relationship. Offspring genetic variation, on the contrary,
did not play a role in the association between mppBMI and ΔBMI. One
possible explanation may be that epigenetic processes, linking envi-
ronmental and genetic factors, as opposed to genetics alone, are
playing a role in this association. Epigenetics are now recognized as
important components in the connection between the intrauterine
environment and offspring health in later life (11,30,31), particularly
for environmental exposures present before the intrauterine develop-
mental stage (32,33). It has been suggested that the obesogenic envi-
ronment experienced prior to and during conception and early preg-
nancy may induce methylation differences (32,33), causing changes
in gene expression, tissue structure, and organ development and
resulting in subsequent cardiometabolic health consequences in
the adult offspring (34). mppBMI may provide an estimate for a precon-
ceptional maternal exposure, and thus, timing-specific epigenetic
processes, and gene–environment interactions, may play a role in
the association between mppBMI and ΔBMI. More research is nec-
essary to further explore this possibility.

Strengths and limitations
The major strength of our study is the combination of high-quality
detailed records of pre- and perinatal maternal and offspring charac-
teristics with offspring genetic data as well as long-term follow-up
data at ages 17 and 32 years after birth. Availability of information
collected in early life, including both pregnancy-related factors and
lifestyle and socio-demographic characteristics, together with charac-
teristics of offspring at early adulthood, improved the characteriza-
tion of the environment during pregnancy and birth as well as in
adulthood, permitting control for these important factors.

There are several limitations to our study. First, it includes only a
sample of offspring from the original 1974-1976 JPS cohort who
were invited to participate in the follow-up study. However, using a
stratified sampling approach and over-sampling in the ends of the
distribution ensured that offspring with a full range of mppBMI and
birth weight were included in our study. Second, both mppBMI and
GWG were reported by mothers in interviews conducted by nurses
while hospitalized after delivery. Verification from clinical records
was not available. Nevertheless, the associations demonstrated in
this study between reported maternal attributes and ΔBMI >30 years
later, as well as with long-term clinical outcomes in mothers
described previously in this cohort (35), together with the agreement
with findings from studies in other populations (e.g., (8,9)), lend
support to the validity of the data. Additionally, studies have shown
that maternal recollection of pre-pregnancy weight and height is
reproducible and valid (36,37). High correlation was reported
between documented and maternal self-reported GWG when recall
was within 9 months of delivery (38). Importantly, evaluation of the
impact of misclassification in GWG on associations with various
pregnancy outcomes has demonstrated that associations were attenu-
ated when GWG was based on recall rather than on measurement,
indicating a bias towards the null (39,40). In our study, it seems rea-
sonable to assume that given the timing of the interview, that is,
within several days of delivery, the majority of mothers could

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FIGURE 1 Adjusted means of offspring change in BMI by quartiles of maternal pre-pregnancy body mass index (mppBMI) and gestational weight gain (GWG). mppBMI and GWG were grouped by quartiles (Q) of distribution: mppBMI Q1, <20.8 kg/m²; Q2, 20.8-23.4 kg/m²; Q3, >23.4-26.2 kg/m², and Q4, >26.2 kg/m²; GWG Q1, <9 kg; Q2, 9-11 kg; Q3, >11-14 kg; and Q4, >14 kg. Estimates for the categorical variables from linear regression models (models 1 and 2) were used to determine adjusted means and SEs for offspring change in BMI for all subjects within the same quartile. Error bars represent SEs. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
provide valid information on GWG, yet even if reporting error was present it most likely resulted in an underestimation in our findings. Additionally, our measure of ΔBMI is based on weight and height at only two points in time. We, therefore, cannot accurately assess weight fluctuations or intrapersonal variation over time, but rather evaluate the simple change from ages 17 to 32 years. Further studies that examine weight fluctuations at multiple points throughout the life cycle should be conducted.

**Implications**

This study points to the strong relationship between maternal excess weight and weight gain in pregnancy with offspring increases in weight from adolescence to adulthood. In addition, the study points to a potential genetic component in the relationship between GWG and ΔBMI. These findings broaden previous observations indicating that maternal obesity-related phenotypes have long-term consequences for offspring health and support the need to further explore genetic and/or environmental mechanisms underlying these associations.

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