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Adiposity in 277 young adult male offspring of women with diabetes compared with controls: A Danish population-based cohort study

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Abstract

Objective—To examine the associations of maternal diabetes, overall and stratified according to treatment of diabetes, with weight-related outcomes at the time of military conscription, at age 18–20 years.

Design and setting—Cohort study of 277 Danish male offspring of mothers with recognized pre-gestational or gestational diabetes. As population-based controls we selected 870 men matched from the Civil Registration Office.

Methods—Data on weight-related outcomes were retrieved from the Danish military conscription registry.

Main outcome measures—Military rejection due to adiposity and body mass index (BMI) at conscription.

Results—Army rejection rate due to adiposity was 5.8% ($n = 16$) among 277 diabetes mellitus-exposed men compared with 3.1% ($n = 27$) in 870 controls (risk difference 2.7 (95% confidence interval (CI) -0.3 – 5.7)) and mean BMI at conscription was 1.4 kg/m^2 (95%CI 0.8 – 2.0) higher among those diabetes mellitus-exposed men. In analyses adjusted for birthweight and gestational age, compared with controls, the BMI was 0.6 kg/m^2 (95%CI -0.3 – 1.5) higher in sons of mothers with pre-gestational and 2.7 kg/m^2 (95% (CI): 0.9 – 4.5) higher with gestational diabetes. The

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Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

greatest BMI difference was in offspring of mothers with gestational diabetes in whom insulin was initiated during pregnancy. We found no difference in conscript height.

Conclusions—Compared with controls, male offspring of women with diabetes had a higher rejection rate due to adiposity and higher adult BMI. Subgroup analyses showed that the association was most pronounced in sons of mothers with gestational diabetes, whereas pre-gestational diabetes was only weakly associated with higher offspring BMI.

Keywords

Adiposity; conscription; male; maternal diabetes; offspring body mass index

Introduction

Previous studies have found a positive association between birthweight and body mass index (BMI) attained later in life, suggesting that early life factors may be determinants of later obesity (1–3). One of these factors may be maternal diabetes during pregnancy. Offspring of women with diabetes are exposed to an altered intrauterine metabolism with maternal hyperglycemia and fetal hyperinsulinemia leading to higher birthweights (4). These intrauterine influences may program the fetus to be at increased risk of obesity later in childhood or in adulthood (5). Few studies, however, have addressed long-term height and weight outcomes of offspring of mothers with diabetes, and the results have been divergent. Two Scandinavian studies reported that offspring of mothers with type 1 and gestational diabetes had higher BMI in young adulthood compared with controls (6,7). Lawlor et al. found a positive association between maternal gestational diabetes and offspring obesity at age 9–11 years, but did not find this in offspring of mothers with pre-existing diabetes (8). In a study of offspring of USA nurses, Gillman et al. (9) found a moderately increased risk of adolescent obesity among offspring of mothers with gestational diabetes compared with no diabetes, but adjustment for maternal BMI attenuated the association. In a sib-pair analysis, which controlled for genetic differences, Dabelea et al. (10) found higher BMI from adolescence to young adulthood among sibs exposed compared with those unexposed to diabetes in utero. However, that study was among Pima Indians, who have a higher risk of obesity and diabetes, making the generalizability of the results questionable. In a multiethnic USA population of nearly 10 000 mother–child pairs in which universal screening for gestational diabetes was performed, Hillier et al. (11) observed that increasing maternal hyperglycemia in pregnancy was associated with an increased weight-for-age percentile at age 5–7 years, and in women receiving treatment for hyperglycemia the risk of obesity in offspring was reduced. However, in a follow-up of a randomized trial, Gillman et al. (12) found no effect of treatment of mild gestational diabetes in pregnant women on the BMI of 4- to 5-year-old children.

Our present knowledge about the association of exposure to a diabetic intrauterine environment with adult offspring obesity is thus divergent. The prevalence of both diabetes and obesity is increasing, with major consequences in terms of morbidity. We therefore found it of interest to examine these associations further, especially to distinguish effects of pre-gestational vs. gestational diabetes.

The aim of this study therefore was to examine in a cohort of young Danish men, compared with a control group, the associations of exposure to recognized diabetes in utero, overall and according to whether the diabetes was pre-gestational or gestational, with army rejection rate due to adiposity, and with height, weight and body mass index at time of military conscription.

Material and methods

From the medical records of the obstetrics departments in two Danish hospitals (Rigshospitalet, Copenhagen, and Aalborg Hospital, North Jutland County), we identified all boys born between 1976 and 1984 to women with pre-gestational or gestational diabetes (DM-exposed). In Denmark, at that time all pregnant women were routinely offered regular and free outpatient care and hospitalization if necessary. Care of pregnant women with diabetes in eastern Denmark (1.5 million inhabitants) and North Jutland County (0.5 million inhabitants) was confined to these two hospitals. The diabetic pregnancies were classified according to the Rigshospitalet University Hospital modification of the White classification (13). The DM-exposed cohort was stratified according to time of diagnosis of diabetes in relation to pregnancy. We divided the pre-gestational group ($n = 185$) into a type 1 group ($n = 151$) and a diet-only treated group ($n = 34$). In the gestational diabetes group ($n = 34$), diabetes was diagnosed for the first time during pregnancy, and we divided them into diet-treated ($n = 22$) and diet plus insulin treatment ($n = 12$) during the pregnancy.

In the study period, Danish guidelines recommended that pregnant women be screened for diabetes with an oral glucose challenge test (OGTT) in gestational weeks 24–26 if they met one of the following criteria: (1) previous birth of a baby with birthweight >4500 g; (2) maternal overweight $>130\%$; (3) family history of diabetes; (4) glucosuria or (5) previous obstetrical complications or late miscarriage. In the case of abnormal OGTT, the woman was admitted to hospital to monitor blood glucose and/or instructed in home monitoring of blood glucose, and she received dietary instructions. Depending on blood glucose values the obstetrician decided whether dietary interventions were sufficient (diet-only group) or insulin therapy was warranted (insulin-initiated group). Because of missing data, six women with diabetes during pregnancy could not be classified into pre-gestational or gestational diabetes.

We collected data on birthweight and gestational age on all DM-exposed and controls from hospital records and the Danish Medical Birth Registry (14). This Registry contains information on all births in Denmark since 1 January 1973 from the official reports filed by the midwives, who attend all deliveries in Denmark.

From the nationwide Central Office of Civil Registration we randomly identified three control pregnancies with singleton male offspring matched per DM-exposed woman, delivered within one year before or after the birth day of the exposed male offspring and in which the pregnant women lived in the same municipality as the mother with diabetes.

Weight and height at Draft Board examination

It is mandatory that all Danish men register with the military Draft Board sometime between the ages of 18 and 20 years. At the time of conscription, all young men complete a health questionnaire in which they can report chronic health problems that could preclude military service, such as asthma or low back pain. The Draft Board verifies such reports with health care providers, and men deemed unfit for military service are exempt from further examination. Conscription test results are thus unavailable for these men (non-presenters) but we have access to the medical diagnosis leading to rejection. We report the number of exempted men due to adiposity (International Classification of Diseases, version 10: E66 'overweight and obesity') among DM-exposed and controls as one of our study outcomes.

The remaining men (presenters) go through a standardized medical examination at the Draft Board including measuring height and weight. Height was measured without shoes and weight was recorded in underwear only on a standard scale. All data regarding health conditions are filed in the Conscript Registry, from which we retrieved data on height and weight for all presenters.

Statistical analyses

All Danes receive a 10-digit personal registration number at birth or upon immigration, permitting unambiguous linkage between different registries. Having linked data we first cross-tabulated the study variables and outcomes and reported recorded height, weight and BMI in DM-exposed and controls. The difference in rejection rate for military service was reported as risk difference with associated 95% confidence interval. The difference in mean BMI at conscription was assessed by an unpaired t-test. For each infant, we calculated birthweight adjusted for sex and gestational age based on Danish standard tables (15). Z-scores were calculated from the formula (observed weight–expected weight)/standard deviation, where expected birthweight and standard deviation were taken from these standard tables. For BMI as an outcome, we used multiple linear regression models before and after adjustment for gestational age (weeks) and birthweight (g). The results are reported with 95% confidence intervals. The study was approved by the Regional Ethics Committee, file no. 2-16-4-5-95. We used version 9.0SE of STATA software for all analyses (16).

Results

The DM-exposed cohort consisted of 277 male 18–20-year-old offspring of women with diabetes, of whom 225 had valid data on height and weight at conscription; for 216 we also had data on gestational age and birthweight (Table 1). The control group consisted of 870 men of the same age of whom 737 had valid data on height and weight at conscription; 637 also had data on gestational age and birthweight in the registries (Table 1). Mean gestational age at birth among DM-exposed was 36.8 weeks compared with 38.8 among controls, giving an absolute difference of 2.0 weeks ((95% confidence interval (CI) 1.7–2.4)).

Among 277 DM-exposed men, 147 (53%) were rejected for any reason compared with 395 of 870 (45%) controls, giving a risk difference of 7.7% (95% CI 0.9–14.4). Based on 16 men (5.8%) rejected due to adiposity in the DM-exposed group and 27 (3.1%) among controls,

the risk difference of rejection due to adiposity was 2.7% (95%CI -0.3–5.7, $p = 0.04$). In the pre-gestational group the risk difference was 1.6% (95%CI -1.3–4.6) compared with 4.8% (95%CI -3.9–13.4) in the gestational group. For 41 of these 43 men rejected due to adiposity, we had data on height and weight. Mean BMI of these DM-exposed and controls was 35.1 and 35.8 kg/m², respectively. The following four categories accounted for 64% of all rejections among 185 non-presenters: respiratory (25%), behavioral (16%), musculoskeletal (12%) and hearing loss (10%).

The observed mean difference in BMI at conscription between all DM-exposed ($n = 225$) and controls ($n = 737$) was 1.4 kg/m² (95%CI 0.8–2.0), equivalent to 4.7 kg for a height of 180.3 cm, which was the mean in both groups. In the pre-gestational and gestational groups, BMI at conscription was 1.1 kg/m² (95%CI 0.4–1.7) and 2.9 kg/m² (95%CI 1.5–4.3) higher than in controls, respectively (Table 2).

When birthweight adjusted for sex and gestational age was added to the models, these differences were attenuated to 0.6 kg/m² (95%CI -0.3–1.5) in the pre-gestational group and to 2.7 kg/m² (95%CI 0.9–4.5) in the gestational group. This 2.7 kg/m² difference is equivalent to 6.3 kg for a man with the mean height of 180.3 cm. Sons of women with pre-gestational type 1 diabetes had the smallest difference in BMI (0.5 kg/m²; 95%CI -0.5–1.5) compared with controls, whereas the largest increase in adult BMI was seen among offspring of women with gestational diabetes in whom insulin had been instituted (4.0 kg/m²; 95%CI 1.5–6.6).

Discussion

We found that sons of mothers with diabetes had higher military rejection rates due to adiposity and that among those presenting at the Draft Board, the mean BMI was 2.7 kg/m² higher among those exposed to gestational diabetes in utero compared with controls. Exposure to pre-gestational type 1 diabetes was only weakly associated with a higher BMI at conscription.

Our findings add to previous studies that have raised the possibility of a stronger effect of gestational than pre-gestational diabetes on offspring adiposity, but these studies have not been able to address the question as directly as our study has. Clausen et al. (6) found that offspring of women with gestational diabetes had an additional BMI of 1.3 kg/m² at the age of 18–27 years, whereas maternal type 1 diabetes was associated with an additional 1.1 kg/m². With a shorter observational period of 9–16 years, both Gillman et al. (9) and Väärasmäki et al. (7) have reported higher BMI and percentages of overweight individuals in offspring of women with gestational diabetes compared with non-diabetic controls, but they did not include pre-gestational diabetes. In a study of 40 type 1 diabetic pregnancies and 53 with gestational diabetes pregnancies, Lawlor et al. (8) likewise found higher odds of obesity at 9–11 years of age in offspring of gestational as compared with pre-gestational diabetes, but the sample size was limited. In a cohort of Pima Indians, Dabelea et al. (10) reported that mean adolescent BMI was 2.6 kg/m² higher in sibling offspring of diabetic pregnancies compared with siblings born before the mother developed type 2 diabetes; however, they did not include women with pre-gestational diabetes.

Within the gestational group, we found the strongest association with adult BMI among those men in whom maternal insulin treatment was initiated during pregnancy. The decision to begin insulin treatment was based primarily on actual blood glucose values. It therefore seems reasonable to assume that these 12 women had higher blood glucose values during pregnancy than the ones remaining on a diet-only regimen. Some of these women may have had undiagnosed diabetes for a substantial time before pregnancy. This could indicate a dose–response association between intrauterine blood glucose levels and adult BMI.

Our study extends the observations of the previously cited studies by including offspring of women with both pre-gestational and gestational diabetes and, within the gestational group, we had data on initiation of insulin treatment as an indirect measure of severity of maternal diabetes. Compared with previous studies, the strengths of our study include the relatively large number of women exposed to type 1 diabetes, the long observational time with limited loss to follow-up, the ability to differentiate between women with pre-gestational and gestational diabetes, and the use of contemporary population-based controls. However, due to our observational design we cannot determine whether our findings represent a causal association or merely a risk marker.

Several potential study weaknesses deserve discussion. The primary limitation is lack of data on maternal pre-pregnancy BMI and weight gain during pregnancy, which are major risk factors for gestational diabetes and is related to offspring adiposity. Adjustment for birthweight (also associated with maternal BMI) and gestational age, which attenuated estimates slightly, can only partially overcome this weakness. Differences in reasons for rejection in non-presenters could introduce selection bias if they were related to obesity. The majority of non-presenters were rejected due to asthma, behavioral and musculoskeletal diagnoses or hearing loss. We do not find it likely that these conditions are so strongly related to obesity that selection bias from non-presenters will invalidate our conclusions.

We do not have data on maternal metabolic control during pregnancy, and the White classification was our only available variable to classify the severity of pre-gestational diabetes. In women with type 1 diabetes this classification mainly reflects maternal age at time of debut and duration of diabetes. As these factors may be of limited value in the actual pregnancy, we did not stratify this group according to White classes. In the gestational group, we could only separate women treated by diet from those in whom insulin treatment was initiated during actual pregnancy, but no further refinement was possible. Our analyses in this group were also hampered by low numbers. One reason for this could be an incomplete adherence of the recommended screening procedure, so that some women with gestational diabetes may not have been diagnosed. But despite this possibility, associations with offspring BMI were present for the entire gestational group and in the even smaller group in which insulin was initiated.

Our registry-based dataset lacked information about several other factors that could confound the observed associations if they were unevenly distributed by maternal diabetes status. In addition to maternal pre-pregnancy BMI, these include gestational weight gain, maternal smoking and co-morbidities, breastfeeding, parental socioeconomic status, dietary habits, level of physical activity, and height and weight at various times between birth and

time of conscription, all of which have been identified as predictors of offspring weight by several authors (2,17,18). Except for maternal BMI, however, the other factors, even gestational weight gain, may not be strongly related to risk of gestational diabetes (19). Our outcomes were also restricted to height and weight without detailed data on body composition, which may be more informative about the risk of insulin resistance and subsequent cardiovascular morbidity (20).

Conclusion

In a cohort of 277 Danish men aged 18–20 years born to women with diabetes recognized before or during pregnancy, we found a higher army-rejection rate due to adiposity compared with population controls. Conscripts with measured weight and height data whose mothers had gestational diabetes were on average almost 6 kg heavier, but not taller or shorter, than their counterparts whose mothers did not have diabetes during pregnancy. Maternal type 1 diabetes was only weakly associated with adult offspring BMI.

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Abbreviations

BMI	body mass index
DM	pre-gestational or gestational diabetes
CI	confidence interval
SD	standard deviation
RD	risk difference

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Key Message

Male offspring of women with diabetes have a higher army rejection rate due to adiposity and higher adult body mass index than controls. The association is most pronounced in the case of gestational diabetes, whereas pre-gestational diabetes is only weakly associated with offspring body mass index.

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Table 1

Selection process with number of exclusions in DM-exposed and control cohorts

	DM-exposed	Controls
Men aged 18–20 years for evaluation at Draft Board, <i>n</i>	277	870
Non-presenters rejected based on report of chronic health problems precluding military service, therefore no data on height and weight, <i>n</i> (%)	52 (19)	133 (15)
Men with data on height and weight at conscription, <i>n</i>	225	737
Rejected due to adiposity, <i>n</i>	16	27
Rejected due to adiposity, percent	5.8	3.1
Men with missing data on birthweight or gestational age, <i>n</i>	9	100
Men with data on height and weight at conscription plus birthweight and gestational age, <i>n</i>	216	637

DM, pre-gestational or gestational diabetes.

Table 2

Descriptive data and differences in body mass index between Danish male conscripts unexposed (controls) and exposed to diabetes in utero, overall and by subcategories of diabetes exposure

	Controls	All DM-exposed	Pre-gestational			Gestational		
			All	Type 1 diabetes	Diet only	All	Diet only	Insulin initiated
Number of subjects	737	225	185 [/]	151	34	34 [/]	22	12
Birthweight, mean g	3482	3395	3327	3356	3199	3803	4005	3435
Birthweight, SD	551	708	648	668	543	780	731	759
Gestational age, mean weeks	38.8	36.8	36.5	36.3	37.5	38.9	39.4	37.8
Gestational age, SD	2.0	2.1	1.8	1.7	2.1	1.9	1.9	1.5
Height at conscription, mean cm	180.3	180.3	180.3	180.7	179.2	179.9	180.8	178.3
Height at conscription, SD	6.6	7.0	6.8	7.1	5.3	8.2	8.2	8.3
Weight at conscription, mean kg	75.8	80.5	79.5	79.5	79.4	85.5	84.3	87.7
Weight, at conscription SD	14.0	16.2	14.5	14.5	14.8	21.9	21.0	24.3
BMI at conscription, mean kg/m ²	23.3	24.7	24.4	24.3	24.7	26.2	25.6	27.3
BMI at conscription, SD	4.0	4.5	4.2	4.2	4.1	5.6	5.3	6.3
<i>Crude analyses</i>								
BMI difference DM-exposed vs. control, mean kg/m ² ,	0	1.4	1.1	1.0	1.4	2.9	2.3	4.1
95% confidence interval	(Ref.)	0.8–2.0	0.4–1.7	0.3–1.7	0.0–2.8	1.5–4.3	0.6–4.0	1.8–6.4
<i>Adjusted analyses</i>								
Number included in adjusted analyses	637	216	177 [/]	145	32	33 [/]	22	11
BMI difference DM-exposed vs. control, mean kg/m ² , adjusted ²	0	1.0	0.6	0.5	1.0	2.7	1.9	4.0
95% confidence interval	(Ref.)	0.1–1.8	–0.3–1.5	–0.5–1.5	–0.5–2.5	0.9–4.5	–0.8–4.6	1.5–6.6

¹ Six cases could not be categorized and were thus omitted from the analyses stratified according to subtype of diabetes.

² Linear regression models adjusted for gestational age (weeks) and birthweight (g).

DM, pre-gestational or gestational diabetes; SD, standard deviation; BMI, body mass index.