High Prevalence of Type 2 Diabetes and Pre-Diabetes in Adult Offspring of Women With Gestational Diabetes Mellitus or Type 1 Diabetes

The role of intrauterine hyperglycemia

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OBJECTIVE — The role of intrauterine hyperglycemia and future risk of type 2 diabetes in human offspring is debated. We studied glucose tolerance in adult offspring of women with either gestational diabetes mellitus (GDM) or type 1 diabetes, taking the impact of both intrauterine hyperglycemia and genetic predisposition to type 2 diabetes into account.

RESEARCH DESIGN AND METHODS — The glucose tolerance status following a 2-h 75-g oral glucose tolerance test (OGTT) was evaluated in 597 subjects, primarily Caucasians, aged 18–27 years. They were subdivided into four groups according to maternal glucose metabolism during pregnancy and genetic predisposition to type 2 diabetes: *1*) offspring of women with diet-treated GDM (O-GDM), *2*) offspring of genetically predisposed women with a normal OGTT (O-NoGDM), *3*) offspring of women with type 1 diabetes (O-type 1), and *4*) offspring of women from the background population (O-BP).

RESULTS — The prevalence of type 2 diabetes and pre-diabetes (impaired glucose tolerance or impaired fasting glucose) in the four groups was 21, 12, 11, and 4%, respectively. In multiple logistic regression analysis, the adjusted odds ratios (ORs) for type 2 diabetes/pre-diabetes were 7.76 (95% CI 2.58–23.39) in O-GDM and 4.02 (1.31–12.33) in O-type 1 compared with O-BP. In O-type 1, the risk of type 2 diabetes/pre-diabetes was significantly associated with elevated maternal blood glucose in late pregnancy: OR 1.41 (1.04–1.91) per mmol/l.

CONCLUSIONS — A hyperglycemic intrauterine environment appears to be involved in the pathogenesis of type 2 diabetes/pre-diabetes in adult offspring of primarily Caucasian women with either diet-treated GDM or type 1 diabetes during pregnancy.

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The rapid global rise in the prevalence of type 2 diabetes constitutes a health threat to the individual and is a major burden for health economy. Therefore, it is crucial to identify specific risk groups, targeting preventive strategies. Studies of developmental origins of health and disease have focused on the possible role of intrauterine hyperglycemia in the pathogenesis of type 2 diabetes (1). Maternal glucose crosses placenta easily, and maternal hyperglycemia leads to intrauterine hyperglycemia, fetal hyperinsulinemia, and possible modification of growth and development of the fetus (2).

Pronounced hyperglycemia in relation to pregnancies of women with type 1 diabetes as well as mild hyperglycemia, as seen among women with gestational diabetes mellitus (GDM), are both associated with increased fetal growth and perinatal morbidity (3,4). Also, less severe forms of glucose intolerance are associated with increased feto-maternal morbidity (5).

In animal studies, intrauterine hyperglycemia increases the risk of abnormal glucose tolerance, diabetes, overweight, and insulin resistance in offspring (6–10). Despite very convincing animal studies, questions still exist concerning the long-term impact of intrauterine hyperglycemia in humans, especially regarding the impact in adult Caucasians. Observational and prospective studies among the Pima Indians and from the Chicago group support the findings of animal studies (11–18). The studies of the Pima Indians examine children and adult offspring in contrast to the majority of the other studies, in which offspring before the end of puberty are investigated (14–16,18). Because of the very specific genetics of the Pima Indians, the results are not directly applicable to other populations (11–13,19). Furthermore, some of the other studies have limitations: small number of participants (17), high number of dropouts during follow-up (14,15), and analyses including maternal type 1 and type 2 diabetes together (16). Only one follow-up study of children from a small randomized trial in women with GDM has been performed—without definitive conclusions (20).

Thus, in the present paper we aimed to evaluate the prevalence of type 2 dia-

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Abbreviations: GAD65ab, GAD65 autoantibody; GDM, gestational diabetes mellitus; LGA, large for gestational age; OGTT, oral glucose tolerance test; SGA, small for gestational age.

betes and pre-diabetes in young adult offspring of women with either diet-treated GDM or type 1 diabetes in a mainly Nordic Caucasian population, taking the impact of both intrauterine hyperglycemia and genetic predisposition to type 2 diabetes into account.

RESEARCH DESIGN AND METHODS

— Through 2002–2005, we conducted a follow-up study of 597 adult offspring born to women with GDM or type 1 diabetes and from two control groups. All subjects were born at the Department of Obstetrics, Rigshospitalet, Denmark, from 1978 to 1985, and coupling between mother and child was possible through the Danish Civil Registrar System. We included singletons only, and if more than one sibling from the study period met criteria for inclusion, only the oldest was invited.

Protocol was in accordance with the Declaration of Helsinki and approved by the local ethical committee. All participants gave a written consent before taking part in the survey.

We sought a model to evaluate the possible impact of exposure to intrauterine hyperglycemia both in subjects with a relatively high genetic predisposition to type 2 diabetes and in subjects with a relatively low genetic predisposition. Because there was no universal screening for GDM during 1978–1985 and because there currently are no available tools for adequate genetic testing for type 2 diabetes, our model is based on certain assumptions concerning phenotypic traits and genetic predisposition to type 2 diabetes.

From 1978 to 1985, Danish routine screening of pregnant women for GDM was based on risk indicators (family history of diabetes [unspecified], ≥20% overweight prepregnancy, previous GDM, previous delivery of a macrosomic baby [≥4.500 g], and glucosuria) and fasting blood glucose (21). Women with risk indicators and two consecutive fasting capillary blood glucose measurements ≥4.1 mmol were offered a 3-h 50-g oral glucose tolerance test (OGTT). Until September 1982, glucose during OGTT was measured in venous plasma, while capillary whole blood was used thereafter as previously published (22). The OGTT was defined as abnormal if more than two of seven values during the test exceeded the mean + 3 SDs for a reference group of normal-weight nonpregnant women without a family history of diabetes (23).

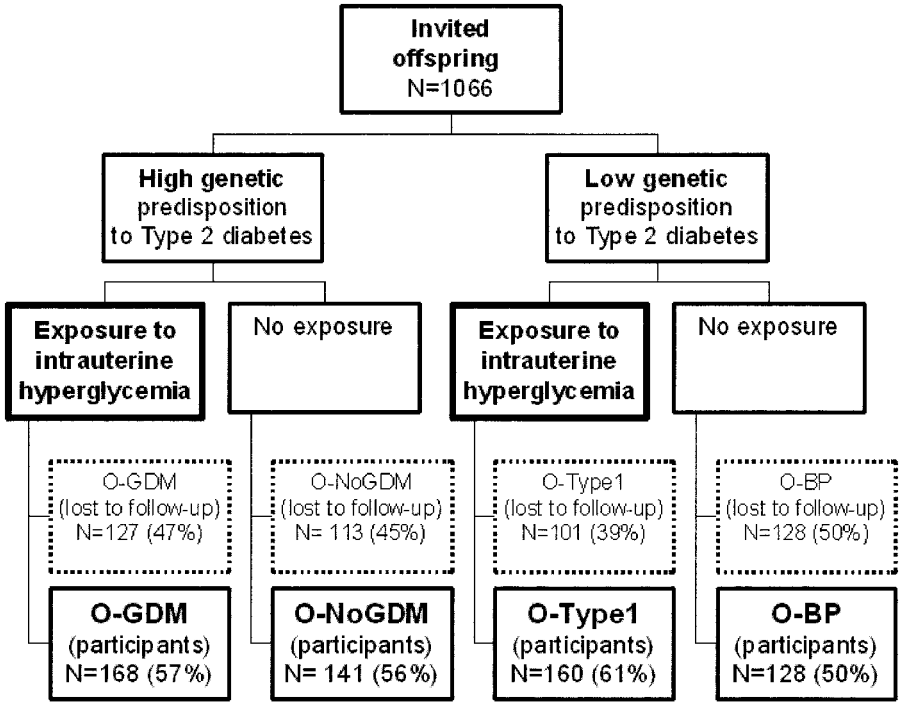

Figure 1—*Subjects in the study stratified according to relative genetic predisposition to type 2 diabetes and exposure to intrauterine hyperglycemia.*

We assumed all women, examined by an OGTT on this background, to have a relatively high genetic predisposition to type 2 diabetes independently of the result of the OGTT. The prevalence of GDM was 2% (21), meaning that 98% did not have GDM. Accordingly, the background population was regarded as having a relatively low genetic risk of developing type 2 diabetes. Women with type 1 diabetes were regarded as having comparably low genetic risk of developing type 2 diabetes.

Based on these assumptions, our model consists of four groups enriched with different combinations of intrauterine hyperglycemia and genetic predisposition to type 2 diabetes (Fig. 1): *1*) offspring of women with GDM (O-GDM) (intrauterine hyperglycemia and a relatively high genetic predisposition to type 2 diabetes), *2*) offspring of women who were screened for GDM because of risk indicators and elevated fasting blood glucose but had a normal OGTT (O-NoGDM) (no intrauterine hyperglycemia and a relatively high genetic predisposition to type 2 diabetes), *3*) offspring of women with type 1 diabetes (O-type 1) (intrauterine hyperglycemia and a relatively low genetic predisposition to type 2 diabetes), and *4*) offspring of women from the background population (O-BP) (no intrauterine hyperglycemia and a relatively low genetic predisposition to type 2 diabetes).

All mothers of O-GDM were diet-treated only. Mothers of O-NoGDM had all glucose values during the OGTT below the mean + 2 SDs of the reference group (23). Mothers of O-type 1 fulfilled three criteria: onset of diabetes at age ≤40 years, a classical history, and insulin treatment started ≤6 months after diagnosis. The background population was defined as women from the local community referred for antenatal care and delivery.

Examination at follow-up

After an overnight fast, participants without known diabetes had a 2-h 75-g OGTT with venous sampling at 0 and 120 min. Participants with known diabetes only had fasting venous samples. Weight and height were measured in light clothing and without shoes, and a questionnaire regarding information on occupation, health, medication, smoking, physical activity (24), and paternal diabetes status was filled in.

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

either the enzymatic ultraviolet 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 C-peptide was measured automatically by a fluoroimmunoassay using monoclonal antibodies (AutoDELFIA C-peptide kit; Perkin-Elmer Life and Analytical Sciences, Wallac Oy, Turku, Finland). GAD65 autoantibodies (GAD65abs) were detected by ELISA (GAD65 Autoantibody ELISA kit; RSR, Cardiff, U.K.) and defined as positive when ≥5 units/ml.

Covariates

Outcome. The prevalence of either type 2 diabetes or pre-diabetes in the offspring at follow-up was our primary outcome. The OGTTs were evaluated according to World Health Organization criteria of 1999 (25). Classification of diabetes type was based on history, medical records, and levels of fasting C-peptide and GAD65ab. Pre-diabetes was defined as either impaired glucose tolerance or impaired fasting glucose.

Exposure. We used group (O-GDM, O-NoGDM, O-type 1, and O-BP) as an estimate of different levels of intrauterine hyperglycemia in analyses including all offspring. In a subanalysis of offspring born to women having an OGTT during pregnancy, we included either fasting or 2-h blood glucose from this OGTT in the analyses. In women with type 1 diabetes, estimates of mean blood glucose in the first trimester and in late pregnancy were available, and the predictive value of these variables were tested for O-type 1.

Potential confounding covariates. Socioeconomic position was based on the highest occupational status of the parents at present and coded into family social class I–V in accordance with the standards of the Danish National Institute of Social Research, similar to the British Registrar General's Classification I–V. We added a social class VI representing people on transfer income, including sickness benefits and disability pension (26), and dichotomized the variable into family social class (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). Paternal diabetes was defined as unspecified diabetes at follow-up (yes vs. no). Maternal family history of diabetes was defined as unspecified diabetes in a first-degree relative on the maternal side (yes vs. no).

Maternal smoking during pregnancy was entered (≥1 cigarette/day, yes vs. no), as were age at delivery (<25 vs. ≥25 years), parity (≥1 partus versus nulliparity), and pregestational BMI (≥25 vs. <25 kg/m^2) of mothers. Offspring sex was entered (male vs. female), as were physical activity (≥30 vs. <30 min/day), current smoking (≥1 cigarette/day, yes vs. no), and age (years) of offspring. We considered offspring BMI (≥25 vs. <25 kg/m^2), to be a possible mediating covariate in the casual pathway from exposure to intrauterine hyperglycemia to glucose metabolism in offspring.

Offspring were defined as small or large for gestational age (SGA and LGA, respectively) according to a Danish standard population (27). In O-GDM and especially in O-type 1 birth weight, gestational age and offspring risk of becoming LGA were extensively influenced by factors attributed to the disease as well as to interventions related to treatment. Therefore, we considered the following covariates as both potential mediators and proxy variables for the two treated groups (O-GDM and O-type 1): preterm delivery (<37 weeks' gestation; yes vs. no), birth weight (grams), gestational age (days), SGA (yes vs. no) and LGA (yes vs. no). For this, we studied the possible effect of these variables on offspring risk of type 2 diabetes/pre-diabetes without the "group" covariate in the model. We performed analyses including offspring from all four groups together but also analyses separately for offspring in the two treated groups (O-GDM and O-type 1) and offspring in the two untreated groups (O-NoGDM and O-BP).

Statistical analyses

Continuous variables are given as mean ± SDs or median (2.5th–97.5th percentiles). Differences between groups were analyzed with the χ^2 test, ANOVA, Student's *t* test, Kruskal-Wallis test, or the Mann-Whitney test when appropriate. Post hoc tests were corrected for multiple comparisons using the Bonferroni method. *P* values were multiplied by four as we compared O-BP with the other three groups, as well as O-GDM with O-NoGDM. First we did simple logistic regression analyses, giving the unadjusted odds ratio (OR) of having type 2 diabetes/pre-diabetes for each of the covariates. Secondly, we used a "change-in-estimate method" (28) to assess confounding. Covariates that altered the unadjusted ORs of type 2 diabetes/pre-diabetes by more than 10% were considered confounders. Multiple logistic regression models included only confounders, and they were not reduced. The results of the logistic regression analyses are expressed as ORs (95% CI). All tests were two tailed, and a significance level of 0.05 was chosen. Data were processed using SPSS (version 13.0; SPSS, Chicago, IL).

RESULTS

Characteristics of the study population

The overall participation rate in the study was 56% (597 of 1,066) (Fig. 1). Among the subjects lost to follow-up, 40% did not respond, 34% refused to participate, 10% had emigrated, 6% did not show up, 5% had died, and 5% had other reasons not to participate. The participation rate was comparable in the four groups.

Table 1 gives baseline data from the original medical records on the pregnant women in the four groups. There was no difference between participants and subjects lost to follow-up except for 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%, $P < 0.001$).

OGTTs were performed at 33 weeks' gestation (17–39 weeks). The prevalence of risk indicators in mothers of O-GDM and O-NoGDM was comparable according to family history of diabetes (30 vs. 35%, $P = 0.4$), ≥20% overweight prepregnancy (30 vs. 24%, $P = 0.3$), previous delivery of a macrosomic baby (5 vs. 11%, $P = 0.08$), and glucosuria (41 vs. 42%, $P = 0.8$). Also, the prevalence of more than one risk indicator was comparable (21 vs. 15%, $P = 0.2$), but slightly more mothers of O-GDM had GDM previously (9 vs. 2%, $P = 0.02$). As expected, women with GDM had a higher fasting (5.2 vs. 4.7 mmol/l) and 2-h (7.8 vs. 5.2 mmol/l) glucose ($P < 0.001$).

Women with type 1 diabetes had 12 years (1–26 years) duration of diabetes, and 52% had late diabetic complications (retinopathy or nephropathy). The majority was on two or four intakes of insulin per day, with insulin dosage increasing from 43 IU (13 IU) to 74 IU (20 IU) daily during pregnancy. Twice during pregnancy, women with type 1 diabetes were hospitalized for 3 days and blood glucose measured seven times per day in capillary

Table 1—*Baseline data on mothers and offspring, as well as offspring follow-up characteristics*

	O-GDM	O-NoGDM	O-Type1	O-BP	*P**
n	168	141	160	128	
Maternal data					
Age at delivery (years)	29.5 ± 5.4†	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)†	92 (118/128)	0.02
Maternal family history of diabetes	30 (51/168)†	35 (45/130)†	20 (32/157)	16 (20/126)	0.001
Smoking during pregnancy	37 (54/146)	42 (49/117)	60 (88/148)	48 (54/113)	0.001
Multiparity (≥1 partus)	58 (97/168)	53 (75/141)	46 (73/160)	45 (57/128)	0.06
Pregestational BMI (kg/m^2)‡	23.0 (17.2–38.8)†§	21.4 (16.7–32.8)†	21.6 (17.3–26.1)	20.9 (15.9–29.1)	<0.001
Pregestational BMI ≥25 (kg/m^2)	38 (64/168)†§	23 (28/121)†	6 (9/152)	11 (14/126)	<0.001
Birth data					
Male sex	54 (91/168)	45 (63/141)	45 (72/160)	49 (63/128)	0.3
Birth weight (g)	3410 (530)	3492 (497)	3269 (760)†	3474 (481)	0.004
SGA	5 (8/168)	6 (9/141)	3 (5/160)	7 (9/127)	0.4
LGA	22 (37/168)	16 (22/141)	49 (79/160)†	16 (20/127)	<0.001
Gestational age (days)‡	273 (247–284)†§	281 (254–302)	260 (202–269)†	280 (253–298)	<0.001
Preterm delivery (<37 weeks' gestation)	8 (14/168)	4 (6/141)	43 (69/160)†	4 (5/127)	<0.001
Offspring follow-up data					
Glucose tolerance status					
Type 2 diabetes/pre-diabetes	21 (36/168)†	12 (17/139)	11 (17/160)	4 (5/128)	<0.001
Type 2 diabetes	4 (7/168)	0 (0/141)	2 (3/160)	1 (1/128)	0.04
Pre-diabetes (IGT or IFG)	17 (29/168)†	12 (17/139)†	9 (14/160)	3 (4/128)	0.001
IGT	11 (19/168)†	5 (7/139)	5 (8/160)	2 (3/128)	0.009
IFG	6 (10/168)	7 (10/140)	4 (6/160)	1 (1/128)	0.06
Type 1 diabetes	0 (0/168)	1 (2/141)	4 (7/160)	0 (0/128)	0.004
Glucose estimates					
Fasting plasma glucose (mmol/l)¶	5.5 ± 0.9†	5.3 ± 0.5†	5.2 ± 0.5	5.1 ± 0.4	<0.001
2-h plasma glucose (mmol/l)¶	5.9 ± 2.1†	5.6 ± 1.3	5.8 ± 1.6†	5.3 ± 1.3	0.005
Other					
Age (years)	21.6 ± 1.8†	21.1 ± 2.1†	22.5 ± 2.2	22.9 ± 2.2	<0.001
BMI (kg/m^2)‡	23.7 (18.2–41.1)†	23.8 (17.7–39.0)	23.5 (18.3–41.7)†	22.4 (18.5–32.9)	0.005
Paternal diabetes	8 (13/164)	8 (11/136)	5 (8/157)	9 (11/125)	0.6
GAD65ab positive (≥5 units/ml)‖	1 (2/166)	4 (5/138)	4 (6/152)	2 (3/128)	0.4
Family social class V or VI	27 (45/167)†	18 (25/140)	18 (29/160)†	8 (10/128)	<0.001
Physical activity (≥30 min/day)	56 (94/168)	56 (79/141)	48 (77/160)	50 (64/128)	0.4
Offspring current smoker	46 (77/168)	42 (59/141)	36 (57/160)	35 (45/128)	0.2

Data are means ± SD or percentages (*n*) unless otherwise indicated. For some of the variables, numbers are changing as a result of missing data. *Analyses of differences between means, medians, and proportions were performed by ANOVA, Kruskal-Wallis, or the χ^2 test, respectively. †Compared with the O-BP group, $P < 0.05$ (post hoc test: Student's *t* test, Mann-Whitney test, or the χ^2 test; *P* values multiplied by four). ‡Data are median (2.5th–97.5th percentiles), as data was not normally distributed. §Compared with the O-NoGDM group, $P < 0.05$ (post hoc test: Student's *t* test, Mann-Whitney test, or the χ^2 test; *P* values multiplied by four). ¶Including individuals with normal glucose tolerance (NGT), impaired fasting glucose (IFG) (fasting plasma glucose [FPG] ≥6.1 mmol/l but <7.0 mmol/l and 2-h plasma glucose <7.8 mmol/l), impaired glucose tolerance (IGT) (FPG <7.0 mmol/l and 2-h plasma glucose ≥7.8 mmol/l but <11.1 mmol/l), or screen-detected treatment-naive type 2 diabetes; *n*: 167, 139, 153, and 128, respectively. ‖Positive GAD65 autoantibodies were found in 3% (16 of 588) of offspring without type 1 diabetes. One O-GDM and 1 O-NoGDM had impaired fasting glucose; the remaining 14 had normal glucose tolerance and C-peptide. Positive GAD65 autoantibodies were found in 89% of offspring with type 1 diabetes (8 of 9).

whole blood. In the first trimester, mean blood glucose was 8.9 ± 2.8 mmol/l, and in late pregnancy, within the last 4 weeks before the estimated date of delivery, it was 6.8 ± 1.8 mmol/l.

Data at follow-up. Table 1 and online appendix 1 (available at http://dx.doi.org/10.2337/dc07-1596) give data on offspring at follow-up. The prevalence of type 2 diabetes/pre-diabetes was 21% in O-GDM, 12% in O-NoGDM, and 11% in O-type 1 compared with 4% in O-BP. Only one of the 11 cases of type 2 diabetes was known before the study, the remaining diagnosed during the study. Two of the nine cases of type 1 diabetes were diagnosed during the study. Both were O-type 1, presenting with classical hyperglycemic symptoms, 2-h plasma glucose >30 mmol/l, and ketonuria.

O-GDM had significantly higher fasting and 2-h plasma glucose than O-BP. Also, O-NoGDM had significantly higher fasting plasma glucose than O-BP. Finally, O-type 1 had significantly higher 2-h plasma glucose than O-BP. BMI was significantly higher in O-GDM, O-NoGDM, and O-type 1 than in O-BP.

Online appendix 2 shows risk of type 2 diabetes/pre-diabetes in the four offspring groups and effects of the potential confounding covariates. The unadjusted OR for type 2 diabetes/pre-diabetes was markedly increased in O-GDM, O-NoGDM, and O-type 1 compared with that in O-BP. Adjustment for maternal family history of diabetes, maternal overweight, and offspring age (Model 1) slightly reduced this association; ORs were as follows: 7.76 (95% CI 2.58–23.39) in O-GDM, 4.46 (1.38–14.46) in O-NoGDM, and 4.02 (1.31–12.33) in O-type 1 compared with O-BP. When O-GDM was compared with O-NoGDM, the OR was 1.74 (0.89–3.40). Additional adjustment for offspring overweight (Model 2) further decreased the association but did not change the pattern.

In O-type 1, risk of type 2 diabetes/pre-diabetes was significantly associated with elevated maternal glucose in late pregnancy (OR 1.41 [95% CI 1.04–1.91]) per millimole when adjusted for covariates included in Model 1. Further adjustment for offspring overweight did not change this.

Maternal age at delivery, ethnicity, smoking during pregnancy, parity, paternal diabetes status at follow-up, family social class, sex, offspring physical activity, and offspring smoking habits were not found to be confounders and had no effect on offspring risk of type 2 diabetes/pre-diabetes when entered in multiple logistic regression models. We found no interaction between groups and covariates in the two models.

No associations between birth weight, gestational age, preterm delivery, LGA, or SGA and offspring risk of type 2 diabetes/pre-diabetes were found, neither when all offspring were studied together nor when offspring were studied in subgroups. Furthermore, ORs for type 2 diabetes/pre-diabetes did not change significantly when these variables were forced into the logistic regression models.

CONCLUSIONS — We found a high prevalence of type 2 diabetes/pre-diabetes among adults exposed to a hyperglycemic intrauterine environment. More than 20% of offspring born to mothers with diet-treated GDM and more than 10% of offspring born to mothers with type 1 diabetes had type 2 diabetes/pre-diabetes at the age of 22 years. Compared with offspring from the background population, the adjusted risks of type 2 diabetes/pre-diabetes were eight- and fourfold increased, respectively, and this was not explained by differences in offspring overweight, birth weight, or gestational age. Furthermore, we found an association between elevated maternal blood glucose in late pregnancy and type 2 diabetes/pre-diabetes in offspring of women with type 1 diabetes.

Strengths and limitations of this study

We had a high number of subjects with long-term follow-up, a high participation rate, an internal control group, and data on many potential confounding covariates, including paternal diabetes status, social class, physical activity, and levels of C-peptide and GAD65abs in offspring. A low prevalence of GDM in our background population has previously been documented in O-BP (21), suggesting that the majority of mothers had a normoglycemic intrauterine milieu. Undiagnosed cases of GDM among mothers of O-BP would only push our results toward the null hypothesis and thus underrate the difference between the O-BP and the three other groups. Pregnant women with type 1 diabetes had documented high glucose values during pregnancy, and although we did not document high glucose levels continuously during pregnancy in the diet-treated GDM mothers, we have previously demonstrated an impact of a hyperglycemic milieu on the fetus in a similar group of diet-treated women with GDM (29), suggesting a hyperglycemic environment also in O-GDM. However, we are aware that diet treatment after diagnosis of GDM may reduce the predictive value of glycemia during OGTT, leading to an underestimation of the difference between O-GDM and O-NoGDM. Nevertheless group and fasting or 2-h glucose values are crude estimates of maternal glucose metabolism during pregnancy. In the two groups with a relatively high genetic predisposition in our model, we have documented a higher prevalence of maternal family history of diabetes (30 and 35%) compared with the two groups with a low genetic predisposition (16 and 20%). According to our model, the observed differences in the prevalence of type 2 diabetes/pre-diabetes between O-GDM and O-NoGDM (21 vs. 12%) and between O-type 1 and O-BP (11 vs. 4%) may be interpreted as an effect of maternal hyperglycemia, whereas the differences between O-GDM and O-type 1 (21 vs. 11%) and between O-NoGDM and O-BP (12 vs. 4%) may be interpreted as an effect of genetics (online appendix 1). These indications of an effect of maternal hyperglycemia are supported by multiple logistic regression analysis, as ORs for type 2 diabetes/pre-diabetes were higher in O-type 1 compared with O-BP (4.02 [95% CI 1.31–12.33]) and in O-GDM compared with O-NoGDM (1.74 [0.89–3.40]), even though the latter didn't reach the level of significance. Finally, the significant association between higher glucose levels in late pregnancy and type 2 diabetes/pre-diabetes in O-type 1 supports the hypothesis that intrauterine hyperglycemia plays a role in the pathogenesis of type 2 diabetes in offspring. We find that bias from losses to follow-up is unlikely. Long-term studies of the risk of type 2 diabetes in normoglycemic women with risk indicators for GDM (the O-NoGDM group) are lacking, and whether the observed difference in the prevalence of type 2 diabetes/pre-diabetes between O-GDM and O-NoGDM is due to a more pronounced intrauterine hyperglycemia in O-GDM, stronger genetic predisposition, postnatal environmental factors, or a combination cannot be further elucidated from our data. A more ideal control group of O-GDM might have been discordant siblings, but that model wasn't feasible in our

population, with its low GDM rate and the screening program used.

The high prevalence of type 2 diabetes/pre-diabetes in adult offspring of women with type 1 diabetes has not previously been documented but is in accordance with studies of children born to women with type 1 diabetes (14,16). Furthermore, a small study found a higher prevalence of impaired glucose tolerance and decreased insulin secretion among adult offspring of mothers compared with offspring of fathers with type 1 diabetes (17).

The significant association between higher glucose levels in late pregnancy in mothers with type 1 diabetes and the incidence of type 2 diabetes/pre-diabetes in offspring has not been reported previously but is supported by the finding of an association between maternal 2-h glucose during OGTT and offspring glucose metabolism in glucose-tolerant Pima Indians (30).

This study is the first to show a high prevalence of type 2 diabetes/pre-diabetes in adult offspring of mothers with GDM in a primarily Caucasian population. This finding is in accordance with results from high-risk populations (11) and studies of children from Caucasian populations (14,16).

Abnormal glucose tolerance is associated with either decreased insulin secretion, decreased insulin sensitivity, or a combination of both. The few human studies looking into this in offspring of diabetic women give various results with decreased insulin sensitivity reported by some authors (14,31–33) and decreased insulin secretion by others (14,17,34).

In conclusion, the prevalence of type 2 diabetes/pre-diabetes is markedly increased among adult, primarily Nordic Caucasian, offspring born to women with hyperglycemia during pregnancy, as seen in diet-treated GDM and type 1 diabetes. Our findings support the hypothesis that a hyperglycemic intrauterine environment plays a role in the pathogenesis of type 2 diabetes. Identification of risk groups gives unique opportunities for lifestyle interventions; furthermore, aiming at a normoglycemic intrauterine environment in pregnant women may reduce the risk of type 2 diabetes in future generations.

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