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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000601
Article Type:	Research
Date Submitted by the Author:	10-Nov-2011
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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Epidemiology
Keywords:	Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, Fetal medicine < OBSTETRICS

Pre- pregnancy body mass index and the risk of adverse outcome in type 1 diabetic pregnancies - a population based cohort study.

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Short running title: Overweight in type 1 diabetic pregnancies

Word count: 3,675 words (abstract 300 words) excluding references, 1 figure and 4 tables

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Article summary

Article focus

To assess the risk of obstetric and perinatal complications in overweight and obese women with and without type 1 diabetes (T1DM).

Key findings

- High pre-pregnancy BMI is an important risk factor for adverse outcome in type 1 diabetic pregnancies.
- The combined effect of both type 1 diabetes and overweight or obesity constitutes the greatest risk.
- T1DM is a significant effect modifier of the association between BMI and LGA, major malformations and preeclampsia ($p<0.001$).

Strengths and Limitations

The present study is to our knowledge, the first to present risk estimates of several obstetric and perinatal complications in women with type 1 diabetes, stratified by BMI category and compared with a non-diabetic reference population. The population based study design, including a very large cohort of T1DM pregnancies offers a unique possibility to provide solid data on risks associated with high BMI, including comparatively rare outcomes such as perinatal mortality. A potential limitation is that the study design did not allow assessment of the impact of maternal glycemic control on the association between exposure and outcome.

Abstract

Objective To assess the risk of perinatal complications in overweight and obese women with and without type 1 diabetes (T1DM).

Research Design Prospective population-based cohort study.

Setting This study was based on data from the Swedish Medical Birth Registry from 1998 - 2007.

Participants 3,457 T1DM and 764,498 non-diabetic pregnancies were included. T1DM was identified based on ICD code O24.0. Mothers were categorized according to pre-pregnancy body mass index (BMI:weight in kg/height in m²) as normal weight (BMI 18.5-24.9), over weight (BMI 25-29.9) or obese (BMI≥30). Only women with singleton pregnancies and with data on BMI were included.

Outcomes The primary outcome was large-for-gestational age (LGA: birth weight>90th percentile) infants. Secondary outcomes were major malformations, preeclampsia (PE), preterm delivery, perinatal mortality, delivery by Cesarean section and neonatal overweight. Logistic regression analysis was performed with normal weight non-diabetic women as the reference category and also within the diabetic cohort with normal weight type 1 diabetic women as the reference. The odds ratio´s (OR) were adjusted for ethnicity, maternal age, height, parity, smoking and chronic hypertension.

Results 35% of women with T1DM were overweight and 18% were obese, as compared to 26% and11%, respectively, in non-diabetic pregnancies. The incidences of adverse outcome increased with greater BMI category. As compared with non-diabetic normal weight women, the adjusted OR for obese T1DM for LGA was [adj OR: 13.26 (11.27-15.59), major malformations [adj OR 4.11 (2.99-5.65)] and PE [adj OR: 14.19 (11.50-17.50). T1DM was a significant effect modifier of the association between BMI and LGA, major malformations and PE (p<0.001).

Conclusion High pre-pregnancy BMI is an important risk factor for adverse outcome in type 1 diabetic pregnancies. The combined effect of both type 1 diabetes and overweight or obesity constitutes the greatest risk. It seems prudent to strive towards normal pre-pregnancy BMI in women with T1DM.

Introduction

Body mass index (BMI) has increased among fertile women in many countries, including Sweden (1). Maternal overweight and obesity are well known risk factors for adverse pregnancy outcome. High pre-pregnancy BMI has been associated with increased risk for stillbirth, foetal malformations, large-for-date neonates, neonatal and infant death, pregnancy induced hypertension and preeclampsia, maternal diabetes, delivery by Cesarean section as well as increased numbers of days spent in hospital for both mother and infant (2-11). The pathophysiological mechanism behind the increased risk of adverse pregnancy outcome in obese women is not fully understood. Increased insulin resistance and a state of inflammation associated with obesity (12) are likely important contributing factors.

Given the links between overweight, insulin resistance and adverse pregnancy outcome, any additional pregnancy risks in overweight women with diabetes are important to disclose, especially since overweight and obesity are more prevalent among diabetic women than in the general obstetric population (13).Increased risks of neonatal and maternal morbidity have been reported in overweight and obese women with gestational diabetes (14-16).In contrast, data is very limited regarding the impact of high maternal BMI on the risk of adverse pregnancy outcome in women with type 1 diabetes. An interaction between maternal diabetes, including both pre-gestational and gestational diabetes, and obesity has been suggested to increase the risk of malformations in the offspring (17). However, the majority of women in

that study had gestational diabetes and no separate analysis was performed in women with type 1 diabetes.

The aim of the present study was to analyse the association between maternal overweight and obesity and the risk of fetal and obstetric complications in type 1diabetic pregnancies, with special reference to the high and increasing incidence of large-for-gestational age infants (13). This study includes a large national cohort of more than 3,000 type 1 diabetic pregnancies and the risk of adverse outcome in relation to maternal BMI was also compared with non- diabetic pregnancies. Our hypothesis was that maternal overweight/obesity and maternal type 1 diabetes have independent impact on the risk of adverse outcome and that the combination of the two constitutes the greatest risk.

Research design, material and methods

This population based cohort study was based on data from the Swedish Medical Birth Registry (MBR). The MBR prospectively collects information on maternal medical history, obstetric and neonatal diagnoses and covers more than 99% of all pregnancies in Sweden. The quality of data has been found high (18).

Maternal and neonatal diagnoses are classified according ICD-10. All diagnoses are made by a physician before hospital discharge and copies of the records are forwarded to the MBR. Maternal characteristics included in the present study were mother's age, parity, pre-pregnancy weight, height, chronic hypertension, smoking habits, and whether the mother was born in one of the Nordic countries (Sweden, Finland, Denmark, Norway or Iceland) or elsewhere. Chronic hypertensive disease ICD-10: I10 or O10.0) was defined as blood pressure above 140/90 mmHg diagnosed before pregnancy or before 20 weeks of gestation. Maternal

height and pre-pregnancy weight were recorded by recall and body mass index (BMI) was calculated as weight in kg divided by the square of the height in meters. Exposure in women with and without T1DM was defined as overweight (BMI≥25-29.9 kg/m²) or obese (BMI≥30 kg/m²) and pregnancy outcomes were compared with that of normal weight women (BMI 18.5-24.9 kg/m²). Women with BMI< 18.5 kg/m² (under-weight) and records with missing data on BMI were excluded as well as records with extreme values on maternal age (<13 or >54 years) maternal weight (<40 or > 200 kg) or maternal height (<120 or >200 cm). We applied the same limits for data acceptance of birth weight and birth length as in the Swedish Perinatal Quality Registry: i.e. records with birth weight < 200 or > 9998 grams or birth length <15 or >65 cm, were excluded.

Study cohort

Infants from singleton pregnancies and born to mothers with type 1 diabetes in Sweden between 1998 and 2007 were included, in total n=3,457. Type 1 diabetic pregnancies were indentified based on ICD10 code O240.

Non-diabetic cohort

The reference group (n= 764,498) included all singleton pregnancies to mothers without a diagnosis of diabetes (based on ICD 10 codes type 1 diabetes: O240, type 2 diabetes all codes starting with E11 and E 177-119, O241: or gestational diabetes codes O244 A, B, X) and born in the same time period as the study cohort. Percentiles for birth weight were based on all live born, singleton infants, without major malformations, to mothers without a diagnosis of diabetes. Birth weight percentiles were adjusted for sex and gestational age.

Primary outcome

Foetal macrosomia, i.e. giving birth to a large-for-gestational age (LGA) infant was the primary outcome of this study (LGA was defined as a birth weight >90th percentile adjusted for sex and gestational age).

Secondary outcomes

Secondary outcomes were major malformations, preeclampsia, preterm delivery, perinatal mortality, delivery by Cesarean section (emergency and elective) and neonatal overweight. Major malformations were pre-defined in the MBR as fatal or potentially life threatening malformations or if the malformation would likely lead to a serious handicap or major cosmetic defect if not surgically corrected.Preeclampsia was defined as a blood pressure above 140/90 mmHg after 20 weeks of gestation and proteinuria (at least 0.3 g/day or > 1+ on a urine dipstick, ICD-10 codes: O14.0, O14.1 and O15). Preterm birth was defined as delivery before 37 gestational weeks. Perinatal mortality was defined as intrauterine death after the 28th week of gestation or death during the first week of postnatal life.Neonatal overweight was defined as birth weight and ponderal index (PI: birth weight in grams/length cm³) above the 90th percentile adjusted for sex and gestational age.

Statistical methods

Comparison between groups were made using Kruskall Wallis test for continous data and χ^2 test and χ^2 test for trend for binary and categorical data as appropriate. Unconditional logistic regression was used to explore associations between maternal BMI categories and adverse outcomes with normal weight (BMI 18.5-24.9 kg/m²) women as the reference category as follows: the odds ratios of adverse outcomes in relation to BMI category were estimated in women with type 1 diabetes with 1) normal weight women with type 1 diabetes as reference category and 2) with normal weight non-diabetic women as reference category and in non-

diabetic women with normal weight non-diabetic women as reference category. Crude and adjusted odds ratios (OR) were calculated. The following variables were included in the final regression model for LGA as possible confounders because of their established association with the primary outcome: Nordic origin (yes/no), maternal age, height, parity, smoking and chronic hypertension. The final regression models for the secondary outcomes included covariates significantly associated with the outcomes in univariate analysis. Missing indicator variables were used for maternal age and height. The likely hood ratio test was used to explore potential interaction between BMI categories and T1DM for the risk of the adverse outcomes. A p-value <0.05 was considered significant. All statistical analyses were performed using STATA 10.1 SE.

Results

Between 1998 and 2007, there were 947,096 deliveries in Sweden, including 4,208 (0.4%) deliveries to mothers with type 1 diabetes. Of all pregnancies, we excluded 441 records (0.05%) with extreme values on maternal age, maternal weight or height. No records were excluded due to extreme values on birth weight but 3,402 records were missing for this variable. We excluded 90 records (0.01%) due to extreme values on birth length and 14,544 were missing for birth length. In women with type 1 diabetes, 652 records (15%) were excluded due to missing data on maternal BMI or BMI<18.5 and 116 (2.8%) due to multiple pregnancies. The final study cohort comprised 3,457 infants (1,758 male infants, 51%) born to mothers with type 1 diabetes. The reference population included 764,498 singleton pregnancies to mothers without a diagnosis of diabetes, excluding 28,018 records from multiple pregnancies and 147,835 records with missing data on maternal BMI or BMI<18.5.

Reference percentiles for birth weight, birth length and ponderal index were formed using records from all non-diabetic pregnancies and excluding stillborn infants (0.31%), infants with major malformations (1.84%) and multiple pregnancies (3.01%).

Maternal and infant characteristics

Mothers with type 1 diabetes had a significantly higher median pre-pregnancy BMI (25.1 kg/m²) compared to the non-diabetic group (23.6 kg/m²), ($p<0.001$). In the type 1 diabetic cohort, 35% (n= 1,195) of women were overweight and 18% (n=618) were obese as compared with 26% (n=200,600) and 11% (n=82,331), respectively, in the non-diabetic population, Figure 1.Women with type 1 diabetes were also more often of Nordic origin, had a higher prevalence of chronic hypertension and smoking during the first trimester compared to women without diabetes (p-value for all comparisons <0.01). Infants to mothers with diabetes type 1 were born at a significantly lower median gestational age and preterm birth was four times as common compared to non-diabetic offspring (p-value for all comparisons <0.001). The median birth weight was significantly higher in infants to mothers with type 1 diabetes than in the reference group, Table 1.

Adverse outcomes in relation to body mass index category

Overall, the incidence of all adverse outcomes was significantly higher in women with type 1 diabetes, irrespective of BMI category. The incidence of the primary outcome was highest in obese women; however the difference did not reach statistical significance within the diabetes cohort. The incidence of all secondary outcomes was highest in obese women with and without type 1 diabetes, except for PMR in type 1 diabetic pregnancies with the highest recorded frequency in overweight women. Within the non-diabetic pregnancies, the incidence

of all outcomes increased significantly with greater BMI category (chi square test for trends for all outcomes p<0.001), Table 2.

There was a similar pattern of increasing odds ratio for adverse outcome with greater BMI category in women with and without type 1 diabetes. Inclusion of maternal covariates in the regression models did not significantly change these estimates. Relative to a normal weight non-diabetic woman, the adjusted OR for the risk of having a LGA infant in overweight or obese women with type 1 diabetes was approximately 13, as compared with approximately 2 in overweight and obese non-diabetic women, Table 3. In relation to a normal weight woman without diabetes, obesity in women with type 1 diabetes was associated with an adjusted OR for major malformation of [4.11 (2.99-5.65)] as compared with [1.15 (1.09-1.22)] in women with obesity only. Compared with a normal weight non-diabetic woman, the adjusted odds ratios for PE in a woman with type 1 diabetes of normal weight was [7.17 (6.04-8.50)] and in combination with overweight [9.91 (8.61-11.40)] and in the obese woman [14.19 (11.50-17.50)].The corresponding estimates for a non-diabetic woman with overweight or obesity were [1.74(1.69-1.80)] and [3.37 (3.25-3.49)], respectively. The OR for Cesarean section increased with BMI category in both women with and without type 1 diabetes, Table 3.

Table 4 shows the OR for adverse outcome in women with type 1diabetes by BMI category with normal weight women with type 1 diabetes as the reference category. In obese women the adjusted OR of major malformations [1.77 (1.18-2.65)] and preeclampsia [1.74(1.35-2.25)] were significantly increased compared with normal weight women. The OR of Cesarean section was significantly increased in both overweight and obese women, Table 4

Discussion

This study shows that high maternal pre-pregnancy BMI is a very important risk factor for adverse pregnancy outcome in women with and without type 1 diabetes. High maternal BMI and type 1 diabetes are independent risk factors for maternal and perinatal complications. However, type 1 diabetes remains a stronger risk factor for adverse outcome than obesity. The risk of adverse outcome in women with concomitant type 1 diabetes and obesity exceeds that of either condition alone, indicating synergism between the two exposures. Obesity in type 1 diabetes is associated with significantly increased risk of PE, major malformations and Cesarean section as compared with type 1 diabetic women with normal BMI.

The prevalence of overweight and obesity in pregnant women is increasing in Sweden and worldwide (1, 12) and the harmful effects of high maternal BMI on pregnancy outcome are well established in the general obstetric population (2-11). On the other hand, data on the potential association between high maternal BMI and adverse pregnancy outcome in women with type 1 diabetes is scarce (17, 19-20). In a cohort of 46 women with type 1 diabetes and nephropathy, maternal overweight was identified as an important risk factor for poor pregnancy outcome (19). In mixed populations of women with pre-gestational diabetes, maternal obesity has been associated with pregnancy complications (20) and increased risk of birth defects (17). These two studies however, do not separate women with diabetes type 1 from those with diabetes type 2 and do not include any comparable data from a non-diabetic reference population.

The present study is to our knowledge, the first to present risk estimates of obstetric and perinatal complications in a large cohort of women with exclusively type 1 diabetes, stratified by BMI category and compared with a non-diabetic reference population. The large sample size enabled risk estimation of rare outcomes such as perinatal mortality and major malformations in relation to subgroups of maternal BMI. The population based study design

provides unanimous risk estimates for overweight and obese women with and without type1 diabetes. The vast majority of our study population is of Nordic origin. The study population is also homogenous with respect to medical care in pregnancy. In Sweden, healthcare is free of charge as well as insulin, test strips for home monitoring of glucose and equipment for insulin administration. The care of pregnant women with type 1 diabetes is uniform over the whole country and pregnancy outcome does not differ with geographical area (13).

Some limitations with the present study should be noted. Body mass index was calculated from recalled data on pre-pregnancy weight and height. Women tend to underestimate their weight and it has been demonstrated that this bias increases directly with the degree of overweight (21). A potential misclassification of women to lower BMI categories would lead to an underestimation of our findings of increased risks associated with high maternal BMI. The Swedish MBR does not collect data on maternal glycemic control, duration of diabetes, insulin regimens nor data on diet and physical activity. Consequently, the impact of diet, physical activity and level of control on the risk of adverse outcome could not be assessed. It is plausible that the achieved level of metabolic control differed between normal weight, overweight and obese type 1 diabetic women. In a study on pregnancies complicated by gestational diabetes, the fasting glucose levels were significantly higher in obese compared with overweight and normal weight women (14). However, results from the HAPO study confirm that maternal BMI and glycemia exert independent effects on the risk of adverse pregnancy outcome (2).

In the present study, obese women with type 1 diabetes had significantly increased risks of major malformations and preeclampsia as compared with normal weight women with type 1 diabetes. This is in line with the finding of an interaction between maternal diabetes and

obesity on the risk of adverse outcome in a mixed population of women with different types of diabetes (17). However, the increased risk of major malformations in relation to BMI in the present analysis should be interpreted with caution as maternal overweight and obesity rend ultrasound assessment of fetal anatomy difficult (22) and we do not have data on the number of induced abortions due to malformations. Maternal hyperglycemia in early pregnancy is a well known risk factor for major malformations and preeclampsia (23). Obesity is associated with increased insulin resistance (12) and one could speculate that women with obesity had a poorer level of control in early pregnancy than women with normal or slightly elevated BMI. In line with previous studies, we found increased risks of PE and major malformations in obese non diabetic women (5, 6, 10). In the present study, the risks of these complications were also significantly elevated in non- diabetic women with overweight. Obesity is associated with decreased insulin sensitivity and already slightly elevated levels of fasting glucose, within the upper normal range, are associated with increased risk of preeclampsia in women without diabetes (24). In Sweden, there is no uniform screening for gestational diabetes. It is possible that the increased risk of PE and major malformations in overweight and obese women in the reference group is partly due to undetected cases of impaired glucose tolerance or diabetes. Interestingly, maternal pre pregnancy BMI has been demonstrated as a stronger predictor of major malformations than severity of gestational diabetes (25).

In women with type 1 diabetes, the incidence of LGA was very high in all weight classes and increased with greater BMI category. However, the odds ratio for an LGA outcome did not differ significantly with BMI category, as opposed to in non-diabetic women. On the contrary, the risk of delivering a disproportionate LGA infant (PI > 90th percentile) was significantly increased in obese women within the type 1 diabetic cohort. In accordance with the study by Ehrenberg our findings indicate that maternal overweight is an important risk factor for LGA,

but maternal diabetes has an even greater impact (26). A possible contributing factor to this finding could also be the increasing prevalence of preeclampsia with greater BMI category.

This study confirms the observations in non-diabetic pregnancies (2-5) that increasing maternal BMI is associated with increased risk of delivery by Cesarean section also in women with type 1 diabetes. The increased incidence of complications such as preeclampsia and LGA in these groups most likely contributes to this finding.

The majority of perinatal deaths were stillbirths in all BMI categories and in both women with and without type 1 diabetes. The risk of perinatal mortality was independent of BMI category within the type 1 diabetic cohort but increased significantly with higher BMI in the reference group. This finding is in line with previous studies, reporting increased risk of both stillbirth and neonatal mortality in obese, non-diabetic women even after adjusting for maternal and perinatal risk factors (7, 8, 9). The lack of a significantly increased risk of perinatal mortality with increasing BMI category within the diabetes cohort, indicate that diabetes is a stronger risk factor for perinatal mortality than maternal overweight/obesity.

In the present study, we found an increasing risk of preterm delivery with greater BMI category in both women with and without type 1 diabetes.
Results from some earlier studies have shown an increased risk of preterm delivery in obese non-diabetic women (3, 4) while others have reported the opposite association (2, 5).

It is hypothesized that the increased risk of pregnancy complications in overweight and obese women is due to increased maternal fat mass. In the present study, pre pregnancy BMI was used as a proxy for maternal fat mass. This assumption is a potential limitation, however there

is a strong correlation (r^2= 0.86) between pre pregnancy BMI and maternal fat mass in women without diabetes (27). More importantly, BMI does not provide information on the localization of fat mass. One hypothesized link between high maternal pre pregnancy BMI and increased risk of adverse outcome is the visceral fat mass. The visceral fat mass is associated with increased insulin resistance, inflammation and lipotoxicity with potential harmful effects on maternal vascular and placental function and fetal development (28). The pathophysiological mechanism behind the increased risk of adverse pregnancy outcome in overweight/obese mothers is not clear but is most likely complex. Genetic- and socioeconomic factors, maternal diet and physical activity are probable contributing factors. However, the similar pattern, in both women with and without type 1 diabetes, with increased risk of adverse outcome with higher maternal BMI implies that BMI per se is an important risk factor to address. It is reasonable to assume that preventive measures, aiming at normal pre pregnancy BMI, may reduce the risk of complications in type 1 diabetic pregnancies.

In conclusion, this population based study on more than 3000 type 1 diabetic pregnancies demonstrates a strong association between maternal pre-pregnancy BMI and elevated risk of adverse pregnancy outcome. Type 1 diabetes in combination with overweight or obesity constitutes a higher risk than either condition alone. Striving towards normal pre pregnancy BMI in women with type 1 diabetes could hopefully reduce the risk of adverse outcome.

Acknowledgement

This study was supported by the Swedish Order of Freemasons and the Stockholm County Council. DP was funded by the National Institute of Health Research (NIHR), UK and the Tommy´s Charity. The funding consisted of salary for the researchers MP and DP. We appreciate the help from the Swedish Medical Birth Registry to provide us with data.

Disclosure of interest

The authors have no potential conflicts of interest.

Author contributions

MP. DP.UH.MW.MN; contributions of design and interpretation of data
MP. UH; Data acquisition
MP. DP; Data analyses
MP. DP.UH.MW. MN; Interpretation of results
MP. MN; Drafted the manuscript
MN; Handled funding and supervision
MP. DP. UH. MW.MN; Critical revision of the manuscript and final approval of the version to be published

Ethics Approval

This study was approved by the Regional Ethical Review Board in Uppsala, Sweden. Date of approval: 22/7 2009, reference number: 2009/187

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Data sharing statement

No additional data available.

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Strobe

This manuscript was written according to the guidelines given by STROBE. The study hypothesis arose before inspection of the data.

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Table 1) Maternal characteristics, type 1 diabetes and reference population

Numbers and percentages

	Type 1 diabetes N=3,457	**Non-diabetic population** N=764,498
Maternal characteristics		
Nordic, n (%)	3,194 (92)	643,608 (84)
Maternal age, years (median, IQR)	30 (27-34)	30(27-33)
Smoking first trimester, n (%)	384 (11)	72,766 (10)
Primipara, n (%)	1,559 (45)	337,199 (44)
BMI, kg/m² (median, IQR)	25.1 (23.0-28.4)	23.6 (21.6-26.4)
Over weight (BMI ≥ 25-29.9), n(%)	1,195 (35%)	200,600 (26%)
Obese (BMI ≥30), n(%)	618 (18%)	82,331 (11%)
Height, cm (median,IQR)	167 (162-170)	167 (162-170)
Chronic hypertension, n (%)	92 (2.7)	2,472 (0.32)
Infant characteristics		
Male, n (%)	1,758 (51%)	393,324 (51%)
Gestational age, weeks (md,IQR)	38 (37-39)	40 (39-41)
Preterm delivery (n, %)	741 (21%)	35,878 (4.7%)
Birth weight, g (md,IQR)	3805 (3350-4265)	3575 (3240-3915)
Birth length, cm (md,IQR)	51 (49-52)	51 (49-52)
LGA, BW >90 percentile, n (%)	1,694 (49)	81,142 (11)
AGA, BW 10-90 percentile, n (%)	1,661 (48%)	614,784 (80%)
SGA, BW <10 percentile, n (%)	109 (3.2%)	76,214 (10)

Table 2) Outcomes, type 1 diabetes and non-diabetic population

Numbers and percentages

	BMI 18.5-24.9	BMI 25-29.9	BMI≥30	P value
LGA				
Type 1 diabetes	778 (47)	603 (50)	313 (51)	0.170
Non-diabetic	39,265 (8.2)	26,828 (13)	15,049 (18)	<0.001
Major malformations				
Type 1 diabetes	65 (4.0)	44 (3.7)	41 (6.6)	0.008
Non-diabetic	8,186 (1.7)	3,736 (1.9)	1,610 (2.0)	<0.001
Preelampsia				
Type 1 diabetes	222 (14)	185 (15)	114 (18)	0.012
Non-diabetic	9,872 (2.1)	6,529 (3.3)	4,810 (5.8)	<0.001
Preterm delivery				
Type 1 diabetes	322 (20)	275 (23)	144 (23)	0.041
Non-diabetic	21,714 (4.5)	9,464 (4.7)	4,700 (5.7)	<0.001
Perinatal mortality				
Type 1 diabetes	14 (0.85)	15 (1.3)	6 (0.97)	0.566
Non-diabetic	1,554 (0.32)	948 (0.47)	593 (0.72)	<0.001
Cesarean section				
Type 1 diabetes	748 (46)	639 (53)	362 (59)	<0.001
Non-diabetic	64,131 (13)	34,081 (17)	18,166 (22)	<0.001
Neonatal overweight				
Type 1 diabetes	351 (21)	288 (24)	166 (27)	0.016
Non-diabetic	15,359 (3)	10,430 (5)	6,466 (8)	<0.001

*Chi square test, Kruskall Wallis test, Chi square test for trends

Table 3) Crude and Adjusted* Odds ratios (CI) for outcomes in T1DM and non-diabetic population

	Non-diabetic BMI 18.5-24.9	T1DM BMI 18.5-24.9	BMI 25-29.9	BMI≥30	Interaction# P value
LGA, T1DM					
Crude	1.0	10.16 (9.10-11.36)	12.40 (11.22-13.70)	12.29 (10.50-14.40)	<0.001
Adjusted	1.0	10.72 (9.56-12.01)	13.55 (12.23-15.02)	13.26 (11.27-15. 59)	<0.001
LGA, ref					
Crude	1.0	-	1.74 (1.71-1.77)	2.52 (2.47-2.57)	<0.001
Adjusted	1.0	-	1.76 (1.73-1.79)	2.60 (2.55-2. 66)	<0.001
Major malformations,T1DM					
Crude	1.0	2.28 (1.71-3.04)	2.34 (1.81-3.02)	4.11 (2.99-5.65)	0.03
Adjusted	1.0	2.28 (1.71-3.04)	2.34 (1.81-3.03)	4.11 (2.99-5.65)	0.03
Major malformations, ref					
Crude	1.0	-	1.10 (1.06-1.14)	1.15 (1.09-1.22)	0.03
Adjusted	1.0	-	1.10 (1.06-1.14)	1.15 (1.09-1.22)	0.03
Preeclampsia, T1DM					
Crude	1.0	7.12 (6.02-8.42)	9.30 (8.11-10.67)	11.23 (9.15-13.77)	<0.001
Adjusted	1.0	7.17 (6.04-8.50)	9.91(8.61-11.40)	14.19 (11.50-17.50)	<0.001
Preeclamspia, ref					
Crude	1.0	-	1.61(1.56-1.66)	2.96 (2.86-3.07)	<0.001
Adjusted	1.0	-	1.74 (1.69-1.80)	3.37 (3.25-3.49)	<0.001
Preterm delivery, T1DM					
Crude	1.0	4.86 (4.22-5.60)	6.23 (5.53-7.02)	6.39 (5.30-7.71)	0.16
Adjusted	1.0	4.72 (4.09-5.44)	5.98 (5.31-6.74)	5.97 (4.94-7.21)	0.15
Preterm delivery, ref					
Crude	1.0	-	1.05 (1.02-1.07)	1.28 (1.24-1.32)	0.16
Adjusted	1.0	-	1.04 (1.02-1.07)	1.26 (1.22-1.30)	0.15
PMR,T1DM					
Crude	1.0	2.55 (1.36-4.76)	3.93 (2.49-6.19)	3.14 (1.40-7.04)	0.29
Adjusted	1.0	2.46 (1.32-4.60)	3.72 (2.36-5.89)	2.86 (1.27-6.44)	0.31
PMR, ref					
Crude	1.0	-	1.47 (1.35-1.59)	2.24 (2.04-2.46)	0.29
Adjusted	1.0	-	1.46 (1.35-1.59)	2.22 (2.03-2.44)	0.31

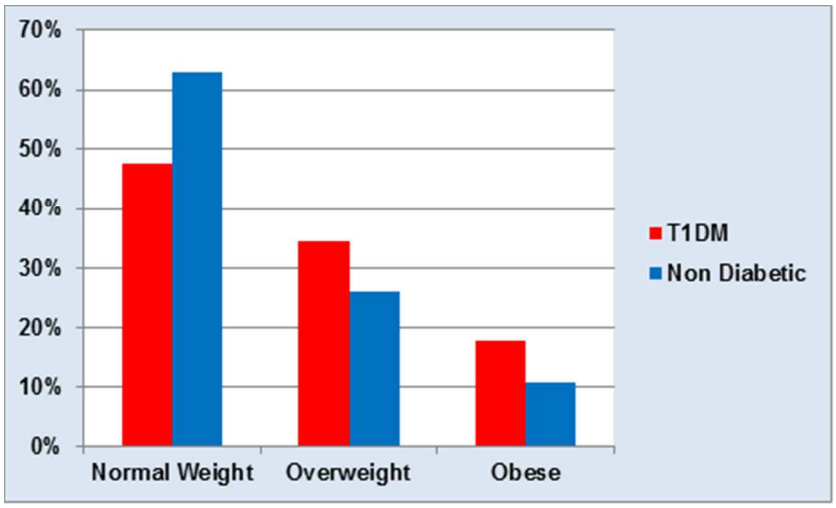
Cesarean section,T1DM					
Crude	1.0	5.59 (5.00-6.25)	7.09 (6.42-7.83)	9.44 (8.04-11.08)	0.42
Adjusted	1.0	5.69 (5.09-6.37)	7.12 (6.44-7. 88)	9.35 (7.95-11.00)	0.36
Cesarean section, ref					
Crude	1.0	-	1.33 (1.31-1.35)	1.84 (1.81-1.88)	0.42
Adjusted	1.0	-	1.34 (1.32-1.36)	1.87 (1.83-1.90)	0.36
Neonatal overweight,T1DM					
Crude	1.0	8.46 (7.39-9.70)	9.93 (8.83-11.17)	11.71 (9.79-14.00)	<0.001
Adjusted	1.0	8.40 (7.32-9.64)	9.86 (8.76-11.11)	11.29 (9.42-13.53)	<0.001
Neonatal overweight, ref					
Crude	1.0	-	1.66 (1.62-1.71)	2.59 (2.51-2.67)	<0.001
Adjusted	1.0	-	1.65 (1.61-1.69)	2.55 (2.48-2.63)	<0.001

*Adjusted for ethnicity, maternal age, height, parity, smoking first trimester, chronic hypertension #Interaction between BMI category and T1DM

Table 4) Crude and Adjusted* Odds ratios (CI), type 1 diabetes

	BMI 18.5-24.9	BMI 25-29.9	BMI≥30
LGA,T1DM			
Crude	1.0	1.13 (0.98-1.32)	1.14 (0.95-1.37)
Adjusted	1.0	1.18 (1.01-1.38)	1.21 (1.00-1.47)
Major malformations, T1DM			
Crude	1.0	0.93 (0.63-1.37)	1.73 (1.15-2.58)
Adjusted	1.0	0.92 (0.62-1.36)	1.77 (1.18-2.65)
Preeclampsia, T1DM			
Crude	1.0	1.17 (0.95-1.45)	1.45 (1.13-1.86)
Adjusted	1.0	1.21 (0.98-1.50)	1.74 (1.35-2.25)
Preterm delivery,T1DM			
Crude	1.0	1.23 (1.02-1.47)	1.25 (1.00-1.56)
Adjusted	1.0	1.22 (1.02-1.47)	1.25 (1.00-1.56)
PMR T1DM			
Crude	1.0	1.48 (0.71-3.08)	1.14 (0.44-2.98)
Adjusted	1.0	1.47 (0.70-3.03)	1.08 (0.41-2.83)
Cesarean section,T1DM			
Crude	1.0	1.38 (1.19-1.60)	1.69 (1.40-2.04)
Adjusted	1.0	1.37 (1.18-1.60)	1.67 (1.38-2.03)
Neonatal overweight, T1DM			
Crude	1.0	1.17 (0.98-1.40)	1.35 (1.09-1.67)
Adjusted	1.0	1.19 (0.99-1.42)	1.36 (1.09-1.69)

*Adjusted for ethnicity, maternal age, height, parity, smoking first trimester, chronic hypertension



Body mass index categories in women with T1DM and in non-diabetic subjects
153x92mm (96 x 96 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
	X	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2X	Explain the scientific background and rationale for the investigation being reported
Objectives	3X	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4x	Present key elements of study design early in the paper
Setting	5x	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6x	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7x	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*x	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9x	Describe any efforts to address potential sources of bias
Study size	10x	Explain how the study size was arrived at
Quantitative variables	11x	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12x	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*x	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*x	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*x	Report numbers of outcome events or summary measures over time
Main results	16x	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17x	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18x	Summarise key results with reference to study objectives
Limitations	19x	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20x	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21x	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22x	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Pre-pregnancy body mass index and the risk of adverse outcome in type 1 diabetic pregnancies- a population based cohort study.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000601.R1
Article Type:	Research
Date Submitted by the Author:	05-Jan-2012
Complete List of Authors:	Persson, Martina; Karolinska Institute, Department of Clinical Science, Intervention and Technology Pasupathy, Dharmintra; Division of Women's Health, NIHR Biomedical Research Centre, Kings Health´s Partners, King´s College London, Maternal and Fetal Medicin Hanson, Ulf; Department of Woman and Child Health, Uppsala University, Sweden., Westgren, Magnus; Karolinska Institute, Department of Clinical Science, Intervention and Technology Norman, Mikael; Karolinska Institute, Department of Clinical Science, Intervention and Technology
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Epidemiology, Reproductive medicine, obstetrics and gynaecology
Keywords:	Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, Fetal medicine < OBSTETRICS

PRE-PREGNANCY BODY MASS INDEX AND THE RISK OF ADVERSE OUTCOME IN TYPE 1 DIABETIC PREGNANCIES-A POPULATION BASED COHORT

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Short running title: Overweight in type 1 diabetic pregnancies

Word count: 3,773 words (abstract 294 words) excluding references, 1 figure and 4 tables

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Article summary

Article focus

To assess the risk of obstetric and perinatal complications in overweight and obese women with and without type 1 diabetes (T1DM).

Key findings

- High pre-pregnancy BMI is an important risk factor for adverse outcome in type 1 diabetic pregnancies.
- The combined effect of both type 1 diabetes and overweight or obesity constitutes the greatest risk.
- T1DM is a significant effect modifier of the association between BMI and LGA, major malformations and preeclampsia ($p<0.001$).

Strengths and Limitations

The present study is to our knowledge, the first to present risk estimates of several obstetric and perinatal complications in women with type 1 diabetes, stratified by BMI category and compared with a non-diabetic reference population. The population based study design, including a very large cohort of T1DM pregnancies offers a unique possibility to provide solid data on risks associated with high BMI, including comparatively rare outcomes such as perinatal mortality. A potential limitation is that the study design did not allow assessment of the impact of maternal glycaemic control on the association between exposure and outcome.

ABSTRACT

Objective To assess the risk of perinatal complications in overweight and obese women with and without type 1 diabetes (T1DM).

Design Prospective population-based cohort study.

Setting This study was based on data from the Swedish Medical Birth Registry from 1998 - 2007.

Participants 3,457 T1DM and 764,498 non-diabetic pregnancies were included. T1DM was identified based on ICD code O24.0. Mothers were categorized according to pre-pregnancy body mass index (BMI: weight in kg/height in m²) as normal weight (BMI 18.5-24.9), over-weight (BMI 25-29.9) or obese (BMI≥30). Only women with singleton pregnancies and with data on BMI were included.

Primary/secondary outcomes The primary outcome was large for gestational age (LGA: birth weight>90th percentile) infants. Secondary outcomes were major malformations, preeclampsia (PE), preterm delivery, perinatal mortality, delivery by Caesarean section and neonatal overweight. Logistic regression analysis was performed with normal weight non-diabetic women as the reference category and also within the diabetic cohort with normal weight type 1 diabetic women as the reference. The odds ratio´s (OR) were adjusted for ethnicity, maternal age, height, parity, smoking and chronic hypertension.

Results 35% of women with T1DM were overweight and 18% were obese, as compared to 26% and 11%, respectively, in non-diabetic pregnancies. The incidences of adverse outcome increased with greater BMI category. As compared with non-diabetic normal weight women, the adjusted OR for obese T1DM for LGA was 13.26 (11.27-15.59), major malformations 4.11 (2.99-5.65) and PE 14.19 (11.50-17.50). T1DM was a significant effect modifier of the association between BMI and LGA, major malformations and PE (p<0.001).

Conclusion High pre-pregnancy BMI is an important risk factor for adverse outcome in type 1 diabetic pregnancies. The combined effect of both type 1 diabetes and overweight or obesity constitutes the greatest risk. It seems prudent to strive towards normal pre-pregnancy BMI in women with T1DM.

Introduction

Body mass index (BMI) has increased among fertile women in many countries, including Sweden (1). Maternal overweight and obesity are well known risk factors for adverse pregnancy outcome. High pre-pregnancy BMI has been associated with increased risk for stillbirth, fetal malformations, large for date neonates, neonatal and infant death, pregnancy induced hypertension and preeclampsia, maternal diabetes, delivery by Caesarean section as well as increased numbers of days spent in hospital for both mother and infant (2-11). The pathophysiological mechanism behind the increased risk of adverse pregnancy outcome in obese women is not fully understood. Increased insulin resistance and a state of inflammation associated with obesity (12) are likely important contributing factors.

Given the links between overweight, insulin resistance and adverse pregnancy outcome, any additional pregnancy risks in overweight women with diabetes are important to disclose, especially since overweight and obesity are more prevalent among diabetic women than in the general obstetric population (13). Increased risks of neonatal and maternal morbidity have been reported in overweight and obese women with gestational diabetes (14-16). In contrast, data is very limited regarding the impact of high maternal BMI on the risk of adverse pregnancy outcome in women with type 1 diabetes. An interaction between maternal diabetes, including both pre-gestational and gestational diabetes, and obesity has been suggested to increase the risk of malformations in the offspring (17). However, the majority of women in that study had gestational diabetes and no separate analysis was performed in women with type 1 diabetes.

The aim of the present study was to analyse the association between maternal overweight and obesity and the risk of fetal and obstetric complications in type 1diabetic pregnancies, with

special reference to the high and increasing incidence of large for gestational age infants (13). This study includes a large national cohort of more than 3,000 type 1 diabetic pregnancies and the risk of adverse outcome in relation to maternal BMI was also compared with non-diabetic pregnancies. Our hypothesis was that maternal overweight/obesity and maternal type 1 diabetes have independent impact on the risk of adverse outcome and that the combination of the two constitutes the greatest risk.

Research design, material and methods

This population based cohort study was based on data from the Swedish Medical Birth Registry (MBR). The MBR prospectively collects information on maternal medical history, obstetric and neonatal diagnoses and covers more than 99% of all pregnancies in Sweden. Until 2008, the MBR did only collect data on pregnancies from $28^{0/7}$ weeks of gestation and did not register data on earlier fetal losses or induced abortions. The quality of data in the registry is continuously evaluated by the National Board of Health and the conclusion of the latest extensive validation in 2002 was that quality of data is high (18).Maternal and neonatal diagnoses were classified according to ICD-10, introduced in Sweden in 1997. ICD 9 codes were also included to ensure that no patients would be missed. All diagnoses were made by a physician before hospital discharge and copies of the records were forwarded to the MBR. Maternal characteristics included in the present study were mother's age, parity, pre-pregnancy weight, height, chronic hypertension, smoking habits, and whether the mother was born in one of the Nordic countries (Sweden, Finland, Denmark, Norway or Iceland) or elsewhere. Chronic hypertensive disease ICD-10: I10 or O10.0) was defined as blood pressure above 140/90 mmHg diagnosed before pregnancy or before 20 weeks of gestation. Maternal height and pre-pregnancy weight were recorded by recall and body mass index (BMI) was calculated as weight in kg divided by the square of the height in meters. Exposure in women

with and without T1DM was defined as overweight (BMI≥25-29.9 kg/m²) or obese (BMI≥30 kg/m²) and pregnancy outcomes were compared with that of normal weight women (BMI 18.5-24.9 kg/m²). Women with BMI< 18.5 kg/m² (under-weight) and records with missing data on BMI were excluded as well as records with extreme values on maternal age (<13 or >54 years) maternal weight (<40 or > 200 kg) or maternal height (<120 or >200 cm). We applied the same limits for data acceptance of birth weight and birth length as in the National Perinatal Quality Registry in Sweden: i.e., records with birth weight <200 or >9998 grams or birth length <15 or >65 cm, were excluded.

Study cohort

Infants from singleton pregnancies and born to mothers with type 1 diabetes in Sweden between 1998 and 2007 were included, in total n=3,457. Type 1 diabetic pregnancies were indentified based on ICD10 code O240 and ICD 9 code 250 for pre-gestational diabetes.

Non-diabetic cohort

The reference group (n= 764,498) included all singleton pregnancies to mothers without a diagnosis of diabetes [based on ICD 10 and 9 codes for type 1 diabetes (O240, 250x1/x3), type 2 diabetes (O241) and all codes starting with E11 and E 177-119,250x0/x2 or gestational diabetes codes (O244 A, B, X, 648.8)] and born in the same time period as the study cohort. Percentiles for birth weight were based on all live born, singleton infants, without major malformations, to mothers without a diagnosis of diabetes. Birth weight percentiles were adjusted for sex and gestational age.

Primary outcome

Fetal macrosomia, i.e. giving birth to a large for gestational age (LGA) infant was the primary outcome of this study. LGA was defined as a birth weight >90th percentile for sex and gestational age.

Secondary outcomes

Secondary outcomes were major malformations, preeclampsia, preterm delivery, perinatal mortality, delivery by Caesarean section (emergency and elective) and neonatal overweight. Major malformations were pre-defined in the MBR as fatal or potentially life threatening malformations or if the malformation would likely lead to a serious handicap or major cosmetic defect if not surgically corrected. Preeclampsia was defined as a blood pressure above 140/90 mmHg after 20 weeks of gestation and proteinuria (at least 0.3 g/day or > 1+ on a urine dipstick, ICD-10 codes: O14.0, O14.1 and O15/ICD 9 codes: 642.4, 642.5 and 642.6). Preterm birth was defined as delivery before 37 gestational weeks. Perinatal mortality was defined as intrauterine death after 28$^{0/7}$ weeks of gestation or death during the first week of postnatal life. Neonatal overweight was defined as birth weight and ponderal index (PI: birth weight in grams/length cm)^3 above the 90th percentile for sex and gestational age.

This study was approved by the Regional Ethical Review Board in Uppsala, Sweden.

Statistical methods

Comparison between groups were made using Kruskall Wallis test for continuous data and χ^2 test and χ^2 test for trend for binary and categorical data as appropriate. Unconditional logistic regression was used to explore associations between maternal BMI categories and adverse outcomes with normal weight (BMI 18.5-24.9 kg/m^2) women as the reference category as follows: the odds ratios of adverse outcomes in relation to BMI category were estimated in

women with type 1 diabetes with 1) normal weight women with type 1 diabetes as reference category and 2) with normal weight non-diabetic women as reference category. Crude and adjusted odds ratios (OR) were calculated. The following variables were included in the final regression model for LGA as possible confounders because of their established association with the primary outcome: Nordic origin (yes/no), maternal age, height, parity, smoking and chronic hypertension. The final regression models for the secondary outcomes included covariates significantly associated with the outcomes in univariate analysis. Missing indicator variables were used for maternal age and height. The likely hood ratio test was used to explore potential interaction between BMI categories and T1DM for the risk of the adverse outcomes. A p-value <0.05 was considered significant. All statistical analyses were performed using STATA 10.1 SE.

Results

Between 1998 and 2007, there were 947,096 deliveries in Sweden, including 4,208 (0.4%) deliveries to mothers with type 1 diabetes. Of all pregnancies, we excluded 441 records (0.05%) with extreme values on maternal age, maternal weight or height. No records were excluded due to extreme values on birth weight but 3,402 records were missing for this variable. We excluded 90 records (0.01%) due to extreme values on birth length and 14,544 were missing for birth length. In women with type 1 diabetes, 652 records (15%) were excluded due to missing data on maternal BMI or BMI<18.5 and 116 (2.8%) due to multiple pregnancies. 17 records were identified as both missing for BMI and with multiple pregnancies, thus giving a final study cohort of 3,457 infants (1,758 male infants, 51%) born to mothers with type 1 diabetes. The reference population included 764,498 singleton pregnancies to mothers without a diagnosis of diabetes, excluding 28,018 records from multiple pregnancies and 147,835 records with missing data on maternal BMI or BMI<18.5.

Reference percentiles for birth weight, birth length and ponderal index were formed using records from all non-diabetic pregnancies and excluding stillborn infants (0.31%), infants with major malformations (1.84%) and multiple pregnancies (3.01%).

Maternal and infant characteristics

Mothers with type 1 diabetes had a significantly higher median pre-pregnancy BMI (25.1 kg/m²) compared to the non-diabetic group (23.6 kg/m², p<0.001). In the type 1 diabetic cohort, 35% (n= 1,195) of women were overweight and 18% (n=618) were obese as compared with 26% (n=200,600) and 11% (n=82,331), respectively, in the non-diabetic population. Women with type 1 diabetes were also more often of Nordic origin, had a higher prevalence of chronic hypertension and smoking during the first trimester compared to women without diabetes (p-value for all comparisons <0.01). Infants to mothers with diabetes type 1 were born at a significantly lower median gestational age and preterm birth was four times as common compared to non-diabetic offspring (p-value for all comparisons <0.001). The median birth weight was significantly higher in infants delivered by mothers with type 1 diabetes than in the reference group, Table 1.

Table 1) Maternal and infant characteristics, type 1 diabetes and non-diabetic reference population

	Type 1 diabetes N=3,457	**Non-diabetic population** N=764,498	**P-value**
Maternal characteristics			
Nordic, n (%)	3,194 (92)	643,608 (84)	<0.001
Swedish origin, n (%)	3,151 (91)	628,534 (82)	<0.001
Maternal age, years (median, IQR)	30 (27-34)	30(27-33)	<0.001
Smoking first trimester, n (%)	384 (11)	72,766 (10)	0.001
Primipara, n (%)	1,559 (45)	337,199 (44)	0.242
BMI, kg/m² (median, IQR)	25.1 (23.0-28.4)	23.6 (21.6-26.4)	<0.001
Over weight (BMI ≥ 25-29.9), n (%)	1,195 (35%)	200,600 (26%)	<0.001
Obese (BMI ≥30), n (%)	618 (18%)	82,331 (11%)	<0.001
Height, cm (median,IQR)	167 (162-170)	167 (162-170)	0.250
Chronic hypertension, n (%)	92 (2.7)	2,472 (0.32)	<0.001
Infant characteristics			
Male, n (%)	1,758 (51%)	393,324 (51%)	0.485
Gestational age, weeks (md,IQR)	38 (37-39)	40 (39-41)	<0.001
Preterm delivery n (%)	741 (21%)	35,878 (4.7%)	<0.001
Birth weight, g (md,IQR)	3805 (3350-4265)	3575 (3240-3915)	<0.001
Birth length, cm (md,IQR)	51 (49-52)	51 (49-52)	0.576
LGA, BW >90 percentile, n (%)	1,694 (49)	81,142 (11)	<0.001
AGA, BW 10-90 percentile, n (%)	1,661 (48%)	614,784 (80%)	<0.001
SGA, BW <10 percentile, n (%)	109 (3.2%)	76,214 (10)	<0.001

Adverse outcomes in relation to body mass index category (Table 2)

Overall, the incidence of all adverse outcomes was significantly higher in women with type 1 diabetes, irrespective of BMI category. The incidence of the primary outcome LGA was highest in obese T1DM women; however the differences between BMI categories did not reach statistical significance within the diabetes cohort. The incidence of all secondary outcomes was highest in obese women with type 1 diabetes, except for PMR in type 1 diabetic pregnancies with the highest recorded frequency in overweight women. Within the non-diabetic pregnancies, the incidence of all outcomes increased significantly with greater BMI category (chi square test for trends for all outcomes $p<0.001$), Table 2.

Table 2) Perinatal outcomes for pregnant women with or without type 1 diabetes and stratified on pre-pregnancy BMI. Data are presented as numbers (percentages).

	BMI 18.5-24.9	BMI 25-29.9	BMI≥30	P-value
LGA-infant				
Type 1 diabetes	778 (47)	603 (50)	313 (51)	0.170
Non-diabetic	39,265 (8.2)	26,828 (13)	15,049 (18)	<0.001
Major malformations				
Type 1 diabetes	65 (4.0)	44 (3.7)	41 (6.6)	0.008
Non-diabetic	8,186 (1.7)	3,736 (1.9)	1,610 (2.0)	<0.001
Preeclampsia				
Type 1 diabetes	222 (14)	185 (15)	114 (18)	0.012
Non-diabetic	9,872 (2.1)	6,529 (3.3)	4,810 (5.8)	<0.001
Preterm delivery				
Type 1 diabetes	322 (20)	275 (23)	144 (23)	0.041
Non-diabetic	21,714 (4.5)	9,464 (4.7)	4,700 (5.7)	<0.001
Perinatal mortality				
Type 1 diabetes	14 (0.85)	15 (1.3)	6 (0.97)	0.566
Non-diabetic	1,554 (0.32)	948 (0.47)	593 (0.72)	<0.001
Caesarean section				
Type 1 diabetes	748 (46)	639 (53)	362 (59)	<0.001
Non-diabetic	64,131 (13)	34,081 (17)	18,166 (22)	<0.001
Neonatal overweight				
Type 1 diabetes	351 (21)	288 (24)	166 (27)	0.016
Non-diabetic	15,359 (3)	10,430 (5)	6,466 (8)	<0.001

*Chi square test, Kruskall Wallis test, Chi square test for trends

There was a similar pattern of increasing odds ratio for adverse outcome with greater BMI category in women with and without type 1 diabetes. Inclusion of maternal covariates in the regression models did not significantly change these estimates. Relative to a normal weight non-diabetic woman, the adjusted OR for the risk of having a LGA infant in overweight or obese women with type 1 diabetes was approximately 13, as compared with approximately 2 in overweight and obese non-diabetic women, Table 3. In relation to a normal weight woman without diabetes, obesity in women with type 1 diabetes was associated with an adjusted OR for major malformation of 4.11 (2.99-5.65) as compared with 1.15 (1.09-1.22) in non-diabetic women with obesity. Compared with a normal weight non-diabetic woman, the adjusted odds ratios for PE in a woman with type 1 diabetes of normal weight was 7.17 (6.04-8.50) and in combination with overweight 9.91 (8.61-11.40) and in obese T1DM women the adjusted OR was 14.19 (11.50-17.50).The corresponding estimates for a non-diabetic woman with overweight or obesity were 1.74(1.69-1.80) and 3.37 (3.25-3.49), respectively. The OR for Caesarean section increased with BMI category, both in women with and without type 1 diabetes, Table 3.

Table 3) Crude and adjusted* odds ratios (OR; 95%CI) for adverse perinatal outcomes in pregnant women with and without type 1 diabetes (T1DM) and stratified on pre-pregnancy BMI. Reference group: non-diabetic women with normal pre-pregnancy BMI.

	BMI 18.5-24.9	BMI 25-29.9	BMI≥30	Interaction# P-value
LGA-infant				
T1DM; Crude	10.16 (9.10-11.36)	12.40 (11.22-13.70)	12.29 (10.50-14.40)	<0.001
Adjusted	10.72 (9.56-12.01)	13.55 (12.23-15.02)	13.26 (11.27-15. 59)	<0.001
Non-diabetic ; Crude	1.0	1.74 (1.71-1.77)	2.52 (2.47-2.57)	<0.001
Adjusted	1.0	1.76 (1.73-1.79)	2.60 (2.55-2. 66)	<0.001
Major malformations				
T1DM; Crude	2.28 (1.71-3.04)	2.34 (1.81-3.02)	4.11 (2.99-5.65)	0.03
Adjusted	2.28 (1.71-3.04)	2.34 (1.81-3.03)	4.11 (2.99-5.65)	0.03
Non-diabetic; Crude	1.0	1.10 (1.06-1.14)	1.15 (1.09-1.22)	0.03
Adjusted	1.0	1.10 (1.06-1.14)	1.15 (1.09-1.22)	0.03
Preeclampsia				
T1DM; Crude	7.12 (6.02-8.42)	9.30 (8.11-10.67)	11.23 (9.15-13.77)	<0.001
Adjusted	7.17 (6.04-8.50)	9.91(8.61-11.40)	14.19 (11.50-17.50)	<0.001
Non-diabetic; Crude	1.0	1.61(1.56-1.66)	2.96 (2.86-3.07)	<0.001
Adjusted	1.0	1.74 (1.69-1.80)	3.37 (3.25-3.49)	<0.001
Preterm delivery				
T1DM; Crude	4.86 (4.22-5.60)	6.23 (5.53-7.02)	6.39 (5.30-7.71)	0.16
Adjusted	4.72 (4.09-5.44)	5.98 (5.31-6.74)	5.97 (4.94-7.21)	0.15
Non-diabetic; Crude	1.0	1.05 (1.02-1.07)	1.28 (1.24-1.32)	0.16
Adjusted	1.0	1.04 (1.02-1.07)	1.26 (1.22-1.30)	0.15

Perinatal mortality				
T1DM; Crude	2.55 (1.36-4.76)	3.93 (2.49-6.19)	3.14 (1.40-7.04)	0.29
Adjusted	2.46 (1.32-4.60)	3.72 (2.36-5.89)	2.86 (1.27-6.44)	0.31
Non-diabetic ; Crude	1.0	1.47 (1.35-1.59)	2.24 (2.04-2.46)	0.29
Adjusted	1.0	1.46 (1.35-1.59)	2.22 (2.03-2.44)	0.31
Caesarean section				
T1DM; Crude	5.59 (5.00-6.25)	7.09 (6.42-7.83)	9.44 (8.04-11.08)	0.42
Adjusted	5.69 (5.09-6.37)	7.12 (6.44-7. 88)	9.35 (7.95-11.00)	0.36
Non-diabetic; Crude	1.0	1.33 (1.31-1.35)	1.84 (1.81-1.88)	0.42
Adjusted	1.0	1.34 (1.32-1.36)	1.87 (1.83-1.90)	0.36
Neonatal overweight				
T1DM; Crude	8.46 (7.39-9.70)	9.93 (8.83-11.17)	11.71 (9.79-14.00)	<0.001
Adjusted	8.40 (7.32-9.64)	9.86 (8.76-11.11)	11.29 (9.42-13.53)	<0.001
Non-diabetic; Crude	1.0	1.66 (1.62-1.71)	2.59 (2.51-2.67)	<0.001
Adjusted	1.0	1.65 (1.61-1.69)	2.55 (2.48-2.63)	<0.001

*Adjusted for ethnicity, maternal age, height, parity, smoking first trimester, chronic hypertension

#Interaction between BMI category and T1DM

Table 4 shows the OR for adverse outcome in women with type 1diabetes by BMI category with normal weight women with type 1 diabetes as the reference category. In obese T1DM women the adjusted OR of major malformations [1.77 (1.18-2.65)] and preeclampsia [1.74(1.35-2.25)] were significantly increased compared with normal weight T1DM women. The OR of Caesarean section was significantly increased in both overweight and obese T1DM women, Table 4. The OR for LGA did not differ significantly between the different

BMI categories. However, the adjusted OR for delivering a disproportionate LGA-infant with neonatal overweight (ponderal index >90th percentile) was significantly increased in obese T1DM women 1.36 (1.09-1.69).

Table 4) Crude and Adjusted* Odds ratios (OR; 96%CI) for adverse perinatal outcome in pregnant women with type 1 diabetes (T1DM) and stratified on BMI. Reference group: T1DM women with normal pre-pregnancy BMI.

	T1DM BMI 18.5-24.9	T1DM BMI 25-29.9	T1DM BMI≥30
LGA-infant			
Crude	1.0	1.13 (0.98-1.32)	1.14 (0.95-1.37)
Adjusted	1.0	1.18 (1.01-1.38)	1.21 (1.00-1.47)
Major malformations			
Crude	1.0	0.93 (0.63-1.37)	1.73 (1.15-2.58)
Adjusted	1.0	0.92 (0.62-1.36)	1.77 (1.18-2.65)
Preeclampsia			
Crude	1.0	1.17 (0.95-1.45)	1.45 (1.13-1.86)
Adjusted	1.0	1.21 (0.98-1.50)	1.74 (1.35-2.25)
Preterm delivery			
Crude	1.0	1.23 (1.02-1.47)	1.25 (1.00-1.56)
Adjusted	1.0	1.22 (1.02-1.47)	1.25 (1.00-1.56)
Perinatal mortality			
Crude	1.0	1.48 (0.71-3.08)	1.14 (0.44-2.98)
Adjusted	1.0	1.47 (0.70-3.03)	1.08 (0.41-2.83)
Caesarean section			
Crude	1.0	1.38 (1.19-1.60)	1.69 (1.40-2.04)
Adjusted	1.0	1.37 (1.18-1.60)	1.67 (1.38-2.03)
Neonatal overweight			
Crude	1.0	1.17 (0.98-1.40)	1.35 (1.09-1.67)
Adjusted	1.0	1.19 (0.99-1.42)	1.36 (1.09-1.69)

*Adjusted for ethnicity, maternal age, height, parity, smoking first trimester, chronic hypertension

Discussion

This study shows that high maternal pre-pregnancy BMI is a very important risk factor for adverse pregnancy outcome in women with and without type 1 diabetes. High maternal BMI and type 1 diabetes are independent risk factors for maternal and perinatal complications. However, type 1 diabetes remains a stronger risk factor for adverse outcome than obesity. The risk of adverse outcome in women with concomitant type 1 diabetes and obesity exceeds that of either condition alone, indicating synergism between the two exposures. Obesity in type 1 diabetes is associated with significantly increased risk of PE, major malformations and Caesarean section as compared with type 1 diabetic women with normal BMI.

The prevalence of overweight and obesity in pregnant women is increasing in Sweden and worldwide (1, 12) and the harmful effects of high maternal BMI on pregnancy outcome are well established in the general obstetric population (2-11). On the other hand, data on the potential association between high maternal BMI and adverse pregnancy outcome in women with type 1 diabetes is scarce (17, 19-20). In a cohort of 46 women with type 1 diabetes and nephropathy, maternal overweight was identified as an important risk factor for poor pregnancy outcome (19). In mixed populations of women with pre-gestational diabetes, maternal obesity has been associated with pregnancy complications (20) and increased risk of birth defects (17). These two studies however, do not separate women with diabetes type 1 from those with diabetes type 2 and do not include any comparable data from a non-diabetic reference population.

The present study is to our knowledge, the first to present risk estimates of obstetric and perinatal complications in a large cohort of women with exclusively type 1 diabetes, stratified by BMI category and compared with a non-diabetic reference population. The large sample

size enabled risk estimation of rare outcomes such as perinatal mortality and major malformations in relation to subgroups of maternal BMI. The population based study design provides unanimous risk estimates for overweight and obese women with and without type1 diabetes. The vast majority of our study population is of Nordic origin and 91% were Swedish. The study population is also homogenous with respect to medical care in pregnancy. In Sweden, healthcare is free of charge as well as insulin, test strips for home monitoring of glucose and equipment for insulin administration. The care of pregnant women with type 1 diabetes is uniform over the whole country and pregnancy outcome does not differ with geographical area (13).

Some limitations with the present study should be noted. Body mass index was calculated from recalled data on pre-pregnancy weight and height. Women tend to underestimate their weight and it has been demonstrated that this bias increases directly with the degree of overweight (21). A potential misclassification of women to lower BMI categories would lead to an underestimation of our findings of increased risks associated with high maternal BMI. The Swedish MBR does not collect data on maternal glycaemic control, duration of diabetes, insulin regimens nor data on diet and physical activity. Data on socioeconomic factors is also very limited. Consequently, the impact of socioeconomic factors, diet, physical activity and level of control on the risk of adverse outcome could not be assessed. It is plausible that the achieved level of metabolic control differed between normal weight, overweight and obese type 1 diabetic women. In a study on pregnancies complicated by gestational diabetes, the fasting glucose levels were significantly higher in obese compared with overweight and normal weight women (14). However, results from the HAPO study confirm that maternal BMI and glycaemia exert independent effects on the risk of adverse pregnancy outcome (2).

In the present study, obese women with type 1 diabetes had significantly increased risks of major malformations and preeclampsia as compared with normal weight women with type 1 diabetes. This is in line with the finding of an interaction between maternal diabetes and obesity on the risk of adverse outcome in a mixed population of women with different types of diabetes (17). However, the increased risk of major malformations in relation to BMI in the present analysis should be interpreted with caution as maternal overweight and obesity rend ultrasound assessment of fetal anatomy difficult (22) and we do not have data on the number of induced abortions due to malformations. Maternal hyperglycaemia in early pregnancy is a well known risk factor for major malformations and preeclampsia (23). Obesity is associated with increased insulin resistance (12) and one could speculate that women with obesity had a poorer level of control in early pregnancy than women with normal or slightly elevated BMI. In line with previous studies, we found increased risks of PE and major malformations in obese non diabetic women (5, 6, 10). In the present study, the risks of these complications were also significantly elevated in non- diabetic women with overweight. Obesity is associated with decreased insulin sensitivity and already slightly elevated levels of fasting glucose, within the upper normal range, are associated with increased risk of preeclampsia in women without diabetes (24). In Sweden, there is no uniform screening for gestational diabetes. It is possible that the increased risk of PE and major malformations in overweight and obese women in the reference group is partly due to undetected cases of impaired glucose tolerance or diabetes. Interestingly, maternal pre-pregnancy BMI has been demonstrated as a stronger predictor of major malformations than severity of gestational diabetes (25).

In women with type 1 diabetes, the incidence of LGA was very high in all weight classes and increased with greater BMI category. However, the odds ratio for an LGA outcome did not differ significantly between BMI categories, as opposed to in non-diabetic women. This is in

accordance with findings in two recent studies (26, 27). On the contrary, the risk of delivering a disproportionate, overweight LGA infant (PI > 90th percentile) was significantly increased in obese women within the type 1 diabetic cohort. In accordance with the study by Ehrenberg our findings indicate that maternal overweight is an important risk factor for LGA, but maternal diabetes has an even greater impact (28). A possible contributing factor to this finding could also be the increasing prevalence of preeclampsia with greater BMI category.

This study confirms the observations in non-diabetic pregnancies (2-5) that increasing maternal BMI is associated with increased risk of delivery by Caesarean section also in women with type 1 diabetes. The increased incidence of complications such as preeclampsia and LGA in these groups most likely contributes to this finding.

The majority of perinatal deaths were stillbirths in all BMI categories and in both women with and without type 1 diabetes. The risk of perinatal mortality was independent of BMI category within the type 1 diabetic cohort but increased significantly with higher BMI in the reference group. This finding is in line with previous studies, reporting increased risk of both stillbirth and neonatal mortality in obese, non-diabetic women even after adjusting for maternal and perinatal risk factors (7, 8, 9). The lack of a significantly increased risk of perinatal mortality with increasing BMI category within the diabetes cohort, indicate that diabetes is a stronger risk factor for perinatal mortality than maternal overweight/obesity.

In the present study, we found an increasing risk of preterm delivery with greater BMI category, both in women with and without type 1 diabetes. Results from some earlier studies have shown an increased risk of preterm delivery in obese non-diabetic women (3, 4) while others have reported the opposite association (2, 5).

It is hypothesized that the increased risk of pregnancy complications in overweight and obese women is related to increased maternal fat mass. In the present study, pre-pregnancy BMI was used as a proxy for maternal fat mass as there is a strong correlation (r^2= 0.86) between pre-pregnancy BMI and maternal fat mass in women without diabetes (29). However, BMI does not provide information on the localization of fat mass. One suggested link between high maternal pre-pregnancy BMI and increased risk of adverse outcome pregnancy is a large visceral fat mass. The visceral fat mass is associated with increased insulin resistance, inflammation and lipotoxicity with potential harmful effects on maternal vascular and placental function and fetal development (30). Other pathophysiological mechanisms behind the increased risk of adverse pregnancy outcome in overweight/obese mothers are not clear but are most likely complex. Genetic- and socioeconomic factors, maternal diet and physical activity are probable contributing factors.

In conclusion, this population based study on more than 3000 type 1 diabetic pregnancies demonstrates a strong association between maternal pre-pregnancy BMI and elevated risk of adverse pregnancy outcome. Type 1 diabetes in combination with overweight or obesity constitutes a higher risk than either condition alone. Striving towards normal pre-pregnancy BMI in women with type 1 diabetes could hopefully reduce the risk of adverse outcome.

Acknowledgement

This study was supported by the Swedish Order of Freemasons and the Stockholm County Council. DP was funded by the National Institute of Health Research (NIHR), UK and the Tommy´s Charity. The funding consisted of salary for the researchers MP and DP. We appreciate the help from the Swedish Medical Birth Registry to provide us with data.

Disclosure of interest

The authors have no potential conflicts of interest.

Author contributions

MP. DP.UH.MW.MN; contributions of design and interpretation of data
MP. UH; Data acquisition
MP. DP; Data analyses
MP. DP.UH.MW. MN; Interpretation of results
MP. MN; Drafted the manuscript
MN; Handled funding and supervision
MP. DP. UH. MW.MN; Critical revision of the manuscript and final approval of the version to be published

Ethics Approval

This study was approved by the Regional Ethical Review Board in Uppsala, Sweden. Date of approval: 22/7 2009, reference number: 2009/187

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Data sharing statement

No additional data available.

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Table 1) Maternal and infant characteristics, type 1 diabetes and non-diabetic reference population

	Type 1 diabetes N=3,457	Non-diabetic population N=764,498	P-value
Maternal characteristics			
Nordic, n (%)	3,194 (92)	643,608 (84)	<0.001
Swedish origin, n (%)	3,151 (91)	628,534 (82)	<0.001
Maternal age, years (median, IQR)	30 (27-34)	30(27-33)	<0.001
Smoking first trimester, n (%)	384 (11)	72,766 (10)	0.001
Primipara, n (%)	1,559 (45)	337,199 (44)	0.242
BMI, kg/m² (median, IQR)	25.1 (23.0-28.4)	23.6 (21.6-26.4)	<0.001
Over weight (BMI ≥ 25-29.9), n (%)	1,195 (35%)	200,600 (26%)	<0.001
Obese (BMI ≥30), n (%)	618 (18%)	82,331 (11%)	<0.001
Height, cm (median,IQR)	167 (162-170)	167 (162-170)	0.250
Chronic hypertension, n (%)	92 (2.7)	2,472 (0.32)	<0.001
Infant characteristics			
Male, n (%)	1,758 (51%)	393,324 (51%)	0.485
Gestational age, weeks (md,IQR)	38 (37-39)	40 (39-41)	<0.001
Preterm delivery n (%)	741 (21%)	35,878 (4.7%)	<0.001
Birth weight, g (md,IQR)	3805 (3350-4265)	3575 (3240-3915)	<0.001
Birth length, cm (md,IQR)	51 (49-52)	51 (49-52)	0.576
LGA, BW >90 percentile, n (%)	1,694 (49)	81,142 (11)	<0.001
AGA, BW 10-90 percentile, n (%)	1,661 (48%)	614,784 (80%)	<0.001
SGA, BW <10 percentile, n (%)	109 (3.2%)	76,214 (10)	<0.001

Table 2) Perinatal outcomes for pregnant women with or without type 1 diabetes and stratified on pre-pregnancy BMI. Data are presented as numbers (percentages).

	BMI 18.5-24.9	BMI 25-29.9	BMI≥30	P-value
LGA-infant				
Type 1 diabetes	778 (47)	603 (50)	313 (51)	0.170
Non-diabetic	39,265 (8.2)	26,828 (13)	15,049 (18)	<0.001
Major malformations				
Type 1 diabetes	65 (4.0)	44 (3.7)	41 (6.6)	0.008
Non-diabetic	8,186 (1.7)	3,736 (1.9)	1,610 (2.0)	<0.001
Preeclampsia				
Type 1 diabetes	222 (14)	185 (15)	114 (18)	0.012
Non-diabetic	9,872 (2.1)	6,529 (3.3)	4,810 (5.8)	<0.001
Preterm delivery				
Type 1 diabetes	322 (20)	275 (23)	144 (23)	0.041
Non-diabetic	21,714 (4.5)	9,464 (4.7)	4,700 (5.7)	<0.001
Perinatal mortality				
Type 1 diabetes	14 (0.85)	15 (1.3)	6 (0.97)	0.566
Non-diabetic	1,554 (0.32)	948 (0.47)	593 (0.72)	<0.001
Cesarean section				
Type 1 diabetes	748 (46)	639 (53)	362 (59)	<0.001
Non-diabetic	64,131 (13)	34,081 (17)	18,166 (22)	<0.001
Neonatal overweight				
Type 1 diabetes	351 (21)	288 (24)	166 (27)	0.016
Non-diabetic	15,359 (3)	10,430 (5)	6,466 (8)	<0.001

*Chi square test, Kruskall Wallis test, Chi square test for trends

Table 3) Crude and adjusted* odds ratios (OR; 95%CI) for adverse perinatal outcomes in pregnant women with and without type 1 diabetes (T1DM) and stratified on pre-pregnancy BMI. Reference group: non-diabetic women with normal pre-pregnancy BMI.

	BMI 18.5-24.9	BMI 25-29.9	BMI≥30	Interaction# P-value
LGA-infant				
T1DM; Crude	10.16 (9.10-11.36)	12.40 (11.22-13.70)	12.29 (10.50-14.40)	<0.001
Adjusted	10.72 (9.56-12.01)	13.55 (12.23-15.02)	13.26 (11.27-15. 59)	<0.001
Non-diabetic ; Crude	1.0	1.74 (1.71-1.77)	2.52 (2.47-2.57)	<0.001
Adjusted	1.0	1.76 (1.73-1.79)	2.60 (2.55-2. 66)	<0.001
Major malformations				
T1DM; Crude	2.28 (1.71-3.04)	2.34 (1.81-3.02)	4.11 (2.99-5.65)	0.03
Adjusted	2.28 (1.71-3.04)	2.34 (1.81-3.03)	4.11 (2.99-5.65)	0.03
Non-diabetic; Crude	1.0	1.10 (1.06-1.14)	1.15 (1.09-1.22)	0.03
Adjusted	1.0	1.10 (1.06-1.14)	1.15 (1.09-1.22)	0.03
Preeclampsia				
T1DM; Crude	7.12 (6.02-8.42)	9.30 (8.11-10.67)	11.23 (9.15-13.77)	<0.001
Adjusted	7.17 (6.04-8.50)	9.91(8.61-11.40)	14.19 (11.50-17.50)	<0.001
Non-diabetic; Crude	1.0	1.61(1.56-1.66)	2.96 (2.86-3.07)	<0.001
Adjusted	1.0	1.74 (1.69-1.80)	3.37 (3.25-3.49)	<0.001
Preterm delivery				
T1DM; Crude	4.86 (4.22-5.60)	6.23 (5.53-7.02)	6.39 (5.30-7.71)	0.16
Adjusted	4.72 (4.09-5.44)	5.98 (5.31-6.74)	5.97 (4.94-7.21)	0.15
Non-diabetic; Crude	1.0	1.05 (1.02-1.07)	1.28 (1.24-1.32)	0.16
Adjusted	1.0	1.04 (1.02-1.07)	1.26 (1.22-1.30)	0.15

Perinatal mortality				
T1DM; Crude	2.55 (1.36-4.76)	3.93 (2.49-6.19)	3.14 (1.40-7.04)	0.29
Adjusted	2.46 (1.32-4.60)	3.72 (2.36-5.89)	2.86 (1.27-6.44)	0.31
Non-diabetic ; Crude	1.0	1.47 (1.35-1.59)	2.24 (2.04-2.46)	0.29
Adjusted	1.0	1.46 (1.35-1.59)	2.22 (2.03-2.44)	0.31
Cesarean section				
T1DM; Crude	5.59 (5.00-6.25)	7.09 (6.42-7.83)	9.44 (8.04-11.08)	0.42
Adjusted	5.69 (5.09-6.37)	7.12 (6.44-7. 88)	9.35 (7.95-11.00)	0.36
Non-diabetic; Crude	1.0	1.33 (1.31-1.35)	1.84 (1.81-1.88)	0.42
Adjusted	1.0	1.34 (1.32-1.36)	1.87 (1.83-1.90)	0.36
Neonatal overweight				
T1DM; Crude	8.46 (7.39-9.70)	9.93 (8.83-11.17)	11.71 (9.79-14.00)	<0.001
Adjusted	8.40 (7.32-9.64)	9.86 (8.76-11.11)	11.29 (9.42-13.53)	<0.001
Non-diabetic; Crude	1.0	1.66 (1.62-1.71)	2.59 (2.51-2.67)	<0.001
Adjusted	1.0	1.65 (1.61-1.69)	2.55 (2.48-2.63)	<0.001

*Adjusted for ethnicity, maternal age, height, parity, smoking first trimester, chronic hypertension

#Interaction between BMI category and T1DM

Table 4) Crude and Adjusted* Odds ratios (OR; 96%CI) for adverse perinatal outcome in pregnant women with type 1 diabetes (T1DM) and stratified on BMI. Reference group: T1DM women with normal pre-pregnancy BMI.

	T1DM BMI 18.5-24.9	T1DM BMI 25-29.9	T1DM BMI≥30
LGA-infant			
Crude	1.0	1.13 (0.98-1.32)	1.14 (0.95-1.37)
Adjusted	1.0	1.18 (1.01-1.38)	1.21 (1.00-1.47)
Major malformations			
Crude	1.0	0.93 (0.63-1.37)	1.73 (1.15-2.58)
Adjusted	1.0	0.92 (0.62-1.36)	1.77 (1.18-2.65)
Preeclampsia			
Crude	1.0	1.17 (0.95-1.45)	1.45 (1.13-1.86)
Adjusted	1.0	1.21 (0.98-1.50)	1.74 (1.35-2.25)
Preterm delivery			
Crude	1.0	1.23 (1.02-1.47)	1.25 (1.00-1.56)
Adjusted	1.0	1.22 (1.02-1.47)	1.25 (1.00-1.56)
Perinatal mortality			
Crude	1.0	1.48 (0.71-3.08)	1.14 (0.44-2.98)
Adjusted	1.0	1.47 (0.70-3.03)	1.08 (0.41-2.83)
Cesarean section			
Crude	1.0	1.38 (1.19-1.60)	1.69 (1.40-2.04)
Adjusted	1.0	1.37 (1.18-1.60)	1.67 (1.38-2.03)
Neonatal overweight			
Crude	1.0	1.17 (0.98-1.40)	1.35 (1.09-1.67)
Adjusted	1.0	1.19 (0.99-1.42)	1.36 (1.09-1.69)

*Adjusted for ethnicity, maternal age, height, parity, smoking first trimester, chronic hypertension

PRE-PREGNANCY BODY MASS INDEX AND THE RISK OF ADVERSE OUTCOME IN TYPE 1 DIABETIC PREGNANCIES-A POPULATION BASED COHORT

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Short running title: Overweight in type 1 diabetic pregnancies

Word count: 3,773 words (abstract 294 words) excluding references, 1 figure and 4 tables

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Article summary

Article focus

To assess the risk of obstetric and perinatal complications in overweight and obese women with and without type 1 diabetes (T1DM).

Key findings

- High pre-pregnancy BMI is an important risk factor for adverse outcome in type 1 diabetic pregnancies.
- The combined effect of both type 1 diabetes and overweight or obesity constitutes the greatest risk.
- T1DM is a significant effect modifier of the association between BMI and LGA, major malformations and preeclampsia ($p<0.001$).

Strengths and Limitations

The present study is to our knowledge, the first to present risk estimates of several obstetric and perinatal complications in women with type 1 diabetes, stratified by BMI category and compared with a non-diabetic reference population. The population based study design, including a very large cohort of T1DM pregnancies offers a unique possibility to provide solid data on risks associated with high BMI, including comparatively rare outcomes such as perinatal mortality. A potential limitation is that the study design did not allow assessment of the impact of maternal glycaemic control on the association between exposure and outcome.

ABSTRACT

Objective To assess the risk of perinatal complications in overweight and obese women with and without type 1 diabetes (T1DM).

Design Prospective population-based cohort study.

Setting This study was based on data from the Swedish Medical Birth Registry from 1998 - 2007.

Participants 3,457 T1DM and 764,498 non-diabetic pregnancies were included. T1DM was identified based on ICD code O24.0. Mothers were categorized according to pre-pregnancy body mass index (BMI: weight in kg/height in m²) as normal weight (BMI 18.5-24.9), over-weight (BMI 25-29.9) or obese (BMI≥30). Only women with singleton pregnancies and with data on BMI were included.

Primary/secondary outcomes The primary outcome was large for gestational age (LGA: birth weight>90th percentile) infants. Secondary outcomes were major malformations, preeclampsia (PE), preterm delivery, perinatal mortality, delivery by Caesarean section and neonatal overweight. Logistic regression analysis was performed with normal weight non-diabetic women as the reference category and also within the diabetic cohort with normal weight type 1 diabetic women as the reference. The odds ratio´s (OR) were adjusted for ethnicity, maternal age, height, parity, smoking and chronic hypertension.

Results 35% of women with T1DM were overweight and 18% were obese, as compared to 26% and 11%, respectively, in non-diabetic pregnancies. The incidences of adverse outcome increased with greater BMI category. As compared with non-diabetic normal weight women, the adjusted OR for obese T1DM for LGA was 13.26 (11.27-15.59), major malformations 4.11 (2.99-5.65) and PE 14.19 (11.50-17.50). T1DM was a significant effect modifier of the association between BMI and LGA, major malformations and PE (p<0.001).

4

Conclusion High pre-pregnancy BMI is an important risk factor for adverse outcome in type 1 diabetic pregnancies. The combined effect of both type 1 diabetes and overweight or obesity constitutes the greatest risk. It seems prudent to strive towards normal pre-pregnancy BMI in women with T1DM.

Introduction

Body mass index (BMI) has increased among fertile women in many countries, including Sweden (1). Maternal overweight and obesity are well known risk factors for adverse pregnancy outcome. High pre-pregnancy BMI has been associated with increased risk for stillbirth, fetal malformations, large for date neonates, neonatal and infant death, pregnancy induced hypertension and preeclampsia, maternal diabetes, delivery by Caesarean section as well as increased numbers of days spent in hospital for both mother and infant (2-11). The pathophysiological mechanism behind the increased risk of adverse pregnancy outcome in obese women is not fully understood. Increased insulin resistance and a state of inflammation associated with obesity (12) are likely important contributing factors.

Given the links between overweight, insulin resistance and adverse pregnancy outcome, any additional pregnancy risks in overweight women with diabetes are important to disclose, especially since overweight and obesity are more prevalent among diabetic women than in the general obstetric population (13). Increased risks of neonatal and maternal morbidity have been reported in overweight and obese women with gestational diabetes (14-16). In contrast, data is very limited regarding the impact of high maternal BMI on the risk of adverse pregnancy outcome in women with type 1 diabetes. An interaction between maternal diabetes, including both pre-gestational and gestational diabetes, and obesity has been suggested to increase the risk of malformations in the offspring (17). However, the majority of women in that study had gestational diabetes and no separate analysis was performed in women with type 1 diabetes.

The aim of the present study was to analyse the association between maternal overweight and obesity and the risk of fetal and obstetric complications in type 1diabetic pregnancies, with

special reference to the high and increasing incidence of large for gestational age infants (13). This study includes a large national cohort of more than 3,000 type 1 diabetic pregnancies and the risk of adverse outcome in relation to maternal BMI was also compared with non--diabetic pregnancies. Our hypothesis was that maternal overweight/obesity and maternal type 1 diabetes have independent impact on the risk of adverse outcome and that the combination of the two constitutes the greatest risk.

Research design, material and methods

This population based cohort study was based on data from the Swedish Medical Birth Registry (MBR). The MBR prospectively collects information on maternal medical history, obstetric and neonatal diagnoses and covers more than 99% of all pregnancies in Sweden. Until 2008, the MBR did only collect data on pregnancies from $28^{0/7}$ weeks of gestation and did not register data on earlier fetal losses or induced abortions. The quality of data in the registry is continuously evaluated by the National Board of Health and the conclusion of the latest extensive validation in 2002 was that quality of data is high (18).Maternal and neonatal diagnoses were classified according to ICD-10, introduced in Sweden in 1997. ICD 9 codes were also included to ensure that no patients would be missed. All diagnoses were made by a physician before hospital discharge and copies of the records were forwarded to the MBR. Maternal characteristics included in the present study were mother's age, parity, pre-pregnancy weight, height, chronic hypertension, smoking habits, and whether the mother was born in one of the Nordic countries (Sweden, Finland, Denmark, Norway or Iceland) or elsewhere. Chronic hypertensive disease ICD-10: I10 or O10.0) was defined as blood pressure above 140/90 mmHg diagnosed before pregnancy or before 20 weeks of gestation. Maternal height and pre-pregnancy weight were recorded by recall and body mass index (BMI) was calculated as weight in kg divided by the square of the height in meters. Exposure in women

Comment [MP1]: R2, comment1

Comment [MP2]: R2, comment 2

Comment [MP3]: R1"Some comments", nb1

with and without T1DM was defined as overweight (BMI≥25-29.9 kg/m²) or obese (BMI≥30 kg/m²) and pregnancy outcomes were compared with that of normal weight women (BMI 18.5-24.9 kg/m²). Women with BMI< 18.5 kg/m² (under-weight) and records with missing data on BMI were excluded as well as records with extreme values on maternal age (<13 or >54 years) maternal weight (<40 or > 200 kg) or maternal height (<120 or >200 cm). We applied the same limits for data acceptance of birth weight and birth length as in the National Perinatal Quality Registry in Sweden: i.e., records with birth weight <200 or >9998 grams or birth length <15 or >65 cm, were excluded.

Study cohort

Infants from singleton pregnancies and born to mothers with type 1 diabetes in Sweden between 1998 and 2007 were included, in total n=3,457. Type 1 diabetic pregnancies were indentified based on ICD10 code O240 and ICD 9 code 250 for pre-gestational diabetes.

Non-diabetic cohort

The reference group (n= 764,498) included all singleton pregnancies to mothers without a diagnosis of diabetes [based on ICD 10 and 9 codes for type 1 diabetes (O240, 250x1/x3), type 2 diabetes (O241) and all codes starting with E11 and E 177-119,250x0/x2 or gestational diabetes codes (O244 A, B, X, 648.8)] and born in the same time period as the study cohort. Percentiles for birth weight were based on all live born, singleton infants, without major malformations, to mothers without a diagnosis of diabetes. Birth weight percentiles were adjusted for sex and gestational age.

Primary outcome

Fetal macrosomia, i.e. giving birth to a large for gestational age (LGA) infant was the primary outcome of this study. LGA was defined as a birth weight >90th percentile for sex and gestational age.

Secondary outcomes

Secondary outcomes were major malformations, preeclampsia, preterm delivery, perinatal mortality, delivery by Caesarean section (emergency and elective) and neonatal overweight. Major malformations were pre-defined in the MBR as fatal or potentially life threatening malformations or if the malformation would likely lead to a serious handicap or major cosmetic defect if not surgically corrected. Preeclampsia was defined as a blood pressure above 140/90 mmHg after 20 weeks of gestation and proteinuria (at least 0.3 g/day or > 1+ on a urine dipstick, ICD-10 codes: O14.0, O14.1 and O15/ICD 9 codes: 642.4, 642.5 and 642.6). Preterm birth was defined as delivery before 37 gestational weeks. Perinatal mortality was defined as intrauterine death after 28$^{0/7}$ weeks of gestation or death during the first week of postnatal life. Neonatal overweight was defined as birth weight and ponderal index (PI: birth weight in grams/length cm)^3 above the 90th percentile for sex and gestational age.

This study was approved by the Regional Ethical Review Board in Uppsala, Sweden.

Comment [MP4]: *R1 first comment*

Statistical methods

Comparison between groups were made using Kruskall Wallis test for continuous data and χ^2 test and χ^2 test for trend for binary and categorical data as appropriate. Unconditional logistic regression was used to explore associations between maternal BMI categories and adverse outcomes with normal weight (BMI 18.5-24.9 kg/m^2) women as the reference category as follows: the odds ratios of adverse outcomes in relation to BMI category were estimated in

women with type 1 diabetes with 1) normal weight women with type 1 diabetes as reference category and 2) with normal weight non-diabetic women as reference category. Crude and adjusted odds ratios (OR) were calculated. The following variables were included in the final regression model for LGA as possible confounders because of their established association with the primary outcome: Nordic origin (yes/no), maternal age, height, parity, smoking and chronic hypertension. The final regression models for the secondary outcomes included covariates significantly associated with the outcomes in univariate analysis. Missing indicator variables were used for maternal age and height. The likely hood ratio test was used to explore potential interaction between BMI categories and T1DM for the risk of the adverse outcomes. A p-value <0.05 was considered significant. All statistical analyses were performed using STATA 10.1 SE.

Results

Between 1998 and 2007, there were 947,096 deliveries in Sweden, including 4,208 (0.4%) deliveries to mothers with type 1 diabetes. Of all pregnancies, we excluded 441 records (0.05%) with extreme values on maternal age, maternal weight or height. No records were excluded due to extreme values on birth weight but 3,402 records were missing for this variable. We excluded 90 records (0.01%) due to extreme values on birth length and 14,544 were missing for birth length. In women with type 1 diabetes, 652 records (15%) were excluded due to missing data on maternal BMI or BMI<18.5 and 116 (2.8%) due to multiple pregnancies. 17 records were identified as both missing for BMI and with multiple pregnancies, thus giving a final study cohort of 3,457 infants (1,758 male infants, 51%) born to mothers with type 1 diabetes. The reference population included 764,498 singleton pregnancies to mothers without a diagnosis of diabetes, excluding 28,018 records from multiple pregnancies and 147,835 records with missing data on maternal BMI or BMI<18.5.

Comment [MP5]: R2, comment 3

Reference percentiles for birth weight, birth length and ponderal index were formed using records from all non-diabetic pregnancies and excluding stillborn infants (0.31%), infants with major malformations (1.84%) and multiple pregnancies (3.01%).

Maternal and infant characteristics

Mothers with type 1 diabetes had a significantly higher median pre-pregnancy BMI (25.1 kg/m²) compared to the non-diabetic group (23.6 kg/m², p<0.001). In the type 1 diabetic cohort, 35% (n= 1,195) of women were overweight and 18% (n=618) were obese as compared with 26% (n=200,600) and 11% (n=82,331), respectively, in the non-diabetic population. Women with type 1 diabetes were also more often of Nordic origin, had a higher prevalence of chronic hypertension and smoking during the first trimester compared to women without diabetes (p-value for all comparisons <0.01). Infants to mothers with diabetes type 1 were born at a significantly lower median gestational age and preterm birth was four times as common compared to non-diabetic offspring (p-value for all comparisons <0.001). The median birth weight was significantly higher in infants delivered by mothers with type 1 diabetes than in the reference group, Table 1.

Table 1) Maternal and infant characteristics, type 1 diabetes and non-diabetic reference population

	Type 1 diabetes N=3,457	Non-diabetic population N=764,498	P-value
Maternal characteristics			
Nordic, n (%)	3,194 (92)	643,608 (84)	<0.001
Swedish origin, n (%)	3,151 (91)	628,534 (82)	
Maternal age, years (median, IQR)	30 (27-34)	30(27-33)	<0.001
Smoking first trimester, n (%)	384 (11)	72,766 (10)	0.001
Primipara, n (%)	1,559 (45)	337,199 (44)	0.242
BMI, kg/m² (median, IQR)	25.1 (23.0-28.4)	23.6 (21.6-26.4)	<0.001
Over weight (BMI ≥ 25-29.9), n (%)	1,195 (35%)	200,600 (26%)	<0.001
Obese (BMI ≥30), n (%)	618 (18%)	82,331 (11%)	<0.001
Height, cm (median,IQR)	167 (162-170)	167 (162-170)	0.250
Chronic hypertension, n (%)	92 (2.7)	2,472 (0.32)	<0.001
Infant characteristics			
Male, n (%)	1,758 (51%)	393,324 (51%)	0.485
Gestational age, weeks (md,IQR)	38 (37-39)	40 (39-41)	<0.001
Preterm delivery n (%)	741 (21%)	35,878 (4.7%)	<0.001
Birth weight, g (md,IQR)	3805 (3350-4265)	3575 (3240-3915)	<0.001
Birth length, cm (md,IQR)	51 (49-52)	51 (49-52)	0.576
LGA, BW >90 percentile, n (%)	1,694 (49)	81,142 (11)	<0.001
AGA, BW 10-90 percentile, n (%)	1,661 (48%)	614,784 (80%)	<0.001
SGA, BW <10 percentile, n (%)	109 (3.2%)	76,214 (10)	<0.001

Comment [MP6]: R1 "Some comments" no 6.

Comment [MP7]: R1"Some comments" no 2.

Adverse outcomes in relation to body mass index category (Table 2)

Overall, the incidence of all adverse outcomes was significantly higher in women with type 1 diabetes, irrespective of BMI category. The incidence of the primary outcome LGA was highest in obese T1DM women; however the differences between BMI categories did not reach statistical significance within the diabetes cohort. The incidence of all secondary outcomes was highest in obese women with type 1 diabetes, except for PMR in type 1 diabetic pregnancies with the highest recorded frequency in overweight women. Within the non-diabetic pregnancies, the incidence of all outcomes increased significantly with greater BMI category (chi square test for trends for all outcomes $p<0.001$), Table 2.

Table 2) Perinatal outcomes for pregnant women with or without type 1 diabetes and stratified on pre-pregnancy BMI. Data are presented as numbers (percentages).

Comment [MP8]: R1"Minor comment" no1

	BMI 18.5-24.9	BMI 25-29.9	BMI≥30	P-value
LGA-infant				
Type 1 diabetes	778 (47)	603 (50)	313 (51)	0.170
Non-diabetic	39,265 (8.2)	26,828 (13)	15,049 (18)	<0.001
Major malformations				
Type 1 diabetes	65 (4.0)	44 (3.7)	41 (6.6)	0.008
Non-diabetic	8,186 (1.7)	3,736 (1.9)	1,610 (2.0)	<0.001
Preeclampsia				
Type 1 diabetes	222 (14)	185 (15)	114 (18)	0.012
Non-diabetic	9,872 (2.1)	6,529 (3.3)	4,810 (5.8)	<0.001
Preterm delivery				
Type 1 diabetes	322 (20)	275 (23)	144 (23)	0.041
Non-diabetic	21,714 (4.5)	9,464 (4.7)	4,700 (5.7)	<0.001
Perinatal mortality				
Type 1 diabetes	14 (0.85)	15 (1.3)	6 (0.97)	0.566
Non-diabetic	1,554 (0.32)	948 (0.47)	593 (0.72)	<0.001
Caesarean section				
Type 1 diabetes	748 (46)	639 (53)	362 (59)	<0.001
Non-diabetic	64,131 (13)	34,081 (17)	18,166 (22)	<0.001
Neonatal overweight				
Type 1 diabetes	351 (21)	288 (24)	166 (27)	0.016
Non-diabetic	15,359 (3)	10,430 (5)	6,466 (8)	<0.001

*Chi square test, Kruskall Wallis test, Chi square test for trends

There was a similar pattern of increasing odds ratio for adverse outcome with greater BMI category in women with and without type 1 diabetes. Inclusion of maternal covariates in the regression models did not significantly change these estimates. Relative to a normal weight non-diabetic woman, the adjusted OR for the risk of having a LGA infant in overweight or obese women with type 1 diabetes was approximately 13, as compared with approximately 2 in overweight and obese non-diabetic women, Table 3. In relation to a normal weight woman without diabetes, obesity in women with type 1 diabetes was associated with an adjusted OR for major malformation of 4.11 (2.99-5.65) as compared with 1.15 (1.09-1.22) in non-diabetic women with obesity. Compared with a normal weight non-diabetic woman, the adjusted odds ratios for PE in a woman with type 1 diabetes of normal weight was 7.17 (6.04-8.50) and in combination with overweight 9.91 (8.61-11.40) and in obese T1DM women the adjusted OR was 14.19 (11.50-17.50).The corresponding estimates for a non-diabetic woman with overweight or obesity were 1.74(1.69-1.80) and 3.37 (3.25-3.49), respectively. The OR for Caesarean section increased with BMI category, both in women with and without type 1 diabetes, Table 3.

Table 3) Crude and adjusted* odds ratios (OR; 95%CI) for adverse perinatal outcomes in pregnant women with and without type 1 diabetes (T1DM) and stratified on pre-pregnancy BMI. Reference group: non-diabetic women with normal pre-pregnancy BMI.

Comment [MP9]: R2, last comment

	BMI 18.5-24.9	BMI 25-29.9	BMI≥30	Interaction# P-value
LGA-infant				
T1DM; Crude	10.16 (9.10-11.36)	12.40 (11.22-13.70)	12.29 (10.50-14.40)	<0.001
Adjusted	10.72 (9.56-12.01)	13.55 (12.23-15.02)	13.26 (11.27-15. 59)	<0.001
Non-diabetic ; Crude	1.0	1.74 (1.71-1.77)	2.52 (2.47-2.57)	<0.001
Adjusted	1.0	1.76 (1.73-1.79)	2.60 (2.55-2. 66)	<0.001
Major malformations				
T1DM; Crude	2.28 (1.71-3.04)	2.34 (1.81-3.02)	4.11 (2.99-5.65)	0.03
Adjusted	2.28 (1.71-3.04)	2.34 (1.81-3.03)	4.11 (2.99-5.65)	0.03
Non-diabetic; Crude	1.0	1.10 (1.06-1.14)	1.15 (1.09-1.22)	0.03
Adjusted	1.0	1.10 (1.06-1.14)	1.15 (1.09-1.22)	0.03
Preeclampsia				
T1DM; Crude	7.12 (6.02-8.42)	9.30 (8.11-10.67)	11.23 (9.15-13.77)	<0.001
Adjusted	7.17 (6.04-8.50)	9.91(8.61-11.40)	14.19 (11.50-17.50)	<0.001
Non-diabetic; Crude	1.0	1.61(1.56-1.66)	2.96 (2.86-3.07)	<0.001
Adjusted	1.0	1.74 (1.69-1.80)	3.37 (3.25-3.49)	<0.001
Preterm delivery				
T1DM; Crude	4.86 (4.22-5.60)	6.23 (5.53-7.02)	6.39 (5.30-7.71)	0.16
Adjusted	4.72 (4.09-5.44)	5.98 (5.31-6.74)	5.97 (4.94-7.21)	0.15
Non-diabetic; Crude	1.0	1.05 (1.02-1.07)	1.28 (1.24-1.32)	0.16
Adjusted	1.0	1.04 (1.02-1.07)	1.26 (1.22-1.30)	0.15

Perinatal mortality				
T1DM; Crude	2.55 (1.36-4.76)	3.93 (2.49-6.19)	3.14 (1.40-7.04)	0.29
Adjusted	2.46 (1.32-4.60)	3.72 (2.36-5.89)	2.86 (1.27-6.44)	0.31
Non-diabetic ; Crude	1.0	1.47 (1.35-1.59)	2.24 (2.04-2.46)	0.29
Adjusted	1.0	1.46 (1.35-1.59)	2.22 (2.03-2.44)	0.31
Caesarean section				
T1DM; Crude	5.59 (5.00-6.25)	7.09 (6.42-7.83)	9.44 (8.04-11.08)	0.42
Adjusted	5.69 (5.09-6.37)	7.12 (6.44-7. 88)	9.35 (7.95-11.00)	0.36
Non-diabetic; Crude	1.0	1.33 (1.31-1.35)	1.84 (1.81-1.88)	0.42
Adjusted	1.0	1.34 (1.32-1.36)	1.87 (1.83-1.90)	0.36
Neonatal overweight				
T1DM; Crude	8.46 (7.39-9.70)	9.93 (8.83-11.17)	11.71 (9.79-14.00)	<0.001
Adjusted	8.40 (7.32-9.64)	9.86 (8.76-11.11)	11.29 (9.42-13.53)	<0.001
Non-diabetic; Crude	1.0	1.66 (1.62-1.71)	2.59 (2.51-2.67)	<0.001
Adjusted	1.0	1.65 (1.61-1.69)	2.55 (2.48-2.63)	<0.001

*Adjusted for ethnicity, maternal age, height, parity, smoking first trimester, chronic hypertension

#Interaction between BMI category and T1DM

Table 4 shows the OR for adverse outcome in women with type 1diabetes by BMI category with normal weight women with type 1 diabetes as the reference category. In obese T1DM women the adjusted OR of major malformations [1.77 (1.18-2.65)] and preeclampsia [1.74(1.35-2.25)] were significantly increased compared with normal weight T1DM women. The OR of Caesarean section was significantly increased in both overweight and obese T1DM women, Table 4. The OR for LGA did not differ significantly between the different

BMI categories. However, the adjusted OR for delivering a disproportionate LGA-infant with neonatal overweight (ponderal index >90th percentile) was significantly increased in obese T1DM women 1.36 (1.09-1.69).

Comment [MP10]: R1 "Some comments" nb 5

Table 4) Crude and Adjusted* Odds ratios (OR; 96%CI) for adverse perinatal outcome in pregnant women with type 1 diabetes (T1DM) and stratified on BMI. Reference group: T1DM women with normal pre-pregnancy BMI.

Comment [MP11]: R2, last comment

	T1DM BMI 18.5-24.9	T1DM BMI 25-29.9	T1DM BMI≥30
LGA-infant			
Crude	1.0	1.13 (0.98-1.32)	1.14 (0.95-1.37)
Adjusted	1.0	1.18 (1.01-1.38)	1.21 (1.00-1.47)
Major malformations			
Crude	1.0	0.93 (0.63-1.37)	1.73 (1.15-2.58)
Adjusted	1.0	0.92 (0.62-1.36)	1.77 (1.18-2.65)
Preeclampsia			
Crude	1.0	1.17 (0.95-1.45)	1.45 (1.13-1.86)
Adjusted	1.0	1.21 (0.98-1.50)	1.74 (1.35-2.25)
Preterm delivery			
Crude	1.0	1.23 (1.02-1.47)	1.25 (1.00-1.56)
Adjusted	1.0	1.22 (1.02-1.47)	1.25 (1.00-1.56)
Perinatal mortality			
Crude	1.0	1.48 (0.71-3.08)	1.14 (0.44-2.98)
Adjusted	1.0	1.47 (0.70-3.03)	1.08 (0.41-2.83)
Caesarean section			
Crude	1.0	1.38 (1.19-1.60)	1.69 (1.40-2.04)
Adjusted	1.0	1.37 (1.18-1.60)	1.67 (1.38-2.03)
Neonatal overweight			
Crude	1.0	1.17 (0.98-1.40)	1.35 (1.09-1.67)
Adjusted	1.0	1.19 (0.99-1.42)	1.36 (1.09-1.69)

*Adjusted for ethnicity, maternal age, height, parity, smoking first trimester, chronic hypertension

Discussion

This study shows that high maternal pre-pregnancy BMI is a very important risk factor for adverse pregnancy outcome in women with and without type 1 diabetes. High maternal BMI and type 1 diabetes are independent risk factors for maternal and perinatal complications. However, type 1 diabetes remains a stronger risk factor for adverse outcome than obesity. The risk of adverse outcome in women with concomitant type 1 diabetes and obesity exceeds that of either condition alone, indicating synergism between the two exposures. Obesity in type 1 diabetes is associated with significantly increased risk of PE, major malformations and Caesarean section as compared with type 1 diabetic women with normal BMI.

The prevalence of overweight and obesity in pregnant women is increasing in Sweden and worldwide (1, 12) and the harmful effects of high maternal BMI on pregnancy outcome are well established in the general obstetric population (2-11). On the other hand, data on the potential association between high maternal BMI and adverse pregnancy outcome in women with type 1 diabetes is scarce (17, 19-20). In a cohort of 46 women with type 1 diabetes and nephropathy, maternal overweight was identified as an important risk factor for poor pregnancy outcome (19). In mixed populations of women with pre-gestational diabetes, maternal obesity has been associated with pregnancy complications (20) and increased risk of birth defects (17). These two studies however, do not separate women with diabetes type 1 from those with diabetes type 2 and do not include any comparable data from a non-diabetic reference population.

The present study is to our knowledge, the first to present risk estimates of obstetric and perinatal complications in a large cohort of women with exclusively type 1 diabetes, stratified by BMI category and compared with a non-diabetic reference population. The large sample

size enabled risk estimation of rare outcomes such as perinatal mortality and major malformations in relation to subgroups of maternal BMI. The population based study design provides unanimous risk estimates for overweight and obese women with and without type1 diabetes. The vast majority of our study population is of Nordic origin and 91% were Swedish. The study population is also homogenous with respect to medical care in pregnancy. In Sweden, healthcare is free of charge as well as insulin, test strips for home monitoring of glucose and equipment for insulin administration. The care of pregnant women with type 1 diabetes is uniform over the whole country and pregnancy outcome does not differ with geographical area (13).

Some limitations with the present study should be noted. Body mass index was calculated from recalled data on pre-pregnancy weight and height. Women tend to underestimate their weight and it has been demonstrated that this bias increases directly with the degree of overweight (21). A potential misclassification of women to lower BMI categories would lead to an underestimation of our findings of increased risks associated with high maternal BMI. The Swedish MBR does not collect data on maternal glycaemic control, duration of diabetes, insulin regimens nor data on diet and physical activity. Data on socioeconomic factors is also very limited. Consequently, the impact of socioeconomic factors, diet, physical activity and level of control on the risk of adverse outcome could not be assessed. It is plausible that the achieved level of metabolic control differed between normal weight, overweight and obese type 1 diabetic women. In a study on pregnancies complicated by gestational diabetes, the fasting glucose levels were significantly higher in obese compared with overweight and normal weight women (14). However, results from the HAPO study confirm that maternal BMI and glycaemia exert independent effects on the risk of adverse pregnancy outcome (2).

Comment [MP12]: *R1 "Some comments" nb 4*

In the present study, obese women with type 1 diabetes had significantly increased risks of major malformations and preeclampsia as compared with normal weight women with type 1 diabetes. This is in line with the finding of an interaction between maternal diabetes and obesity on the risk of adverse outcome in a mixed population of women with different types of diabetes (17). However, the increased risk of major malformations in relation to BMI in the present analysis should be interpreted with caution as maternal overweight and obesity rend ultrasound assessment of fetal anatomy difficult (22) and we do not have data on the number of induced abortions due to malformations. Maternal hyperglycaemia in early pregnancy is a well known risk factor for major malformations and preeclampsia (23). Obesity is associated with increased insulin resistance (12) and one could speculate that women with obesity had a poorer level of control in early pregnancy than women with normal or slightly elevated BMI. In line with previous studies, we found increased risks of PE and major malformations in obese non diabetic women (5, 6, 10). In the present study, the risks of these complications were also significantly elevated in non- diabetic women with overweight. Obesity is associated with decreased insulin sensitivity and already slightly elevated levels of fasting glucose, within the upper normal range, are associated with increased risk of preeclampsia in women without diabetes (24). In Sweden, there is no uniform screening for gestational diabetes. It is possible that the increased risk of PE and major malformations in overweight and obese women in the reference group is partly due to undetected cases of impaired glucose tolerance or diabetes. Interestingly, maternal pre-pregnancy BMI has been demonstrated as a stronger predictor of major malformations than severity of gestational diabetes (25).

In women with type 1 diabetes, the incidence of LGA was very high in all weight classes and increased with greater BMI category. However, the odds ratio for an LGA outcome did not differ significantly between BMI categories, as opposed to in non-diabetic women. This is in

accordance with findings in two recent studies (26, 27). On the contrary, the risk of delivering a disproportionate, overweight LGA infant (PI > 90th percentile) was significantly increased in obese women within the type 1 diabetic cohort. In accordance with the study by Ehrenberg our findings indicate that maternal overweight is an important risk factor for LGA, but maternal diabetes has an even greater impact (28). A possible contributing factor to this finding could also be the increasing prevalence of preeclampsia with greater BMI category.

Comment [MP13]: R1_RE: ref by Murphy

This study confirms the observations in non-diabetic pregnancies (2-5) that increasing maternal BMI is associated with increased risk of delivery by Caesarean section also in women with type 1 diabetes. The increased incidence of complications such as preeclampsia and LGA in these groups most likely contributes to this finding.

The majority of perinatal deaths were stillbirths in all BMI categories and in both women with and without type 1 diabetes. The risk of perinatal mortality was independent of BMI category within the type 1 diabetic cohort but increased significantly with higher BMI in the reference group. This finding is in line with previous studies, reporting increased risk of both stillbirth and neonatal mortality in obese, non-diabetic women even after adjusting for maternal and perinatal risk factors (7, 8, 9). The lack of a significantly increased risk of perinatal mortality with increasing BMI category within the diabetes cohort, indicate that diabetes is a stronger risk factor for perinatal mortality than maternal overweight/obesity.

In the present study, we found an increasing risk of preterm delivery with greater BMI category, both in women with and without type 1 diabetes. Results from some earlier studies have shown an increased risk of preterm delivery in obese non-diabetic women (3, 4) while others have reported the opposite association (2, 5).

It is hypothesized that the increased risk of pregnancy complications in overweight and obese women is related to increased maternal fat mass. In the present study, pre--pregnancy BMI was used as a proxy for maternal fat mass as there is a strong correlation (r^2= 0.86) between pre-pregnancy BMI and maternal fat mass in women without diabetes (29). However, BMI does not provide information on the localization of fat mass. One suggested link between high maternal pre-pregnancy BMI and increased risk of adverse outcome pregnancy is a large visceral fat mass. The visceral fat mass is associated with increased insulin resistance, inflammation and lipotoxicity with potential harmful effects on maternal vascular and placental function and fetal development (30). Other pathophysiological mechanisms behind the increased risk of adverse pregnancy outcome in overweight/obese mothers are not clear but are most likely complex. Genetic- and socioeconomic factors, maternal diet and physical activity are probable contributing factors.

In conclusion, this population based study on more than 3000 type 1 diabetic pregnancies demonstrates a strong association between maternal pre-pregnancy BMI and elevated risk of adverse pregnancy outcome. Type 1 diabetes in combination with overweight or obesity constitutes a higher risk than either condition alone. Striving towards normal pre--pregnancy BMI in women with type 1 diabetes could hopefully reduce the risk of adverse outcome.

Acknowledgement

This study was supported by the Swedish Order of Freemasons and the Stockholm County Council. DP was funded by the National Institute of Health Research (NIHR), UK and the Tommy´s Charity. The funding consisted of salary for the researchers MP and DP. We appreciate the help from the Swedish Medical Birth Registry to provide us with data.

Disclosure of interest

The authors have no potential conflicts of interest.

Author contributions

MP. DP.UH.MW.MN; contributions of design and interpretation of data
MP. UH; Data acquisition
MP. DP; Data analyses
MP. DP.UH.MW. MN; Interpretation of results
MP. MN; Drafted the manuscript
MN; Handled funding and supervision
MP. DP. UH. MW.MN; Critical revision of the manuscript and final approval of the version to be published

Ethics Approval

This study was approved by the Regional Ethical Review Board in Uppsala, Sweden. Date of approval: 22/7 2009, reference number: 2009/187

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Data sharing statement

No additional data available.

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Table 1) Maternal and infant characteristics, type 1 diabetes and non-diabetic reference population

	Type 1 diabetes N=3,457	Non-diabetic population N=764,498	P-value
Maternal characteristics			
Nordic, n (%)	3,194 (92)	643,608 (84)	<0.001
Swedish origin, n (%)	3,151 (91)	628,534 (82)	
Maternal age, years (median, IQR)	30 (27-34)	30(27-33)	<0.001
Smoking first trimester, n (%)	384 (11)	72,766 (10)	0.001
Primipara, n (%)	1,559 (45)	337,199 (44)	0.242
BMI, kg/m² (median, IQR)	25.1 (23.0-28.4)	23.6 (21.6-26.4)	<0.001
Over weight (BMI ≥ 25-29.9), n (%)	1,195 (35%)	200,600 (26%)	<0.001
Obese (BMI ≥30), n (%)	618 (18%)	82,331 (11%)	<0.001
Height, cm (median,IQR)	167 (162-170)	167 (162-170)	0.250
Chronic hypertension, n (%)	92 (2.7)	2,472 (0.32)	<0.001
Infant characteristics			
Male, n (%)	1,758 (51%)	393,324 (51%)	0.485
Gestational age, weeks (md,IQR)	38 (37-39)	40 (39-41)	<0.001
Preterm delivery n (%)	741 (21%)	35,878 (4.7%)	<0.001
Birth weight, g (md,IQR)	3805 (3350-4265)	3575 (3240-3915)	<0.001
Birth length, cm (md,IQR)	51 (49-52)	51 (49-52)	0.576
LGA, BW >90 percentile, n (%)	1,694 (49)	81,142 (11)	<0.001
AGA, BW 10-90 percentile, n (%)	1,661 (48%)	614,784 (80%)	<0.001
SGA, BW <10 percentile, n (%)	109 (3.2%)	76,214 (10)	<0.001

Comment [MP14]: R1 "Some comments" no 6.

Comment [MP15]: R1"Some comments" no 2.

Table 2) Perinatal outcomes for pregnant women with or without type 1 diabetes and stratified on pre-pregnancy BMI. Data are presented as numbers (percentages).

Comment [MP16]: R1"Minor comment" no1

	BMI 18.5-24.9	BMI 25-29.9	BMI≥30	P-value
LGA-infant				
Type 1 diabetes	778 (47)	603 (50)	313 (51)	0.170
Non-diabetic	39,265 (8.2)	26,828 (13)	15,049 (18)	<0.001
Major malformations				
Type 1 diabetes	65 (4.0)	44 (3.7)	41 (6.6)	0.008
Non-diabetic	8,186 (1.7)	3,736 (1.9)	1,610 (2.0)	<0.001
Preeclampsia				
Type 1 diabetes	222 (14)	185 (15)	114 (18)	0.012
Non-diabetic	9,872 (2.1)	6,529 (3.3)	4,810 (5.8)	<0.001
Preterm delivery				
Type 1 diabetes	322 (20)	275 (23)	144 (23)	0.041
Non-diabetic	21,714 (4.5)	9,464 (4.7)	4,700 (5.7)	<0.001
Perinatal mortality				
Type 1 diabetes	14 (0.85)	15 (1.3)	6 (0.97)	0.566
Non-diabetic	1,554 (0.32)	948 (0.47)	593 (0.72)	<0.001
Cesarean section				
Type 1 diabetes	748 (46)	639 (53)	362 (59)	<0.001
Non-diabetic	64,131 (13)	34,081 (17)	18,166 (22)	<0.001
Neonatal overweight				
Type 1 diabetes	351 (21)	288 (24)	166 (27)	0.016
Non-diabetic	15,359 (3)	10,430 (5)	6,466 (8)	<0.001

*Chi square test, Kruskall Wallis test, Chi square test for trends

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Table 3) Crude and adjusted* odds ratios (OR; 95%CI) for adverse perinatal outcomes in pregnant women with and without type 1 diabetes (T1DM) and stratified on pre-pregnancy BMI. Reference group: non-diabetic women with normal pre-pregnancy BMI.

Comment [MP17]: R2, last comment

	BMI 18.5-24.9	BMI 25-29.9	BMI≥30	Interaction# P-value
LGA-infant				
T1DM; Crude	10.16 (9.10-11.36)	12.40 (11.22-13.70)	12.29 (10.50-14.40)	<0.001
Adjusted	10.72 (9.56-12.01)	13.55 (12.23-15.02)	13.26 (11.27-15. 59)	<0.001
Non-diabetic ; Crude	1.0	1.74 (1.71-1.77)	2.52 (2.47-2.57)	<0.001
Adjusted	1.0	1.76 (1.73-1.79)	2.60 (2.55-2. 66)	<0.001
Major malformations				
T1DM; Crude	2.28 (1.71-3.04)	2.34 (1.81-3.02)	4.11 (2.99-5.65)	0.03
Adjusted	2.28 (1.71-3.04)	2.34 (1.81-3.03)	4.11 (2.99-5.65)	0.03
Non-diabetic; Crude	1.0	1.10 (1.06-1.14)	1.15 (1.09-1.22)	0.03
Adjusted	1.0	1.10 (1.06-1.14)	1.15 (1.09-1.22)	0.03
Preeclampsia				
T1DM; Crude	7.12 (6.02-8.42)	9.30 (8.11-10.67)	11.23 (9.15-13.77)	<0.001
Adjusted	7.17 (6.04-8.50)	9.91(8.61-11.40)	14.19 (11.50-17.50)	<0.001
Non-diabetic; Crude	1.0	1.61(1.56-1.66)	2.96 (2.86-3.07)	<0.001
Adjusted	1.0	1.74 (1.69-1.80)	3.37 (3.25-3.49)	<0.001
Preterm delivery				
T1DM; Crude	4.86 (4.22-5.60)	6.23 (5.53-7.02)	6.39 (5.30-7.71)	0.16
Adjusted	4.72 (4.09-5.44)	5.98 (5.31-6.74)	5.97 (4.94-7.21)	0.15
Non-diabetic; Crude	1.0	1.05 (1.02-1.07)	1.28 (1.24-1.32)	0.16
Adjusted	1.0	1.04 (1.02-1.07)	1.26 (1.22-1.30)	0.15

Perinatal mortality				
T1DM; Crude	2.55 (1.36-4.76)	3.93 (2.49-6.19)	3.14 (1.40-7.04)	0.29
Adjusted	2.46 (1.32-4.60)	3.72 (2.36-5.89)	2.86 (1.27-6.44)	0.31
Non-diabetic ; Crude	1.0	1.47 (1.35-1.59)	2.24 (2.04-2.46)	0.29
Adjusted	1.0	1.46 (1.35-1.59)	2.22 (2.03-2.44)	0.31
Cesarean section				
T1DM; Crude	5.59 (5.00-6.25)	7.09 (6.42-7.83)	9.44 (8.04-11.08)	0.42
Adjusted	5.69 (5.09-6.37)	7.12 (6.44-7. 88)	9.35 (7.95-11.00)	0.36
Non-diabetic; Crude	1.0	1.33 (1.31-1.35)	1.84 (1.81-1.88)	0.42
Adjusted	1.0	1.34 (1.32-1.36)	1.87 (1.83-1.90)	0.36
Neonatal overweight				
T1DM; Crude	8.46 (7.39-9.70)	9.93 (8.83-11.17)	11.71 (9.79-14.00)	<0.001
Adjusted	8.40 (7.32-9.64)	9.86 (8.76-11.11)	11.29 (9.42-13.53)	<0.001
Non-diabetic; Crude	1.0	1.66 (1.62-1.71)	2.59 (2.51-2.67)	<0.001
Adjusted	1.0	1.65 (1.61-1.69)	2.55 (2.48-2.63)	<0.001

*Adjusted for ethnicity, maternal age, height, parity, smoking first trimester, chronic hypertension

#Interaction between BMI category and T1DM

Table 4) Crude and Adjusted* Odds ratios (OR; 96%CI) for adverse perinatal outcome in pregnant women with type 1 diabetes (T1DM) and stratified on BMI. Reference group: T1DM women with normal pre-pregnancy BMI.

Comment [MP18]: R2, last comment

	T1DM BMI 18.5-24.9	T1DM BMI 25-29.9	T1DM BMI≥30
LGA-infant			
Crude	1.0	1.13 (0.98-1.32)	1.14 (0.95-1.37)
Adjusted	1.0	1.18 (1.01-1.38)	1.21 (1.00-1.47)
Major malformations			
Crude	1.0	0.93 (0.63-1.37)	1.73 (1.15-2.58)
Adjusted	1.0	0.92 (0.62-1.36)	1.77 (1.18-2.65)
Preeclampsia			
Crude	1.0	1.17 (0.95-1.45)	1.45 (1.13-1.86)
Adjusted	1.0	1.21 (0.98-1.50)	1.74 (1.35-2.25)
Preterm delivery			
Crude	1.0	1.23 (1.02-1.47)	1.25 (1.00-1.56)
Adjusted	1.0	1.22 (1.02-1.47)	1.25 (1.00-1.56)
Perinatal mortality			
Crude	1.0	1.48 (0.71-3.08)	1.14 (0.44-2.98)
Adjusted	1.0	1.47 (0.70-3.03)	1.08 (0.41-2.83)
Cesarean section			
Crude	1.0	1.38 (1.19-1.60)	1.69 (1.40-2.04)
Adjusted	1.0	1.37 (1.18-1.60)	1.67 (1.38-2.03)
Neonatal overweight			
Crude	1.0	1.17 (0.98-1.40)	1.35 (1.09-1.67)
Adjusted	1.0	1.19 (0.99-1.42)	1.36 (1.09-1.69)

*Adjusted for ethnicity, maternal age, height, parity, smoking first trimester, chronic hypertension

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
	X	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2X	Explain the scientific background and rationale for the investigation being reported
Objectives	3X	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4x	Present key elements of study design early in the paper
Setting	5x	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6x	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7x	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*x	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9x	Describe any efforts to address potential sources of bias
Study size	10x	Explain how the study size was arrived at
Quantitative variables	11x	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12x	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*x	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*x	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*x	Report numbers of outcome events or summary measures over time
Main results	16x	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17x	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18x	Summarise key results with reference to study objectives
Limitations	19x	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20x	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21x	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22x	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.