

Association of Maternal Diabetes Mellitus in Pregnancy With Offspring Adiposity Into Early Adulthood

Sibling Study in a Prospective Cohort of 280 866 Men From 248 293 Families

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Background—Maternal diabetes mellitus in pregnancy results in greater offspring adiposity at birth. It is unclear whether it is associated with greater adiposity into adulthood, and if so, whether this is via intrauterine mechanisms or shared familial characteristics.

Methods and Results—A record-linkage prospective cohort study of 280 866 singleton-born Swedish men from 248 293 families was used to explore the intrauterine effect of maternal diabetes mellitus on offspring body mass index (BMI) in early adulthood. Maternal diabetes mellitus during pregnancy was associated with greater mean BMI at age 18 in their sons. The difference in BMI was similar within brothers and between nonsiblings. BMI of men whose mothers had diabetes mellitus during their pregnancy was on average 0.94 kg/m² greater (95% confidence interval [CI], 0.35 to 1.52) than in their brothers born before their mother was diagnosed with diabetes, after adjustment for birth year, maternal age, parity and education, birth weight, gestational age, and age at assessment of BMI. Early-pregnancy BMI was positively associated with son's BMI between nonsiblings, but there was no association within brothers. Adjustment of the maternal diabetes–offspring BMI association for maternal BMI did not alter the association either within brothers or between nonsiblings. Results were also robust to sensitivity analyses restricting the within-sibling analyses to siblings born within 3 years of each other.

Conclusion—Maternal diabetes mellitus has long-term consequences for greater BMI in offspring; this association is likely to be via intrauterine mechanisms, and is independent of maternal BMI in early pregnancy. (*Circulation*. 2011;123:258-265.)

Key Words: pregnancy ■ diabetes mellitus ■ overnutrition ■ obesity ■ epidemiology

Gestational diabetes mellitus is associated with greater fetal adiposity.^{1,2} Among nondiabetic mothers there is a linear association between fasting and postchallenge glucose and greater birth size.³ Fuel-mediated teratogenesis, also known as developmental overnutrition, has been suggested as the likely mechanism for these associations.^{4–6}

Clinical Perspective on p 265

Developmental overnutrition, resulting from maternal hyperglycemia/diabetes mellitus, may also program offspring to life-long increased adiposity.⁷ In studies of Pima Indians, mean body mass index (BMI) is greater from birth to 20 years in offspring born to mothers who had diabetes mellitus during their pregnancy compared with either the offspring of mothers who developed diabetes later in their lives or those who never developed diabetes.^{8–10} In a sibling study (182 individuals from 52 families) conducted in the Pima Indians, obesity was greater among offspring born after the mother had been

diagnosed with diabetes mellitus than in their siblings born before their mother's diagnosis, suggesting that, in this population, exposure to maternal diabetes in utero has long-term effects on the offspring via intrauterine mechanisms.¹¹ The Pima Indians are a population at very high risk of obesity, type-2 diabetes, and gestational diabetes, and findings in this population may not generalize to other populations.

The long-term consequences of exposure to maternal hyperglycemia/diabetes mellitus in utero beyond the Pima Indian population has been less well studied.⁷ In a review of the subject published in 2007, 2 studies in non-Pima populations were identified that examined the association of diabetes mellitus in pregnancy with future (beyond birth) offspring adiposity.^{12,13} We have identified a further 7 studies of this association.^{14–20} The majority,^{12–15,18–20} though not all,^{12,16,17} report greater offspring BMI or obesity in those whose mothers had diabetes (any of gestational, type 1, or type 2 diabetes) in pregnancy. In the studies finding an association,

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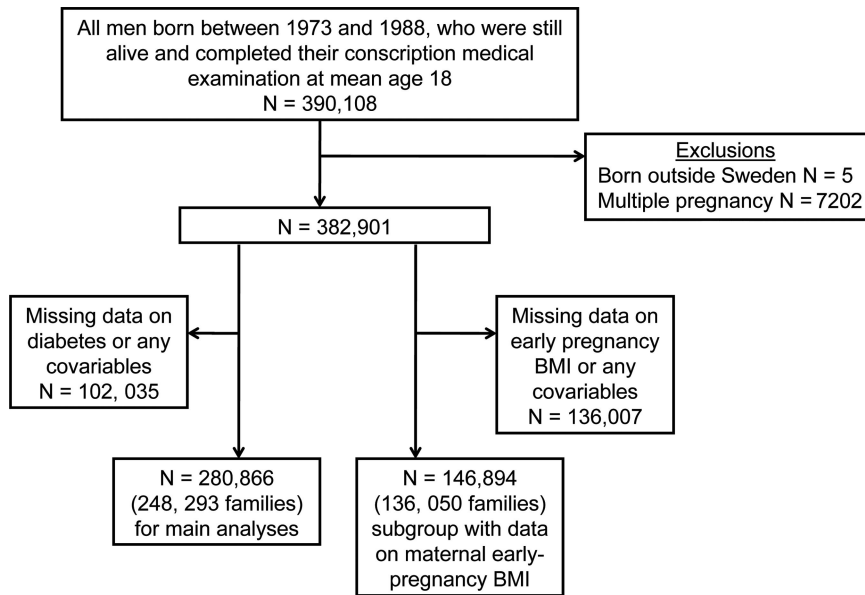


Figure. Sampling frame, eligible cohort, and numbers included in analyses.

this persisted after adjustment for maternal early pregnancy BMI in most, but in 2 studies, the association attenuated to the null with this adjustment.^{13,20} The majority of these studies are small, with all except 2^{13,18} including <100 mothers with diabetes mellitus.

The association of diabetes mellitus with later offspring adiposity might be explained by shared familial genetic variation and lifestyle characteristics related to greater adiposity, the major risk factor for gestational and type 2 diabetes. None of the studies in non-Pima populations have compared associations within and between siblings to more directly explore the likely contribution of intrauterine mechanisms.¹¹ This is important because, if intrauterine exposure to maternal diabetes in pregnancy is causally related to later offspring obesity via intrauterine pathways, this could result in an acceleration of the increase in population levels of diabetes mellitus and obesity that would continue across several generations even with improvements to the obesogenic environment.²¹

The aim of this study was to examine the associations of diabetes mellitus in pregnancy with offspring BMI (at mean age 18) in a general European population. We further aimed to use a sibling study design to explore the extent to which intrauterine mechanisms are likely to play a causal role in any associations. This is a form of natural experiment, and is a powerful approach for testing causal inference by dealing with unmeasured confounders that are identical or very similar in siblings.²² In recent years, it increasingly has been used to explore causality in a wide range of epidemiological studies,^{23–26} including for exploring whether gestational diabetes mellitus is causally related via intrauterine mechanisms to offspring BMI in Pima Indians.¹¹ If siblings exposed to maternal diabetes have higher BMI compared with their siblings who were not exposed to maternal diabetes, this supports a causal intrauterine mechanism. Such an association could not be explained by mechanisms such as familial socioeconomic position and shared lifestyle or maternal genotype, which will be the same for siblings.

Methods

We used data from the mandatory national conscription examination for offspring BMI, and hence included men only, because only men complete this examination. The study consisted of all men born in Sweden between 1973 and 1988 who were still alive and completed their conscription medical examination during the period 1990 to 2005 (N=390 108). Date of birth of the index participant, together with mother's age at birth and parents' unique identity numbers (used to generate a family ID for the purpose of identifying full siblings) were extracted from the Swedish Multi-Generation Register. A linkage was made between these data and the Swedish Medical Birth Register,^{27,28} the Swedish Military Service Conscription Register, and the Population and Housing Censuses of 1990. The Regional Ethics Committee, Stockholm, approved these linkages.

We excluded anyone born outside of Sweden, multiple births, and anyone with missing data on any variables included in this study. After these exclusions, the study population comprised 280 866 men (73% of eligible men) for analyses of diabetes mellitus in pregnancy and 146 894 (38%) for analyses with maternal early-pregnancy BMI. The Figure shows the derivation of the eligible cohort and final analysis cohort and subgroup.

Data on maternal weight and height (used to calculate BMI) at first antenatal clinic assessment, which took place around 10 weeks gestation, birth weight, parity, and diabetes mellitus in pregnancy were measured by midwives, obstetricians, or other physicians as part of normal clinical practice. Information on these were taken directly from the obstetric records and entered into the Medical Birth Register. Gestational age was assessed from the first day of the last menstrual period for 80% of the cohort, with ultrasound scan results being used in the remainder. Diabetes mellitus during pregnancy was entered onto the Medical Birth Register, with no distinction made between gestational and existing diabetes mellitus, and therefore we use the term "maternal diabetes" in pregnancy for this exposure. Highest maternal education (4 categories: primary and lower secondary only; upper secondary only; postsecondary or university education) was obtained from the 1990 census.

During the years covered by this study it was a legal requirement that all Swedish men attend the Swedish military service conscription examination; there were almost no exclusions to this requirement. Only individuals with severe mental retardation, being hospitalized for severe psychiatric morbidity, or imprisoned for severe criminality were exempt. At the conscription units across Sweden, height and weight were measured by trained personnel using standard procedures with the men in underclothes and without shoes.

Statistical Analyses

We compared distributions of characteristics between men who were included in the study and those excluded because of missing data, using χ^2 , t , and F tests, as appropriate. To compare the within-sibling and between-unrelated family associations, we used fixed and between-cluster linear regression models, using the `xtreg` command in Stata (StataCorp, College Station, TX).²⁹ This approach runs 2 regression models simultaneously, the within-sibling fixed-effect model and the between-clusters (here, unrelated families) model. The random effect is then obtained as the weighted average of the regression coefficients from these 2 models. For all models our outcome is offspring BMI at age 18. For our main analyses, the exposure of interest is maternal diabetes mellitus in pregnancy, and in a subgroup, we also have examined maternal early-pregnancy BMI as an exposure. The equations for the models are provided in the online-only Data Supplement.

The fixed-effect regression coefficient provides the within-sibling association. This coefficient represents the association of maternal diabetes mellitus with offspring BMI, having controlled for fixed maternal characteristics (eg, socioeconomic background, lifestyle, and genes). A positive association here supports an intrauterine effect because it would suggest that the sibling exposed to maternal diabetes in utero (with all fixed maternal characteristics controlled for) has a higher BMI than the sibling born before the mother had diabetes. The between-cluster regression coefficient represents the between-nonsiblings effect. This coefficient represents the association of maternal diabetes with offspring BMI between unrelated individuals. The estimate still uses data from all participants, but relates the mean offspring BMI within a cluster (family) to mean exposure within clusters (family); the clusters are independent of each other. A Hausman statistic is used to compare these 2 models.²⁹ If the within-sibling and between-unrelated-clusters coefficients are consistent with each other, and in both there is an association of maternal diabetes with offspring BMI, this suggests that the association is importantly driven by intrauterine mechanisms. If the between-unrelated-clusters coefficient is greater than the within-sibling coefficient, it suggests that much of this association is driven by characteristics that are shared within families (maternal genotype, background socioeconomic position), given that, once these are controlled for in the fixed within-sibling association, the coefficient is weaker. The random effects regression coefficient (overall association) is then obtained as the weighted average of the within-sibling and between-nonsibling effects, each coefficient weighted by the inverse of its variance.²⁹ This latter represents the overall association between the maternal diabetes mellitus and offspring BMI at mean age 18, taking family clustering into account in the estimation of 95% confidence intervals.

In the basic model (model 1) we adjusted only for year of birth (of all siblings). We then additionally adjusted for potential confounding by maternal age at birth, parity, and education (model 2). Note that maternal education does not contribute in the within-sibling analyses because it is the same for both siblings. These potential confounding factors were chosen on the basis of previous knowledge of their associations with the exposure (maternal diabetes mellitus) and outcome (offspring BMI). In model 3, we explored for possible mediation of associations by gestational age and birth weight. As noted in the introduction, maternal diabetes mellitus is associated with greater fetal and infant (at birth) adiposity, with evidence that this is due to intrauterine mechanisms related to fetal insulin secretion. It is also known that birth weight is positively correlated with later BMI. Therefore, we wanted to examine whether any association of maternal pregnancy diabetes with later offspring BMI was explained by greater adiposity at birth that persisted into adulthood. Finally, after exploring possible interactions, we adjusted for maternal early-pregnancy BMI in the subgroup with these data. Maternal early-pregnancy BMI is an established key risk factor for gestational diabetes mellitus and is also associated with offspring BMI and therefore could be a confounder in the association we are examining. We explored whether there was any evidence of interaction between maternal early-pregnancy BMI (categorized at normal weight [<24.9 kg/m²], overweight (25 to 30 kg/m²), or obese (>30 kg/m²) and diabetes mellitus in pregnancy in their associations

with offspring BMI by including interaction terms in the regression models. Finally, we undertook a sensitivity analyses in which we restricted analyses only to those brothers who were born within 3 years of each other, as done in the previous sibling study undertaken in Pima Indians.¹¹

Results

The 280 866 males in the cohort used for exploring associations of maternal diabetes mellitus with offspring BMI belonged to 248 293 families: A total of 81 139 men had at least 1 brother within the cohort. The 146 894 men in the subgroup with information on maternal early-pregnancy BMI belonged to 136 050 families: A total of 46 066 men had at least 1 brother within the cohort. Characteristics of the cohort and differences between those included and those excluded because of missing data are shown in Table 1. The mothers in this study are a relatively lean population, with just 2% being obese and 13% overweight. The differences between those included and excluded were small with respect to effect sizes. However, the large sample size made most of these statistically significant. For example, the prevalence of maternal diabetes in pregnancy in those included in the main analyses was 0.5% and in those excluded because of missing data it was 0.6%. Mean early-pregnancy BMI in those included in the analyses was 21.9 kg/m² and was 22.0 kg/m² in those excluded. However, P -values for both of these differences were ≤ 0.002 . Similar small differences (again statistically significant) were also present when we compared the subgroup with data available on maternal BMI to all others (results available from authors on request).

Table 2 shows correlations between maternal and offspring anthropometric measurements. Maternal early-pregnancy BMI was weakly positively associated with birth weight and moderately positively associated with offspring BMI at age 18. Maternal BMI in early pregnancy was positively associated with odds of diabetes mellitus in pregnancy; the odds ratio per 1 U greater BMI was 1.08 (95% CI, 1.07 to 1.09); the odds ratio comparing overweight to normal-weight women was 2.23 (95% CI, 1.95 to 2.56), and the odds ratio comparing obese women to normal-weight women was 5.25 (95% CI, 4.28 to 6.43).

Table 3 shows the overall within-brother and between-unrelated individuals associations of maternal diabetes mellitus in pregnancy and early-pregnancy BMI with offspring BMI at mean age 18. Overall in the cohort, with control for clustering within families, offspring BMI was on average 1.00 kg/m² (95% CI, 0.81 to 1.18) greater in men whose mothers had diabetes in pregnancy compared with those who did not. Similar results were found for the within-sibling and between-nonsibling analyses. Thus, BMI was 0.89 kg/m² (95% CI, 0.31 to 1.47) greater at mean age 18 years in men whose mothers had diabetes during their pregnancy compared with their older brothers who were in utero before their mothers were diagnosed with diabetes. Adjustment for maternal age, parity, education, gestational age, and birth weight had little impact on any of these associations.

In the subgroup with data on maternal early-pregnancy BMI, there was no evidence that associations of maternal diabetes with offspring BMI varied by maternal overweight/obesity status in early pregnancy (P values for interactions in models 1 to 3 were all >0.8). The associations in this subgroup for models 1 to 3 were essentially the same as those presented in Table 3 for the whole cohort (results available on request). With further adjust-

Table 1. Characteristics of Men Included in Analyses With Maternal-Pregnancy Diabetes Mellitus as Exposure (N=280 866) and Those Excluded Because of Missing Data

	Number With Data in Excluded Category	Excluded Men*	Included Men	P
Maternal characteristic				
Diabetes in pregnancy	101 412			0.002
No		101 412 (99.4)	279 391 (99.5)	
Yes		623 (0.4)	1475 (0.5)	
Maternal early-pregnancy BMI categories	77 259			<0.001
Normal		64 971 (84.1)	125 748 (85.6)	
Overweight		10 450 (13.5)	18 297 (12.5)	
Obese		1838 (2.4)	2849 (1.9)	
Mean early pregnancy BMI, kg/m ²	77 259	22.0 (3.2)	21.9 (3.1)	<0.001
Weight gain in pregnancy, kg	77 259	14.2 (4.5)	14.1 (4.3)	<0.001
Height, cm	79 428	165.7 (5.8)	166.1 (5.7)	<0.001
Age at birth, y	102 035	27.6 (5.2)	27.8 (5.0)	<0.001
Parity	102 014			<0.001
1		40 936 (40.1)	117 792 (41.9)	
2		36 956 (36.2)	103 604 (36.9)	
3		17 139 (16.8)	44 492 (15.8)	
4		4931 (4.8)	11 100 (4.0)	
5		1379 (1.4)	2724 (1.0)	
≥6		673 (0.7)	1154 (0.4)	
Highest education	100 328			<0.001
Primary or lower secondary		25 133 (25.0)	55 696 (19.8)	
Upper secondary		51 441 (51.3)	140 598 (50.0)	
Post-secondary		23 586 (23.5)	83 938 (29.9)	
University		168 (0.2)	634 (0.2)	
Son's characteristic				
Birth weight, kg	100 572	3563 (558)	3596 (541)	<0.001
Gestational age, d	100 852	279 (13)	279 (12)	<0.001
Age at conscription, y	102 035	17.88 (0.59)	17.83 (0.52)	<0.001
Weight at conscription, kg	3192	73.6 (12.9)	74.0 (12.8)	0.15
Height at conscription, cm	3192	180.0 (6.5)	180.2 (6.5)	0.007
BMI at conscription, kg/m ²	3192	22.7 (3.7)	22.7 (3.6)	0.77
BMI category at conscription	3192			0.59
Normal		2548 (79.8)	224 655 (80.0)	
Overweight		483 (15.1)	43 095 (15.3)	
Obese		161 (5.0)	13 116 (4.7)	

Continuous variables are expressed as mean (SD); categorical variables as n (%).

*Excluded because of some missing data.

ment for maternal early-pregnancy BMI, the overall and between-nonsibling association of maternal diabetes mellitus with offspring BMI at mean age 18 was weakened somewhat, but the within-sibling association was strengthened (model 4 in Table 3). However, in all models there was no strong statistical evidence that associations within siblings differed from those between nonsiblings for the association of maternal diabetes mellitus with offspring BMI. Maternal early-pregnancy BMI was positively associated with offspring BMI overall in the cohort and between nonsiblings, but there was no association within siblings (Table 3).

On average, brothers were born 1.71 (95% CI, 1.69 to 1.74) years apart from each other. When we restricted the analyses to those who were born ≤3 years between each other, 278 240 individuals from 248 153 families remained in the main analyses. The results in this group did not differ from those presented in Tables 2 and 3.

Discussion

In this large family-based study of men born in Sweden, we found that offspring BMI at mean age 18 years is greater in those whose mothers had diabetes mellitus during their pregnancy

Table 2. Correlations of Maternal and Son's Anthropometric Data Among 146 894 Mothers and Sons Born in Sweden

	Maternal Height*	Maternal Weight*	Maternal BMI*	Son's Birth Weight	Son's Height†	Son's Weight†	Son's BMI†
Maternal height*	1						
Maternal weight*	0.38	1					
Maternal BMI*	-0.12	0.86	1				
Son's birth weight	0.17	0.22	0.15	1			
Son's height†	0.17	0.32	0.25	0.18	1		
Son's weight†	0.46	0.23	0.02	0.27	0.39	1	
Son's BMI†	-0.02	0.25	0.27	0.08	0.91	-0.03	1

*Measured at first antenatal clinic visit when mothers were largely 10 weeks gestation.

†Measured at conception examination when sons were mean age 18.

All *P* values <0.001.

than in those who did not. The similarity of associations within siblings differentially exposed to maternal diabetes mellitus in utero and between unrelated individuals suggests that this association is not fully explained by factors that are fixed (identical or very similar) in siblings. For example, the association is unlikely to be explained by background socioeconomic position or by familial behaviors that are shared by siblings up to age 18 years. Furthermore, it cannot be explained by maternal genotype because these would be identical in full siblings. Clearly, the maternal intrauterine environment differed for siblings whose mother had diabetes mellitus during her pregnancy compared with their sibling conceived before she was diagnosed with diabetes, and our sibling analyses support an intrauterine mechanism for the association of maternal diabetes with greater

BMI in her offspring. This finding is consistent with 1 previous sibling study of this association that was conducted in the Pima Indian population, but with a considerably smaller sample size than here.¹¹

Whereas we found a positive association of maternal early pregnancy BMI with offspring BMI in the cohort overall and between unrelated individuals, there was no such association within siblings. These findings suggest that the general (overall) association seen in this study and in other studies that have found positive associations of early-pregnancy BMI with offspring BMI^{30–33} might be explained by confounding due to characteristics that are the same or very similar in siblings, including maternal genotype, background socioeconomic position, and familial behaviors such as diet and

Table 3. Associations of Maternal Diabetes Mellitus in Pregnancy and Early-Pregnancy BMI With Offspring BMI at Mean Age 18 years, Within Sibling Groups and Between Unrelated Individuals

Maternal Exposure and Model	No. Included in Analyses	Mean Difference in Offspring BMI by Maternal Exposure, kg/m ² (95% CI)			<i>P</i> Value for Difference Within and Between Siblings*
		Overall	Within Siblings	Between Nonsiblings	
Diabetes in pregnancy, yes vs no					
Model 1	280 866	1.00 (0.81 to 1.18)	0.89 (0.31 to 1.47)	1.01 (0.81 to 1.21)	0.68
Model 2	280 866	1.00 (0.81 to 1.18)	0.90 (0.31 to 1.48)	1.01 (0.81 to 1.21)	0.68
Model 3	280 866	0.88 (0.69 to 1.07)	0.94 (0.35 to 1.52)	0.87 (0.68 to 1.07)	0.81
Model 4	146 894	0.46 (0.21 to 0.72)	1.23 (0.11 to 2.36)	0.41 (0.15 to 0.67)	0.14
Early-pregnancy BMI, per 1 kg/m ²					
Model 1	146 894	0.31 (0.30 to 0.31)	-0.04 (-0.07 to -0.01)	0.32 (0.31 to 0.33)	<0.001
Model 2	146 894	0.30 (0.29 to 0.31)	-0.04 (-0.07 to -0.01)	0.32 (0.31 to 0.32)	<0.001
Model 3	146 894	0.30 (0.29 to 0.30)	-0.04 (-0.07 to -0.01)	0.31 (0.30 to 0.31)	<0.001
Model 4	146 894	0.30 (0.29 to 0.30)	-0.04 (-0.07 to -0.01)	0.31 (0.30 to 0.31)	<0.001

All results are mean differences in kg/m²; the null value is 0.

Model 1: Adjusted for year of birth.

Model 2: As model 1, plus additional adjustment for maternal age at birth, parity, and education.

Model 3: As model 2, plus additional adjustment for birth weight and gestational age.

Model 4: As model 3, plus mutual adjustment of each of the 2 exposures for each other.

*Obtained from the Hausman Test, testing the null hypothesis that the within-sibling and between-nonsibling associations are identical.

physical activity. These findings are consistent with a study showing that paternal BMI around the time of pregnancy was associated with later offspring BMI with the same magnitude of association as that of maternal pre-/early-pregnancy BMI and offspring BMI.³⁴ Our results are also consistent with findings from a study in which maternal genetic variation in the fat mass and obesity-associated (*FTO*) gene was used as an instrumental variable to explore the causal intrauterine effect of her BMI on offspring adiposity.³⁵ In contrast, our results are inconsistent with a small sibling study in which offspring born to mothers with extreme obesity ($>40\text{kg/m}^2$) after they had lost weight after bariatric surgery had lower mean BMI than their siblings born before the mother had this surgery.³⁶ Although maternal behavior is likely to have changed after surgery, this changed behavior will have been present for the majority of both siblings' childhoods, given their close ages. What clearly differed between the siblings was the intrauterine environment and early infancy. It is possible that maternal extreme obesity during pregnancy does result in greater offspring adiposity in later life, but variation in maternal BMI at lower levels does not. It is notable that in our study, mothers were relatively slender, with only 2% classified as obese. In contemporary Western populations levels of obesity in early pregnancy have been found to be as high as 16% to 20%.³⁷ That said, it is also notable that in this lean population, as well as in the Pima population that has very high rates of obesity,¹¹ there is evidence for intrauterine mechanisms linking maternal diabetes mellitus in pregnancy to later-life offspring BMI.

Several mechanisms could explain the association of pregnancy diabetes mellitus with offspring BMI. First, it could be explained by maternal genotype and shared familial lifestyles related to adiposity. For example, mothers with adiposity related genotypes will be more likely to have type-2 and gestational diabetes mellitus, and if this genotype is inherited by their offspring they will have on average greater BMI. Thus, maternal adiposity-related genotypes could explain the association. Similarly, mothers with unhealthy diets and low levels of physical activity will have greater BMI and diabetes risk, and if these lifestyles are adopted by their offspring, they, too will have greater BMI. Our within-sibling analyses account for this because maternal genotype and lifestyle during offspring's early life will be identical for siblings.

Second, an interuterine causal relationship could occur as a result of tracking of greater adiposity from birth to adulthood. Glucose crosses the placenta from mother to developing fetus freely, whereas insulin does not.⁵ Consequently, the fetus of a mother with diabetes mellitus will be exposed to greater levels of glucose than a mother without diabetes, which will result in increased fetal insulin secretion.⁵ This, in turn, acts as a growth hormone, resulting in the birth of babies with on average greater birth weight and greater fat mass than those of mothers without diabetes mellitus.² Babies born with greater adiposity may simply remain more adipose throughout life. Our results, and those of a previous study,⁷ suggest that this is not the case because adjustment for birth weight and gestational age did not importantly attenuate associations. In a recent study, cord leptin (a marker of neonatal fat mass³⁸) was found to be elevated in infants of mothers with type-1 diabetes mellitus, and was higher

in children of those mothers who were later (age 7) obese or overweight.¹⁹ This might suggest a role for tracking of fat mass from birth. However, in that study none of the control group (offspring of mothers without diabetes mellitus) were overweight/obese, and whether cord leptin did mediate associations of maternal type-1 diabetes with later overweight/obesity could not be explored.

Lastly, it has been suggested that increased fetal secretion of insulin leads to life-long hyperphagia, and hence, later, greater adiposity that is independent of size at birth.³⁸ Most research in this area to date has been in animal models, but recent evidence from human studies provides some support for this mechanism. Thus, there is evidence that greater amniotic fluid and cord blood insulin are related to later offspring adiposity.¹⁴ Our results support an intrauterine mechanisms for the association of maternal diabetes with offspring greater adiposity that is not mediated by birth weight, but further work is required to determine the exact mechanisms involved.

The main strengths of our study are its very large sample size and the ability to examine associations within siblings in addition to unrelated individuals. This made it possible to explore the extent to which associations were explained by familial (maternal genetic or shared family lifestyle) confounding as opposed to causal intrauterine effects. We were unable to distinguish between gestational diabetes or existing type-1 or type-2 diabetes mellitus, because birth register information simply notes whether the mother had diabetes or not during a particular pregnancy. In general, any form of diabetes would have similar developmental overnutrition effects in terms of exposing the developing fetus to higher levels of glucose with a resultant increase in fetal insulin secretion, and studies to date that have reported associations of maternal diabetes with later offspring BMI have included mothers with type-1, type-2, gestational, or a mixture of diabetes types.^{12–15;18–20} However, women with a known diagnosis of type-1 or type-2 diabetes before becoming pregnant may have been better controlled medically than those who developed gestational diabetes. With actual measurements of diabetes control during pregnancy, it is possible we could have identified even stronger associations than those reported here for a heterogeneous group of mothers with diabetes mellitus. We used BMI as a measure of adiposity in offspring at age 18 years and for maternal early-pregnancy adiposity; this may not accurately reflect total fat mass. Babies born to mothers with diabetes mellitus have greater fat mass at birth even when they have similar birth weights to those born to mothers without diabetes mellitus.² However, there are strong correlations between directly assessed fat mass and BMI in childhood, adolescence and adulthood.⁴⁰ Furthermore, the magnitude of the association of BMI assessed in childhood with cardiovascular disease risk factors assessed in adolescence/young adulthood is the same as the equivalent association for either directly assessed fat mass or waist circumference.⁴⁰ These findings suggest that BMI is a good proxy for fat mass in European populations. Finally, this study is of male offspring only, and findings may not necessarily generalize to women.

In conclusion, our study suggests that in a relatively lean European population, as in the Pima Indian population, maternal diabetes mellitus in pregnancy is associated with greater offspring BMI in late adolescence/early adulthood, and that this is

not due to familial confounding, but most likely to intrauterine mechanisms. The strong association of maternal pregnancy diabetes mellitus with offspring BMI that we have found within siblings and between nonsiblings in the entire population highlights the importance of identifying and appropriately treating pregnancy diabetes mellitus, not only for immediate perinatal reasons, but also for the long-term health of the offspring. These findings support long-term funding of randomized, controlled trials of pregnancy diabetes treatment to determine the effect of such treatments on the long-term risk of greater adiposity and associated consequences in offspring.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Maternal diabetes mellitus in pregnancy results in greater offspring adiposity at birth. However, it is unclear whether it results in greater adiposity into adulthood in humans. We undertook a large record-linkage prospective-cohort study of 280 866 singleton-born Swedish men from 248 293 families in order to explore the intrauterine effect of maternal diabetes mellitus on offspring body mass index (BMI) in early adulthood. Maternal diabetes mellitus during pregnancy was associated with greater mean BMI at age 18 in their sons. The difference in BMI was similar within brothers and between unrelated individuals. BMI of men whose mothers had diabetes mellitus during their pregnancy was on average 0.94kg/m² greater (95% confidence interval, 0.35 to 1.52) than in their brothers born before their mother was diagnosed with diabetes. This association was independent of maternal early-pregnancy BMI. Our results show that maternal diabetes mellitus in pregnancy has long-term consequences that are, at least in part, driven by intrauterine mechanisms for greater BMI in offspring. These findings highlight the clinical importance of identifying and adequately treating gestational diabetes mellitus not only for the short-term health benefit of mother and baby, but also potentially for the longer-term prevention of obesity in offspring.

Association of Maternal Diabetes Mellitus in Pregnancy With Offspring Adiposity Into Early Adulthood: Sibling Study in a Prospective Cohort of 280 866 Men From 248 293 Families

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SUPPLEMENTAL MATERIAL

Maternal diabetes in pregnancy programmes greater offspring adiposity into early adulthood: Sibling study in a prospective cohort of 280,866 men from 248,293 families.

Debbie A Lawlor (MB ChB, FFPH, PhD), Paul Lichtenstein (PhD), Niklas Långström (PhD).

Supplementary methods

Details of regression models used in main analyses

The models used in our analyses are as follows

Fixed effect (within sibling) regression:

$$Y_{it} - \bar{Y}_i = \beta_w(X_{it} - \bar{X}_i) + \sum_j \gamma_j (Z_{jit} - \bar{Z}_{ji}) + (\varepsilon_{it} - \bar{\varepsilon}_i)$$

Between sibling regression:

$$\bar{Y}_i = \alpha + \beta_b \bar{X}_i + \sum_j \gamma_j \bar{Z}_{ji} + v_i + \bar{\varepsilon}_i$$

Random effects regression:

This is obtained as the weighted average of the regression coefficients from the fixed effect and between sibling models. The random effects model is expressed as:

$$Y_{it} = \alpha + \beta_r X_{it} + \sum_j \gamma_j Z_{jit} + v_i + \varepsilon_{it}$$

Where

Y_{it} is the outcome (offspring BMI at age 18) in sibling t of family i

\bar{Y}_i is the mean outcome (offspring BMI at age 18) of family i

α is the constant / intercept

β_w is the within sibling regression coefficient of the association of the main exposure with outcome

β_b is the between sibling regression coefficient of the association of the main exposure with outcome

β_r is the random effect regression coefficient giving the overall association of the main exposure with outcome having taken account of clustering within families

X_{it} is the exposure (maternal pregnancy diabetes or maternal early pregnancy BMI) for sibling t of family i

\bar{X}_i is the mean exposure (maternal pregnancy diabetes or maternal early pregnancy BMI) for family i

Z_{jit} $j = 1, \dots, j$ is the j^{th} covariable included in the model when controlling for covariables for sibling t of family i

\bar{Z}_{ji} is the mean of the j^{th} covariable included in the model

ε_{it} is the error term (residual variation in outcome not explained by the exposure or covariables) for sibling t of family i

$\bar{\varepsilon}_i$ is the mean error term for family i

v_i terms are the unobserved cluster-specific effects that are fixed within clusters (sibling groups)