Associations of Maternal Prepregnancy Body Mass Index and Gestational Weight Gain With Adult Offspring Cardiometabolic Risk Factors

The Jerusalem Perinatal Family Follow-Up Study

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Background—Accumulating evidence demonstrates that both maternal prepregnancy body mass index (mppBMI) and gestational weight gain (GWG) are associated with adult offspring adiposity. However, whether these maternal attributes are related to other cardiometabolic risk factors in adulthood has not been comprehensively studied.

Methods and Results—We used a birth cohort of 1400 young adults born in Jerusalem who had extensive archival data and clinical information at 32 years of age to prospectively examine the associations of mppBMI and GWG with adiposity and related cardiometabolic outcomes. Greater mppBMI, independently of GWG and confounders, was significantly associated with higher offspring BMI, waist circumference, systolic and diastolic blood pressures, insulin, and triglycerides and with lower high-density lipoprotein cholesterol. For example, the effect sizes were translated to nearly 5 kg/m² higher mean BMI, 8.4 cm higher waist circumference, 0.13 mmol/L (11.4 mg/dL) higher triglycerides, and 0.10 mmol/L (3.8 mg/dL) lower high-density lipoprotein cholesterol among offspring of mothers within the upper mppBMI quartile (mppBMI ≥ 26.4 kg/m²) compared with the lower quartile (mppBMI < 21.0 kg/m²). GWG, independently of mppBMI, was positively associated with offspring adiposity; differences of 1.6 kg/m² in BMI and 2.4 cm in waist were observed when offspring of mothers in the upper (GWG ≥ 14 kg) and lower (GWG < 9 kg) quartiles of GWG were compared. Further adjustment for offspring adiposity attenuated the observed associations to the null.

Conclusions—Maternal size both before and during pregnancy is associated with cardiometabolic risk factors in young adult offspring. The associations appear to be driven mainly by offspring adiposity. Future studies that explore mechanisms underlying the intergenerational cycle of obesity are warranted to identify potentially novel targets for cardiometabolic risk-reduction interventions. (Circulation. 2012;125:1381-1389.)

Key Words: cohort study ▪ obesity ▪ pregnancy ▪ risk factors ▪ cardiovascular diseases

The prevalence of overweight and obesity is rising worldwide, affecting all age groups, including women of reproductive age. Together with associated cardiometabolic outcomes such as hypertension, hypercholesterolemia, and diabetes mellitus, overweight and obesity have become a major public health concern globally.1,2

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Accumulating evidence suggests that overweight and obesity in adult life and related cardiometabolic risk factors are influenced by the intrauterine environment. In recent years, emerging data from animal and human studies suggest that maternal overnutrition, reflected in part by greater maternal prepregnancy body mass index (mppBMI) and gestational weight gain (GWG), may affect offspring adiposity later in life.1,2 Population-based studies assessing whether the relationships between these maternal attributes and offspring cardiometabolic health extend into adulthood are limited and are restricted mainly to offspring adiposity,3–8 with 1 study examining young adult offspring blood pressure (BP) levels as well.9 We are unaware of previous studies that have examined long-term associations of mppBMI and GWG with other related offspring cardiometabolic outcomes measured in early adulthood such as levels of glucose, insulin, lipids, and lipoproteins.

Using the Jerusalem Perinatal Family Follow-Up Study birth cohort, we extend previous studies by examining the associations of mppBMI and GWG with a range of
cardiometabolic risk factors in offspring (BMI, waist circumference [WC], BP, and plasma levels of fasting glucose, insulin, lipids and lipoproteins) 32 years after birth, taking into account characteristics of both early and current environments, and assessing to what extent the possible relationships of mppBMI and GWG with offspring cardiometabolic outcomes are independent of offspring adiposity.

Methods
The Jerusalem Perinatal Study (JPS) population-based cohort includes a subcohort of all 17,003 births to residents of Jerusalem between 1974 and 1976.\textsuperscript{10–12} 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, smoking status, height, prepregnancy weight, end of pregnancy weight, and gynecological history, was collected by interviewing mothers on the first or second postpartum day. Detailed information on data collection has previously been described.\textsuperscript{10–12} Through data linkage with the Israeli military draft records, information from medical examinations at 17 years of age, including BMI, was obtained for \( \sim 70\% \) of the JPS cohort.\textsuperscript{13}

The JPS Family Follow-Up study includes a sample of 1400 offspring from the original 1974 to 1976 birth cohort who were interviewed and examined between 2007 and 2009. Sampling frame included singletons and term (gestational age \( \geq 36 \) weeks) births without congenital malformations. We obtained a stratified sample of eligible individuals; the strata were defined by mppBMI and birth weight. Both low (\( \leq 2500 \) g) and high (\( \geq 4000 \) g) birth weight and overweight and obese mothers (BMI \( \geq 27 \) kg/m\(^2\)) 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 scale), WC (at the midaxillary line; Seca measurement tape), and BP (measured 3 consecutive times in the right arm in the sitting position after a 5-minute rest; Omron M7 automatic sphygmomanometer). Blood samples at fasting (at least 8 hours of fasting) were taken with standard procedures. Samples were immediately spun, and biochemical measurements were assayed in plasma. Insulin levels were determined by radioimmunoassay with the Human Insulin-Specific RIA Kit (Millipore), and analyses of glucose, high-density lipoprotein cholesterol (HDL-C), and triglycerides were preformed on the VITROS 5.1FS Chemistry System (Ortho Clinical Diagnostics).

Individuals who reported taking BP-lowering medication (n = 11), lipid-lowering medication (n = 13), or medication to treat diabetes mellitus (n = 13) were excluded from the corresponding analyses.

Study Variables
The following cardiometabolic outcomes measured at 32 years of age were examined: BMI (calculated by dividing weight [kg] by squared height [m\(^2\])], WC (mean of 2 consecutive measurements [cm]), systolic and diastolic BP (SBP and DBP; mean of 3 consecutive measures [mm Hg]), glucose (mmol/L), insulin (mean of 2 repeated measures [pmol/L], log-transformed [base 10] because of asymmetrical distribution), low-density lipoprotein cholesterol (LDL-C, mmol/L), and triglycerides (mmol/L, log-transformed [base 10] because of asymmetrical distribution). All cardiometabolic outcomes were treated as continuous variables. The following explanatory variables were examined: mppBMI (calculated as prepregnancy weight [kg] divided by squared height [m\(^2\]), continuous variable and categorical grouped by quartiles of distribution) and GWG (simple difference between end of pregnancy weight and prepregnancy weight [kg], continuous variable and categorical grouped by quartiles of distribution).

All models were adjusted for offspring sex and ethnicity. Following an approach suggested by Thomas and Witte,\textsuperscript{14} ethnicity of offspring was classified on the basis of country of origin of all 4 grandparents with the use of 9 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 giving the proportion of grandparents derived from each of the 9 ethnic groups (ranging from 0 to 1, reflecting none or all 4 grandparents originating from the specific ethnic group, respectively) and then included these covariates as adjustment variables in a multiple regression (excluding 1 strata [Ashkenazi] to eliminate complete multicollinearity).

We addressed potential confounders at 2 time points in offspring life, at birth and at 32 years of age, reflecting the early environment (ie, prenatal and perinatal periods) and the environment at young adulthood, respectively. Potential confounders at the time of birth were (1) parity (continuous), (2) mother’s age at child birth (continuous), (3) maternal smoking during the pregnancy (current smoker versus never smoked or smoked in the past), (4) socioeconomic status based on the father’s occupation at the time of birth (grouped into 3 categories: low, medium, high), (5) mother’s years of education at time of birth (continuous), (6) maternal medical condition (dichotomous; based on whether the mother had ever suffered from any of the following diseases: diabetes mellitus, hypertension, heart disease, toxemia), (7) birth weight (continuous), and gestational week (continuous, to adjust for residual confounding within term pregnancies). Potential confounders at 32 years of age were (1) smoking status (current smoker versus never smoked or smoked in the past), (2) physical activity (dichotomous, based on the question, During leisure time, are you engaged in moderate or vigorous physical activity that lasts at least 20 minutes 3 or more times a week?), and (3) years of education (continuous).

BMI and WC at 32 years of age were also assessed as potential mediators in the associations with the other cardiometabolic outcomes.

Statistical Analyses
Analyses were carried out with the SPSS version 17.0 statistical package (SPSS, Inc, Chicago, IL) and Stata 10.0 (StataCorp, College Station, TX).

Linear regression models were used to investigate the associations of mppBMI and GWG, independently of each other, with cardiometabolic outcomes measured at 32 years of age after controlling for potential confounders. Two sets of models were constructed. Model 1 included both mppBMI and GWG adjusted for ethnicity, sex, maternal and offspring characteristics at the time of birth (ie, parity, mother’s age, maternal smoking, socioeconomic status, mother’s years of education, maternal medical condition, birth weight, and gestational week) and offspring characteristics at 32 years of age (ie, smoking status, physical activity, years of education). In model 2, we assessed whether BMI at 32 years of age mediates, at least in part, the associations of mppBMI and GWG with all other cardiometabolic outcomes by further adjusting model 1 for BMI. Coefficients presented in the table indicate increment (positive or negative) in cardiometabolic outcome per 1-unit increase in mppBMI (kg/m\(^2\)) or GWG (kg).

Sex interactions with mppBMI and GWG on all cardiometabolic outcomes examined were assessed by introducing both multiplicative terms (ie, 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 outcomes, 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; quartile 1, < 21.0 kg/m\(^2\); quartile 2, 21.0–23.8 kg/m\(^2\); quartile 3, 23.9–26.4 kg/m\(^2\); quartile 4, > 26.4 kg/m\(^2\); GWG: quartile 1, < 9 kg; quartile 2, 9–11 kg; quartile 3, 12–14 kg; quartile 4, > 14 kg). We used estimates for these categorical variables from linear regressions adjusted for confounders described above (in model 1) to determine adjusted means and SEs for offspring cardiometabolic outcomes for all subjects within the same quartile. All models used inverse probability weighting to account for the stratified sampling.

As a result of a limited number of missing values for several potential confounders at the time of birth and at 32 years of age, a
total of 180 offspring could not be included in analyses. To reduce possible bias, we imputed missing data using observed data and assuming that data were missing at random. Linear regression models were repeated with imputed data and yielded regression coefficients and SEs similar to those obtained by excluding missing values. The following analyses are therefore based on subjects with complete data: 1250 for adiposity and BP and 1130 for blood assays.

This study was approved by the Institutional Review Board of the Hadassah-Hebrew University Medical Center and by the University of Washington Human Subject Review Committee. All participants provided informed consent.

### Results

Maternal and offspring characteristics obtained at birth and offspring characteristics and cardiometabolic outcomes at 32 years of age are listed in Table 1.
The relationships of mppBMI with WC, BP, insulin, HDL-C, and triglycerides and those of GWG with WC and triglycerides were not independent of concurrent BMI; all significant associations were attenuated to the null with further adjustment for BMI at 32 years of age (Table 2, top and bottom, model 2). Analyses were repeated with further adjustment for WC instead of BMI, yielding similar results (data not shown).

Additional support for a potential mediating role of BMI was provided among a subsample of 991 men and women for whom, in addition to the data at 32 years of age, BMI at 17 years of age was available. In this subsample, the effect size of mppBMI on SBP at 32 years of age without adjusting for BMI (β=0.426, P=0.008) was attenuated (β=0.306, P=0.06) after further adjustment for BMI at 17 years of age.

To further illustrate the effects sizes presented in Table 2, we compared adjusted means of selected offspring cardiometabolic outcomes at 32 years of age; the coefficient indicates the increment (positive or negative) in cardiometabolic outcome per 1-unit increase in maternal prepregnancy BMI (kg/m²) or gestational weight gain (kg).

*Linear regression models. Coefficient indicates increment (positive or negative) in cardiometabolic outcome per 1-unit increase in mppBMI on SBP at 32 years of age without adjusting for BMI (P<0.0001), WC (P<0.0001), SBP (P=0.003), DBP (P=0.017), insulin (P=0.007), and triglycerides (P=0.02) and negatively associated with HDL-C (P=0.03). These associations were independent of GWG and of characteristics at birth and at 32 years of age (Table 2, top, model 1). For example, the coefficients presented in Table 2 can also be interpreted as an increase of 1.8 kg/m² in offspring BMI, 3.5 cm in WC, and 1.7 and 1.1 mm Hg in SBP and DBP per increase of 1 SD in mppBMI. GWG adjusted for mppBMI and all confounders was also positively associated with offspring adiposity traits, including BMI (P=0.0001) and WC (P=0.024), and with triglycerides (P=0.04; Table 2, bottom, model 1).

### Table 2. Associations* of Maternal Prepregnancy Body Mass Index and Gestational Weight Gain With Offspring Cardiometabolic Outcomes at 32 Years of Age

<table>
<thead>
<tr>
<th>Exposure: maternal prepregnancy BMI</th>
<th>Model 1†</th>
<th>Model 2†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficient</td>
<td>95% CI</td>
<td>P</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.481</td>
<td>0.377 to 0.585</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>0.927</td>
<td>0.668 to 1.185</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>0.441</td>
<td>0.149 to 0.732</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>0.287</td>
<td>0.051 to 0.523</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>−0.001</td>
<td>−0.019 to 0.016</td>
</tr>
<tr>
<td>Insulin, μU/mL</td>
<td>0.008</td>
<td>0.002 to 0.014</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>0.012</td>
<td>−0.008 to 0.031</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>−0.010</td>
<td>−0.019 to −0.0007</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.007</td>
<td>0.001 to 0.012</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exposure: gestational weight gain</th>
<th>Model 1†</th>
<th>Model 2†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficient</td>
<td>95% CI</td>
<td>P</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.178</td>
<td>0.088 to 0.267</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>0.277</td>
<td>0.036 to 0.518</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>0.206</td>
<td>0.003 to 0.408</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>0.174</td>
<td>−0.004 to 0.353</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>0.005</td>
<td>−0.008 to 0.019</td>
</tr>
<tr>
<td>Insulin, μU/mL</td>
<td>0.002</td>
<td>−0.003 to 0.008</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>0.007</td>
<td>−0.010 to 0.023</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>−0.006</td>
<td>−0.014 to 0.002</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.005</td>
<td>0.0001 to 0.009</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; and HDL-C, high-density lipoprotein cholesterol.

*Linear regression models. Coefficient indicates increment (positive or negative) in cardiometabolic outcome per 1-unit increase in maternal prepregnancy BMI (kg/m²) or gestational weight gain (kg).

†Model 1: includes both maternal prepregnancy BMI and gestational weight gain adjusted for ethnicity and sex, characteristics at the time of birth (ie, parity, mother’s age, maternal smoking, SES, mother’s years of education, maternal medical condition, birth weight, and gestational week), and offspring characteristics at 32 years of age (ie, smoking status, physical activity, years of education). Model 2: model 1 plus additional adjustment for offspring BMI at 32 years of age.

‡Individuals who reported taking antihypertensive medication (n=11) were excluded from analysis.

§Individuals who reported taking lipid-lowering medication (n=13) were excluded from analysis.

¶Log-transformed values (base 10) because of asymmetrical distribution.

#Conversions: glucose, mg/dL=(mmol/L)/0.0555; insulin, μU/mL=(pmol/L)/6.945; triglycerides, mg/dL=(mmol/L)/0.0113; HDL-C and LDL-C, mg/dL=(mmol/L)/0.259.
outcomes between quartiles of mppBMI and GWG (the Figure). This assessment revealed that the BMI of offspring whose mothers were in the upper quartile of mppBMI (mppBMI $\geq 26.4$ kg/m$^2$) was nearly 5 kg/m$^2$ higher compared with that of the offspring of mothers in the lower quartile (mppBMI $<21.0$ kg/m$^2$), a difference corresponding to 0.9 SD of offspring BMI. WC was 8.4 cm higher among the offspring of mothers in the upper quartile compared with the offspring of mothers in the lower quartile (0.64 SD of WC). The differences in mean BP levels between the 2 quartiles were 5.2 mm Hg for SBP and 3.0 mm Hg for DBP (corresponding to ~0.4 SD and 0.35 SD, respectively). The effect sizes for the associations of mppBMI with insulin and triglycerides were translated to 17.4 pmol/L (2.5 $\mu$U/mL) higher insulin and 0.13 mmol/L (11.4 mg/dL) higher triglycerides among offspring of mothers within the upper mppBMI quartile compared with the offspring of mothers in the lower quartile (the Figure). Mean HDL-C level among offspring of mothers within the upper quartile of mppBMI was 0.10 mmol/L (3.8 mg/dL) lower compared with the offspring of mothers in the lower quartile, corresponding to 0.26 SD of HDL-C (data not shown). The differences in BMI and WC among offspring of mothers in the upper (GWG $\geq 14$ kg) and
lower (GWG < 9 kg) quartiles of GWG were 1.6 kg/m² in BMI and 2.4 cm in WC (the Figure).

We have additionally explored whether there was evidence for sex differences in the associations between mppBMI and GWG with offspring cardiometabolic outcomes. Except for the statistically significant sex interaction with GWG on BP (FInteraction=0.004 and FInteraction=0.001 for SBP and DBP, respectively), there was little evidence to suggest interactions of sex with either mppBMI or GWG for the other cardiometabolic outcomes (data not shown).

Finally, we investigated whether the associations of mppBMI with any of the cardiometabolic outcomes examined were modified by GWG. However, we found no support for such interactions (data not shown).

Discussion

Summary of Findings
This study investigated the associations between maternal prepregnancy body size and weight gain during pregnancy with a range of offspring cardiometabolic risk factors in early adulthood. We demonstrated that mppBMI was independently and positively associated with offspring BMI and WC at 32 years of age. We extend previous studies by demonstrating that greater mppBMI was also significantly associated with higher offspring SBP, DBP, insulin, and triglycerides levels and lower HDL-C. Additionally, we have shown that GWG, independently of mppBMI, was positively associated with offspring adiposity. The observed associations were independent of characteristics reflecting the prenatal, perinatal, and postnatal environments, including current measures of socioeconomic status and lifestyle. Furthermore, the associations appear to be driven mainly by offspring adiposity.

Associations With Offspring Adiposity
Our finding that mppBMI was positively associated with offspring adiposity in early adulthood is in accordance with other studies.3–8 Recently, several studies examined the association between GWG and offspring adiposity in adulthood, reflected primarily by offspring BMI, and have generally demonstrated a positive association.5–7,9,15,16

Associations With Offspring BP
There have been only a few investigations of the association of mppBMI or GWG with offspring BP, and because of the scarcity of long follow-up data, most have examined BP in childhood only. Nevertheless, similar to our findings in adults, positive associations of mppBMI and GWG with offspring BP measured in childhood were demonstrated in several studies.17–22 A previous study based on 10 883 subjects from the JPS 1974 to 1976 birth cohort examined the association of several prenatal characteristics with offspring BP at adolescence (17 years of age) and found mppBMI to be positively associated with offspring BP, whereas GWG was not related to BP.23 In an Australian population-based cohort of 2432 individuals 21 years of age, greater GWG was shown to be associated with increased SBP.24 Although this association was not statistically significant, the authors argue that its magnitude is consistent with the associations of GWG with BMI and of BMI with BP. In agreement with the aforementioned studies,9,23 we have shown that the association between mppBMI and BP at 32 years of age was significant, whereas GWG was not significantly associated with BP. A possible explanation for the lack of association seen for GWG and BP may be the presence of a significant GWG-sex interaction. However, we acknowledge that our interaction finding may be due to chance and therefore requires replication in other cohorts.

Associations With Offspring Fasting Glucose and Insulin
We have shown that mppBMI was associated with offspring fasting insulin levels, whereas GWG was not associated with either insulin or glucose level. Data on the associations between mppBMI and GWG with offspring fasting levels of glucose and insulin are scarce. A small case-control study of 52 young adult offspring of obese mothers (BMI ≥ 30 kg/m² before and during pregnancy) and 15 offspring of normal-weight mothers demonstrated that the offspring of obese mothers were more likely to be overweight and obese and more insulin resistant compared with the control subjects.24

Associations With Offspring Fasting Lipids and Lipoproteins
We have shown that mppBMI was significantly associated with HDL-C and triglycerides. No associations of GWG with lipids and lipoproteins were observed (borderline significance with triglycerides, P=0.044). We are unaware of other studies examining these associations with offspring lipids and lipoproteins in young adults. The only previous study that investigated similar associations is a recent study of 9-year-old children from the United Kingdom that examined relationships of mppBMI and GWG with a wide range of offspring cardiovascular risk factors.19 With some similarity to our findings, the UK study showed that both greater mppBMI and GWG were significantly associated with lower HDL-C, whereas associations with triglyceride levels were positive but confidence intervals were wide. The variation in the findings may be attributed to differences in characteristics of participants (eg, age) between studies.

Mediating Role of Adiposity
Our analyses suggest that the significant associations of mppBMI and GWG with BP, insulin, and lipids appeared to be largely mediated by offspring concurrent body size, reflected by both BMI and WC.

Similar to our findings in adults, a case-control study comprising offspring 6 to 13 years of age suggested that, independently of maternal diabetes status, greater mppBMI was associated with raised BP and that this association was mediated by BMI.22 A recent study of 30 461 mother-child pairs examining whether intrauterine and/or childhood growth mediate the associations between prenatal factors and SBP at 7 years of age demonstrated that the association of mppBMI with SBP was independent of intrauterine growth restriction and was attenuated to the null after adjustment for offspring BMI trajectory.21 Additional support for our findings comes from the UK study in children; those authors reported that the significant relationships demonstrated for
Mechanisms Underlying the Observed Associations

Several pathways may underlie the associations of mppBMI and GWG with offspring adiposity. First, mppBMI and GWG are correlated with birth weight; therefore, their association with offspring body size may simply reflect tracking of body size throughout life. However, consistent with other studies, adjustment for birth weight did not alter the observed associations. Second, shared genetic and environmental characteristics between mother and offspring that are related to both adiposity and weight gain may account for these relationships. This study did not assess the contribution of directly measured genetic factors to the observed associations. Yet, we have attempted to account for various shared environmental characteristics by adjusting for characteristics reflecting the early environment such as socioeconomic status and maternal smoking, as well as for characteristics of the environment in early adulthood, including offspring level of education, smoking, and physical activity. Our models demonstrated significant associations that were independent of the various environmental characteristics. Third, intrauterine mechanisms may account for the long-term associations with offspring adiposity. This was examined in a recent study of ~150 000 Swedish male conscripts (18 years of age) using a unique study design to compare within-sibling and between-nonsibling associations. The authors reported that, among overweight and obese mothers, intrauterine mechanisms contribute to the association between weight gain during pregnancy and later offspring obesity in addition to shared genetic and environmental factors.

Intrauterine mechanisms explaining long-term associations with offspring obesity and related cardiometabolic outcomes have been proposed by the developmental overnutrition hypothesis. Greater fat during pregnancy (owing to higher mppBMI or greater GWG) results in greater delivery of glucose, amino acids, and free fatty acids from mother to fetus and thus may lead to permanent changes in appetite control, neuroendocrine functioning, and energy metabolism in the developing fetus with long-term consequences on risk of adiposity and related cardiometabolic disease. Relevant here is the concept of developmental origins of health and disease, in which ample evidence exists linking birth weight, a surrogate measure of intrauterine growth and development, with cardiometabolic outcomes in adult life such as obesity, hypertension, and diabetes mellitus. As mentioned, taking birth weight into account did not attenuate the observed associations of maternal attributes with offspring cardiometabolic outcomes. This finding can imply that birth weight does not measure the intrauterine environment well enough, although in our data birth weight appears to be associated to some extent with several of the cardiometabolic outcomes examined (eg, adiposity, BP, insulin, triglycerides) and with clinical outcomes such as mortality demonstrated in previous studies in this cohort. Alternatively, it could suggest that the associations of maternal adiposity (both mppBMI and GWG) and birth weight with offspring cardiometabolic outcomes reflect different pathways linking early life events with adult health.

Finally, there is increasing recognition that epigenetic processes, linking environmental and genetic factors, are important components in the transmission of acquired information from the uterus to the offspring in later life. It has been suggested that the obesogenic environment experienced in utero may induce epigenetic modifications, causing changes in gene expression, tissue structure, and organ development and resulting in subsequent cardiometabolic health consequences in the adult offspring. In support of epigenetic mechanisms, it should be noted that although adiposity and related risk factors show significant heritability (~50%), common genetic variation identified thus far appears to have a modest impact on these traits. Furthermore, in our cohort, mothers were noticeably leaner than their offspring when they were at childbearing age. Clearly, the genetic makeup did not change during these years, but the environment has changed dramatically; Jerusalem during the last 3 decades has gradually become a more affluent society. It may therefore be the difference between the environment experienced by the offspring in utero and the environment experienced later in life that has interacted with genes to exert the observed intergenerational changes.

On a more specific note, in the recent study of 9-year-old children from the United Kingdom, it was suggested that long-term associations of GWG and offspring cardiometabolic outcomes may vary between outcomes, depending on the timing during gestation, possibly pointing to differences in underlying mechanisms between traits. In the UK study, GWG at all stages of gestation was found to be associated with offspring adiposity, whereas other cardiometabolic outcomes such as lipids and inflammatory profiles were related to GWG only in mid to late gestation. The influence of timing of intrauterine exposures has also been demonstrated in the Dutch famine cohort, where people exposed to famine in late or mid gestation showed a different cardiometabolic risk pattern in adulthood than those exposed in early gestation, and these differences may involve persistent changes in DNA methylation that depend on gestational timing. Thus, a possible explanation for the fact that, in the present study, GWG was found to be associated with adiposity traits and not with other cardiometabolic outcomes is that it may reflect mechanistic differences in which obesity is affected more robustly by weight gain at any time during the pregnancy, whereas other outcomes are sensitive to weight gain in specific time windows in gestation. We were unable to examine this possibility because repeated measures of GWG were unavailable.

Study Strengths and Limitations

The major strength of our study is the combination of high-quality detailed records of prenatal and perinatal maternal and offspring characteristics with comprehensive long-term follow-up data 32 years after birth. Availability of information collected in early life, including both pregnancy-related factors and lifestyle and sociodemographic characteristics, together with characteristics of offspring at early adulthood, improved the characterization of the environment during pregnancy and birth and in adulthood, permitting control for these important factors.

Our study has several limitations. First, it includes only a sample of offspring from the original 1974 to 1976 JPS cohort
who were invited to participate in the follow-up study. However, using a stratified sampling approach and oversampling 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 the present study between reported maternal attributes and measured cardiometabolic traits >30 years later and with long-term clinical outcomes in mothers described previously in this cohort,29 together with the agreement with findings from studies in other populations (eg, see References 5, 9, and 16), lend support to the validity of the data. Additionally, studies have shown that maternal recollection of prepregnancy weight and height is reproducible and valid.39—44 High correlation was also reported between documented and maternal self-reported GWG when recall was within 9 months of delivery.42 Importantly, evaluation of the impact of misclassification in GWG on associations with various pregnancy outcomes has demonstrated that associations were attenuated when GWG was based on recall rather than on measurement, indicating a bias toward the null.43,44 In our study, it seems reasonable to assume that, given the timing of the interview, ie, within several days of delivery, the majority of mothers could provide valid information on GWG, yet even if reporting error was present, it most likely resulted in an understimation in our findings. Additionally, we were not able to examine the associations of GWG at various stages of pregnancy with offspring cardiometabolic outcomes because repeated measures of GWG were not available. Finally, this study did not assess the impact of direct measurements of genetic and epigenetic factors on the associations examined. Further studies that examine whether genetic and/or epigenetic variation may account for the observed associations are warranted.

**Implications**

Our study adds to and extends accumulating evidence of long-term relationships of maternal excess weight and weight gain in pregnancy with offspring cardiometabolic health in adulthood. It should be emphasized that, at the time this birth cohort was established, obesity was not near its current magnitude. Therefore, the distribution of mppBMI in our study reflects a much leaner population than the current population, and this is likely true for GWG, given its rising trends.45 Nevertheless, significant associations with mppBMI and GWG were demonstrated for a range of cardiometabolic risk factors in offspring, with clinically significant effect sizes on offspring adiposity in particular. Furthermore, the associations appear to be driven mainly by offspring adiposity, emphasizing the potential impact that maternal adiposity may have through offspring adiposity on various predictors of subclinical and clinical disease, including diabetes mellitus, myocardial infarction, and stroke. Whether this predicts even worse outcomes for the next generation is unknown, but the possibility is nonetheless concerning.

Future studies should explore mechanisms underlying the relationships between these maternal pregnancy-related characteristics and cardiometabolic outcomes in offspring. Achieving a better understanding of the mechanisms underlying the intergenerational cycle of obesity may help facilitate the identification of novel targets for cardiometabolic risk-reduction interventions.

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**Disclosures**

None.

**References**

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**CLINICAL PERSPECTIVE**

Accumulating evidence suggests that maternal prepregnancy body mass index (mBMI) and gestational weight gain (GWG) may affect adult offspring adiposity. However, whether these maternal attributes are associated with other offspring cardiometabolic risk factors in adulthood remains unclear. We have prospectively examined the independent associations of mBMI and GWG with offspring cardiometabolic risk factors at 32 years of age using a birth cohort of 1400 young adults born in Jerusalem. Greater mBMI was significantly associated with higher offspring BMI, waist circumference, systolic and diastolic blood pressures, insulin, and triglycerides and with lower levels of high-density lipoprotein cholesterol. GWG was positively associated with offspring adiposity, including BMI and waist circumference. Translating these associations into mean differences of cardiometabolic outcomes between quartiles of mBMI and GWG distributions reveals clinically meaningful differences. For example, offspring of mothers within the upper mBMI quartile (mBMI >26.4 kg/m²) had 4.6 kg/m² higher BMI, 11.4 mg/dL higher triglycerides, and 3.8 mg/dL lower high-density lipoprotein cholesterol compared with offspring of mothers within the lower quartile (mBMI <21.0 kg/m²). Differences of 1.6 kg/m² in BMI and 2.4 cm in waist circumference were observed when offspring of mothers in the upper (GWG >14 kg) and lower (GWG <9 kg) quartiles of GWG were compared. The associations appear to be driven mainly by offspring adiposity, emphasizing the potential impact that maternal adiposity may have via offspring adiposity on predictors of long-term cardiometabolic health outcomes in offspring. Further studies that explore the mechanisms that account for these associations and clinical trials monitoring maternal size both before and during pregnancy are warranted to identify potentially novel targets for cardiometabolic risk-reduction interventions.
Associations of Maternal Prepregnancy Body Mass Index and Gestational Weight Gain With Adult Offspring Cardiometabolic Risk Factors: The Jerusalem Perinatal Family Follow-Up Study
Hagit Hochner, Yechiel Friedlander, Ronit Calderon-Margalit, Vardiella Meiner, Yael Sagy, Meytal Avgil-Tsadok, Ayala Burger, Bella Savitsky, David S. Siscovick and Orly Manor

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