Overweight and the Metabolic Syndrome in Adult Offspring of Women with Diet-Treated Gestational Diabetes Mellitus or Type 1 Diabetes

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Context: In animal studies, exposure to intrauterine hyperglycemia increases the risk of cardiovascular disease through only partly understood epigenetic mechanisms. Human long-term follow-up studies on the same topic are few.

Objective: The aim was to study the risk of overweight and the metabolic syndrome in adult offspring of women with diet-treated gestational diabetes mellitus (GDM) or type 1 diabetes, and additionally to study associations between estimates of maternal hyperglycemia and outcome in the offspring.

Design and Setting: We conducted a follow-up study of 1066 primarily Caucasian women aged 18–27 yr in the Center for Pregnant Women with Diabetes, Rigshospitalet, Copenhagen, Denmark.

Participants: Offspring of women with diet-treated GDM (n = 168) and an unexposed reference group (n = 141) participated, as well as offspring of women with type 1 diabetes (n = 160) and offspring from the background population representing an unexposed reference group (n = 128). The follow-up rate was 56% (597 of 1066).

Main Outcome Measures: Women with body mass index of at least 25 kg/m^2 were considered overweight. The metabolic syndrome was determined by the International Diabetes Federation 2006 criteria.

Results: The risk of overweight was doubled in offspring of women with diet-treated GDM or type 1 diabetes compared with offspring from the background population, whereas the risk of the metabolic syndrome was 4- and 2.5-fold increased, respectively. Offspring risk of the metabolic syndrome increased significantly with increasing maternal fasting blood glucose as well as 2-h blood glucose (during oral glucose tolerance test).

Conclusions: Adult offspring of women with diet-treated GDM or type 1 diabetes are risk groups for overweight and the metabolic syndrome. Intrauterine hyperglycemia may in addition to genetics and other factors contribute to the pathogenesis of overweight and the metabolic syndrome. **(*J Clin Endocrinol Metab* 94: 2464–2470, 2009)**

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Abbreviations: AGA, Appropriate for gestational age; BMI, body mass index; CI, confidence interval; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein; LGA, large for gestational age; O-BP, control offspring of women from the background population; O-GDM, offspring of women with diet-treated GDM; OGTT, oral glucose tolerance test; O-NoGDM, control offspring of women with risk indicators for GDM but a normal OGTT; OR, odds ratio; O-Type1, offspring of women with type 1 diabetes; SDS, SD score; SGA, small for gestational age.

Worldwide the incidence of overweight, type 2 diabetes, and other conditions associated with cardiovascular disease is rapidly increasing and having a major impact on public health. Therefore, knowledge of pathogenesis and risk groups is urgently needed to target preventive strategies (1).

The metabolic syndrome is a cluster of medical disorders associated with increased risk of cardiovascular disease. The risk of overweight, type 2 diabetes, and the metabolic syndrome depends on genetic susceptibility but is modulated by postnatal environmental factors. Furthermore, studies in recent years have also shown that prenatal environmental events or stimuli have lasting effects on offspring metabolism through only partly understood epigenetic mechanisms (2).

According to the "Pedersen hypothesis" and the hypothesis of "fuel-mediated teratogenesis," maternal glucose crosses the placenta easily and leads to intrauterine hyperglycemia, fetal hyperinsulinemia, and possible modification of growth and development of the fetus (3, 4).

In animal studies, intrauterine hyperglycemia increases the risk of abnormal glucose tolerance, diabetes, overweight, insulin resistance, and cardiovascular disease in the offspring, an effect that can be prevented through normalization of maternal metabolism before the last trimester of gestation (5).

We have recently reported an increased risk of either type 2 diabetes or prediabetes (impaired fasting glucose or impaired glucose tolerance) in adult offspring of women with diet-treated gestational diabetes mellitus (GDM) or type 1 diabetes (6).

Only a few studies in adult offspring of women with diabetes during pregnancy have focused on overweight and other cardiovascular risk factors (7–12). Most of the studies are in Pima Indians (10–12) and findings are not fully consistent because some find increased prevalence of overweight in diabetes-exposed offspring (7, 9–12) whereas one study does not (8), and the same conflicts are seen in relation to blood pressure and waist-hip ratio. None of the studies include data on lipid metabolism in the offspring, and only studies in the Pima Indians include data on maternal glucose metabolism during pregnancy (11, 12). A recent review concludes that studies including adult offspring of women with diabetes during pregnancy from other populations than American Indians are lacking (13).

The present paper evaluates the risk of overweight and the metabolic syndrome in adult offspring of women with GDM or type 1 diabetes compared with two reference groups of offspring not exposed to diabetes while *in utero* using a primarily Caucasian population. Moreover, the study evaluates the association between the severity of maternal glucose intolerance in pregnancy and offspring outcome.

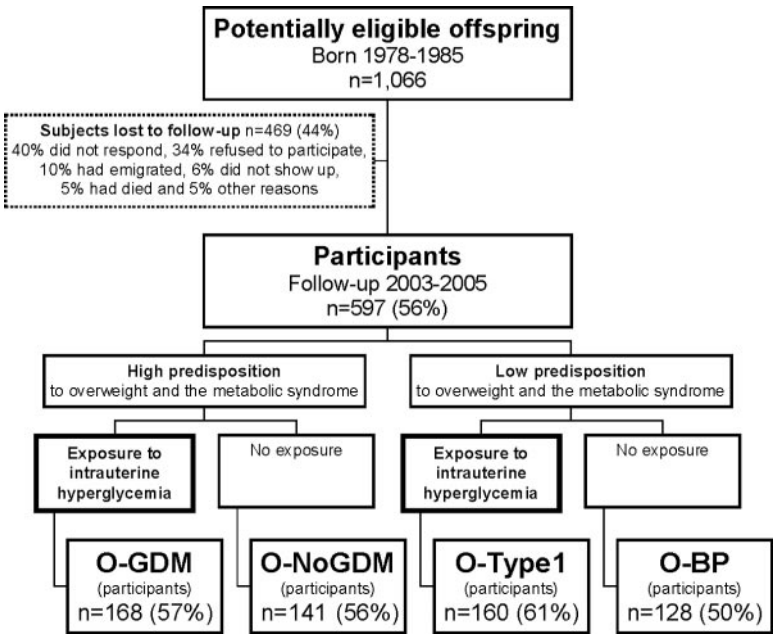

FIG. 1. Flow chart.

Subjects and Methods

During 2003–2005, we conducted a follow-up study of 1,066 subjects aged 18–27 yr. The study population was offspring of women with either diet-treated GDM or type 1 diabetes or from two reference groups not exposed to hyperglycemia during pregnancy (Fig. 1). All subjects were born at the Department of Obstetrics, Rigshospitalet, from 1978 to 1985, and coupling between mother and child was possible through the Danish Civil Registrar System. Only the oldest sibling from the study period and singletons were included. We extracted baseline data from original medical records.

Protocol was in accordance with the Declaration of Helsinki and was approved by the local ethical committee (KF 01-061/03). All participants gave written consent before taking part in the survey.

Screening procedure for GDM in the mothers (1978–1985)

GDM, defined as "carbohydrate intolerance of varying severity with onset or first recognition during pregnancy" (14), complicated 1–2% of pregnancies in Denmark during 1978–1985 (15). The routine screening procedure for GDM was, and still is, risk indicator-based and not universal (15–17).

In 1978–1985, screening was based on fasting blood glucose as well as the following risk indicators: family history of diabetes, at least 20% prepregnancy overweight, previous GDM, previous delivery of a macrosomic baby (≥4.500 g), and glucosuria (15, 18). Women with risk indicators and two consecutive fasting blood glucose values of at least 4.1 mmol were tested by a 3-h 50-g oral glucose tolerance test (OGTT).

GDM was diagnosed if at least two of seven glucose values exceeded the mean + 3 SD values for a reference group of normal-weight nonpregnant women without a family history of diabetes (16, 19).

The OGTT was defined as normal if all glucose values were below the mean + 2 SD values of the reference group (16).

Selection of subjects

The subjects were assigned to four different groups according to maternal characteristics during pregnancy (Fig. 1).

1) Offspring of women with diet-treated GDM (O-GDM; n = 168). We excluded women with insulin-treated GDM to limit inclusion of women with undiagnosed pregestational type 2 diabetes and maturity onset diabetes of the young.

2) An unexposed reference group of offspring born to women with risk indicators for GDM but a normal OGTT (O-NoGDM; n = 141). Based on risk indicators for GDM, we expect this group to have a relatively high predisposi-

tion to type 2 diabetes, overweight, and the metabolic syndrome, which is comparable with the O-GDM group.

3) Offspring of women with type 1 diabetes, who fulfilled three criteria: onset of diabetes of 40 yr or less, classical history, and insulin treatment starting 6 months or less after the diagnosis (O-Type1; n = 160).

4) An unexposed reference group of offspring born to women from the background population, defined as unselected women from the local community referred for antenatal care and delivery (O-BP; n = 128). Because the background risk of GDM was 1–2% (15), we expected the majority of women to be normoglucemic and the group to have a relatively low predisposition to type 2 diabetes, overweight, and the metabolic syndrome, which is comparable with the O-Type1 group. Eight of these women had a normal OGTT, whereas the remaining, according to our screening procedure, were not tested.

Examination of subjects at follow-up (2003–2005)

Venous samples were drawn after an overnight fast. Weight, height, waist circumference, and blood pressure were measured, and a questionnaire with information on occupation, health, medication, smoking habits, and level of physical activity (20) as well as paternal diabetes status was completed.

Biochemical methods

Blood samples for glucose measurements were drawn in heparin-sodium fluoride vials, kept on ice, centrifuged, plasma separated within 30 min, and analyzed on a Cobas Mira analyzer by the enzymatic UV test, HK/G-6PHD method (ABX Diagnostics Glucose HK 125; Horiba-ABX, Montpellier, France), or the glucose dehydrogenase catalyzed oxidation method (Gluc-DH Method, Merck, Darmstadt, Germany). Serum levels of triglycerides and high-density lipoprotein (HDL)-cholesterol were measured on a Cobas Mira by enzymatic colorimetric methods (triglycerides and HDL-cholesterol direct, Horiba-ABX, Montpellier, France).

Variables

Main outcome measures

1) Overweight was defined as body mass index (BMI) of at least 25 kg/m^2. 2) The metabolic syndrome was determined according to the International Diabetes Federation 2006 (21), based on central obesity (waist circumference, women ≥80 cm; men ≥94 cm) plus any two of four additional factors: elevated triglyceride level (≥1.7 mmol/liter), reduced HDL-cholesterol (women <1.29 mmol/liter; men <1.03 mmol/liter), hypertension/elevated blood pressure (systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg) or elevated fasting plasma glucose (≥5.6 mmol/liter).

Exposure variables

We used five different estimates of intrauterine hyperglycemia. In analyses based on all participants, the assignment into four groups (O-GDM, O-NoGDM, O-Type1, and O-BP) was used as surrogate measure of different levels of intrauterine hyperglycemia. In subanalyses of offspring of women who underwent an OGTT during pregnancy (n = 317), we used maternal fasting glucose and 2-h blood glucose. Women with type 1 diabetes were routinely hospitalized twice during pregnancy for 3 d (in the first trimester and again in the third trimester no more than 4 wk before estimated date of delivery), measuring capillary whole blood glucose seven times daily. In subanalyses of O-Type1 (n = 160), we used mean maternal blood glucose in the first and third trimesters as exposure variable.

Potential confounders, risk factors, and mediators

Socioeconomic position was measured by a standardized measure of occupational social classes I–V in accordance with standards of the Danish National Institute of Social Research (22). We added a social class VI representing people out of the labor market (23). Family occupational social class was based on information on the parental occupational status at follow-up (2003–2005). We classified according to the parent with the highest position and dichotomized (V–VI *vs.* I–IV).

Ethnic origin was defined as Nordic Caucasian if the mother originated from Denmark, Norway, Sweden, or Iceland (yes *vs.* no). Other maternal covariates were: age at delivery (years), parity (≥1 partus *vs.* nulliparity), pregestational BMI (≥25 *vs.* <25 kg/m^2), hypertension at first hospital visit (≥140/90 *vs.* <140/90 mm Hg), and family history of diabetes, defined as unspecified diabetes in a first-degree relative on the maternal side (yes *vs.* no). Paternal diabetes was defined as unspecified diabetes at follow-up (2003–2005) (yes *vs.* no). Covariates associated with the offspring were: gender, level of physical activity (≥30 *vs.* <30 min daily), current smoking status (smoker *vs.* nonsmoker), and age at follow-up (years).

Birth weight SD score (SDS) was calculated as the deviation from the population mean value in SD units adjusted for sex and gestational age (24). The offspring were defined as: large for gestational age (LGA, ≥ 90th percentile), appropriate for gestational age (AGA), or small for gestational age (SGA, ≤ 10th percentile). Maternal gestational weight gain was the difference between maternal weight within 1 wk before delivery and self-reported prepregnancy weight. The following covariates were studied in separate models because they were considered possible mediators: maternal gestational weight gain (kilograms), birth weight SDS (SD units), LGA/AGA/SGA and preterm delivery (<37 wk gestation, yes *vs.* no).

Statistical analyses

Normally distributed continuous data are presented as mean (SD), whereas non-normally distributed data are presented as median (2.5–97.5th percentiles). Differences between groups were analyzed with ANOVA, Kruskal-Wallis, χ^2, Fisher's exact, Student's *t*, or Mann-Whitney test when appropriate. To correct for multiple comparisons, we multiplied *P* values in *post hoc* test by 4 because we compared O-BP with the other three groups as well as O-GDM with O-NoGDM (Bonferroni method).

In multiple logistic regression analyses, we entered only confounders and risk factors that were associated at the 0.1 level with both outcome and the exposure variable of primary interest because these models had limited degrees of freedom. Models were not reduced. Results are presented as odds ratio (OR), 95% confidence interval (CI), and *P* values.

All tests were two-tailed, and a significance level of 0.05 was chosen. Data were processed using SPSS version 13.0 (SPSS Inc., Chicago, IL).

Results

Baseline data on mothers and offspring (1978–1985)

The overall participation rate of the study population was 56% (597 of 1066), and the participation rate did not differ between the four groups (Fig. 1).

Table 1 presents baseline data on participants in the four groups. Participants and subjects lost to follow-up were comparable according to: maternal age at delivery, family history of diabetes, smoking and blood glucose values during pregnancy, parity, gender, birth weight, and gestational age, but there was a slightly lower pregestational maternal BMI (21.7 *vs.* 21.9 kg/m^2; $P = 0.04$) and a higher rate of Nordic Caucasian mothers among participants (94 *vs.* 86%; $P < 0.001$).

Maternal OGTTs were performed at 33 wk gestation (17–39 wk). The prevalence of risk indicators in mothers of O-GDM and O-NoGDM was comparable with regard to: family history of diabetes (30 *vs.* 35%; $P = 0.4$), ≥20% prepregnancy overweight (30 *vs.* 24%; $P = 0.3$), previous delivery of a macrosomic baby (5 *vs.* 11%; $P = 0.08$), glucosuria (41 *vs.* 42%; $P = 0.8$) and

TABLE 1. Baseline data on mothers and offspring (1978–1985)

Variables	O-GDM (n = 168)	O-NoGDM (n = 141)	O-Type1 (n = 160)	O-BP (n = 128)	P[a]
Maternal data					
Age at delivery (yr)	29.5 (5.4)[b]	28.2 (5.0)	26.5 (4.2)	27.6 (4.3)	**<0.001**
Nordic Caucasian	91% (153/168)	92% (130/141)	99% (158/160)[b]	92% (118/128)	**0.02**
Maternal family history of diabetes	30% (51/168)[b]	35% (45/130)[b]	20% (32/157)	16% (20/126)	**0.001**
Multiparity (≥1)	58% (97/168)	53% (75/141)	46% (73/160)	45% (57/128)	0.06
Pregestational BMI ≥25 kg/m^2	38% (64/168)[b,c]	23% (28/121)[b]	6% (9/152)	11% (14/126)	**<0.001**
Gestational weight gain (kg)	10.5 (5.5)[b,c]	14.1 (4.4)	12.0 (4.1)[b]	13.7 (4.6)	**0.005**
Hypertension at first visit (≥140/90 mm Hg)	10% (16/166)	5% (6/123)	23% (36/159)[b]	5% (6/127)	**<0.001**
Offspring birth data					
Men	54% (91/168)	45% (63/141)	45% (72/160)	49% (63/128)	0.3
Birth weight (g)	3410 (530)	3492 (497)	3269 (760)[b]	3474 (481)	**0.004**
Birth weight SDS	0.18 (1.33)	−0.18 (1.16)	1.16 (1.78)[b]	−0.18 (1.10)	**<0.001**
SGA (<10th percentile)	11% (18/168)	15% (21/141)	6% (9/160)	14% (18/127)	**0.04**
LGA (>90th percentile)	17% (29/168)	12% (17/141)	42% (67/160)[b]	11% (14/127)	**<0.001**
Gestational age (d)[d]	273 (247–284)[b,c]	281 (254–302)	260 (202–269)[b]	280 (253–298)	**<0.001**
Preterm delivery (<37 wk gestation)	8% (14/168)	4% (6/141)	43% (69/160)[b]	4% (5/127)	**<0.001**

Data are mean (SD) or proportion (number) if not otherwise stated. For some of the variables, numbers are changing due to missing data. $P < 0.05$ are *bold*.

[a] Overall analysis of difference between the four groups (ANOVA, Kruskal-Wallis, or χ^2 test).

[b] Compared with O-BP group, $P < 0.05$ (*post hoc*, Student's *t*, Mann-Whitney, or χ^2 test. *P* values multiplied by 4).

[c] Compared with O-NoGDM group, $P < 0.05$ (*post hoc*, Student's *t*, Mann-Whitney, or χ^2 test. *P* values multiplied by 4).

[d] Data are median (2.5–97.5th percentiles).

presence of more than one risk indicator (21 *vs.*15%; $P = 0.2$), but slightly more mothers of O-GDM had GDM previously (9 *vs.* 2%; $P = 0.02$). Per definition, women with GDM had a higher fasting (5.2 *vs.* 4.7 mmol/liter) and 2-h glucose (7.8 *vs.* 5.2 mmol/liter) ($P < 0.001$).

Women with type 1 diabetes had 12-yr (1–26 yr) duration of diabetes, and 52% had late diabetic complications (retinopathy or nephropathy). The maternal mean blood glucose was 8.9 mmol/liter (2.8 mmol/liter) in the first trimester and 6.8 mmol/liter (1.8 mmol/liter) in the third trimester.

Follow-up data on offspring (2003–2005)

The prevalence of offspring overweight was 40% in O-GDM, 30% in O-NoGDM, 41% in O-Type1, and 24% in O-BP, whereas the prevalence of the metabolic syndrome was 24, 15%, 14, and 6%, respectively (Table 2).

In multiple logistic regression analysis (Table 3), the risk of overweight was significantly higher in O-GDM and O-Type1 but not in O-NoGDM compared with O-BP when adjusted for: maternal age at delivery, maternal pregestational BMI, offspring age, family occupational social class, and maternal hypertension

TABLE 2. Follow-up data (2003–2005)

Variables	O-GDM (n = 168)	O-NoGDM (n = 141)	O-Type1 (n = 160)	O-BP (n = 128)	P[a]
Offspring					
Age (yr)	21.6 (1.8)[b]	21.1 (2.1)[b]	22.5 (2.2)	22.9 (2.2)	**<0.001**
BMI ≥25 kg/m^2	40% (67/168)[b]	30% (42/141)	41% (66/160)[b]	24% (31/128)	**0.005**
BMI ≥30 kg/m^2	13% (21/168)	11% (16/141)	10% (16/160)	5% (6/128)	0.1
Metabolic syndrome[c]	24% (40/168)[b]	15% (21/141)[b]	14% (23/160)	6% (7/128)	**<0.001**
Central obesity (M ≥94 cm; W ≥80 cm)	39% (66/168)	38% (54/141)	43% (68/160)	29% (37/128)	0.1
Triglycerides ≥1.7 mmol/liter	16% (26/167)[b]	14% (20/140)[b]	6% (10/159)	5% (6/128)	**0.002**
Reduced HDL (M <1.03; W <1.29 mmol/liter)	37% (62/167)[b]	31% (43/140)[b]	20% (32/159)	13% (17/128)	**<0.001**
Diastolic blood pressure ≥85 mm Hg	4% (6/167)	2% (3/141)	5% (8/160)	2% (2/128)	0.3
Systolic blood pressure ≥130 mm Hg	37% (62/167)	31% (44/141)	41% (66/160)[b]	24% (31/128)	**0.02**
Fasting plasma glucose ≥5.6 mmol/liter	41% (69/167)[b]	30% (42/138)[b]	25% (39/155)[b]	10% (13/128)	**<0.001**
Physical activity (≥30 min/d)	56% (94/168)	56% (79/141)	48% (77/160)	50% (64/128)	0.4
Smokers	46% (77/168)	42% (59/141)	36% (57/160)	35% (45/128)	0.2
Parents					
Paternal diabetes	8% (13/164)	8% (11/136)	5% (8/157)	9% (11/125)	0.6
Family occupational social class V or VI	27% (45/167)[b]	18% (25/140)	18% (29/160)[b]	8% (10/128)	**<0.001**

Data are mean (SD) or proportion (number) if not otherwise stated. For some of the variables, numbers are changing due to missing data. M, Men; W, women. $P < 0.05$ are *bold*.

[a] Overall analysis of difference between the four groups (ANOVA, Kruskal-Wallis, or χ^2 test).

[b] Compared with O-BP group, $P < 0.05$ (*post hoc*, Student's *t*, Mann-Whitney, or χ^2 test. *P* values multiplied by 4).

[c] Metabolic syndrome defined in accordance with the International Diabetes Federation 2006 (21).

TABLE 3. Multiple logistic regression analyses showing the risk of overweight (BMI ≥25 kg/m^2) and the metabolic syndrome (the International Diabetes Federation 2006) in O-GDM, O-NoGDM, and O-Type1 using O-BP as reference

Outcome measures	O-GDM (n = 167)	O-NoGDM (n = 121)	O-Type1 (n = 152)	O-BP (n = 126)
Overweight (n = 566)				
Unadjusted	**2.09 (1.25–3.50)**	1.36 (0.77–2.39)	**2.15 (1.27–3.62)**	Reference
Adjusted[a]	**1.79 (1.00–3.24)**	1.47 (0.78–2.78)	**2.27 (1.30–3.98)**	Reference
Metabolic syndrome (n = 566)				
Unadjusted	**5.35 (2.31–12.42)**	**3.17 (1.28–7.84)**	**2.73 (1.12–6.64)**	Reference
Adjusted[b]	**4.12 (1.69–10.06)**	**2.74 (1.08–6.97)**	**2.59 (1.04–6.45)**	Reference

Results are given as OR (95% CI). $P < 0.05$ are *bold*.

[a] Adjusted for maternal age at delivery, maternal pregestational BMI, offspring age, family occupational social class, maternal hypertension at first visit. When O-GDM were compared with O-NoGDM, the OR (95% CI) for overweight was 1.22 (0.70–2.11).

[b] Adjusted for maternal age at delivery, maternal pregestational BMI, ethnic origin, family occupational social class. When O-GDM were compared with O-NoGDM the OR (95% CI) for the metabolic syndrome was 1.51 (0.79–2.89).

at first visit. The risk of the metabolic syndrome was significantly higher in O-GDM, O-Type1, as well as in O-NoGDM compared with O-BP, adjusted for: maternal age at delivery, maternal pregestational BMI, ethnic origin, and family occupational social class (Table 3). No significant difference according to risk for overweight (OR = 1.22; 95% CI, 0.70–2.11; $P = 0.49$) or the metabolic syndrome (OR = 1.51; 95% CI, 0.79–2.89; $P = 0.22$) was found between O-GDM and O-NoGDM, adjusted for confounders mentioned above. Further adjustment for the potential mediators birth weight SDS, gestational weight gain, LGA/AGA/SGA, or preterm delivery did not change estimates significantly.

Subanalyses including maternal glucose values

In unadjusted analyses of the 317 women who had an OGTT during pregnancy, we found that for each 1 mmol/liter increase in maternal fasting blood glucose, the offspring risk of overweight increased 51%, and the risk of the metabolic syndrome increased 80% (Table 4). Likewise, a 1 mmol/liter increase in maternal 2-h blood glucose was associated with a 13% increased risk of overweight and an 18% increased risk of the metabolic syndrome (Table 4). After adjusting for confounders, the association between maternal fasting blood glucose as well as 2-h blood glucose and offspring risk of the metabolic syndrome remained statistically significant (Table 4). Only maternal BMI was found to confound the association between maternal fasting blood glucose or 2-h blood glucose and offspring risk of the metabolic syndrome. To ensure that our confounder selection procedure did not exclude other potent confounders, we fitted additional models including maternal fasting blood glucose or 2-h blood glucose and maternal BMI, plus all the other potential confounders mentioned in *Materials and Methods* one by one without significant changes in the estimates.

Additional adjustment for the potential mediators birth weight SDS, gestational weight gain, LGA/AGA/SGA, and preterm delivery did not change estimates significantly either.

In unadjusted subanalyses of O-Type1, there was a borderline significant association between maternal blood glucose in the third trimester and offspring risk of the metabolic syndrome (Table 4). No other associations between maternal blood glucose in the first or third trimester and offspring risk of overweight or the metabolic syndrome were found.

TABLE 4. Associations between maternal glucose estimates and outcome in the offspring

	Maternal glucose estimates			
	Mothers having an OGTT (n = 317)		Mothers with type 1 diabetes (n = 160)	
Outcome	Fasting glucose	2-h glucose	Mean glucose in 1st trimester	Mean glucose in 3rd trimester
Overweight				
Univariate	**1.51 (1.05 to 2.19)**	**1.13 (1.01 to 1.28)**	1.05 (0.93 to 1.18)	1.13 (0.94 to 1.36)
Adjusted	1.26 (0.83 to 1.90)[a]	1.03 (0.91 to 1.17)[b]	0.99 (0.87 to 1.12)[c]	1.03 (0.85 to 1.26)[c]
Metabolic syndrome				
Univariate	**1.80 (1.17 to 2.79)**	**1.18 (1.03 to 1.36)**	0.91 (0.77 to 1.08)	1.26 (0.99 to 1.59)
Adjusted	**1.64 (1.03 to 2.62)[a]**	**1.15 (1.00 to 1.33)[d]**	0.91 (0.77 to 1.08)[e]	1.26 (0.99 to 1.59)[e]

Results are given as OR (95% CI). $P < 0.05$ are *bold*. Multiple logistic regression analysis shows the risk of overweight (BMI ≥25 kg/m^2) and the metabolic syndrome (the International Diabetes Federation 2006) associated with a 1 mmol/liter increase in maternal glucose estimate. Additional adjusting for possible mediators (maternal gestational weight gain, birth weight SDS, LGA/AGA/SGA, or preterm delivery) did not change estimates.

[a] Adjusted for maternal pregestational BMI.

[b] Adjusted for offspring age, sex, family occupational social class, maternal hypertension at first visit.

[c] Adjusted for offspring age.

[d] Adjusted for family occupational social class.

[e] There were no confounders according to criteria.

Discussion

We found that O-GDM had a 2-fold higher risk of overweight and a 4-fold higher risk of the metabolic syndrome than O-BP. O-Type1 had a more than 2-fold increased risk of both overweight and the metabolic syndrome compared with O-BP. O-GDM did not differ significantly from O-NoGDM.

The risk of the metabolic syndrome in the offspring increased with an increasing level of maternal fasting blood glucose or 2-h blood glucose during OGTT in pregnancy.

Strengths and weaknesses of the study

The study is based on a large sample with long-term follow-up and is powered by two internal unexposed reference groups including offspring from the unselected background population. Furthermore, it has data on many potential confounding covariates.

In contrast to animal studies, it is very difficult to study the effect of hyperglycemia separately from effects of genes in human models. The problem has been met in studies of Pima Indians using discordant siblings (52 families with 183 siblings) (25), as well as in a small and carefully selected study comparing 15 offspring of mothers with type 1 diabetes with 16 offspring of fathers with type 1 diabetes (8). A third study has used individuals with maturity onset diabetes of the young HNF-1a mutations discordant according to diabetes exposure (26). All three studies found indications of an epigenetic effect of exposure to intrauterine hyperglycemia; however, the external validity of outcome estimates from these studies is low.

We are aware that our model may not be optimal for studying the effect of intrauterine hyperglycemia on the offspring; on the other hand, the large sample increases the internal and external validity, and there is no indication of selection bias due to subjects being lost to follow-up. Furthermore, we find that our four groups are enriched with different combinations of exposure to intrauterine hyperglycemia and other risk factors for overweight and the metabolic syndrome, which enables us to some extent to evaluate the possible impact of intrauterine hyperglycemia in a human model. In this context, we hypothesize that differences according to the prevalence of overweight and the metabolic syndrome between O-GDM and O-NoGDM as well as between O-Type1 and O-BP would be partly explained by a lasting effect of intrauterine hyperglycemia; and the difference between O-GDM and O-Type1 as well as between O-NoGDM and O-BP could be interpreted as a reflection of differences according to genetics, other risk factors, and degree of maternal hyperglycemia.

It is a limitation to the study that the GDM screening procedure was not universal. However, it is likely that the vast majority of mothers of O-BP, not tested by an OGTT, had normal glucose metabolism because the prevalence of GDM in Denmark was only 1–2% (15). Furthermore, the study may suffer from information bias related to insufficient estimates of maternal glucose metabolism during pregnancy. Glucose profiles or glycosylated hemoglobin measured longitudinally through pregnancy would probably have been more powerful estimates, but unfortunately this was not used during 1978–1985. Nevertheless, fasting and 2-h glucose measures from the OGTT have been found to be predictive of perinatal complications (27), offspring BMI (28), and offspring glucose tolerance (12) in other studies. Maternal diet treatment during pregnancy in the O-GDM group as well as exclusion of insulin-treated women narrows the glucose variation in the O-GDM group and diminishes exposure difference between O-GDM and O-NoGDM, but we did not include insulin-treated women because this could potentially increase the genetic difference between O-GDM and O-NoGDM. However, all these factors, as well as undiagnosed cases of GDM among mothers of O-BP, would work toward acceptance of the null hypothesis and tend to underestimate the associations between maternal glucose values and offspring outcome.

Our data compared with other studies

This study is the first to evaluate the prevalence of the metabolic syndrome in adult offspring of women with diabetes and furthermore to show an association between maternal blood glucose during pregnancy and offspring risk of the metabolic syndrome. Our study is also the first to report the prevalence of overweight in adult offspring of mothers with GDM in a primarily Caucasian population.

Overall, there are only a few studies evaluating overweight and individual components of the metabolic syndrome in adult offspring of women with diabetes during pregnancy (7–12), and none of these studies included data on lipids. In a study from Prague, 148 offspring of women with type 1 diabetes had significantly higher blood pressure and BMI compared with 31 matched controls of healthy mothers (7). A French study compared 15 offspring of mothers with type 1 diabetes with 16 offspring of fathers with type 1 diabetes and found no difference concerning BMI, fat mass, waist-hip ratio, or blood pressure (8). A register-based study from Sweden using data from conscript found increased blood pressure and weight among 368 men born to women with unspecified diabetes during pregnancy compared with 140,000 offspring born to healthy controls (9). Finally, papers on the prospectively studied Pima Indians have demonstrated diabetes in pregnancy and 2-h blood glucose during OGTT in pregnancy to be strong predictors of overweight in the offspring, but Pima Indians have very specific genetics (10–12).

Our data are in accordance with what has been found in studies of children (13, 29–31).

Genetics plays a major role in development of overweight and the metabolic syndrome, and the present paper suggests that this is also the case in our study. An additional effect of intrauterine hyperglycemia on the pathogenesis of overweight and the metabolic syndrome is indicated by the findings of: 1) a significantly higher risk of overweight and the metabolic syndrome in O-Type1 compared with O-BP (Table 3); 2) a comparable risk of overweight in O-Type1 compared with O-GDM, despite the much higher genetic predisposition in the latter group (Table 3); 3) a significantly higher risk of overweight and the metabolic syndrome in O-GDM compared with O-BP, indicating a combined effect of genes and intrauterine hyperglycemia, because O-NoGDM also had a higher risk compared with O-BP— however lower than O-GDM (Table 3); 4) a higher risk of both overweight and the metabolic syndrome in O-GDM compared with O-NoGDM. Because the difference was not statistically significant this could indicate that there was no effect of intrauterine hyperglycemia in offspring with a high *a priori* risk. However, it could also be due to the lack of power (type 2 error)—a risk that was increased by the treatment of O-GDM

mothers after the diagnostic OGTT potentially leading to information bias and a weaker association between exposure and outcome (Table 3); and 5) a significant association between maternal fasting blood glucose or 2-h blood glucose during OGTT and offspring risk of the metabolic syndrome. In fact, almost all associations between maternal glucose estimates and outcome in the offspring had odds ratios above 1, also in confounder-adjusted associations, and an alternative interpretation of the insignificant associations could be lack of power in part related to information bias according to the exposure variables (Table 4).

An epigenetic effect of intrauterine hyperglycemia has been found in animal studies (5), but randomized trials (*e.g.* comparing outcome in offspring of tightly regulated women with GDM with offspring of women following standard treatment) are needed to clarify whether the observed association between maternal hyperglycemia and cardiovascular risk factors in the offspring can be considered to be causal in humans.

Conclusion

Adult primarily Caucasian offspring of women with diet-treated GDM or type 1 diabetes represent risk groups for overweight and the metabolic syndrome. Our findings indicate that a hyperglycemic intrauterine environment may play a role in the pathogenesis of these conditions, in addition to genetics and other risk factors. Preventive strategies for cardiovascular disease in offspring of women with gestational diabetes or type 1 diabetes should be considered.

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