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ORIGINAL RESEARCH ARTICLE

Risk of gestational diabetes mellitus in relation to early pregnancy and gestational weight gain before diagnosis: A population-based cohort study

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Abstract

Introduction: Gestational diabetes mellitus (GDM) is a common pregnancy complication associated with adverse consequences for the mother and offspring in both short and long term. The aim of this study was to investigate associations between risk of GDM and gestational weight gain in early pregnancy and before diagnosis.

Material and methods: Our population-based cohort study included 131 164 singleton pregnancies in the Stockholm-Gotland region in Sweden from 2008 through 2013. The exposures were weight gain in early pregnancy (<22 weeks) and weight gain before diagnosis, standardized into gestational age-specific *z* scores. The outcome was GDM. We used logistic regression models with a generalized estimating equations method to estimate odds ratios with 95% confidence intervals for GDM, stratified by early-pregnancy body mass index (BMI) category.

Results: Above average weight gain before diagnosis (*z* score >0) was associated with increased risk of GDM among all BMI groups except for obese III. Early gestational weight gain above average was associated with increased risk for GDM in overweight women. Below average weight gain before diagnosis (*z* score <0) was only associated with decreased risk of GDM in obese III. Early gestational weight gain below average was associated with reduced risks of GDM in obese class I, II, and III women.

Conclusions: The risk of GDM increased with higher weight gain before diagnosis in all BMI groups except obese class III, whereas the risk was reduced with lower weight gain before diagnosis in obese III women only. The risk of GDM increased with higher early gestational weight gain in overweight women, while the risk was reduced with lower early gestational weight gain among obese women. Obese women may benefit from lower weight gain, especially in early pregnancy.

Abbreviations: aOR, adjusted odds ratio; ATC, Anatomical Therapeutic Chemical; BMI, body mass index; GDM, gestational diabetes mellitus; ICD, International Classification of Diseases; IOM, the Institute of Medicine; IQR, interquartile range; OGTT, oral glucose-tolerance test; SD, standard deviation.

KEYWORDS
early-pregnancy body mass index, gestational diabetes mellitus, gestational weight gain, gestational weight gain *z* score, insulin-treated gestational diabetes mellitus

1 | INTRODUCTION

Gestational diabetes mellitus (GDM) is associated with many short- and long-term adverse consequences for the mother and offspring, including cesarean section, macrosomia, neonatal hypoglycemia,[1] and later risk of type 2 diabetes (both mother and child) and obesity (offspring).[1,2]

Gestational weight gain is a potential modifiable risk factor for GDM. However, in the current gestational weight gain recommendations, from 2009 by the Institute of Medicine (IOM),[3] GDM was not included as an outcome because of the lack of high-quality studies. Specifically, the committee was concerned that most of the available studies examined total weight gain rather than gestational weight gain up until diagnosis, which could lead to bias from reverse causation (as weight gain patterns after diagnosis might be altered as part of GDM treatment).

Since the formulation of the IOM gestational weight gain recommendations, several studies have evaluated the association of gestational weight gain until diagnosis and/or early gestational weight gain with GDM.[2,4–18] However, only six studies[4,8,10,15–17] stratified the analysis by early/pre-pregnancy body mass index (BMI) categories, which is crucial because the modifying effect of early/pre-pregnancy BMI should be considered in the association between gestational weight gain and GDM.[19] Still, associations between gestational weight gain and risk of GDM are inconsistent across BMI categories. The potential reasons for these unclear findings may be small sample sizes within each BMI group, lack of adjustments for confounders, the inclusion of different study populations, as well as the use of different measures of gestational weight gain.

The objective of the current study was to evaluate the associations between gestational weight gain *z* score (ie, gestational weight gain standardized for gestational age[20]) in early pregnancy and weight gain *z* score before the diagnosis and risk of GDM across BMI categories in a large population-based cohort.

Key message

The risk of gestational diabetes mellitus increased with gestational weight gain before diagnosis in all BMI groups except obese III.

2 | MATERIAL AND METHODS

2.1 | Study population

The study population included singleton pregnancies from the Stockholm-Gotland Obstetric cohort, with births recorded from January 1, 2008 to December 31, 2013 (n = 151 710). The cohort contains all electronic medical records from maternity, delivery, and postnatal care units of the Stockholm and Gotland regions in Sweden.[21] These records were linked to the National Patient Register (containing inpatient and outpatient medical care) and the Prescribed Drug Register, using the unique personal identification number assigned to each Swedish resident.[22]

We excluded pregnancies involving pre-pregnancy diabetes (identified by the Swedish version of the International Classification of Diseases, 10th revision [ICD-10-SE] codes O240–O243, E10–E14, or drug dispensation records of insulin or oral antidiabetic medicine within 6 months before conception, based on the World Health Organization Anatomical Therapeutic Chemical [ATC] classification system codes A10A and A10B), lack of early-pregnancy BMI ($<14^{+0}$ weeks of gestation), cases of GDM where the date of diagnosis was unknown or pregnancies that had fewer than two weight measurements before diagnosis/delivery. After these exclusions, 131 164 pregnancies (86%) remained. Early gestational weight gain was available for 51 207 pregnancies (Figure 1). The characteristics of women with vs without early gestational weight gain are shown in the Supplementary material (Table S1).

2.2 | Exposures

Early gestational weight gain and gestational weight gain up until the diagnosis of GDM were used as exposures. Early gestational weight gain was defined as the last measured weight before 22 weeks of gestation minus weight measured at the first antenatal care (median gestational age week 9, interquartile range [IQR], 8–11). The week cut-off for early gestational weight gain was based on the gestational age threshold that would ensure the cut-off date precedes the screening of plasma blood glucose (starting around gestational week 24). Gestational weight gain before GDM diagnosis was calculated as the last measured weight before the diagnosis minus weight measured at the first antenatal care. Gestational weight gain was standardized for gestational age and expressed as *z* score according to the Swedish BMI-specific weight gain-for-gestational age charts.[20]

Gestational weight gain information was collected from each antenatal care visit. During the study period, the typical schedule of routine antenatal care was at weeks 8 to 12, 24, 29, and 31, and thereafter every second (nulliparous women) or third (parous women) week until birth. Nulliparous women generally have an additional visit in week 20.[21]

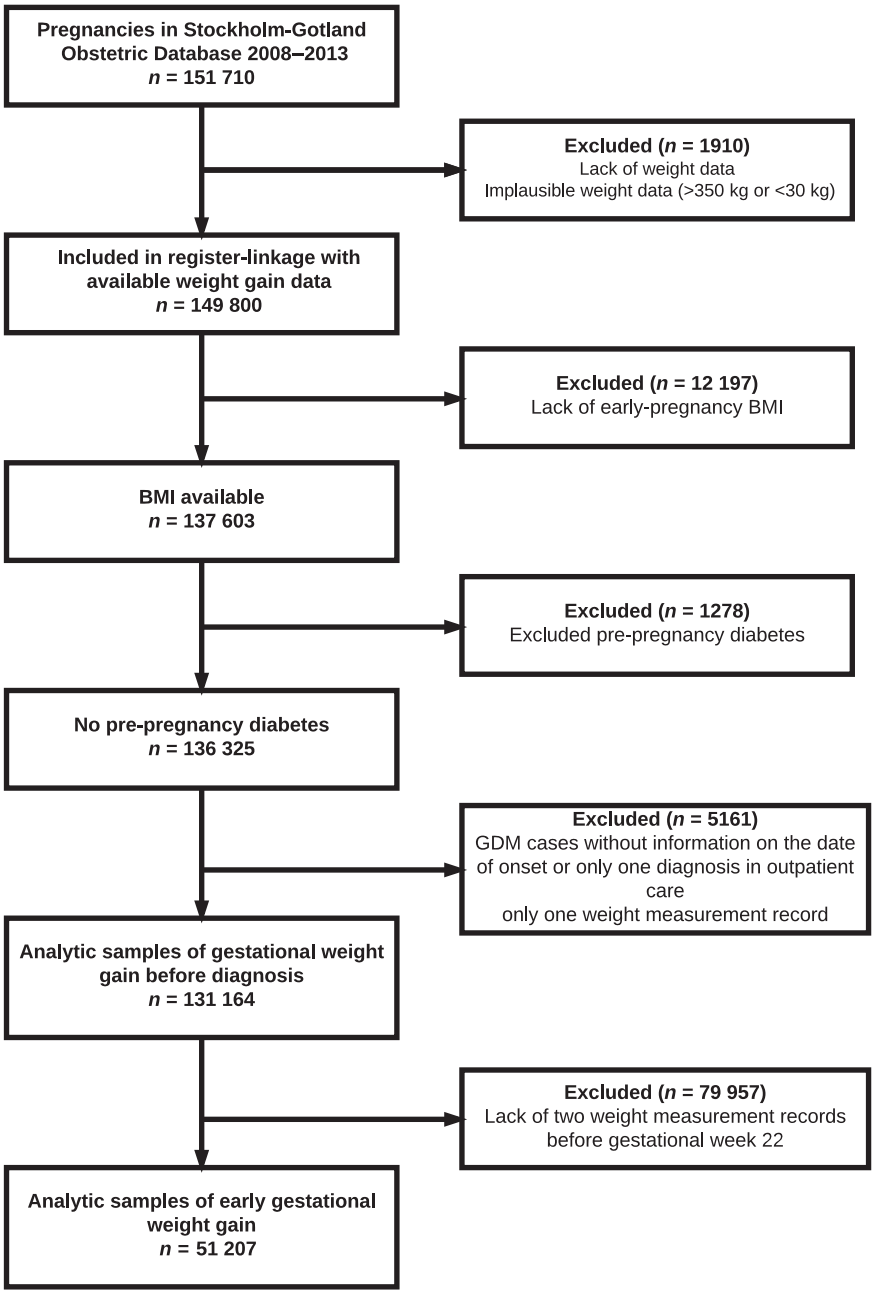

FIGURE 1 Flowchart of women with and without gestational diabetes mellitus in Stockholm-Gotland, Sweden, 2008–2013.

2.3 | Outcomes

GDM was defined by ICD-10 codes O244 in the National Patient Register and ATC codes A10A (ie, insulin) in the Prescribed Drug Register, with any of the following four criteria; one or more ICD-10 codes for GDM from an inpatient admission, one or more incidences of insulin dispensing during pregnancy in the Prescribed Drug Register, two or more outpatient visits listing an ICD-10 code for GDM, or one or more outpatient visits listing an ICD-10 code for GDM followed by a diagnosis in the Stockholm-Gotland Obstetric cohort. The date of diagnosis of GDM was defined as the first recording with an ICD-10 or ATC code from either the National Patient Register or the Prescribed Drug Register, respectively. Insulin-treated GDM was defined as GDM requiring insulin treatment.

2.3.1 | Clinical definition of GDM during the study period

Unlike in other countries, a routine oral glucose-tolerance test (OGTT) is not administered to low-risk women in Sweden. Instead, women generally undergo testing of capillary blood glucose levels at the first antenatal visit and thereafter around gestational weeks 24, 29, 31, and 37/38. If the plasma blood glucose level is 9.0 mmol/L or more, or if accelerated fetal growth or polyhydramnios are observed, then an OGTT is performed. Screening for GDM via an OGTT at gestational weeks 24–28 is only performed in women who belong to a risk group (eg, history of GDM or infant with macrosomia [≥4500 g or 2 standard deviations], BMI ≥35 kg/m^2, OGTT earlier in the current pregnancy but with a normal result). The diagnosis of

GDM during the study period was based on a fasting plasma glucose level of 7.0 mmol/L or more and/or a 2-hour plasma glucose level of 12.2 mmol/L or more during an OGTT.

2.4 | Confounders

Confounders included maternal age at delivery (years), maternal height (cm), parity (nulliparous, 1, ≥2), smoking status at first antenatal visit (non-smoker, smoker, or missing), cohabitation status (living with partner, not living with partner, or missing), and pre-pregnancy hypertension. We also adjusted for early-pregnancy BMI (kg/m^2) as a continuous variable to account for potential residual confounding. We did not adjust for previous GDM as a confounder because adjusting for previous obstetrical history can introduce collider bias.[23,24]

2.5 | Statistical analyses

Characteristics of women were described using means and standard deviation (SD), median and IQR for continuous variables, or counts with percentages for categorical variables.

The associations between gestational weight gain *z*-score before diagnosis (or in early pregnancy) and risk of GDM (or insulin-treated only) were examined by univariate and multivariable logistic regression, with the generalized estimating equations method to account for the possible correlation introduced by repeated pregnancies within the same woman. Results were expressed as crude odds ratios and adjusted odds ratios (aOR) with 95% confidence intervals (CI). The regression models were stratified by early-pregnancy BMI categories (normal weight, 18.5–24.9 kg/m^2; overweight, 25–29.9 kg/m^2; obese class, I 30–34.9 kg/m^2; obese class II, 35–39.9 kg/m^2; or obese class III, kg/m^2). Underweight women were not included because of the small number. For flexible non-linear relations, gestational weight gain *z* score was treated as a continuous variable and modeled by restricted cubic splines with five knots at fixed centiles (5%, 27.5%, 50%, 72.5%, 95%) of the distribution of *z* score for all BMI categories. STATA post-estimation command xblc was used to estimate crude odds ratio and aOR for GDM.[25] We calculated odds ratios for GDM at 0.5 increments of weight gain *z* score in relation to a weight gain *z* score of 0. The risks of GDM across the weight gain continuum estimated in our study were compared with the ranges of weight gain during pregnancy recommended by the IOM.[3] The *z* scores of the IOM recommended weight gain values at weeks 22 and 40 were calculated for each BMI category. For week 40 it was calculated from the recommended total weight gain at week 40 (normal weight: 11.5–16 kg; overweight, 7–11.5 kg, obese [all severity classes] 5–9 kg), whereas for week 22 it was calculated from the first trimester recommended weight gain plus the corresponding recommended weekly weight gain in the second trimester.

2.5.1 | Sensitivity analysis

To test the possible modifying effect of parity, an interaction term between parity and weight gain was included. The date of GDM diagnosis that was retrieved from the first recorded ICD-10 or ATC code was compared with the date of the OGTT for a subset of the cohort for which this was available.

Statistical analyses were performed with STATA 14.0.

2.6 | Ethics statement

The study was approved by the Regional Ethics Committee on April 6, 2009 and June 12, 2013 in Stockholm, Sweden (DNR; 2009/275–31 and 2013/792–32, respectively), and all clinics in the database consented to medical record access.

3 | RESULTS

3.1 | Study characteristics

Table 1 provides characteristics of women with GDM (0.50%; *n* = 658) vs without GDM (99.50%; *n* = 130 506). Compared with women without GDM, women with GDM were more likely to be older, shorter, overweight/obese, have more than two children, live without a partner, have pre-pregnancy hypertension, develop pre-eclampsia, have a cesarean delivery, and deliver at an earlier gestational age. The neonates of women with GDM were more likely to have neonatal hypoglycemia and macrosomia. The median gestational week for GDM diagnosis was 33 (IQR 29–36), and was similar for all BMI categories (Figure S1).

In Table S2 the characteristics of women with insulin-treated GDM (58%; *n* = 382) vs non-insulin-treated GDM (42%; *n* = 276) are compared.

3.2 | Gestational weight gain before diagnosis and risk of GDM

Gestational weight gain *z* score below average (ie, *z* score <0) was associated with decreased risk of GDM among obese class III women, but not among any other BMI categories. The risk was reduced starting from a *z* score of −1 compared with a *z* score of 0 (Figure 2 and Table S3).

Above average gestational weight gain *z* scores (ie, *z* score >0) were associated with increased risks of GDM among normal weight, overweight, obese class I, and obese class II women. The risks were increased from *z* scores of 1, 1.5, 1.5, and 2, respectively (Figure 2 and Table S3). For instance, overweight women with a *z* score value of 1.5 (corresponding to a weight gain of 24.3 kg at 40 weeks) had an almost doubled aOR (1.98; 95% CI 1.36–2.87) for GDM compared with overweight women with a *z* score of 0 (corresponding

TABLE 1 Characteristics of 131 164 women with vs without gestational diabetes mellitus in Stockholm-Gotland, Sweden, 2008–2013.

Characteristic	No GDM ($n = 130\,506$)	GDM ($n = 658$)
Maternal age, year, mean ± SD	31.5 ± 5.0	33.1 ± 5.6
Maternal height, cm, mean ± SD	166.4 ± 6.5	162.8 ± 6.8
BMI in early-pregnancy, kg/m^2, *n* (%)		
Underweight (<18.5)	3962 (3.0)	10 (1.5)
Normal weight (18.5–24.9)	88 013 (67.4)	155 (23.6)
Overweight (25.0–29.9)	27 752 (21.3)	246 (37.4)
Obesity I (30.0–34.9)	8041 (6.2)	143 (21.7)
Obesity II (35.0–39.9)	2101 (1.6)	70 (10.6)
Obesity III (≥40)	637 (0.5)	34 (5.2)
Parity, *n* (%)		
Nulliparous	60 493 (46.4)	268 (40.7)
1	48 631 (37.3)	216 (32.8)
≥2	21 382 (16.4)	174 (26.4)
Smoking[a], *n* (%)		
Non-smoker	124 469 (95.4)	620 (94.2)
Smoker	5400 (4.1)	35 (5.3)
Missing	637 (0.5)	3 (0.5)
Living with partner, *n* (%)	122 757 (94.1)	589 (89.5)
Missing	802 (0.6)	5 (0.8)
Pre-pregnancy hypertension, *n* (%)	1048 (0.8)	22 (3.3)
Pre-eclampsia, *n* (%)	3967 (3.0)	41 (6.2)
Neonatal hypoglycemia, *n* (%)	975 (0.8)	42 (6.4)
Macrosomia[b], *n* (%)	4067 (3.1)	65 (9.9)
Cesarean delivery, *n* (%)	25 491 (19.5)	229 (34.8)
Gestational age at delivery (days), median (IQR)	280 (273–286)	274 (267–280)
Gestational age at diagnosis (days), median (IQR)	–	229 (205–250)
No. of weight measurements, median (IQR)[c]	5 (3–7)	4 (2–5)

Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus; IQR, interquartile range; SD, standard deviation.

[a]Smoking status at first antenatal care visit.

[b]Macrosomia referred to birthweight >4500g.

[c]Number of weight measurements for non-GDM until delivery. Number of weight measurements for GDM until diagnosis.

to a weight gain of 13.7 kg at 40 weeks; Table S3). Above average gestational weight gain *z* scores were not associated with GDM risk among obese class III women.

Figure 2 shows the risk of GDM in relation to the IOM gestational weight gain recommendations. At 40 weeks, the IOM-recommended weight gain corresponded to weight gain *z* scores of −0.6 SD to +0.4 SD for normal weight women, −1.3 SD to −0.4 SD for overweight women, −1.1 SD to −0.4 SD for obese I women, −0.7 SD to −0.1 SD for obese class II women, and −0.4 SD to 0.1 SD for obese class III women. Within the weight gain range of the current IOM recommendation there was no increased risk of GDM across the BMI categories. For women with severe obesity (class III), gestational weight gain below the IOM recommendation, however, indicated a reduced risk of GDM.

The association between gestational weight gain *z* score and insulin-treated GDM (Figure S2) was similar as for the overall analysis (Figure 2), except that *z* scores below average were significantly associated with decreased risk of insulin-treated GDM in obese II women only, but the patterns were similar. Further, no association was observed for *z* score above average among normal weight, which was observed for all GDM.

3.3 | Early gestational weight gain and GDM

Early gestational weight gain *z* score below average was associated with a decreased risk of GDM among obese class I, II, and III (but not among normal weight and overweight) women, although some

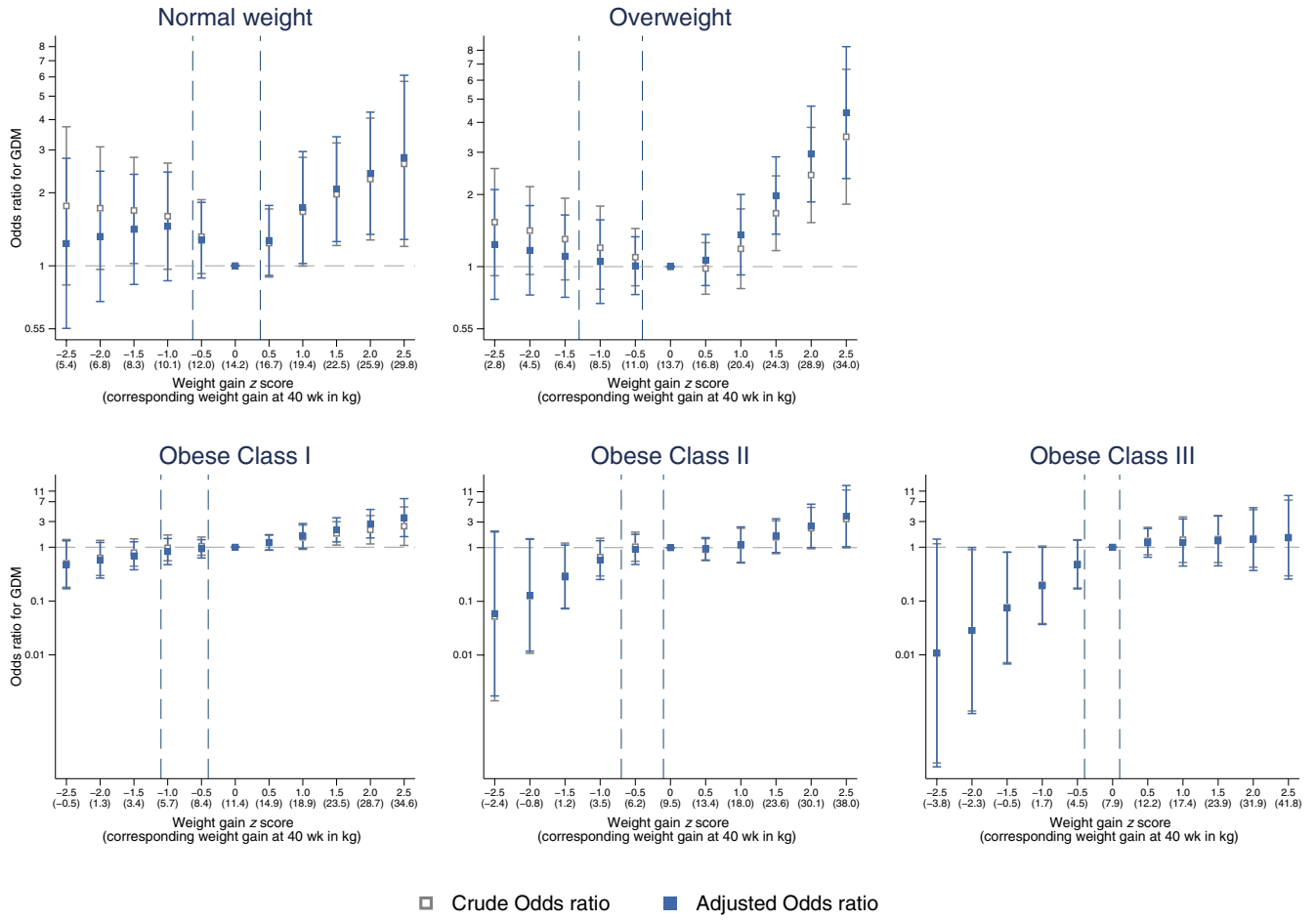

FIGURE 2 Gestational weight gain *z* score before diagnosis and risk of gestational diabetes mellitus (GDM) in normal weight, overweight, and obese women ($n = 127\,192$) in Stockholm-Gotland, Sweden, 2008–2013 (blue vertical dash line refers to Institute of Medicine recommend weight gain range). Crude and adjusted odds ratio (95% CI) for GDM at 0.5 increments of weight gain *z* score in relation to a weight gain *z* score of 0 (normal weight and overweight group had same scales on *y*-axis, while obese I, II, and III had the same scales on *y*-axis). Adjusted for maternal age, height, body mass index, parity, smoking, cohabiting status, and pre-pregnancy hypertension.

of the confidence intervals included or were close to 1. (Figure 3 and Table S4). Gestational weight gain *z* scores above 0 were associated with increased risk of GDM among overweight women starting at a *z* score of 1.5, but not across any of the other BMI categories (Figure 3 and Table S4).

Figure 3 also shows the risk of early GDM in relation to the IOM gestational weight gain recommendations. Within the weight gain window of the current IOM recommendation there was no increased risk of GDM across the BMI categories. However, for women with obesity (classes I–III), risks of GDM were minimized at weight gain values lower than the IOM recommendation.

3.4 | Sensitivity analysis

No statistical interaction was found between gestational weight gain before diagnosis and parity on risk of GDM (Table S5).

Among the 658 GDM cases identified through ICD-10 or ATC codes, 89 women also had an OGTT of 12.2 mmol/L or more available in our database. Compared with the date of diagnosis, the OGTT test date was earlier than the GDM diagnosis date (median 6 days, IQR 3–12 days; Figure S3). However, as the date of the last weight measurement before diagnosis of GDM was identical to the date of the last weight measurement before OGTT test (median 0 days, IQR 0–0 days; Figure S4), suggested that we have identified weight gain measurement before diagnosis of GDM.

4 | DISCUSSION

We found that a gestational weight gain *z* score above average was associated with increased risk of GDM among all BMI groups except for obese class III. In obese class III on the other hand, a weight gain *z* score below average was associated with a decreased risk of GDM (although confidence intervals were wide). Early gestational weight above average gain was only associated with increased risk of GDM in overweight women, while early gestational weight gain below average was associated with a decreased risk for GDM in obese class I, II, and III women (although confidence intervals were wide for obese class III).

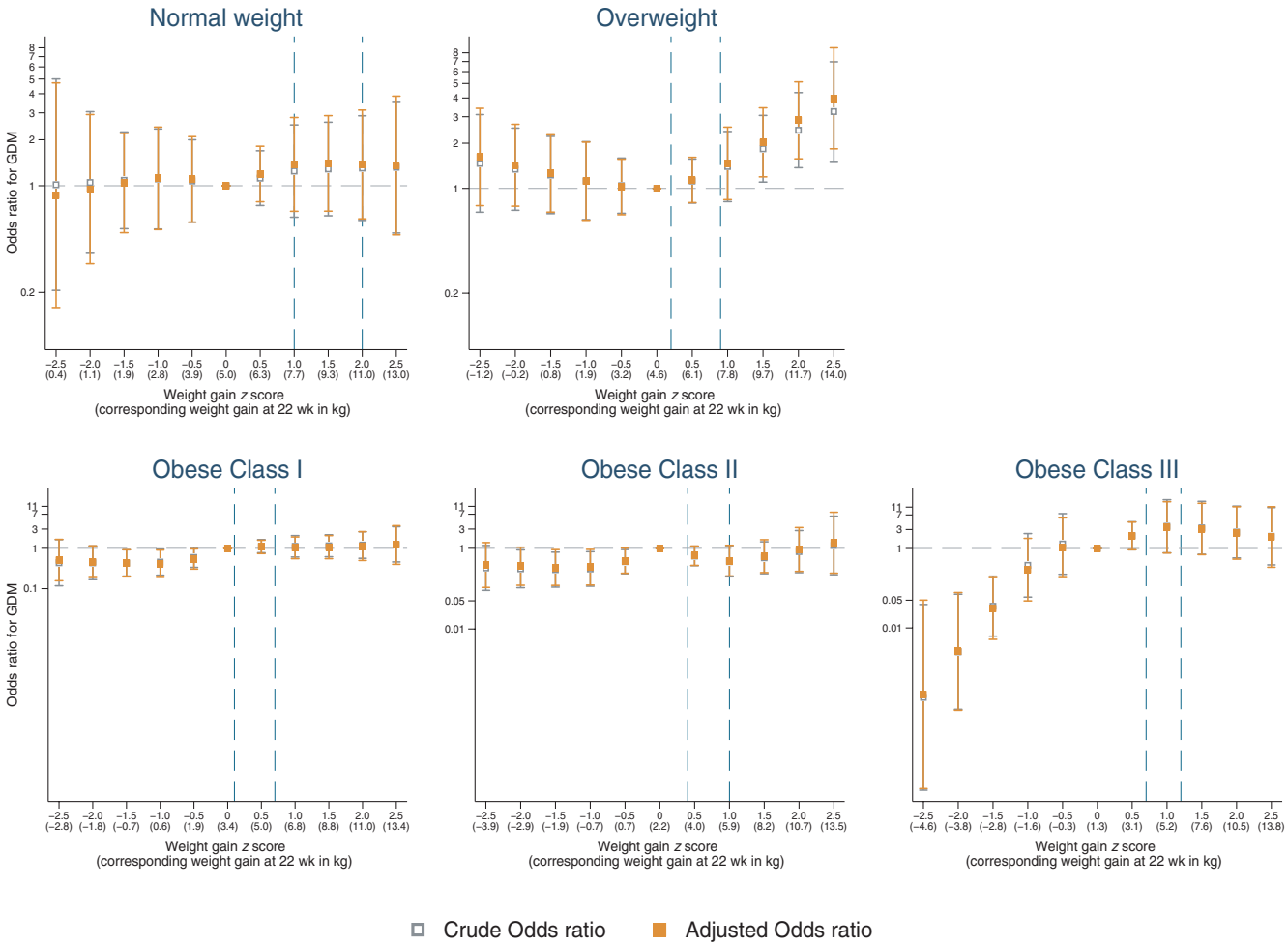

FIGURE 3 Early gestational weight gain *z* score (before week 22) and risk of gestational diabetes mellitus (GDM) in normal weight, overweight, and obese women ($n = 49\,372$) in Stockholm-Gotland, Sweden, 2008–2013 (blue vertical dash line refers to Institute of Medicine recommend weight gain range). Crude and adjusted odds ratio (95% CI) for GDM at 0.5 increments of weight gain *z* score in relation to a weight gain *z* score of 0 (normal weight and overweight group had same scales on *y*-axis, while obese I, II, and III had the same scales on *y*-axis). Adjusted for maternal age, height, body mass index, parity, smoking, cohabiting status, and pre-pregnancy hypertension.

Studies investigating the association between gestational weight gain and GDM according to pre-/early-pregnancy BMI category are rare, and have yielded inconsistent findings (Table S6).[4,8,10,15–17] Among these previous studies, only one study (by MacDonald et al[4]) defined gestational weight gain by *z* scores as we did in the current study. The use of *z* score values allows the comparison of weight gain before the diagnosis of GDM to the weight gain of women without GDM despite differences in gestational age at the time of weight measurements. Our findings agree with those of MacDonald et al's study,[4] that weight gain above average (*z* score >0) before diagnosis increased the risk of GDM in normal weight, and obese class I and II women. We also, in contrast to the MacDonald et al study,[4] found that weight gain above average increased the risk of GDM in overweight women, and a trend towards lower risk of GDM with a weight gain *z* score below average in obese class III women.

Regarding the effect of early gestational weight gain, results are also inconsistent (Table S6).[4,8,16,17] Most previous studies used trimester-specific weight gain, while we used weight gain before 22 gestational weeks to define early gestational weight gain, because we did not have access to weight gain during the first trimester. We found that an association between early gestational weight gain above average (*z* score >0) and increased risk of GDM was restricted to overweight women. We found that all obese women with lower early gestational weight gain had a suggestive lower risk of GDM, but the confidence intervals were close to one for obese class I and II women and were wide for obese class III women. In addition, for women who gained weight within the current IOM recommendations, there was no apparent association between weight gain before diagnosis or early gestational weight gain and GDM. These findings support the IOM recommendation ranges, although the IOM did not take GDM into consideration when establishing the recommendations.[3]

Strengths include that we linked multiple population registries to produce a novel population-based cohort, including gestational weight gain measurements preceding the diagnosis date of GDM. The large sample size allowed us to study the effect of gestational

weight gain on GDM with data stratified by early-pregnancy BMI. Finally, we used gestational weight gain *z* scores, which are, in contrast to weight gain (in kilograms) uncorrelated with gestational age.

Limitations include that we might have misclassified some pre-pregnancy diabetes mellitus cases as GDM, ie, women with an undetected diabetes mellitus diagnosis before pregnancy may have been classified as GDM. However, the median GDM diagnosis date was late in our study (33 weeks of gestation, IQR 29–36 weeks), which indicated that this limitation might be minimal. The late GDM diagnosis may, on the other hand, increase the possibility that extremely preterm (≤27 completed gestational weeks: 0.18%; 235/131 164) and very preterm births (28–31 completed gestational weeks: 0.38%; 499/131 164) would not be at true risk of detection of GDM. However, as the women in our study underwent several capillary blood glucose tests during pregnancy (starting in week 24), the chance of detection of an abnormal blood glucose was high in our study compared with other studies where only OGTT screening was performed once during pregnancy. Hence, a woman delivering extremely or very preterm would still have had the possibility of detection for GDM, unless delivering at or before 24 weeks (which was rare in our study, Figure S5). We used early-pregnancy BMI to represent pre-pregnancy BMI, which could lead to an overestimation of pre-pregnancy BMI. However, weight change in early pregnancy is minimal[26] (median first antenatal visit was at 9 weeks in our study) and most other studies with available pre-pregnancy weights only have access to self-reported pre-pregnancy weight, which often is underestimated and may introduce bias.[27] Further, the prevalence of GDM of 0.5% in our study is substantially lower than reported rates of 6.1% in Europe and of 7.0% in North America and Caribbean,[28] and lower than the prevalence of 2.2% in southern Sweden (ie, the only part of Sweden that conducts routine OGTT for all pregnant women).[29] This difference likely reflects differences in screening routine and diagnostic criteria between jurisdictions, but also differences in risk of GDM with population ethnicity. One disadvantage of not screening all pregnant women for GDM might be that we could have missed those with mild GDM. Nevertheless, we performed a subgroup analysis for insulin-treated GDM, ie, a GDM group that would be detected in all high-income countries independent of the GDM diagnostic criteria and the results were similar to overall GDM analysis except for normal weight. Lastly, only 51 207 women were available for the analysis of early gestational weight gain, and hence a sizeable fraction of the cohort was not included. However, we do not think this will introduce significant bias, as it most likely arises from differences in the timing of routine antenatal visits by parity rather than individual risk profiles. In Sweden, the second scheduled antenatal visit for nulliparous women is usually at week 20, and for parous women it is at week 24. Hence, this resulted in the exclusion of a higher fraction of parous vs nulliparous women from the early gestational weight gain analysis because they did not have their second antenatal care visit until after the cut-off (week 22; Table S1). Another big difference between the included and excluded was early-pregnancy BMI status (Table S1). Since our analyses were conducted separately for each early-pregnancy BMI category, and the interaction analysis showed that parity did not influence the association between gestational weight gain and GDM, we do not believe that this potential selection would have a strong influence on the results.

The biological mechanism behind the observed association between gestational weight gain and risk of GDM is unknown, however it is plausible that it follows the same mechanisms as associations between obesity, type 2 diabetes, and risk of GDM.

Early gestational weight gain has been suggested to be as important for GDM as late gestational weight gain.[3] We observed a particularly beneficial effect of early gestational weight gain below average for all obese classes. Possibly, maternal insulin sensitivity changes are inversely correlated with changes in energy expenditure and fat mass accretion in early but not late pregnancy.[3]

5 | CONCLUSION

Gestational weight gain before diagnosis increased the risk of GDM above average for all BMI groups (except obese class III), whereas early gestational weight gain above average was only associated with increased risk in overweight women. Gestational weight gain below average, and especially early gestational weight gain, was associated with reduced risks among obese class I, II, and III women. Hence, obese women may benefit from a lower gestational weight gain than average, and especially in early pregnancy.

AUTHOR CONTRIBUTIONS

HX, JAH, and KJ designed the study; HX analyzed data or performed statistical analysis, and drafted the manuscript. All authors critically revised the manuscript for important intellectual content. HX and KJ are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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