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The Prevalence of the Metabolic Syndrome in a Danish Population of Women with Previous Gestational Diabetes Mellitus Is Three-Fold Higher than in the General Population

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Context: Diabetes and obesity, components of the metabolic syndrome, are common characteristics of women with prior gestational diabetes mellitus (GDM). Due to increasing incidence of diabetes and obesity, the metabolic syndrome might comprise a major health problem among these women.

Objective: The objective was to estimate the prevalence of the metabolic syndrome by three different criteria [World Health Organization 1999 (WHO), The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001, and European Group for the Study of Insulin Resistance 2002] among women with previous GDM.

Design: We conducted a follow-up study of a Danish cohort of women admitted in 1978–1996 to the Diabetes and Pregnancy Center, Rigshospitalet, Copenhagen University Hospital, with diet-treated GDM. The follow-up took place in 2000–2002 at median 9.8 yr (interquartile range 6.4–17.2) after pregnancy. Results were compared with a control group of 1000 age-matched women from a population-based sample (Inter99).

Participants: Four hundred eighty-one women at median age 43 yr (interquartile range 38–48) participated.

Main Outcome Measures: The main outcome measures were body mass index (BMI), glucose tolerance, blood pressure, lipid profile, and insulin resistance.

Results: Independent of the criteria, the prevalence of the metabolic syndrome was three times higher in the prior GDM group, compared with the control group (*e.g.* WHO: 38.4 *vs.* 13.4%, $P < 0.0005$). Age- and BMI-adjusted odds ratio for having the WHO-defined metabolic syndrome was 3.4 (95% confidence interval 2.5–4.8) for the prior GDM group *vs.* the control group. Obese women (BMI $>$ 30 kg/m^2) with previous GDM had a more than 7-fold increased prevalence of the metabolic syndrome (WHO), compared with normal-weight prior GDM women (BMI $<$ 25 kg/m^2). In glucose-tolerant women, the prevalence was doubled in the prior GDM group, compared with control group.

Conclusion: The prevalence of the metabolic syndrome was three times as high in women with prior diet-treated GDM, compared with age-matched control subjects. **(*J Clin Endocrinol Metab* 90: 4004–4010, 2005)**

OVERWEIGHT AND DIABETES have increased dramatically worldwide during the last decades (1), probably due to a more sedentary lifestyle combined with a relative increase in high-energy food intake. Varying degrees of insulin resistance are present in overweight and obesity and closely related to type 2 diabetes (2). Insulin resistance is associated with increased morbidity and mortality when accompanied by other cardiovascular risk factors such as abnormal glucose tolerance, hypertension, hyperlipidemia, or obesity (3, 4), components of the insulin resistance syndrome or the metabolic syndrome (2). The prevalence of the metabolic syndrome increases with increasing age and body mass index (BMI) (5), and due to the increase in obesity and diabetes in all age groups (1, 6), a significant increase in the prevalence of the metabolic syndrome can therefore be expected also in young obese subjects (7, 8).

Overweight women have an increased risk of developing gestational diabetes mellitus (GDM) (9), which is defined as an abnormal glucose tolerance diagnosed for the first time in pregnancy (10). GDM complicates 2.4% of the pregnancies in Denmark (11) and is associated with a high risk of subsequent overt diabetes mellitus (12). We have recently shown that the incidence of diabetes in Danish women with a history of diet-treated GDM at a median of 6–7 yr after pregnancy had increased from 18 to 40% during the last decade. This increase could primarily be ascribed an increasing prepregnancy BMI (13). Thus, the metabolic syndrome might comprise a major health problem in these women as demonstrated in other populations (14, 15).

The aims of the present study were: 1) to investigate the prevalence of the metabolic syndrome in a Danish population of women with previous diet-treated GDM, compared with a control group of age-matched women applying three different criteria for the metabolic syndrome [World Health

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Abbreviations: BMI, Body mass index; FFA, free fatty acid; GDM, gestational diabetes mellitus; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OR, odds ratio.

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Organization (WHO) 1999 (16), The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) (17) 2001, and European Group for the Study of Insulin Resistance 2002 (EGIR) (18)], and 2) to describe the phenotypic characteristics in women with a history of GDM with or without the metabolic syndrome at follow-up.

Patients and Methods

For the GDM group, in the years 2000–2002, we included 481 women (74% Danish origin) with prior GDM diagnosed during the periods 1978–1985 and 1987–1996 at the Center for Diabetes and Pregnancy, Department of Obstetrics, Rigshospitalet. Our pregnant women were screened for GDM by a risk factor-based method, and the diagnosis GDM was based on Danish criteria (13). All women in the prior GDM group were treated by diet alone. From previous studies from our center, we already know that almost all GDM women who need insulin treatment during pregnancy will subsequently develop diabetes (both types 1 and 2 diabetes) (19, 20). These women were therefore not part of the present study because a major aim was to investigate the incidence of diabetes. At our center treatment with insulin was initiated if mean capillary blood glucose on diet exceeded 7 mmol/liter or single values often surpassed 8 mmol/liter. Home blood glucose was measured four times daily 2 d/wk. Of the total GDM population from the years of the study, 15–16% were treated with insulin. Further details on study design and baseline characteristics have been presented previously (13). Sixty-four percent of the total GDM population diagnosed during the above-mentioned periods was examined at follow-up. The participants were comparable with nonparticipants regarding maternal age at delivery, blood glucose and gestational age at diagnostic oral glucose tolerance test, ethnic origin, and glucose tolerance status post partum. However, the participants had a lower prepregnancy BMI than nonparticipants [median 25.1 (interquartile range 21.9–29.8) and 26.9 kg/m^2 (22.0–31.7), $P = 0.035$] (13). Median follow-up length was 9.8 yr (6.4–17.2). Among the 88.6% answering a questionnaire regarding family history of diabetes, 63.8% had a family history of diabetes (in children, siblings, parents, or grandparents). Known diabetes was reported by 22.0% (13).

For the control group, 1000 age-matched women (95% Danish origin) randomly selected from a population-based study (Inter99) in a neighboring county (21) comprised the control group. The Inter99 is a population-based primary prevention study of cardiovascular disease. An age- and gender-stratified random sample of 12,934 eligible individuals aged 30–60 yr was invited. The participants were invited stratified on age and gender. The participants were born in 1939–1940, 1944–1945, 1949–1950, 1954–1955, 1959–1960, 1964–1965, or 1969–1970. All participants born in the years ending with 4 or 9 were examined in 1999, whereas those ending with 0 or 5 were examined in 2000. Ninety-one percent were parous, 19.6% had a family history of diabetes, and 1.7% reported to have known diabetes.

Plasma glucose, serum insulin, serum high-density lipoprotein (HDL) cholesterol, serum triglycerides, and plasma free fatty acids (FFA) were measured from venous blood samples obtained in the morning after an overnight fast and hemoglobin A_{1c} (HbA_{1c}) from capillary blood (FFA and HbA_{1c} only GDM subjects). Women without known diabetes had a 2-h 75-g oral glucose tolerance test with measurement of 2-h plasma glucose. Glucose tolerance was evaluated according to the criteria by WHO 1999 (16).

Anthropometrical measurements

In the GDM group, anthropometrical measurements included height to nearest centimeter without shoes and weight to nearest 0.1 kg in light clothing. Waist circumference was measured at the level of the narrowest part of the torso and hip circumference at the level of the maximum extension of the buttocks. Waist circumference divided by hip circumference gives the waist to hip ratio. Blood pressure was measured three times using an automatic Kivex 750 with an appropriate-sized cuff on the right arm while sitting and after a 5-min rest. Body fat mass was measured by bioelectrical impedance using a tetrapolar Biodynamics body composition analyzer, model 310e (Biodynamics Corp., Seattle, WA) with a 50 kHz, 1 mAmp device, following the instructions given by the manufacturer.

In the control group, height was measured to the nearest 0.5 cm without shoes and weight to the nearest 0.1 kg in light clothing. Waist circumference was measured midway between the lower rib margin and the iliac crest. Blood pressure was measured twice using a standard mercury sphygmomanometer with an appropriate-sized cuff with participants in a supine position after a 5-min rest.

Blood pressure measured with the automatic device in the sitting position was comparable with the mercury meter in a validity study including 33 women [123/78 (14/10) *vs.* 123/78 (14/10) mm Hg, mean (SD)]. In the supine position the diastolic blood pressure was slightly lower 122/74 (14/11) mm Hg ($P < 0,01$). Hypertension was defined as blood pressure 140/90 mm Hg or more. Women with known antihypertensive medication within the last 2 wk before the examination were considered hypertensive.

BMI was calculated as the weight (kilograms) divided by the height (meters) squared. Overweight was defined as BMI 25 kg/m^2 or more and obesity as BMI 30 kg/m^2 or more (1). Mean systolic and mean diastolic blood pressure was calculated.

Biochemical methods

Blood samples for glucose measurements were taken in heparin-sodium fluoride glasses, immediately put on ice, centrifuged and plasma separated within 30 min, and analyzed by the glucose oxidase method on a Cobas Mira analyzer (Roche, Mannheim, Germany) (for control group on a Hitachi 917, Roche Molecular Biochemicals, Mannheim, Germany). Serum insulin for both the GDM and control groups was measured in the same laboratory on an AutoDelfia (Wallac/PerkinElmer, Turku, Finland) by a fluoroimmunometric assay using monoclonal antibodies (insulin kit K6219, Dako Diagnostics Ltd., Ely, UK). Serum HDL cholesterol, serum triglycerides, and plasma FFAs were measured on a Cobas Mira (control group: Hitachi 917) by colorimetric methods. On the day of examination, the subjects not reporting menstrual bleeding delivered a urine sample. The urine from the prior GDM women was tested with reagent strip (Nephur-Test+Leuco, Roche Molecular Biochemicals) to exclude hematuria and urinary tract infection. The urine from women in the control group was not tested with a reagent strip. Except in cases of hematuria and urinary tract infection, the urine was examined for urinary albumin and creatinine. The urine was analyzed on a Hitachi 917. Urinary albumin concentration (milligrams per liter) was measured using an immunoturbidimetric assay (GDM group: Tina-quant albumin; Roche Diagnostics, Mannheim, Germany; control group: Dako, Glostrup, Denmark) and urinary creatinine concentration (grams per liter), by the Creatinine Jaffé method (Roche). The albumin to creatinine ratio (urinary albumin concentration to urinary creatinine concentration) (milligrams per gram) was calculated in urine from 71.1% of the GDM subjects and 99.8% of the control subjects.

In the GDM group only, HbA_{1c} was analyzed by an antibody immunoassay (DCA 2000 HbA_{1c} reagent kit, Bayer, Elkhart, IN). The normal range in (± 2 SD) in the background population was 4.1–6.4%. Percent body fat was calculated with an equation for female Danes (22) aged 35–65 yr [weight − 0.1815 weight (kilograms) + 0.2789 height^2/resistance (square centimeters per ohm) − 0.0766 age (years) + 0.2305 height (centimeters) − 14.941)]/weight ∗ 100.

Before participation, informed and written consent was obtained from all subjects. The study was approved by the ethical committee of Copenhagen and was in accordance with the principles of the Declaration of Helsinki II.

The metabolic syndrome

Because no single definition for the metabolic syndrome has been accepted worldwide and to give the possibility for comparison with the majority of studies on the same topic, we applied three often used criteria to examine the prevalence of the metabolic syndrome: WHO 1999 (16), ATP III 2000 (17), and EGIR 2002 (18). The various definitions are listed in Table 1. The EGIR criteria relate only to nondiabetic subjects, and due to the fact that diabetes is common among women with previous GDM, we decided to use the WHO-defined metabolic syndrome for more specific analyses. Insulin resistance measured under hyperinsulinemic euglycemic conditions is part of the criteria by WHO. However, in epidemiological studies, insulin resistance can be evaluated by fasting serum insulin (23). Fasting serum insulin was therefore chosen as a measure for insulin resistance in the estimation of the prevalence of the WHO-

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TABLE 1. Components of the metabolic syndrome according to three definitions

WHO 1999	
Either impaired glucose regulation or diabetes	Plasma glucose: fasting ≥ 6.1 mmol/liter or (if measured) 2-h postglucose load ≥ 7.8 mmol/liter Capillary whole blood glucose: fasting ≥ 5.6 mmol/liter or (if measured) 2-h postglucose load ≥ 7.8 mmol/liter
or insulin resistance[a]	Fasting serum insulin ≥ third quartile for women in control group[b]
And at least two of the following:	
Raised arterial pressure	≥ 140/90 mm Hg[c]
Dyslipidemia	Fasting serum triglyceride ≥ 1.7 mmol/liter or HDL < 1.0 mmol/liter
Central obesity	Waist to hip ratio > 0.85 or BMI > 30 kg/m^2
Microalbuminuria	Albumin/creatinine ≥ 30 mg/g
ATP III 2001	
At least three of the following:	
Abdominal obesity	Waist circumference > 88 cm
Hypertension	≥ 130/≥ 85 mm Hg[c]
Abnormal glucose tolerance	Fasting plasma glucose ≥ 6.1 mmol/liter
Triglyceride	Fasting serum triglyceride ≥ 1.7 mmol/liter
HDL cholesterol	Fasting serum HDL cholesterol < 1.3 mmol/liter
EGIR 2002[d]	
Hyperinsulinemia	Fasting serum insulin ≥ third quartile for nondiabetic women in control group[e]
And at least two of the following:	
Hyperglycemia	Fasting plasma glucose ≥ 6.1 mmol/liter or capillary whole blood ≥ 5.6 mmol/liter
Hypertension	Systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg and/or treatment for hypertension
Dyslipidemia	Fasting serum triglyceride > 2.0 mmol/liter and/or HDL < 1.0 mmol/liter and/or treatment for dyslipidemia
Central obesity	Waist circumference > 80 cm

[a] Insulin resistance according to WHO is originally defined as glucose uptake below lowest quartile for background population under hyperinsulinemic, euglycemic conditions.
[b] Third quartile (WHO), 48 pmol/liter.
[c] Treatment for hypertension was originally not included in the definition by WHO and ATP III as is the case by EGIR, although in this study we have chosen to include women on antihypertensive medication in the group with hypertension.
[d] The EGIR insulin resistance syndrome is defined for nondiabetic subjects only: fasting plasma glucose < 7.0 mmol/liter and 2-h plasma glucose < 11.1 mmol/liter if the latter is available.
[e] Third quartile (EGIR), 47 pmol/liter.

defined metabolic syndrome. Insulin resistance was defined as fasting serum insulin equal to or above the third quartile for the background population (the control group): 48 pmol/liter or more. Insulin resistance according to the criteria by EGIR (18) was defined as fasting serum insulin equal to or above the third quartile for the nondiabetic background population (875 women from control group): 47 pmol/liter or more.

Statistics

The χ^2 test was used for comparison of proportions in two groups and trend test for comparison of proportions in more than two groups. The Mann-Whitney test was used for comparison of medians in two groups and Kruskal-Wallis test for comparison in more than two groups. Multiple logistic regression analysis was used for calculating the age and BMI adjusted odds ratio (OR) in the prior GDM group for having the metabolic syndrome, compared with the control group. A two-sided $P < 0.05$ was considered significant. SPSS for Windows (version 11.0; SPSS, Inc., Chicago, IL) was used for statistical analysis.

Results

Table 2 shows the phenotypic characteristics of the 481 women in the prior GDM group and the 1000 age-matched women in the control group. One major difference between the prior GDM group and the control group was that the prevalence of diabetes was more than 10 times higher in the prior GDM group, 39.9 *vs.* 3.3%. In general, the prior GDM group had a cardiovascular profile that was significantly more unfavorable, compared with the control group, with higher levels of serum insulin and triglyceride, lower levels of serum HDL cholesterol, and more obesity. However, the diastolic blood pressure among nonhypertensive women from the control group was marginally higher, compared with the prior GDM group.

The metabolic syndrome was three times as frequent in women with a history of GDM, compared with the control group, independent of the definition (Table 3). After adjustment for BMI and age, the OR for having the metabolic syndrome according to WHO in the previous GDM group, compared with the control group, was 3.4 (95% confidence interval 2.5–4.8).

The prevalence of the metabolic syndrome and the individual components of the metabolic syndrome according to WHO increased with increasing BMI in both the prior GDM group and the control group and was highest in all BMI groups in the prior GDM group (Table 4). Insulin resistance (based on fasting serum insulin) was present in 87% of the obese prior GDM women *vs.* 61% in the obese control group. Median fasting insulin was 75 and 57 pmol/liter ($P < 0.0005$), respectively. Only microalbuminuria was not significantly different between the BMI groups in the control group. Hyper-

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TABLE 2. Phenotypic characteristics of the prior diet-treated GDM group at follow-up 4–23 yr after index pregnancy with GDM as compared with the control group

	Prior GDM group (n = 481)	Control group (n = 1000)	*P*
Age (yr)	42.9 (37.7–47.8)	45.0 (39.9–50.2)	<0.0005
BMI (kg/m^2)	27.9 (24.1–32.9)	24.6 (22.2–27.9)	<0.0005
Waist circumference (cm)	91 (80–100)	78 (71–86)	<0.0005
Waist to hip ratio	0.83 (0.78–0.87)	0.79 (0.76–0.83)	<0.0005
Glucose intolerance	67.6% (325/481)	19.2% (175/910)	<0.0005
IFG	11.0% (53/481)	4.3% (39/910)	<0.0005
IGT	10.6% (51/481)	9.5% (86/910)	0.493
IGT and IFG	6.0% (29/481)	2.2% (20/910)	<0.0005
Diabetes	39.9% (192/481)	3.3% (30/910)	<0.0005
Fasting serum insulin (pmol/liter)	53.8 (34.9–78.3)	31.0 (23.0–48.0)	<0.0005
Systolic BP (mm Hg)[a]	119 (111–126)	120 (110–125)	0.206
Diastolic BP (mm Hg)[a]	73 (66–78)	75 (70–80)	<0.0005
Hypertension (%)	27.8	30.1	0.363
Fasting serum triglyceride (mmol/liter)	1.3 (0.9–1.9)	1.0 (0.7–1.3)	<0.0005
Fasting serum HDL (mmol/liter)	1.4 (1.2–1.7)	1.5 (1.3–1.8)	<0.0005
Urine albumin to creatinine ratio (mg/g)	7.6 (4.6–17.7)	3.0 (3.0–5.0)	<0.0005

Data are presented as median (interquartile range) or proportions (number). BP, Blood pressure.
[a] Nonhypertensive women not taking antihypertensive treatment.

tension was significantly more frequent in the control group with BMI more than 25 kg/m^2, but after adjusting for age and BMI in a multiple logistic regression analysis, there was no significant difference in the prevalence of hypertension between the prior GDM group and the control group. Among women with prior GDM and BMI less than 25 kg/m^2, 50% had impaired glucose regulation and 26% insulin resistance.

The prevalence of the metabolic syndrome increased with increasing deterioration in glucose tolerance in both the prior GDM and control groups (Table 5). However, the prevalence of the metabolic syndrome was more than 2-fold increased among glucose-tolerant women with prior GDM, compared with the control group. BMI was higher (median 25.1 *vs.* 24.2 kg/m^2, $P = 0.031$) and age was lower (41.7 *vs.* 45.0 yr, $P < 0.0005$) in the prior GDM group with normal glucose tolerance, compared with the control group. BMI was equal between the prior GDM and control groups with impaired fasting glucose (IFG)/impaired glucose tolerance (IGT) or diabetes, but the age was significantly higher in the control group: 43.1 *vs.* 50.0 yr, $P < 0.0005$, in women with IGT/IFG and 43.4 *vs.* 49.8 yr, $P < 0.001$, in women with diabetes.

Besides the expected differences regarding the individual components of the metabolic syndrome, the prior GDM women with the metabolic syndrome also differed from women without the metabolic syndrome on several other characteristics (Table 6): higher age; longer follow-up; larger weight gain since index pregnancy; and higher values of fat mass, FFAs, and HbA_{1c}. There was no difference in ethnic origin.

Discussion

The prevalence of the metabolic syndrome was nearly 40% in 43-yr-old women with previous GDM and three times higher than in a population-based sample of age-matched women, independent of the criteria used. The significantly higher risk of the WHO-defined metabolic syndrome in the prior GDM group. compared with the control group, persisted after adjusting for age and BMI (OR 3.4). This equals a longitudinal study by Verma *et al.* (15) in which the prevalence of the metabolic syndrome according to ATP III was three times higher in the GDM group, compared with a control group, 11 yr after pregnancy. Among our glucose-tolerant subjects, the prevalence of the WHO-defined metabolic syndrome was around two times higher in the prior GDM group, compared with the control group, whereas no major differences were found in women with IFG/IGT or diabetes.

In both the prior GDM women and the women from the control group, the prevalence of the metabolic syndrome according to WHO was more than two times higher in overweight

TABLE 3. The prevalence of the metabolic syndrome and its components in women with prior diet-treated GDM according to WHO, ATP III, and EGIR definitions as compared with the prevalence of the metabolic syndrome in the control group

	WHO (Ref. 16)	ATP III (Ref. 17)	EGIR (Ref. 18)
Impaired glucose regulation	67.6 (325/481)	54.9 (252/459)	28.2 (82/291)[a]
Insulin resistance	58.5 (268/458)		56.5 (156/276)
Hypertension	27.8 (128/461)	42.7 (197/461)	20.5 (57/277)
Microalbuminuria	12.0 (41/342)		
Central obesity	54.1 (256/473)	59.5 (279/469)	71.7 (203/283)
Dyslipidemia	35.1 (161/459)	HDL: 34.4 (158/459) Triglyceride: 31.8 (146/459)	18.3 (51/278)
Metabolic syndrome in prior GDM group	38.8 (180/464)	43.5 (199/457)	32.4 (89/275)
Metabolic syndrome in control group	13.4 (134/999)[b]	14.8 (146/987)[b]	11.1 (98/879)[b]

For definitions of the components in the metabolic syndrome, see Table 1. Data are presented as percentage (number with the component/total number with available data on the component).
[a] Only nondiabetic women.
[b] $P < 0.0005$ for the difference in the prevalence of the metabolic syndrome between prior GDM group and control group.

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TABLE 4. The prevalence of the individual components and the metabolic syndrome according to WHO[a] stratified by BMI in the prior diet-treated GDM group and control group

BMI	<25 kg/m^2	25–30 kg/m^2	≥30 kg/m^2	P^b
Prior GDM group				
Age (yr)	43.0 (37.7–49.6)	42.9 (37.3–47.4)	42.5 (38.3–47.2)	0.667
Glucose intolerance	50.3% (<0.0005)	70.0% (<0.0005)	79.1% (<0.0005)	<0.0005
Insulin resistance	25.7% (<0.0005)	57.1% (<0.0005)	86.9% (<0.0005)	<0.0005
Hypertension	13.9% (0.107)	25.2% (0.040)	40.7% (0.018)	<0.0005
Dyslipidemia	17.6% (0.012)	34.6% (0.006)	49.7% (0.009)	<0.0005
Central obesity	14.9% (0.009)	34.1% (0.001)	100.0%	<0.0005
Microalbuminuria	7.4% (0.021)	10.5% (0.001)	16.4% (<0.0005)	0.029
Metabolic syndrome	11.4% (<0.0005)	26.1% (<0.0005)	70.6% (<0.0005)	<0.0005
Total number[c]	149	134	180	
Control group				
Age (yr)	44.9 (39.9–50.1)	45.2 (40.1–54.8)	45.3 (40.1–54.8)	0.002
Glucose intolerance	10.8%	19.3%	37.6%	<0.0005
Insulin resistance	11.7%	29.2%	60.8%	<0.0005
Hypertension	19.8%	33.1%	53.2%	<0.0005
Dyslipidemia	9.7%	21.4%	35.7%	<0.0005
Central obesity	7.5%	19.3%	100.0%	<0.0005
Microalbuminuria	2.6%	2.0%	2.9%	0.909
Metabolic syndrome	2.6%	11.5%	50.0%	<0.0005
Total number[c]	531	296	172	

[a] The definitions are outlined in Table 2. Data are presented as median (interquartile range) or percentage. *P* values in *parentheses* are GDM *vs.* control.
[b] Kruskal-Wallis test for continuous data and trend test for proportions.
[c] Total number of women with sufficient data to evaluate the presence of the metabolic syndrome.

women, compared with normal-weight women. The prevalence was even higher in obese women. Because the proportion of prior GDM women with increased BMI examined in the present study was significantly higher than in the control group, this partly explains the differences in the prevalence of glucose intolerance, because obesity, both central obesity and a significantly increased BMI, is related to the incidence of diabetes (24, 25). Furthermore, in the prior GDM group, the prepregnancy BMI was higher among nonparticipants, compared with participants, so the true prevalence of the metabolic syndrome might be even higher than found in our study. A high energy intake and low energy expenditure in a genetically susceptible individual can result in obesity and increased mortality (1, 26). We have previously shown that pregestational overweight among women with diet-treated GDM is a strong predictor for development of overt diabetes later in life (13). Several studies have shown that simple lifestyle changes such as reduction in energy intake, daily moderate physical activity, or oral hypoglycemic agents can reduce the risk for developing diabetes or diabetes-related complications (27–30). Yet even with intensive instructions regarding modification of diet and exercise, it can be difficult for the patients to sustain the lifestyle changes (31, 32).

Women with severe overweight more often need treatment with insulin during pregnancy due to a higher degree of insulin resistance. This group is therefore expected to develop the metabolic syndrome more often than the diet-treated GDM. Because our study included only women with previous diet-treated GDM, the prevalence of the metabolic syndrome is expected to be even higher in the total GDM population.

The prevalence of the metabolic syndrome was slightly higher when applying the definition by ATP III due to a lower cut-off for hypertension and a higher cut-off for HDL, and the prevalence was slightly lower when applying the criteria by EGIR because only nondiabetic subjects were included. because the incidence of diabetes was 10-fold increased in the prior GDM population (39.1%), many of these women were excluded from evaluation when applying these criteria (18). However, an evaluation of the overall cardiovascular risk profile by defining the metabolic syndrome is also relevant in a diabetic population because it predicts a more than 2-fold increased risk for morbidity and mortality (3). In a nondiabetic population, the metabolic syndrome according to WHO (16) is still more frequent than the syndrome by the EGIR criteria (18), which might be due to the fact that, opposite the ATP III and EGIR definitions, the WHO definition includes both the fasting and 2-h plasma glucose when evaluating the glucose tolerance. The definition by WHO has previously been found to be superior in predicting cardiovascular death, compared with ATP III (4), and could be explained by the 2-h glucose that is a good predictor for increased morbidity (33). To our knowledge the

TABLE 5. The prevalence of the WHO-defined metabolic syndrome according to the glucose tolerance in the prior diet-treated GDM group and the control group

Glucose tolerance[a]	NGT	IFG and/or IGT	Diabetes	*P* for trend
No. GDM/control	153/735	127/145	184/30	
Metabolic syndrome in prior GDM group	12.4%	43.3%	57.6%	<0.0005
Metabolic syndrome in control group	5.3% (0.001)	40.7% (0.662)	76.7% (0.048)	<0.0005

Data are presented as percentage (*P* value for GDM *vs.* control group). NGT, Normal glucose tolerance.
[a] According to the criteria by WHO (16).

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TABLE 6. The phenotype of women with and without the WHO-defined metabolic syndrome 4–23 yr after index pregnancy with gestational diabetes

	The metabolic syndrome by WHO		
	No	Yes	*P*
N	284	180	
Age (yr)	42.1 (36.8–47.4)	43.3 (39.0–48.3)	0.044
BMI (kg/m^2)	25.4 (22.5–28.9)	32.4 (28.6–35.6)	<0.0005
Follow-up length (yr)	8.8 (5.9–17.1)	10.6 (7.1–17.3)	0.032
Danish origin	75.4%	72.8%	0.586
Weight gain since pregnancy (kg)	5.0 (1.2–9.4)	7.1 (1.0–15.4)	0.003
Fat mass (%)	33.9 (28.6–38.8)	42.4 (38.0–45.4)	<0.0005
Waist circumference (cm)	84 (77–93)	100 (94–108)	<0.0005
Systolic BP (mm Hg)	119 (111–128)	139 (125–150)	<0.0005
Diastolic BP (mm Hg)	73 (66–79)	83 (76–92)	<0.0005
Fasting serum insulin (pmol/liter)	43 (29–60)	74 (55–98)	<0.0005
Fasting serum HDL cholesterol (mmol/liter)	1.53 (1.31–1.80)	1.29 (1.08–1.50)	<0.0005
Fasting serum triglyceride (mmol/liter)	1.02 (0.75–1.438)	1.94 (1.42–2.57)	<0.0005
Fasting plasma FFA (mmol/liter)	0.53 (0.40–0.72)	0.60 (0.47–0.79)	0.003
Albumin to creatinine ratio (mg/g)	6.9 (4.3–15.0)	9.2 (4.9–29.9)	<0.001
HbA_{1c} (%)	5.3 (5.0–5.8)	6.0 (5.4–7.4)	<0.0005

Data are presented as median (interquartile range) or percentage. BP, Blood pressure.

EGIR criteria have not yet been evaluated with respect to cardiovascular or all-cause mortality.

The WHO definition includes microalbuminuria, which is positively correlated with hypertension and, when present, is a sign of atherosclerotic damage of the vascular system (34). The criterion hypertension was more often met by the control group, compared with the prior GDM group, although the opposite would be expected because the GDM group otherwise encompasses more cardiovascular risk factors. Furthermore, blood pressure was measured supine in the control group, compared with sitting in the GDM group, and our pilot study found a marginally but significantly lower diastolic blood pressure in the supine position. The higher proportion with hypertension might partly be due to the fact that the control group was slightly older, and after adjusting for age and BMI, the difference in the prevalence of hypertension disappeared. The way of measuring the waist circumference in the GDM and control groups differed slightly, but similar to the differences in blood pressure measurement, this would tend to underestimate the prevalence of the metabolic syndrome in the GDM group (35).

We did not have exact data on the prevalence of GDM in the control group. However, more than 90% of the controls were parous, similar to the Danish background population. With a prevalence of GDM around 2%, approximately 18 women in the control group could be expected to have had GDM. If none in the control group have had GDM, the difference in the prevalence of the metabolic syndrome would be even larger. If the prevalence of GDM in the control group was higher, we would expect a higher prevalence of diabetes in this group. The prevalence of the metabolic syndrome might be lower in nonparous women because pregnancy is an insulin-resistant state, and in the case of GDM, a degree of insulin resistance often persists after pregnancy. Yet the prevalence of the metabolic syndrome is higher among men (36). We have previously shown that within the GDM group, family history, but not parity, was a predictor for type 2 diabetes (13). A family history of diabetes was three times more frequent in the prior GDM group, compared with the control group. Overall the prior GDM group was more likely having the metabolic syndrome. However, we believe the control group corresponds to the general population in Denmark. Because age and BMI are important variables when evaluating the prevalence of the metabolic syndrome and because these variables are included in our analyses, we find the control group suitable for comparison with the GDM group despite the above-mentioned differences in the examination.

The ATP III definition (17) does not include a measure for insulin resistance, which is a crucial abnormality in both GDM diabetes and obesity (2, 14, 37, 38). It therefore seems important to include insulin resistance when evaluating the risk for cardiovascular morbidity and mortality in this population. Also, the ATP III criteria differed markedly from the generally accepted cut-off values for blood pressure and fasting plasma HDL in Denmark, another important fact in the decision of which definition to select when wanting to evaluate a patient's cardiovascular morbidity. A universal set of criteria for the metabolic syndrome is preferable and should ideally be based on data from prospective studies. Obviously, different cut-off values for obesity, blood pressure, and dyslipidemia will define different populations as having the metabolic syndrome as previously shown (4, 39). Furthermore, the prevalence of the metabolic syndrome according to the different definitions differs between different ethnic groups (40). However, ethnicity was not found to be associated with the metabolic syndrome in the present study.

In conclusion, independent of the definition of the metabolic syndrome, we found a 3-fold higher prevalence of the metabolic syndrome in the prior GDM group, compared with the control group. The difference was mainly due to a high proportion with abnormal glucose tolerance and increased BMI in the GDM group. Women with previous diet-treated GDM and the metabolic syndrome at follow-up had a high-risk health profile and hence comprised a group with significantly increased risk for morbidity and mortality. An offer of regular evaluation for vascular disease and early institution of a targeted pharmacological intervention together with education and motivation in healthy lifestyle habits might improve this health risk profile.

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