Original Investigation

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 ($P = 7 \times 10^{-14}$) and −4 g (95% CI, −6 to −2g) per SBP-raising allele ($P = 1 \times 10^{-5}$), 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.[1] 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.[2] Even in the absence of diabetes and when following the same controlled diet, obese women have higher glucose levels than normal-weight women.[3] The association between gestational diabetes and higher birth weight is well documented.[4] Maternal glucose levels below those diagnostic of diabetes also show strong associations with birth weight.[5]

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**).[1,6,7] 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[13,14] 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.

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)[1]; fasting glucose[5]; gestational or type 2 diabetes[32]; triglycerides[9]; HDL-cholesterol[8]; systolic blood pressure[10]; vitamin D status (as indicated by 25-hydroxyvitamin D, 25[OH]D level)[11]; adiponectin.[12]

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 ($P < 5 \times 10^{-8}$) 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.[15] 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.[16,17] 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.[18] Details of

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 [EFSOCH]). 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.

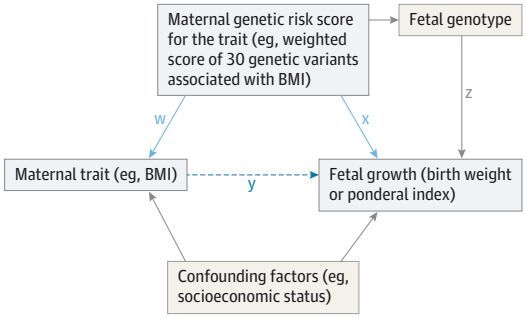
Analyses of Maternal Obesity-Related Traits and Birth Weight

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).

Figure 1. Principle of Mendelian Randomization



If a maternal trait causally influences offspring birth weight, then a risk score of genetic variants associated with that trait will also be associated with birth weight. Because genotype is determined at conception, it should not be associated with factors that normally confound the association between maternal traits and birth weight (eg, socioeconomic status). Estimates of the genetic score–maternal phenotype association (*w*) and the genetic score-birth weight association (*x*) may be used to estimate the association between the maternal trait variation that is due to genetic score and birth weight ($y = x/w$), which is expected to be free from confounding. If the estimated causal relationship, *y*, is different from the observational association between the measured maternal phenotype and birth weight, this would suggest that the observational association is confounded (assuming that the assumptions of the mendelian randomization analyses are valid).[14] The dashed line connecting maternal trait with fetal growth indicates that the causal nature of the association is uncertain. It is important to adjust for possible direct effects of fetal genotype (*z*). Body mass index is calculated as weight in kilograms divided by height in meters squared; ponderal index of neonatal leanness, calculated as birth weight in kilograms divided by birth length in meters cubed.

Maternal BMI, Birth Weight, and Fasting Glucose

To estimate how much of 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 those 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).

Table 1. Key Characteristics of Participants by Study

Source[a]	Study	Country	Offspring Years of Birth	No. of Women With Birth Weight for ≥1 Child	No. of Offspring With Genotype	Mean (SD)		
						Maternal Age at Delivery, y	Maternal Prepregnancy BMI	Offspring Birth Weight, g
Fraser et al,[33] 2013	ALSPAC	United Kingdom	1991-1992	7304	4913	28.5 (4.8)	22.93 (3.73)	3481 (475)
Schlemm et al,[34] 2010	BBC	Germany	2000-2004	1357	1357	30.1 (5.4)	22.78 (3.93)	3472 (511)
Power and Elliott,[35] 2006	B58C-WTCCC	United Kingdom	1972-2000	855	NA	26.2 (5.2)	NA	3325 (483)
Power and Elliott,[35] 2006	B58C-T1DGC	United Kingdom	1972-2000	836	NA	26.1 (5.4)	NA	3379 (469)
Zhao H et al,[36] 2009	CHOP	United States	1987-Present	312	NA	NA	NA	3440 (562)
Bisgaard,[37] 2004	COPSAC-2000	Denmark	1998-2001	282	282	30.4 (4.3)	NA	3560 (505)
Nohr et al,[38] 2009	DNBC-GOYA	Denmark	1996-2002	1805	NA	29.2 (4.2)	23.57 (4.27)	3643 (495)
Olsen et al,[39] 2001	DNBC-PTB-CONTROL	Denmark	1987-2009	1649	975	29.9 (4.2)	23.57 (4.27)	3595 (497)
Knight et al,[40]	EFSOCH	United Kingdom	2000-2004	746	332[b]	30.5 (5.3)	24.07 (4.42)	3512 (480)
Lacroix et al,[41] 2013	GEN-3G	Canada	2010-2013	676	NA	28.4 (4.4)	24.83 (5.63)	3448 (433)
Jaddoe et al, [42] 2012	Generation R	The Netherlands	2002-2006	3810	2196	31.2 (4.5)[c]	23.12 (3.92)	3528 (494)
Metzger et al,[5] 2008 (GWAS)[d]	HAPO	United Kingdom, Canada, Australia	2000-2006	1380	1300	31.5(5.3)[c]	24.5 (5.0)	3557 (517)
Metzger et al,[5] 2008 (non-GWAS)[d]	HAPO	United States, United Kingdom, Canada, Australia	2000-2006	3590	2318	30.4 (5.4)[c]	24.63 (5.33)	3526 (463)
Mangus et al,[43] 2006	MoBa	Norway	1999-2008	650	350	28.5 (3.3)	23.93 (3.94)	3679 (430)
Rantakallio,[44] 1969	NFBC1966	Finland	1987-2001	2035	NA	26.5 (3.7)	NA	3525 (461)
Boomsma et al,[45] 2006	NTR	The Netherlands	1946-2003	706	NA	27.1 (3.7)	NA	3469 (529)
Medland et al,[46] 2009	QIMR	Australia	1929-1990	892	NA	24.5 (4.0)	22.79 (5.13)	3344 (532)
Naiatteru et al,[47] 2013; Moayyeri et al,[48] 2013	TwinsUK	United Kingdom	NA	1602	NA	NA	NA	3365 (581)

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children; BBC, Berlin Birth Cohort; B58C-WTCCC, 1958 British Birth Cohort-Wellcome Trust Case Control Consortium; B58C-T1DGC, 1958 British Birth Cohort-Type 1 Diabetes 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; EFSOCH, 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.

[a] For full details, see eTable 1 in the Supplement.

[b] Fetal genotype in EFSOCH 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.

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.

There was evidence of an association between each genetic score and its corresponding maternal trait measured in pregnancy ($P \leq .003$; **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

Source[a]	No. of Studies	Maternal Obesity-Related Trait	No. of SNPs for Genetic Score	Estimate of % Variance Expalined by Genetic Score in Pregnant Women[b]	No. of Women With Traits Measured During Pregnancy[c]	Estimated Change in Maternal Trait per Average Weighted Trait-Raising or Lowering (95% CI)[d]	*P* Value	*P* for Heterogeneity[e]	I^2,%
Speliotes et al,[49] 2010	5	Prepregnancy BMI	30	1.8, ALSPAC	11 822	0.145 (0.126 to 0.164)	$<2 \times 10^{-16}$	.18	35.8
Dupuis et al,[50] 2010	3	Higher fasting glucose mg/dL[f]	13	5, EFSOCH	5402	0.52 (0.45-0.58)	$<2 \times 10^{-16}$	.70	0
Morris et al,[51] 2012	1	Higher gestational and existing diabetes, mg/dL	55	1.4, ALSPAC	6606[g]	OR, 1.08 (1.03 to 1.14)	.003		
Teslovich et al,[52] 2010	1	Higher triglycerides, mg/dL	17	3, EFSOCH	663	4.9 (2.8 to 6.9)	3×10^{-6}		
Teslovich et al,[52] 2010	1	Lower HDL-C, mg/dL	4	3, EFSOCH	733	−1.9 (−2.8 to −1.0)	1×10^{-5}		
Ehret et al,[53] 2010	2	Higher SBP mm Hg	33	1, ALSPAC	8450	0.186 (0.140 to 0.231)	$<2 \times 10^{-16}$	.04	76.0
Vimaleswaran et al,[6] 2013	1	Lower vitamin D, log transformed[h]	2	0.2, ALSPAC	4767	−0.024 (−0.039 to −0.009)	.002		
Yaghootkar et al,[54] 2013	1	Lower adiponectin, log transformed	3	2,HAPO	1376	−0.17 (−0.23 to −0.11)	1×10^{-8}		

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children[3]; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; EFSOCH, Exeter Family Study of Childhood Health[40]; HAPO, Hyperglycemia and Adverse Pregnancy Outcome study[5]; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio; SBP, systolic blood pressure; SNP, single-nucleotide polymorphism.

SI conversion factors: to convert glucose from mg/dL to mmol/L, multiply by 0.0555; HDL-C from mg/dL to mmol/L, 0.0259; triglycerides from mg/dL to mmol/L, 0.0113.

[a] Genome-wide association studies that originally identified the SNPs used in the genetic scores (studies of nonpregnant individuals).

[b] To estimate the variance in each trait explained by its respective genetic score in pregnant women, the largest available study was used. Further details about the included studies can be found in eTable 4 in the Supplement.

[c] Except BMI, for which the appropriate measurement is before pregnancy.

[d] 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).

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

[f] Removing the 1 study in which the rs10830963 SNP was poorly imputed ($r^2 < 0.8$), we obtained very similar results (n = 4026; effect size = 0.028 (95% CI, 0.024-0.032); $P < 2 \times 10^{-16}$; *P* for heterogeneity = 0.46; $I^2 = 0\%$).

[g] Fifty-four cases, 6552 controls.

[h] 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.[16,17]

dividuals during and outside pregnancy, with the exception of the SBP genetic score, which had a weaker effect during pregnancy (eTable 5 in the Supplement). There was no evidence of association between any genetic score and potentially confounding variables. No individual genetic score was associated with any of the other maternal traits, except for the genetic score for BMI, which was positively associated with SBP (*P* < .003 Bonferroni-corrected for 15 tests; eTable 6 in the Supplement).

Higher Maternal BMI and Higher Birth Weight

The maternal BMI genetic score was associated with higher birth weight (**Table 3**) and ponderal index (eTable 7 in the Supplement) with similar effect sizes before and after adjusting for possible effects of fetal genotype. Using the genetic score to quantify the possible causal association, a 1-SD genetically higher maternal BMI was associated with a 55-g higher offspring birth weight (95% CI, 17-93 g). After adjusting for fetal genotype, the estimated effect was 104-g increase (95% CI, 32-176 g) (**Table 4**). These mendelian randomization causal estimates were similar to the observational association of 62 g per SD of higher maternal BMI (95% CI, 56-70 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) 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).(To convert glucose from mg/dL to mmol/L, multiply by 0.0555.)

Table 3. Associations Between Maternal Genetic Scores and Birth Weight of Offspring

Maternal Trait for Which Genetic Score Was Contructed	No. of Studies	No. of Women	Estimate Change in Offspring Birth Weight per Maternal Trait-Raising/Lowering, Allele (95% CI), to the Nearest g[a]	*P* Value	*P* for Heterogeneity	I^2, %	No. of Studies With Fetal Genotypes	No. of Offspring with Genotypes	Estimated Change in Birth Weight, g, per Maternal Trait-Raising/Lowering Allele Change (95% CI), to the Nearest g[a,b]	*P* Value[c]	*P* for Heterogeneity[%c]	I^2, %[c]
Higher Prepregnancy BMI	16	25 265	2 (0 to 3)	.008	.84	0	7	10 964	4 (1 to 6)	.004	.20	30.5
Higher fasting glucose	15	23 902	8 (6 to 10)	7×10^{-14}	.11	33.3	8	11 493	11 (7 to 14)	7×10^{-9}	.26	21.6
Higher odds of type 2 diabetes	12	18 670	2 (0 to 2)	.06	.22	23.1	5	7769	4 (2 to 6)	.0004	.81	0
Higher odds of type 2 diabetes[d]	6	13 029	2 (1 to 3)	.02	.92	0	4	6210	4 (1 to 6)	.006	.93	0
Higher triglycerides	15	24 985	−2 (−4 to 0)	.12	.83	0	6	11 031	−2 (−7 to 1)	.21	.86	0
Lower HDL-C	15	22 167	0 (−3 to 3)	1	.52	0	6	9176	0 (−5 to 5)	.98	.85	0
Higher SBP[e]	13	20 062	−4 (−6 to −2)	1×10^{-5}	.14	30.4	5	7790	−3 (−6 to 0)	.09	.50	0
Higher SBP[e]	7	13 271	−5 (−7 to −3)	6×10^{-6}	.18	32	4	5488	−4 (−8 to 0)	.04	.16	41.2
Lower vitamin D status	18	30 340	−6 (−12 to 0)	.03	.13	37.1	3	9510	−14 (−25 to 3)	.01	.77	0
Lower adiponectin	9	14 920	−2 (−16 to 12)	.76	.90	0	5	7820	7 (−16 to 30)	.55	.71	0

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.

[a] Estimated change in offspring birth weight per unit change in the maternal genetic score (with sex and gestational age as covariates). The genetic score for each maternal trait was modeled according to its known direction of association with higher BMI (see column 2, above, and the Box). The SD of birth weight averaged over a number of European studies (484 g)[55] was used to generate these estimates from *z* scores. We considered a 2-tailed *P*<.05 to provide evidence against the null hypothesis.

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

[c] Adjusted for fetal genotypes.

[d] Excluding preexisting and gestational diabetes.

[e] Excluding preeclampsia and hypertension.

Maternal Lipids, Adiponectin, and Birth Weight

The maternal triglyceride genetic score was not associated with offspring birth weight (Table 3) or ponderal index (eTable 7 in the Supplement). Using the genetic score to estimate the possible causal relationship, a genetically higher maternal triglyceride level was not associated with offspring birth weight and the 95% CIs around the genetic estimate excluded the observational association between maternal triglycerides and birth weight (*P* = .007 testing difference between genetic and observational association; Table 4; Figure 2). Likewise, the genetic estimate of the possible effect of maternal adiponectin levels on offspring birth weight was different from the observational association (*P* = .002). The genetic score for HDL-C was not associated with birth weight or ponderal index. The analysis was consistent with no causal relationship; however, this could not be distinguished from the negative observational association between maternal HDL-C and birth weight.

Higher SBP and Lower Birth Weight

The maternal SBP genetic score was associated with lower 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 maternal preeclampsia and hypertension. Using the genetic score to estimate the possible causal relationship, 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). After adjusting for fetal genotype, the estimated effect was −151 g (95% CI, −390 to 89 g) (Table 4). The genetic estimate of the association between maternal SBP and birth weight in the full sample of women was in the opposite direction to the observational association (*P* = .01 for difference between genetic and observational associations; Table 4; Figure 2). Similar results were obtained for ponderal index (eTable 8 and eFigure 1 in the Supplement).

The maternal genetic score for lower vitamin D status was associated with lower birth weight (*P* = .03; Table 3). However, the estimated causal relationship was not significantly different from 0 (the estimated change in birth weight for a 10% genetically lower maternal 25[OH]D level was −26 g (95% CI, −54 to 2 g); Table 4, Figure 2).

Consistency Among Studies in the Meta-analysis

Associations between maternal genetic scores and offspring birth weight were similar between studies in the meta-analysis (Table 3; *P* for heterogeneity>.05). When data were combined from observational analyses, the associations between maternal fasting glucose or SBP and birth weight were similar (*P* for heterogeneity>.05), and there was evidence of heterogeneity for the BMI-birth weight observational association (Table 4; *P* for heterogeneity = .03).

Maternal BMI, Maternal Fasting Glucose, and Offspring Birth Weight

To estimate how much of the association between maternal BMI and birth weight might be mediated by fasting glucose, the BMI and fasting glucose genetic scores were used. A 1-SD

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

Study Used for Observational Estimates[a]	Maternal Trait	Value of 1-SD Change in the Trait With Units	No. of Women for Observational Estimat	Observational Estimate of the Change in Birth Weight, g, per 1-SD Change in Maternal Trait, (95% CI)[b]	Genetic Estimate of the Change in Birth Weight, g, per 1-SD Change in Maternal Trait (95% CI), g[c]	*P* Value[d]	Genetic Estimate of Change in Birth Weight, g, per 1-SD Change in Maternal Trait(95% CI)[e]	*P* Value[d]
ALSPAC EFSOCH, HAPO	Higher prepregnancy BMI	4 points	11 969	62 (56 to 70)	55 (17 to 93)	.70	104 (32 to 176)	.28
EFSOCH HAPO	Higher fasting glucose	7.2 mg/dL	6008	92 (80 to 104)	114 (80 to 147)	.28	145 (91 to 199)	.09
EFSOCH	Higher triglycerides	61.9 mg/dL	930	32 (7 to 56)	−24 (−55 to 8)	.007	−33 (−86 to 20)	.03
EFSOCH	Lower HDL-C	19.3 mg/dL	927	30 (3 to 58)	0 (−33 to 34)	.17	−1 (−55 to 54)	.32
ALSPAC HAPO	Lower SPB	10 mm Hg	12 077	24 (15 to 34)	−208 (−394 to −21)	.01	−151 (−390 to 89)	.14
ALSPAC	Lower vitamin D[b]	10%	4710	−4 (−7 to −2)	−26 (−54 to 2)	.13	−56 (−112 to 1)	.07
HAPO	Lower adiponectin[b]	10%	1376	14 (9 to 18)	−1 (−9 to 7)	.002	4 (−9 to 17)	.19

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children[33]; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; EFSOCH, Exeter Family Study of Childhood Health[40]; HAPO, Hyperglycaemia and Adverse Pregnancy Outcomes[5]; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure.

SI conversion factors: to convert glucose from mg/dL mmol/L, multiply by 0.0555; HDL-C from mg/dL to mmol/L, 0.0259; triglycerides from mg/dL to mmol/L, 0.0113.

[a] Heterogeneity statistics from the meta-analyses of observational associations were $P = .03$ and $I^2 = 67.7\%$ for BMI; $P = .09$ and $I^2 = 59.1\%$ for fasting glucose; and $P = .54$ and $I^2 = 0\%$ for SBP.

[b] No. of women included in observational analyses. (No. of women and offspring in genetic analyses is reported in Table 2 and Table 3.) Adjusted for sex and gestational age.

[c] Estimated change in birth weight per SD (or 10%) change in maternal trait (with sex and gestational age as covariates). Birth weight is adjusted for sex and gestational age. Maternal trait is unadjusted for genotype. For 25[OH]D and adiponectin, the estimated change in birth weight per 10% reduction in maternal trait level is presented because these variables were logged for analysis.

[d] *P* values, adjusted for fetal genotype, compare observational with genetic birth weight associations. *P* values <.05 are considered to indicate evidence that the genetic effect size estimate is different from the observational estimate, suggesting that the observational estimate is subject to confounding or bias.

[e] Estimated change in birth weight per SD (or 10%) genetic change in maternal trait (with sex, gestational age, and fetal genotype as covariates). The No. of offspring is the same as listed in Table 1 and Table 2.

genetically 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 a 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.

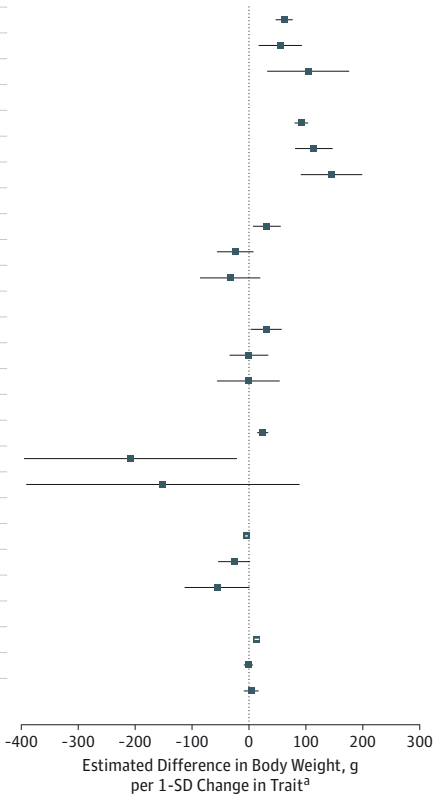
Discussion

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 brith 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.[5] 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,[19,20] leading to increased placental glucose transfer and fetal insulin secretion,[21] and consequently higher birth weight.

Figure 2. Comparison of the Observational With the Genetic Change in Birth Weight (in grams) for an SD Change in Each Maternal Obesity-Related Trait

Source	1-Standard Deviation Change in Trait[a]	No. of Studies	No. of Women	No. of Offspring Genotypes
Prepregnancy BMI				
Observational	4 points higher	3	11969	0
Genetic		16	25265	0
Genetic (adjusted for fetal genotype in subset)		7	10964	10964
Fasting glucose				
Observational	7.2 mg/dL higher	2	6008	0
Genetic		15	23902	0
Genetic (adjusted for fetal genotype in subset)		8	11493	11493
Triglycerides				
Observational	61.9 mg/dL higher	1	930	0
Genetic		15	24985	0
Genetic (adjusted for fetal genotype in subset)		6	11031	11031
HDL cholesterol				
Observational	19.3 mg/dL lower	1	927	0
Genetic		15	22167	0
Genetic (adjusted for fetal genotype in subset)		6	9176	9176
Systolic blood pressure				
Observational	10 mm Hg higher	2	12077	0
Genetic		13	20062	0
Genetic (adjusted for fetal genotype in subset)		5	7790	7790
25(OH)D				
Observational	10% lower	1	4710	0
Genetic		18	30340	0
Genetic (adjusted for fetal genotype in subset)		3	9510	9510
Adiponectin				
Observational	10% lower	1	1376	0
Genetic		9	14920	0
Genetic (adjusted for fetal genotype in subset)		5	7820	7820



[a] For 25[OH]D and adiponectin, we present the change in birth weight for a 10% change in maternal trait level because these variables were logged for analysis. The genetic change was estimated from mendelian randomization analysis, in which a genetic score was used to estimate the possible causal relationship between the maternal trait and birth weight. The genetic estimate is presented twice: in the second case it was adjusted for fetal genotype using a subset of available studies. The error bars represent the 95% CIs around the effect size estimates. For maternal prepregnancy body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) and fasting glucose, the 95% CIs for both the observational and genetic approaches exclude the null, suggesting positive possible causal relationships between maternal BMI and fasting glucose and birth weight. For maternal systolic blood pressure, the observational analysis suggested a weak positive association with birth weight, whereas the genetic analysis showed evidence of a negative possible causal relationship. Observational analyses suggested that higher maternal triglyceride levels, lower maternal adiponectin and lower maternal high-density lipoprotein (HDL) cholesterol levels were associated with higher birth weight, whereas lower maternal vitamin D status was associated with lower birth weight, but none of these was supported by the genetic analyses. To convert glucose from mg/dL to mmol/L, multiply by 0.0555; HDL-C from mg/dL to mmol/L, 0.0259; triglycerides from mg/dL to mmol/L, 0.0113.

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 birth weight were null, in contrast to the observational associations, suggesting that the observational associations seen herein, and in other published studies,[8,9,12] 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.[1] 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[22] and are consistent with laboratory and population studies suggesting a link between hypertensive disorders of pregnancy and impaired fetal growth due to placental pathology.[23] 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,[6] and evidence from multiple observational studies suggests that lower maternal vitamin D is associated with lower birth weight.[11,24] 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.[25] With the potential for high-throughput metabolomic studies and a growing public database of genetic associations,[26-28] 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 conditional 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.[29] 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.[30] 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.[5,10,31]

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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