Genetic Evidence for Causal Relationships Between Maternal Obesity-Related Traits and Birth Weight

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IMPORTANCE Neonates born to overweight or obese women are larger and at higher risk of birth complications. Many maternal obesity-related traits are observationally associated with birth weight, but the causal nature of these associations is uncertain.

OBJECTIVE To test for genetic evidence of causal associations of maternal body mass index (BMI) and related traits with birth weight.

DESIGN, SETTING, AND PARTICIPANTS Mendelian randomization to test whether maternal BMI and obesity-related traits are potentially causally related to offspring birth weight. Data from 30,487 women in 18 studies were analyzed. Participants were of European ancestry from population- or community-based studies in Europe, North America, or Australia and were part of the Early Growth Genetics Consortium. Live, term, singleton offspring born between 1929 and 2013 were included.

EXPOSURES Genetic scores for BMI, fasting glucose level, type 2 diabetes, systolic blood pressure (SBP), triglyceride level, high-density lipoprotein cholesterol (HDL-C) level, vitamin D status, and adiponectin level.

MAIN OUTCOME AND MEASURE Offspring birth weight from 18 studies.

RESULTS Among the 30,487 newborns the mean birth weight in the various cohorts ranged from 3325 g to 3679 g. The maternal genetic score for BMI was associated with a 2-g (95% CI, 0 to 3 g) higher offspring birth weight per maternal BMI-raising allele (P = .008). The maternal genetic scores for fasting glucose and SBP were also associated with birth weight with effect sizes of 8 g (95% CI, 6 to 10 g) per glucose-raising allele (P = 7 × 10⁻¹⁴) and -4 g (95% CI, -6 to -2 g) per SBP-raising allele (P = 1 × 10⁻³⁵), respectively. A 1-SD (≈ 4 points) genetically higher maternal BMI was associated with a 55-g higher offspring birth weight (95% CI, 17 to 93 g). A 1-SD (≈ 7.2 mg/dL) genetically higher maternal fasting glucose concentration was associated with 114-g higher offspring birth weight (95% CI, 80 to 147 g). However, a 1-SD (≈ 10 mm Hg) genetically higher maternal SBP was associated with a 208-g lower offspring birth weight (95% CI, -394 to -21 g). For BMI and fasting glucose, genetic associations were consistent with the observational associations, but for systolic blood pressure, the genetic and observational associations were in opposite directions.

CONCLUSIONS AND RELEVANCE In this mendelian randomization study, genetically elevated maternal BMI and blood glucose levels were potentially causally associated with higher offspring birth weight, whereas genetically elevated maternal SBP was potentially causally related to lower birth weight. If replicated, these findings may have implications for counseling and managing pregnancies to avoid adverse weight-related birth outcomes.


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Neonates born to overweight or obese women are more likely to be large for gestational age. The precise mechanisms underlying this association and the extent to which confounding factors contribute are poorly understood. It is important to understand which maternal traits are causally associated with birth weight because this may facilitate targeted development of interventions to be tested in randomized clinical trials and enable clear, evidence-based recommendations for pregnant women.

Maternal overweight and obesity are key risk factors for gestational diabetes. Even in the absence of diabetes and when following the same controlled diet, obese women have higher glucose levels than normal-weight women. The association between gestational diabetes and higher birth weight is well documented. Maternal glucose levels below those diagnostic of diabetes also show strong associations with birth weight.

The fetus of an overweight or obese woman may be exposed to the consequences of higher maternal triglyceride levels and blood pressure, lower levels of high-density lipoprotein cholesterol (HDL-C) and adiponectin, and lower vitamin D status (Box 1). However, associations are not always consistently observed and may be confounded by maternal socioeconomic status and associated behaviors such as smoking and diet. Furthermore, the high intercorrelation of obesity-related traits complicates determination of causal relationships in an observational setting.

Maternal genotypes may be used in a mendelian randomization approach to provide evidence of a potential causal association between maternal traits and birth outcomes (Figure 1). Mendelian randomization is analogous to a randomized clinical trial: genotypes, which are randomly allocated at conception, are largely free from confounding and can be used to estimate the possible causal effects of maternal traits. In this study, genetic variants were selected to calculate genetic scores representing maternal body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) and each of 7 obesity-related maternal traits. The potential causal relationship between maternal BMI and each related trait was estimated by testing associations between maternal genetic risk scores and offspring birth weights.

Methods

Study Participants

Single-nucleotide polymorphism (SNP) genotype data were used from 30,487 women participating in 18 population- or community-based studies in Europe, North America, or Australia. The birth weight of 1 child per mother was included (see eTable 1 for full details of participant characteristics and eTable 2 for genotyping information, both in the Supplement). Birth weight was measured by trained study personnel (n = 2 studies), from medical records (n = 10 studies), or from maternal report (n = 6 studies). The offspring years of birth were from 1929 to 2013. Multiple births, stillbirths, congenital anomalies, births before 37 weeks’ gestation, and individuals of non-European ancestry were excluded. Informed consent was obtained from all participants, and study protocols were approved by the local, regional, or institutional ethics committees.

Selection of Maternal Obesity-Related Traits and SNPs

In addition to BMI, traits were selected that are associated with maternal obesity and may affect fetal growth through the intrauterine environment. Their effects were modeled in the directions hypothesized by their relationships to maternal BMI (Box 1).

Single-nucleotide polymorphisms known to be robustly associated (P < 5 × 10⁻⁸) with BMI and each obesity-related trait were selected. Full details of the selected SNPs are provided in eTable 3 in the Supplement. Single-nucleotide polymorphisms associated with fasting glucose and type 2 diabetes were used to represent maternal glycemia. The type 2 diabetes SNPs were considered to represent exposure to maternal diabetes in pregnancy, including gestational diabetes, given overlap between type 2 and gestational diabetes’ genetic susceptibility variants. For blood pressure, SNPs were selected that are primarily associated with systolic blood pressure (SBP), although all also show strong evidence of association with diastolic blood pressure. For vitamin D status, 2 SNPs with hypothesized roles in vitamin D synthesis were used to represent 25(OH)D levels (an indicator of overall vitamin D status), as previously recommended. Further details of SNP selection are provided in the eMethods in the Supplement.

A weighted genetic score was calculated for each maternal trait (see eMethods in the Supplement for full details). Very few of the selected SNPs have been tested in pregnancy. Genetic scores were validated by confirming that each was associated with its respective maternal trait, measured during pregnancy (with the exception of BMI, for which the prepregnancy value was used). Maternal prepregnancy BMI was available from registry data (n = 2 studies) or calculated from self-reported weight and height (n = 3 studies). In the Avon Longitudinal Study of Parents and Children (ALSPAC) study, the self-report was validated with a clinic measure. Details of...

Box 1. Maternal Traits That May Affect Her Fetus

Maternal Traits Hypothesized to Increase Fetal Growth

- Higher body mass index
- Higher fasting glucose
- Gestational or type 2 diabetes
- Higher triglycerides
- Lower high-density lipoprotein cholesterol
- Lower adiponectin

Maternal Traits Hypothesized to Decrease Fetal Growth

- High blood pressure
- Lower vitamin D status

The maternal obesity-related traits hypothesized to cause increased or decreased fetal growth, based on observational associations with birth weight: Body mass index (BMI), fasting glucose, gestational or type 2 diabetes, triglycerides, HDL cholesterol, systolic blood pressure, vitamin D status (as indicated by 25-hydroxyvitamin D, 25(OH)D levels), adiponectin.
traits measured in pregnancy and their sources are given in eTable 4 in the Supplement. In each available study, linear regression of the maternal trait (eg, BMI) against the genetic score was performed, adjusting for maternal age. To confirm that associations between each genetic score and its respective maternal trait were similar in the same individuals during and after pregnancy, available data were used from 2 longitudinal studies (ALSPAC and the Exeter Family Study of Childhood Health [EFSOCCH]). To check that the strategy for SNP selection had resulted in genetic scores that were specific to each maternal trait, the association was tested between each of the 8 genetic scores and each maternal trait in addition to indicators of maternal socioeconomic status and smoking.

**Analyses of Maternal Obesity-Related Traits and Birth Weight**

For BMI and each related maternal trait, 2 mendelian randomization approaches were used to test the hypothesis that the trait was causally related to birth weight. First, associations were tested between genetic scores representing maternal traits and offspring birth weight using the maximum number of participants (ie, for each trait, those with genetic score and offspring birth weight data available, irrespective of whether they had the maternal trait measured). An association of the genetic score with birth weight would support a possible causal relationship between the trait (eg, prepregnancy BMI) and birth weight but would not provide information on the size of that association. Second, we performed analyses in those with the measured trait that enabled an estimate of the size of a possible causal relationship. The analyses took into account the association between each genetic score and the maternal trait it represented (eg, BMI), in addition to the association between the same genetic score and birth weight. These 2 results were used to calculate an association between the maternal trait (eg, BMI) and birth weight that was free from confounding. This second approach measures the relationship between variation in maternal BMI (or BMI-related trait) and birth weight that is attributable only to genetic factors (see Figure 1 for an explanation of the method). For each approach, meta-analysis was used to combine data from individual studies (see eMethods in the Supplement).

Using the first approach, we investigated the association between each genetic score and (1) birth weight and (2) ponderal index (an index of neonatal leanness, calculated as birth weight in kilograms divided by birth length in meters cubed). Within each study, birth weight or ponderal index Z scores were regressed against each maternal genetic score, adjusted for offspring sex and gestational age. Analyses using the type 2 diabetes genetic score were repeated after excluding participants with preexisting and gestational diabetes. Analyses using the SBP genetic score were repeated after excluding participants with preeclampsia and existing or gestational hypertension.

The genetic estimate of the association between each maternal trait and birth weight or ponderal index from the second approach was compared with the corresponding observational association. To obtain the observational estimates, linear regression was performed using birth weight or ponderal index as the dependent variable, and each of 7 maternal traits as independent variables, adjusting for sex and gestational age. There was insufficient information on maternal type 2 diabetes prevalence, so it was not possible to estimate the causal relationship for that trait. Full details of the analysis are provided in the eMethods (in the Supplement).

**Maternal BMI, Birth Weight, and Fasting Glucose**

To estimate how much the association between maternal BMI and birth weight might be mediated by fasting glucose, available data were used first to estimate the approximate causal relationship between a 1-SD higher maternal BMI (≈4 points) and (1) fasting glucose and (2) SBP. Then, using each of these estimates, the results of the mendelian randomization analyses were rescaled to represent the effects of fasting glucose and SBP that could be directly compared with the causal relationship between a 1-SD higher maternal BMI and birth weight (see eMethods in the Supplement for a detailed description of the method).

**Correcting for Direct Fetal Genotype Effects**

Genotypes of maternal-fetal pairs were available in up to 8 studies (total for analysis, 11,493). Analyses were repeated including the fetal genotype at each SNP in the model to correct for potential confounding caused by direct effects of the fetal genotype. A 2-sided P value <.05 was considered to provide evidence against the null hypothesis. Statistical software used for data analysis within each individual study is detailed in eTable 2 in the Supplement. All meta-analyses were performed using Stata v.13 (StataCorp).
Results

The characteristics of included participants from the 18 contributing studies are shown in Table 1. Among the 30,487 newborns the mean birth weight ranged from 3325 g to 3679 g. The mean prepregnancy BMI was available in 11 studies and ranged from 22.78 to 24.83. The mean maternal age at delivery, available in 16 studies, ranged from 24.5 years to 31.5 years.

<table>
<thead>
<tr>
<th>Sourcea</th>
<th>Study</th>
<th>Country</th>
<th>Offspring Years of Birth</th>
<th>No. of Women With Birth Weight for ≥1 Child</th>
<th>No. of Offspring With Genotype</th>
<th>Mean (SD) Maternal Age at Delivery, y</th>
<th>Maternal Prepregnancy BMI</th>
<th>Offspring Birth Weight, g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraser et al,33 2013</td>
<td>ALSPAC United Kingdom</td>
<td>1991-1992</td>
<td>7304</td>
<td>4913</td>
<td>28.5 (4.8)</td>
<td>22.93 (3.73)</td>
<td>NA</td>
<td>3481 (475)</td>
</tr>
<tr>
<td>Schlemm et al,34 2010</td>
<td>BBC Germany</td>
<td>2000-2004</td>
<td>1357</td>
<td>1357</td>
<td>30.1 (5.4)</td>
<td>22.78 (3.93)</td>
<td>NA</td>
<td>3472 (511)</td>
</tr>
<tr>
<td>Power and Elliott,35 2006</td>
<td>BSBC-WTCCC United Kingdom</td>
<td>1972-2000</td>
<td>855</td>
<td>NA</td>
<td>26.2 (5.2)</td>
<td>NA</td>
<td>3325 (483)</td>
<td></td>
</tr>
<tr>
<td>Power and Elliott,35 2006</td>
<td>BSBC-T1DGC United Kingdom</td>
<td>1972-2000</td>
<td>836</td>
<td>NA</td>
<td>26.1 (5.4)</td>
<td>NA</td>
<td>3379 (469)</td>
<td></td>
</tr>
<tr>
<td>Zhao H et al,36 2009</td>
<td>CHOP United States</td>
<td>1987-Present</td>
<td>312</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3440 (562)</td>
<td></td>
</tr>
<tr>
<td>Nohr et al,38 2009</td>
<td>DNBC-GOYA Denmark</td>
<td>1996-2002</td>
<td>1805</td>
<td>NA</td>
<td>29.2 (4.2)</td>
<td>23.57 (4.27)</td>
<td>NA</td>
<td>3643 (495)</td>
</tr>
<tr>
<td>Olsen et al,39 2001</td>
<td>DNBC-PTB-CONTROL Denmark</td>
<td>1987-2009</td>
<td>1649</td>
<td>975</td>
<td>29.9 (4.2)</td>
<td>23.57 (4.27)</td>
<td>NA</td>
<td>3595 (497)</td>
</tr>
<tr>
<td>Knight et al,40 2004</td>
<td>EPSOCH United Kingdom</td>
<td>2000-2004</td>
<td>746</td>
<td>332b</td>
<td>30.5 (5.3)</td>
<td>24.07 (4.42)</td>
<td>NA</td>
<td>3512 (480)</td>
</tr>
<tr>
<td>Lacroix et al,41 2013</td>
<td>GEN-3G Canada</td>
<td>2010-2013</td>
<td>676</td>
<td>NA</td>
<td>28.4 (4.4)</td>
<td>24.83 (5.63)</td>
<td>NA</td>
<td>3448 (433)</td>
</tr>
<tr>
<td>Jaddoe et al,42 2012</td>
<td>Generation R The Netherlands</td>
<td>2002-2006</td>
<td>3810</td>
<td>2196</td>
<td>31.2 (4.5)c</td>
<td>23.12 (3.92)</td>
<td>NA</td>
<td>3528 (494)</td>
</tr>
<tr>
<td>Metzger et al,5 2008 (GWAS)d</td>
<td>HAPO United Kingdom, Canada, Australia</td>
<td>2000-2006</td>
<td>1380</td>
<td>1300</td>
<td>31.5 (3.3)c</td>
<td>24.5 (5.0)</td>
<td>NA</td>
<td>3557 (517)</td>
</tr>
<tr>
<td>Metzger et al,5 2008 (non-GWAS)d</td>
<td>HAPO United States, United Kingdom, Canada, Australia</td>
<td>2000-2006</td>
<td>3590</td>
<td>2318</td>
<td>30.4 (5.4)c</td>
<td>24.63 (5.33)</td>
<td>NA</td>
<td>3526 (463)</td>
</tr>
<tr>
<td>Mangus et al,43 2006</td>
<td>MoBa Norway</td>
<td>1999-2008</td>
<td>650</td>
<td>350</td>
<td>28.5 (3.3)</td>
<td>23.93 (3.94)</td>
<td>NA</td>
<td>3679 (430)</td>
</tr>
<tr>
<td>Rantakallio,44 1969</td>
<td>NFBC1966 Finland</td>
<td>1987-2001</td>
<td>2035</td>
<td>NA</td>
<td>26.5 (3.7)</td>
<td>NA</td>
<td>3525 (461)</td>
<td></td>
</tr>
<tr>
<td>Boomsma et al,45 2006</td>
<td>NTR The Netherlands</td>
<td>1946-2003</td>
<td>706</td>
<td>NA</td>
<td>27.1 (3.7)</td>
<td>NA</td>
<td>3469 (529)</td>
<td></td>
</tr>
<tr>
<td>Medland et al,46 2009</td>
<td>QIMR Australia</td>
<td>1929-1990</td>
<td>892</td>
<td>NA</td>
<td>24.5 (4.0)</td>
<td>22.79 (5.13)</td>
<td>NA</td>
<td>3344 (532)</td>
</tr>
<tr>
<td>Naitaturu et al,47 2013; Moayyeri et al,48 2013</td>
<td>TwinsUK United Kingdom</td>
<td>2013-2013</td>
<td>1602</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3365 (581)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children; BBC, Berlin Birth Cohort; BSBC-WTCCC, 1958 British Birth Cohort-Wellcome Trust Case Control Consortium; BSBC-T1DGC, 1958 British Birth Cohort-Non-Diabetic Genetics Consortium; CHOP, Children's Hospital of Philadelphia; DNBC-GOYA, Danish National Birth Cohort-Genetics of Obesity in Young Adults study; DNBC-PTB-CONTROLS, Danish National Birth Cohort Preterm Birth; EPSOCH, Exeter Family Study of Childhood Health; GEN-3G, Genetics of Glycemic Regulation in Gestation and Growth; HAPO, Hyperglycemia and Adverse Pregnancy Outcome; MoBa, the Norwegian Mother and Baby Cohort; NA, not available; NFBC1966, the Northern Finland 1966 Birth Cohort; NTR, Netherlands Twin Registry; QIMR, Queensland Institute of Medical Research.

* For full details, see eTable 1 in the Supplement.

b Fetal genotype in EPSOCH available only for the fasting glucose genetic score.

c In Generation R, maternal age was recorded, on average, at 14.4 weeks of gestation; in HAPO, maternal age was recorded, on average, at 28 weeks of gestation.

d Genome-wide association study.

There was evidence of an association between each genetic score and its corresponding maternal trait measured in pregnancy (P ≤ .003; Table 2). For BMI, fasting glucose, and SBP, data from multiple studies were meta-analyzed, with similar effect estimates among studies for BMI and fasting glucose (P for heterogeneity > .05) and evidence of heterogeneity for SBP (P for heterogeneity = .04). The effect sizes of associations between maternal traits and their respective genetic scores were very similar when compared in the same in-
Table 2. Associations Between Maternal Genetic Scores and Maternal Obesity-Related Traits

<table>
<thead>
<tr>
<th>Sourcea</th>
<th>No. of Studies</th>
<th>Maternal Obesity-Related Trait</th>
<th>No. of SNPs for Genetic Score</th>
<th>Estimate of % Variance Explanied by Genetic Score in Pregnant Womenb</th>
<th>No. of Women With Traits Measured During Pregnancyc</th>
<th>Estimated Change in Maternal Trait per Average Weighted Trait-Raising or Lowering (95% CI)d</th>
<th>P Value</th>
<th>P for Heterogeneitye</th>
<th>P%, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speliotes et al,49 2010</td>
<td>5</td>
<td>Prepregnancy BMI</td>
<td>30</td>
<td>1.8, ALSPAC</td>
<td>11 822</td>
<td>0.145 (0.126 to 0.164)</td>
<td>&lt;2 × 10−16</td>
<td>.18</td>
<td>35.8</td>
</tr>
<tr>
<td>Dupuis et al,50 2010</td>
<td>3</td>
<td>Higher fasting glucose mg/dL</td>
<td>13</td>
<td>5, EFSOCH</td>
<td>5402</td>
<td>0.52 (0.45-0.58)</td>
<td>&lt;2 × 10−16</td>
<td>.70</td>
<td>0</td>
</tr>
<tr>
<td>Morris et al,51 2012</td>
<td>1</td>
<td>Higher gestational and existing diabetes, mg/dL</td>
<td>55</td>
<td>1.4, ALSPAC</td>
<td>6600a</td>
<td>OR, 1.08 (1.03 to 1.14)</td>
<td>.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teslovich et al,52 2010</td>
<td>1</td>
<td>Higher triglycerides, mg/dL</td>
<td>17</td>
<td>3, EFSOCH</td>
<td>663</td>
<td>4.9 (2.8 to 6.9)</td>
<td>3 × 10−6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teslovich et al,52 2010</td>
<td>1</td>
<td>Lower HDL-C, mg/dL</td>
<td>4</td>
<td>3, EFSOCH</td>
<td>733</td>
<td>−1.9 (−2.8 to −1.0)</td>
<td>1 × 10−5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ehret et al,53 2010</td>
<td>2</td>
<td>Higher SBP mm Hg</td>
<td>33</td>
<td>1, ALSPAC</td>
<td>8450</td>
<td>0.186 (0.140 to 0.231)</td>
<td>&lt;2 × 10−16</td>
<td>.04</td>
<td>76.0</td>
</tr>
<tr>
<td>Vimaleswaran et al,54 2013</td>
<td>1</td>
<td>Lower vitamin D, log transformedd</td>
<td>2</td>
<td>0.2, ALSPAC</td>
<td>4767</td>
<td>−0.024 (−0.039 to −0.009)</td>
<td>.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yaghootkar et al,55 2013</td>
<td>1</td>
<td>Lower adiponectin, log transformed</td>
<td>3</td>
<td>2, HAPO</td>
<td>1376</td>
<td>−0.17 (−0.23 to −0.11)</td>
<td>1 × 10−11</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; EFSOCH, Exeter Family Study of Childhood Health; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio; SBP, systolic blood pressure; SNP, single-nucleotide polymorphism.

a Except BMI, for which the appropriate measurement is before pregnancy.

b Estimated change in maternal trait per unit change in the genetic score. The genetic score for each maternal trait was modeled according to its known direction of association with higher BMI (see column 4, above, and the Box). The association was 145 g (95% CI, 91-199 g) (Table 4).

c Evidence of heterogeneity among studies was estimated when more than 1 study contributed to the analysis.

d Removing the 1 study in which the rs10830963 SNP was poorly imputed (i2 < 0.8), we obtained very similar results (n = 4026; effect size = 0.028 (95% CI, 0.024-0.032); P < 2 × 10−16; P for heterogeneity = 0.46; f2 = 0%).

e Fifty-four cases, 6552 controls.

f The 2 SNPs selected for the vitamin D genetic score have a hypothesized role in the synthesis of vitamin D (as opposed to its metabolism) and are recommended for use in mendelian randomization studies.56,57

Although the association between maternal BMI and birth weight may have been influenced by fetal genotype, the effect remained after excluding preexisting and gestational diabetes. Using the genetic score to estimate the possible causal relationship, a 1-SD (7.2 mg/dL) of genetically higher maternal glucose was associated with a 114-g higher birthweight (95% CI, 80-147 g) (Figure 2). Similar results were obtained for ponderal index (eTable 8 and eFigure 1 in the Supplement).

Higher Maternal Fasting Glucose, Higher Birth Weight

The maternal fasting glucose and type 2 diabetes genetic scores were associated with higher birth weight (Table 3) and ponderal index (eTable 7 in the Supplement) with similar effect size estimates before and after adjusting for fetal genotype and before and after excluding preexisting and gestational diabetes. Using the genetic score to estimate the possible causal relationship, a 1-SD (7.2 mg/dL) of genetically higher maternal glucose was associated with a 114-g higher birth weight (95% CI, 80-147 g). After adjusting for fetal genotype, the association was 145 g (95% CI, 91-199 g) (Table 4). These genetic estimates were similar to the observational association of 92 g (95% CI, 80-104 g) per each SD higher maternal glucose (7.2 mg/dL) (Figure 2). Similar results were obtained for ponderal index (eTable 8 and eFigure 1 in the Supplement).
Table 3. Associations Between Maternal Genetic Scores and Birth Weight of Offspring

<table>
<thead>
<tr>
<th>Maternal Trait</th>
<th>No. of Studies</th>
<th>No. of Women</th>
<th>Estimate Change in Offspring Birth Weight per Maternal Trait-Raising/Lowering Allele Change (95% CI), to the Nearest g</th>
<th>P Value</th>
<th>P for Heterogeneity</th>
<th>I²</th>
<th>P for Heterogeneity</th>
<th>I²</th>
<th>P for Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher Prepregnancy BMI</td>
<td>16</td>
<td>25265</td>
<td>2 (0 to 3)</td>
<td>.008</td>
<td>.84</td>
<td>0</td>
<td>7</td>
<td>10964</td>
<td>(1 to 6)</td>
</tr>
<tr>
<td>Higher fasting glucose</td>
<td>15</td>
<td>23902</td>
<td>8 (6 to 10)</td>
<td>7 × 10⁻⁴</td>
<td>.11</td>
<td>33.3</td>
<td>8</td>
<td>11493</td>
<td>(7 to 14)</td>
</tr>
<tr>
<td>Higher odds of type 2 diabetes</td>
<td>12</td>
<td>18670</td>
<td>2 (0 to 2)</td>
<td>.06</td>
<td>.22</td>
<td>23.1</td>
<td>5</td>
<td>7769</td>
<td>(2 to 6)</td>
</tr>
<tr>
<td>Higher trilglycerides</td>
<td>15</td>
<td>24985</td>
<td>2 (1 to 3)</td>
<td>.02</td>
<td>.92</td>
<td>0</td>
<td>4</td>
<td>6210</td>
<td>(1 to 6)</td>
</tr>
<tr>
<td>Lower HDL-C</td>
<td>15</td>
<td>22167</td>
<td>0 (0 to 3)</td>
<td>.12</td>
<td>.83</td>
<td>0</td>
<td>6</td>
<td>11031</td>
<td>(0 to 6)</td>
</tr>
<tr>
<td>Higher SBP</td>
<td>13</td>
<td>20062</td>
<td>−4 (−6 to −2)</td>
<td>1 × 10⁻⁵</td>
<td>.14</td>
<td>30.4</td>
<td>5</td>
<td>7790</td>
<td>(−6 to 0)</td>
</tr>
<tr>
<td>Higher SBP</td>
<td>7</td>
<td>13271</td>
<td>−5 (−7 to −3)</td>
<td>6 × 10⁻⁶</td>
<td>.18</td>
<td>32.4</td>
<td>4</td>
<td>5488</td>
<td>(−8 to 0)</td>
</tr>
<tr>
<td>Lower vitamin D status</td>
<td>18</td>
<td>30340</td>
<td>−6 (−12 to 0)</td>
<td>.03</td>
<td>.13</td>
<td>37.1</td>
<td>3</td>
<td>9510</td>
<td>(−25 to 3)</td>
</tr>
<tr>
<td>Lower adiponectin</td>
<td>9</td>
<td>14920</td>
<td>−2 (−16 to 12)</td>
<td>.76</td>
<td>.90</td>
<td>0</td>
<td>5</td>
<td>7820</td>
<td>(−16 to 10)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure.

*Estimated change in offspring birth weight per unit change in the maternal genetic score (with sex, gestational age and fetal genotype as covariates).

**Adjusted for fetal genotype.

†Excluding preexisting and gestational diabetes.

‡Excluding preclampsia and hypertension.

§Excluding preeclampsia and hypertension.
logically higher maternal BMI was associated with a 0.34 SD (≈ 2.5 mg/dL) higher maternal fasting glucose. From the mendelian randomization analyses, a 1-SD genetically higher maternal fasting glucose was associated with a 114 g higher birth weight (95% CI, 80-147 g). Consequently, it was predicted that a 0.34-SD higher fasting glucose would be associated with a 114 g × 0.34 = 39 g; (95% CI, 27-50 g) higher birth weight. This approximation is broadly similar to the total estimated effect of an SD higher BMI on birth weight (55 g; 95% CI, 17-93 g). However, using the same method with the BMI and SBP genetic scores, we estimated that an SD higher maternal BMI would be associated with a −40 g (95% CI, −75 to −4) lower birth weight via its association with maternal SBP (eFigure 2 in the Supplement), which would oppose the positive association with maternal fasting glucose.

Discussion

This study provides evidence for a possible causal association between maternal BMI and offspring birth weight. A genetically higher maternal BMI of 4 points was associated with a 55 g (95% CI, 17-93 g) higher offspring birth weight. In addition, a genetically higher circulating maternal fasting glucose of 7.2 mg/dL was associated with a 114 g (95% CI, 80-147 g) higher birth weight, whereas genetically higher maternal SBP of 10 mm Hg was associated with a −208 g (95% CI, −394 to −21 g) lower birth weight. These results provide evidence that genetically elevated maternal glucose and SBP may have directionally opposite causal associations with birth weight. The estimated associations between these maternal traits and birth weight (either increased or reduced) are substantial and of clinical importance. They support efforts to maintain healthy gestational glucose and blood pressure levels to ensure healthy fetal growth. The positive association between maternal BMI and birth weight may be partially mediated by the effect of higher BMI on circulating maternal fasting glucose. There was no evidence of association of offspring birth weight with a genetic score for maternal triglycerides, which have also been hypothesized to be important contributors to higher birth weight in overweight or obese women. Other lipids, or specific subclasses of triglycerides, might be important but require further study.

These results provide genetic evidence of a potentially causal association between maternal glycemia and birth weight and ponderal index, even in women with no preexisting or gestational diabetes, which is consistent with published observational data. A possible explanation for this finding is that women with a higher genetic score for type 2 diabetes have relatively higher glucose levels in pregnancy, as a result of inadequate beta-cell compensation in response to gestational insulin resistance, leading to increased placental glucose transfer and fetal insulin secretion, and consequently higher birth weight.

Table 4. Observational and Genetic Associations Between Each Maternal Trait and Offspring Birth Weight

<table>
<thead>
<tr>
<th>Study Used for Observational Estimatesa</th>
<th>Maternal Trait</th>
<th>Value of 1-SD Change in the Trait With Units</th>
<th>No. of Women for Observational Estimate</th>
<th>Observational Estimate of the Change in Birth Weight, g, per 1-SD Change in Maternal Trait, (95% CI)b</th>
<th>Genetic Estimate of the Change in Birth Weight, g, per 1-SD Change in Maternal Trait (95% CI), gc</th>
<th>P Valuea</th>
<th>Genetic Estimate of Change in Birth Weight, g, per 1-SD Change in Maternal Trait (95% CI)c</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALSPAC EFSOCH HAPO</td>
<td>Higher prepregnancy BMI</td>
<td>4 points</td>
<td>11 969</td>
<td>62 (56 to 70)</td>
<td>55 (17 to 93)</td>
<td>.70</td>
<td>104 (32 to 176)</td>
<td>.28</td>
</tr>
<tr>
<td>EFSOCH HAPO</td>
<td>Higher fasting glucose</td>
<td>7.2 mg/dL</td>
<td>6008</td>
<td>92 (80 to 104)</td>
<td>114 (80 to 147)</td>
<td>.28</td>
<td>145 (91 to 199)</td>
<td>.09</td>
</tr>
<tr>
<td>EFSOCH</td>
<td>Higher triglycerides</td>
<td>6.19 mg/dL</td>
<td>930</td>
<td>32 (7 to 56)</td>
<td>−24 (−55 to 8)</td>
<td>.007</td>
<td>−33 (−66 to 20)</td>
<td>.03</td>
</tr>
<tr>
<td>EFSOCH</td>
<td>Lower HDL-C</td>
<td>19.3 mg/dL</td>
<td>927</td>
<td>30 (3 to 58)</td>
<td>0 (−33 to 34)</td>
<td>.17</td>
<td>−1 (−55 to 54)</td>
<td>.32</td>
</tr>
<tr>
<td>ALSPAC HAPO</td>
<td>Lower SBP</td>
<td>10 mm Hg</td>
<td>12 077</td>
<td>24 (15 to 34)</td>
<td>−208 (−394 to −21)</td>
<td>.01</td>
<td>−151 (−390 to 89)</td>
<td>.14</td>
</tr>
<tr>
<td>ALSPAC</td>
<td>Lower vitamin D5d</td>
<td>10%</td>
<td>4710</td>
<td>−4 (−7 to −2)</td>
<td>−26 (−54 to 2)</td>
<td>.13</td>
<td>−56 (−112 to 1)</td>
<td>.07</td>
</tr>
<tr>
<td>HAPO</td>
<td>Lower adiponectinb</td>
<td>10%</td>
<td>1376</td>
<td>14 (9 to 18)</td>
<td>−1 (−9 to 7)</td>
<td>.002</td>
<td>4 (−9 to 17)</td>
<td>.19</td>
</tr>
</tbody>
</table>
These data did not support a causal association between maternal triglyceride, HDL-C or adiponectin levels and birth weight or ponderal index. The genetic associations between maternal triglycerides and adiponectin and birthweight were null, in contrast to the observational associations, suggesting that the observational associations seen herein, and in other published studies, are confounded.

The mendelian randomization analysis showed that the positive observational association between SBP and birth weight is confounded, most likely by BMI, which is both an important risk factor for higher SBP in pregnancy and positively associated with birth weight. Using genetic variants that are independent of confounding by BMI, genetically higher maternal SBP was associated with lower birth weight, even after excluding preeclampsia and hypertension. The precision of our estimate of the change in birth weight per 1 SD in maternal SBP could be affected by the heterogeneity between studies in the genetic score-SBP association ($P = .04$, $I^2 = 76.0\%$; Table 2). However, associations between the SBP genetic score and birth weight were consistent across all 13 meta-analyzed studies ($P = .14$, $I^2 = 30.4\%$; Table 3) and supportive of a causal association between higher maternal SBP and lower birth weight. These findings support observational associations between maternal SBP and birth weight that were adjusted for a wide range of confounders and are consistent with laboratory and population studies suggesting a link between hypertensive disorders of pregnancy and impaired fetal growth due to placental pathology. There are increasing concerns about the effect the obesity epidemic might have on birth size, via greater maternal BMI. However, the focus of that concern has been largely
on increased birth size as a result of greater maternal glucose and other fetal nutrients. Our findings suggest that there may be opposing effects of maternal blood pressure and glucose.

Published mendelian randomization analyses provide evidence that higher BMI is causally associated with lower vitamin D status, and evidence from multiple observational studies suggests that lower maternal vitamin D is associated with lower birth weight. Our analysis of the vitamin D genetic score provided some evidence to support a possible causal association with birth weight, but this requires further exploration in larger numbers of pregnancies.

Socioeconomic factors and related behaviors such as smoking are key confounders of observational associations between maternal BMI (or BMI-related traits) and offspring birth weight, since they are associated with both variables (see eTable 9 in Supplement for a demonstration of these associations in the ALSPAC study). The genetic scores used in our analyses were not associated with socio-economic factors or smoking, and this illustrates a key strength of the mendelian randomization approach: since genotypes are determined at conception, such confounding is avoided.

There are some limitations to this study. Despite attempts to maximize specificity of the genetic scores, we cannot fully exclude the possibility that the selected genetic variants act on more than one maternal trait. Although all available information was used, there was limited power to detect associations between the genetic scores and other traits. For example, the known association between BMI-associated variants and triglyceride levels was not detected. With the potential for high-throughput metabolomic studies and a growing public database of genetic associations, future studies will likely improve the specificity (for different lipid subfractions) of selected genetic variants.

Despite the large sample in this study, statistical power to detect potentially causal relationships was limited for some maternal traits (see eMethods and eTable 10 in Supplement for power calculations). The total sample provided more than 99% power to detect associations at $P < .05$ between birth weight and genetic scores such as fasting glucose and systolic blood pressure that explain at least 0.1% variance in birth weight. However, larger samples (+80 000) will be needed to confidently detect or rule out the association with vitamin D status suggested by our data, or smaller positive or negative causal associations between maternal triglycerides, HDL-C or adiponectin and birth weight.

Although adjusting for the fetal genetic scores was necessary to separate maternal effects from the direct effects of genetic variants in the fetus, this could introduce bias via association with paternal genotypes. Assortative mating for BMI could additionally result in a correlation between maternal and paternal genotypes, leading to similar bias. However, a father’s genetic score would only confound the mendelian randomization estimates if the father’s phenotype were related to birth weight, and we found only very weak associations of fathers BMI and related traits with offspring birth weight (eTable 11 in Supplement). Another potential bias could be induced by the use of the genetic score for SBP, which was derived from a genome-wide association study of blood pressure condition on BMI. Because BMI is also associated with birth weight, this could bias the results. However, similar results were obtained using an alternative genetic score that was unadjusted for BMI (eMethods).

In mendelian randomization analysis, a weak statistical association between a genetic score and a maternal trait (due to low variance explained or small sample size) has the potential to cause weak instrument bias toward the observational results. The proportions of maternal trait variance explained by the genetic scores are modest in our study (Table 2). However, the large overall sample size ensured that the possible causal associations identified are unlikely to be due to weak instrument bias (see eMethods).

Our analyses assume that maternal BMI and related traits are linearly associated with offspring birth weight. We have not tested for nonlinear associations which, in a mendelian randomization design, would require very large numbers. However, for maternal BMI, fasting glucose and SBP, there is observational evidence of such linear associations across the distribution, with no evidence of threshold or curvilinear associations.

Conclusions

In this mendelian randomization study, genetically elevated maternal BMI and blood glucose levels were potentially causally associated with higher offspring birth weight, whereas genetically elevated maternal SBP was potentially causally related to lower birth weight. If replicated, these findings may have implications for counseling and managing pregnancies to avoid adverse weight-related birth outcomes.
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REFERENCES


17. Vimalessarwan KS, Cavadino A, Berry DJ, et al; LifeLines Cohort Study Investigators; International Consortium for Blood Pressure (ICBP); Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium; Global Blood Pressure Genetics (Global BPGen) consortium; Caroline Hayward. Association of vitamin D status with arterial blood pressure and hypertension risk: a mendelian randomisation study. Lancet Diabetes Endocrinol. 2014;2(9):719-729.


