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 off-

spring cardiometabolic outcomes are independent of off-

spring adiposity.

Methods

The Jerusalem Perinatal Study (JPS) population-based cohort in-

cludes a subcohort of all 17 003 births to residents of Jerusalem

between 1974 and 1976.10–12 Data consist of demographic and

socioeconomic information, medical conditions of the mother during

current and previous pregnancies, and offspring birth weight, ab-

tracted 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

reported.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 ~70% of the JPS cohort.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 ≥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 (≤2500 g) and high (>4000 g) birth weight and

overweight and obese mothers (BMI ≥27 kg/m²) 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),

WC (at the midpoint between the lower ribs and iliac crest in 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 automated 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 performed 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 [m²]), WC (mean of 2 consecutive measurements

[cm]), systolic and diastolic BPs (SBP and DBP; mean of 3

consecutive measures [mm Hg]), glucose (mmol/L), insulin (mean of

2 repeated measures [mmol/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 (calcu-
lated as prepregnancy weight [kg] divided by squared height [m²],

continuous variable and categorical grouped by quartiles of distri-

bution) 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. Follow-

ing an approach suggested by Thomas and Witte,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, respecti-

vely) 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

(i.e., 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/m²) 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 multi-

plicative 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/m²; quartile

2, 21.0–23.8 kg/m²; quartile 3, 23.9–26.4 kg/m²; quartile 4, >26.4

kg/m²; 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 confound-

ers 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.

Table 2 presents results of linear regression models examining the associations of mppBMI and GWG with offspring cardiometabolic outcomes.
### 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>Offspring Cardiometabolic Outcomes</th>
<th>Model 1†</th>
<th></th>
<th>Model 2†</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coefficient</strong></td>
<td><strong>95% CI</strong></td>
<td><strong>P</strong></td>
<td><strong>Coefficient</strong></td>
<td><strong>95% CI</strong></td>
</tr>
<tr>
<td><strong>Exposure: maternal prepregnancy BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.481</td>
<td>0.377 to 0.585</td>
<td>&lt;0.0001</td>
<td>-0.094</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>0.927</td>
<td>0.668 to 1.185</td>
<td>&lt;0.0001</td>
<td>-0.016</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>0.441</td>
<td>0.149 to 0.732</td>
<td>0.003</td>
<td>0.078</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>0.287</td>
<td>0.051 to 0.523</td>
<td>0.017</td>
<td>-0.030</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>0.017</td>
<td>0.019 to 0.016</td>
<td>0.875</td>
<td>-0.006</td>
</tr>
<tr>
<td>Insulin, μU/mL</td>
<td>-0.002</td>
<td>0.002 to 0.014</td>
<td>0.007</td>
<td>-0.004</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>0.012</td>
<td>-0.008 to 0.031</td>
<td>0.240</td>
<td>-0.002</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>-0.010</td>
<td>-0.019 to -0.0007</td>
<td>0.033</td>
<td>0.003</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>0.007</td>
<td>0.001 to 0.012</td>
<td>0.020</td>
<td>-0.002</td>
</tr>
<tr>
<td><strong>Exposure: gestational weight gain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.178</td>
<td>0.088 to 0.267</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>0.277</td>
<td>0.036 to 0.518</td>
<td>0.024</td>
<td>-0.100</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>0.206</td>
<td>0.003 to 0.408</td>
<td>0.047</td>
<td>0.063</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>0.174</td>
<td>-0.004 to 0.353</td>
<td>0.055</td>
<td>0.061</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>0.005</td>
<td>-0.008 to 0.019</td>
<td>0.480</td>
<td>0.003</td>
</tr>
<tr>
<td>Insulin, μU/mL</td>
<td>0.002</td>
<td>-0.003 to 0.008</td>
<td>0.339</td>
<td>-0.003</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>0.007</td>
<td>-0.010 to 0.023</td>
<td>0.429</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>-0.006</td>
<td>-0.014 to 0.002</td>
<td>0.164</td>
<td>-0.0004</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>0.005</td>
<td>0.0001 to 0.009</td>
<td>0.044</td>
<td>0.001</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 diabetes 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.

Cardiometabolic outcomes at 32 years of age; the coefficient indicates the increment (positive or negative) in cardiometabolic outcome associated with a 1-unit increase in mppBMI or GWG. mppBMI was positively associated with offspring 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).

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 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 \(26.4 \text{ kg/m}^2\)) was nearly 5 kg/m² higher compared with that of the offspring of mothers in the lower quartile (mppBMI \(<21.0 \text{ kg/m}^2\)), 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 \(\approx 0.4\) 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 \(\mu U/m\)) 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 \(>14 \text{ kg}\)) and

Figure. Adjusted means of offspring selected cardiometabolic outcomes at 32 years of age by quartiles of maternal prepregnancy body mass index (BMI) and gestational weight gain (GWG). Maternal prepregnancy BMI (mppBMI) and GWG were grouped by quartiles (Q) of distribution: mppBMI Q1, \(<21.0 \text{ kg/m}^2\); Q2, 21.0 to 23.8 kg/m²; Q3, 23.9 to 26.4 kg/m²; and Q4, \(\geq 26.4 \text{ kg/m}^2\); GWG Q1, \(<9 \text{ kg}\); Q2, 9 to 11 kg; Q3, 12 to 14 kg; and Q4, \(\geq 14 \text{ kg}\). Estimates for the categorical variables from linear regression models adjusted for ethnicity, sex, characteristics at 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) were used to determine adjusted means and SEs for offspring cardiometabolic outcomes for all subjects within the same quartile. Error bars represent SEs. Difference between each value displayed on the y axis corresponds to \(\approx 2\) SEs of the respective cardiometabolic outcome. Conversions: insulin, \(\mu U/mL=(\text{pmol/L}/6.945)\); triglycerides, mg/dL=(mmol/L)/0.0113. BP indicates blood pressure.
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 ($F_{interaction} = 0.004$ and $F_{interaction} = 0.001$ 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 $\geq 30$ 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
mppBMI and GWG were all attenuated to null after adjustment for various measures of adiposity.\textsuperscript{19}

**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,\textsuperscript{7,9,15,16} 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 \textasciitilde 150,000 Swedish male conscripts (18 years of age) using a unique study design to compare within-sibling and between-nonsibling associations.\textsuperscript{15} 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.\textsuperscript{1} Relevance 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.\textsuperscript{25–28} 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.\textsuperscript{29–31} 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.\textsuperscript{2,3,23} In support of epigenetic mechanisms, it should be noted that although adiposity and related risk factors show significant heritability (\geq 50\%),\textsuperscript{34} common genetic variation identified thus far appears to have a modest impact on these traits.\textsuperscript{35} 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.\textsuperscript{36}

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,\textsuperscript{19} possibly pointing to differences in underlying mechanisms between traits. In the UK study, GWG at all stages of gestation was found to be was associated with offspring adiposity, whereas other cardiometabolic outcomes such as lipids and inflammatory profiles were related to GWG only in mid to late gestation.\textsuperscript{19} 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,\textsuperscript{37} and these differences may involve persistent changes in DNA methylation that depend on gestational timing.\textsuperscript{38} 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.30–41 A 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 underestimation 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.

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**CLINICAL PERSPECTIVE**

Accumulating evidence suggests that maternal prepregnancy body mass index (mpBMI) 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 mpBMI and GWG with offspring cardiometabolic risk factors at 32 years of age using a birth cohort of 1400 young adults born in Jerusalem. Greater mpBMI 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 mpBMI and GWG distributions reveals clinically meaningful differences. For example, offspring of mothers within the upper mpBMI quartile (mpBMI >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 (mpBMI <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. Future 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

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