Risk of pre-eclampsia after gastric bypass: a matched cohort study

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Objective To investigate whether gastric bypass before pregnancy is associated with reduced risk of pre-eclampsia.

Design Nationwide matched cohort study.

Setting Swedish national health care.

Population A total of 843 667 singleton pregnancies without pre-pregnancy hypertension were identified in the Swedish Medical Birth Register between 2007 and 2014, of which 2930 had a history of pre-eclampsia and a pre-surgery weight available from the Scandinavian Obesity Surgery Registry. Two matched control groups (pre-surgery and early-pregnancy body mass index [BMI]) were propensity score matched separately for nulliparous and parous births, to post-gastric bypass pregnancies (\(n_{\text{pre-surgery-BMI}} = 2634/2634/2634/2766/2766\)) on pre-surgery/early-pregnancy BMI, diabetes status (pre-surgery/pre-conception), maternal age, early-pregnancy smoking status, educational level, height, country of birth, delivery year and history of pre-eclampsia.

Main outcome measures Pre-eclampsia categorised into any, preterm onset (<37 weeks) and term onset (≥37 weeks).

Results In post-gastric bypass pregnancies, mean pre-surgery BMI was 42.9 kg/m² and mean BMI loss between surgery and early pregnancy was 14.0 kg/m² (39 kg). Post-gastric bypass pregnancies had lower risk of pre-eclampsia compared with pre-surgery BMI-matched controls (1.7 versus 9.7 per 100 pregnancies; hazard ratio [HR] 0.21, 95% CI 0.15–0.28) and early-pregnancy BMI-matched controls (1.9 versus 5.0 per 100 pregnancies; HR 0.44, 95% CI 0.33–0.60). Although relative risks for pre-eclampsia for post-gastric bypass pregnancies versus pre-surgery matched controls was similar, absolute risk differences (RD) were significantly greater for nulliparous women (RD −13.6 per 100 pregnancies, 95% CI −16.1 to −11.2) versus parous women (RD −4.4 per 100 pregnancies, 95% CI −5.7 to −3.1).

Conclusion We found that gastric bypass was associated with lower risk of pre-eclampsia, with the largest absolute risk reduction among nulliparous women.

Keywords Bariatric surgery, pre-eclampsia, gestational hypertension, hypertension, obesity, overweight, weight loss, weight-loss surgery.

Tweetable abstract In this large study including two comparison groups matched for pre-surgery or early-pregnancy BMI, gastric bypass was associated with lower risk of pre-eclampsia.

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Introduction

Pre-eclampsia is a serious pregnancy-related complication associated with preterm birth, fetal growth restriction, maternal and perinatal mortality, and later cardiovascular and metabolic disorders of the mother. Pre-pregnancy obesity and its co-morbidities are well-established modifiable risk factors of pre-eclampsia. In 2015/16, 35.7% of US women aged 20–39 years were obese (body mass index [BMI] ≥30 kg/m²) and 7.8% had a BMI ≥40 kg/m². Weight loss before pregnancy is expected to reduce the risk of pre-eclampsia. However, effective treatment options for obesity are limited and bariatric surgery is currently the only treatment with proven long-term effects.

The majority of previous studies on bariatric surgery before pregnancy and pre-eclampsia risk have been small...
and inconclusive.\textsuperscript{6–18} Pooling of these studies in meta-analyses has been complicated by the use of heterogeneous control groups. Two meta-analyses\textsuperscript{19,20} that separated the analysis by type of control group found a tendency (although not significant) of a lower risk of pre-eclampsia in the bariatric surgery group compared with both pre-surgery and early-pregnancy BMI-matched controls.

The choice of control group has a major impact on the interpretation of the results.\textsuperscript{21} Inclusion of a pre-surgery BMI-matched control group aims at determining the risk--benefit of undergoing bariatric surgery before pregnancy versus not undergoing surgery for obese women, i.e. in this scenario the controls remain obese while the bariatric surgery group lose weight and improve their metabolic status before pregnancy. In contrast, when using an early-pregnancy BMI-matched control group, the bariatric surgery group and the controls have the same early-pregnancy BMI. In that scenario, the purpose is to inform healthcare personnel as well as patients whether two women with similar current BMI and health status have different prognoses regarding the risk of adverse pregnancy outcomes.

The aim of this large nationwide population-based study was to investigate whether gastric bypass (one of the two most common bariatric surgery procedures) before pregnancy is associated with risk of pre-eclampsia as compared with control pregnancies matched for a number of factors including pre-surgery or early-pregnancy BMI.

Materials and methods

Study design

Data from the Swedish Medical Birth Register were linked to the Scandinavian Obesity Surgery Registry (SOREg), the Swedish National Patient Register and the Swedish Prescribed Drug Register, by using the unique personal identification number assigned to each Swedish citizen and resident with a residence permit (description of registers and eligibility criteria for bariatric surgery in Sweden can be found in the Supplementary Methods and Table S1).

Study population

The study population included 891,077 deliveries recorded in the Swedish Medical Birth Register between 2007 and 2014 (Figure S1). After excluding multiple pregnancies, pregnancies to mothers without a valid personal identification number (because they could not be linked to other registers), pregnancies with missing gestational age and those with pre-existing hypertension (defined according to the International Classification of Diseases tenth revision [ICD-10] or Anatomical Therapeutic Chemical (ATC) codes provided in Table S2), 843,667 singleton pregnancies remained, of which 55,455 had a history of bariatric surgery. Of these, 2,930 had undergone gastric bypass and had pre-surgery BMI available in SOReg (surgery performed between January 2007 and March 2014). From the 838,122 pregnancies in women without gastric bypass, two matched control groups were created.

Outcomes

Pre-eclampsia was defined by ICD-10 codes O14 or O15 identified from the National Patient Register (inpatient or outpatient care) from gestational week 20\textsuperscript{+0} up until 1 week after delivery (to identify possible postpartum pre-eclampsia) or the Medical Birth Register (diagnosis registered at delivery). The following criteria were applied: (1) one inpatient care admission, (2) two outpatient visits, (3) one outpatient visit followed by a diagnosis in the Medical Birth Register and (4) a diagnosis only in the Medical Birth Register. The date of pre-eclampsia diagnosis was defined as the first recording in inpatient care, outpatient care or the Medical Birth Register.

Pre-eclampsia was classified as preterm (<37\textsuperscript{+0} weeks of gestation) or term onset pre-eclampsia (\geq 37\textsuperscript{+0} weeks of gestation). Pre-eclampsia complicated by small-for-gestational age (SGA; defined as a birthweight below the tenth percentile for sex and gestational age) was also investigated.

According to Swedish guidelines, the clinical definition of pre-eclampsia during the study period was new-onset hypertension (systolic/diastolic blood pressure of \geq 140/90 mmHg) with proteinuria (\geq 0.3 g per 24 h or \geq 1 on a urine dipstick on at least two subsequent occasions) developing at gestational week 20\textsuperscript{+0} or later.

Covariates

Pre-surgery BMI was calculated from measured weight and height at the surgical planning visit. Early-pregnancy BMI was calculated from measured weight and self-reported height at the first prenatal visit (median at 9.9 weeks of gestation in the current study). Early-pregnancy self-reported smoking status was registered at the same visit (non-smoker, smoker of one to nine cigarettes/day, or smoker of ten or more cigarettes/day, or missing data). For women giving birth more than once, the median height from all registered pregnancies was used to reduce measurement error and missingness. Information of country of birth of the mother was retrieved from the Total Population Register\textsuperscript{22} and categorised into Nordic (Sweden, Denmark, Norway, Finland and Iceland) or non-Nordic, and education level of the mother (<10 years, 10–12 years, >12 years) was retrieved from the Education Register.\textsuperscript{23}

Gestational age was generally estimated by early second-trimester ultrasound, which has been offered to all pregnant women in Sweden since the 1990s and 95% accept this offer. If ultrasound-estimated date of delivery was not available, gestational age was estimated by using the first day of the last menstrual period.
Diabetes, cardiovascular, psychiatric and substance use disorder status ever before surgery or 6 months before pregnancy were defined according to ICD-10 or ATC codes (Table S2) from the National Patient Register, the Prescribed Drug Register and the Medical Birth Register (only for pre-pregnancy factors).

Propensity score matching
Propensity score matching was used to identify control pregnancies with similar characteristics to the post-gastric bypass pregnancies. Two control groups, matched either for pre-surgery BMI or early-pregnancy BMI, were created by using a 1:1 propensity score matching with nearest neighbour algorithm without replacement allowing a maximum caliper width equal to 0.2 of the pooled standard deviation of the logit of the propensity score.24

The propensity scores for the two matched control groups, were estimated separately in nulliparous and parous women, using a logistic regression model including the following covariates:

1 Pre-surgery BMI matching: pre-surgery BMI as both continuous and in categories (using early-pregnancy BMI in controls; 30–34.9/35–39.9/40–44.9/45–49.9/≥50 kg/m²), pre-surgery diabetes status (before conception in controls).

2 Early-pregnancy BMI matching: early-pregnancy BMI as both continuous and in categories (<18.5/18.5–24.9/25–29.9/30–34.9/35–39.9/≥40 kg/m²), pre-pregnancy diabetes status.

The propensity score models further included maternal age (continuous), early-pregnancy smoking status (non-smoker/one to nine/ten or more daily cigarettes/missing), education level (<10/10–12/>12 years/missing), height (continuous), country of birth (Nordic/non-Nordic), delivery year (2007–2010, 2011–2014) and history of pre-eclampsia.

Standardised differences were calculated for all covariates to assess balance after matching. A characteristic was considered well balanced if the difference was less than 10% (−0.10 < standardised difference < 0.10).

Statistical analysis
Kaplan–Meier survival curves were used to describe time to pre-eclampsia diagnosis for post-gastric bypass pregnancies and the matched control groups. General population pregnancies were added as reference. Cox proportional hazard regression models conditioned on the propensity score matching set, with gestational age as the underlying time-scale, were used to estimate hazard ratios (HRs) for pre-eclampsia in post-gastric bypass pregnancies versus matched controls. Adjustments were made for cardiovascular and psychiatric disease and substance use disorder before surgery or pregnancy. The proportional hazards assumption was assessed for any pre-eclampsia by interacting gastric bypass status and follow-up time in the model using a Wald chi-square test, which showed that the assumption was not violated ($P = 0.85$).

As the analyses were conducted on individual pregnancies, robust standard errors clustering on the ID of the mother were used to account for the possible correlation of having repeated pregnancies in the same mother. The study population was stratified into nulliparous and parous women to further account for the possible dependence, but also because the risk of pre-eclampsia is higher in nulliparous women, and the pre-eclampsia status of the first pregnancy strongly predicts the risks in subsequent pregnancies.1

Additionally, for the pre-surgery matched group, subgroup analyses were conducted by surgery-to-conception interval, pre-surgery BMI, decrease in BMI and weight from surgery to early-pregnancy (below/above the median for all groups) to study potential effect modification of these factors.

Data were analysed using SAS (version 9.4; SAS, Cary, NC, USA) and Stata (version 13; StatCorp, College Station, TX, USA). Two-sided $P$ values less than 0.05 were considered statistically significant.

Results

Study characteristics
Post-gastric bypass pregnancies ($n = 2930$) compared with the general population pregnancies ($n = 838 122$) were older, more likely to be obese, to smoke, have lower educational level, and more likely to have given birth previously (all $P < 0.001$; Table S3). After propensity score 1:1 matching, pre-surgery BMI-matched controls were identified for 2634 post-gastric bypass pregnancies and early-pregnancy matched controls for 2766. After matching, all baseline characteristics (except for psychiatric disease in the early-pregnancy BMI matching) were balanced as evaluated by standardised differences (Table 1).

Mean pre-surgery BMI in post-gastric bypass pregnancies and pre-surgery matched controls (early-pregnancy BMI used in controls) was 42.9 kg/m². In both groups 3% had class I obesity (BMI 30–34.9 kg/m²), 26% had class II obesity (BMI 35–39.9 kg/m²) and 71% had class III obesity (BMI ≥ 40 kg/m²).

Among post-gastric bypass pregnancies, the median surgery-to-conception interval was 1.6 years, with 30% becoming pregnant within the first year after surgery. Mean weight loss between surgery and early pregnancy was 39 kg (Table 1, Figure S2).

Mean early-pregnancy BMI in post-gastric bypass pregnancies and early-pregnancy matched controls was 29.4 kg/m², with 17–18% being normal weight, 42–45% being overweight and 38–39% being obese (Table 1).
Table 1. Maternal characteristics in singleton pregnancies without pre-pregnancy hypertension in Sweden between 2007 and 2014 after gastric bypass and in matched controls

|                                | Pre-surgery BMI matching | Early-pregnancy BMI matching |
|--------------------------------|--------------------------|-----------------------------|
|                                | Pregnancies after gastric bypass | Matched control pregnancies* | Standardised difference | Pregnancies after gastric bypass | Matched control pregnancies** | Standardised difference |
| N                              | 2634                     | 2634                        | 2766                     | 2766                        |
| Surgery-to-conception interval (year), median (IQR) | 1.6 (0.9–2.5)          | 1.6 (0.9–2.5)               | 1.6 (0.9–2.5)           | 1.6 (0.9–2.5)               |
| <1                             | 799 (30.3%)              | 824 (29.8%)                 | 31 ± 5                   | 31 ± 5                     |
| 1 to <2                        | 844 (32.0%)              | 881 (31.9%)                 | 31 ± 6                   | 31 ± 6                     |
| 2 to <5                        | 936 (35.5%)              | 1003 (36.3%)                | 0.000                    | 0.023                      |
| ≥5                             | 55 (2.1%)                | 58 (2.1%)                   |                          |                            |
| Maternal age (year), mean (SD) | 31 ± 5                   | 31 ± 6                     | 43.7 ± 5.5               | 29.0 ± 4.6                 |
| BMI before surgery (kg/m²), mean (SD) | 42.9 ± 5.0              | 42.9 ± 5.7                  | −0.111                   | 29.0 ± 4.6                 |
| 30–34.9                        | 75 (2.8%)                | 59 (2.2%)                   | 0.027                    | 75 (2.8%)                  |
| 35–39.9                        | 691 (26.2%)              | 696 (26.4%)                 | −0.003                   | 696 (26.4%)                |
| 40–44.9                        | 1104 (41.9%)             | 1143 (43.4%)                | −0.021                   | 1143 (43.4%)               |
| 45–49.9                        | 523 (19.9%)              | 510 (19.4%)                 | 0.009                    | 510 (19.4%)                |
| ≥50                            | 241 (9.1%)               | 226 (8.6%)                  | 0.014                    | 226 (8.6%)                 |
| Early pregnancy BMI before (kg/m²), mean (SD) | 29.0 ± 4.6              | 29.0 ± 4.6                  | −3.785                   | 29.0 ± 4.6                 |
| 18.5–24.9                      | 0 (0.0%)                 | 0 (0.0%)                    | 0.019                    | 0 (0.0%)                   |
| 25–29.9                        | 493 (18.7%)              | 493 (18.7%)                 | 0.480                    | 493 (18.7%)                |
| 30–34.9                        | 1118 (42.4%)             | 1118 (42.4%)                | 0.859                    | 1118 (42.4%)               |
| 35–39.9                        | 628 (23.8%)              | 628 (23.8%)                 | 0.479                    | 628 (23.8%)                |
| 40–44.9                        | 220 (8.4%)               | 220 (8.4%)                  | −0.347                   | 220 (8.4%)                 |
| 45–49.9                        | 58 (2.2%)                | 58 (2.2%)                   | −1.454                   | 58 (2.2%)                  |
| ≥40                            | 116 (4.4%)               | 116 (4.4%)                  | 0.215                    | 116 (4.4%)                 |
| Height (cm), mean (SD)         | 167 ± 6                  | 167 ± 6                    | −0.036                   | 167 ± 6                    |
| Smoking status                 |                          |                            |                          |                            |
| Non-smoker                     | 2175 (82.6%)             | 2146 (81.5%)                | 0.020                    | 2146 (81.5%)               |
| 1–9 cigarettes/day             | 277 (10.5%)              | 279 (11.4%)                 | 0.019                    | 279 (11.4%)                |
| ≥10 cigarettes/day             | 104 (3.9%)               | 116 (4.4%)                  | 0.016                    | 116 (4.4%)                 |
| Missing                        | 78 (3.0%)                | 73 (2.8%)                   | 0.008                    | 73 (2.8%)                  |
| Educational level              |                          |                            |                          |                            |
| <10 years                      | 398 (15.1%)              | 397 (15.1%)                 | 0.001                    | 397 (15.1%)                |
| 10–12 years                    | 1586 (60.2%)             | 1612 (61.2%)                | 0.014                    | 1612 (61.2%)               |
| >12 years                      | 641 (24.3%)              | 617 (23.4%)                 | 0.015                    | 617 (23.4%)                |
| Missing                        | 9 (0.3%)                 | 8 (0.3%)                    | 0.005                    | 8 (0.3%)                   |
| Delivery year                  |                          |                            |                          |                            |
| 2007–2010                      | 277 (10.5%)              | 290 (11.0%)                 | 0.011                    | 290 (11.0%)                |
| 2011–2014                      | 2357 (89.5%)             | 2344 (89.0%)                | 0.011                    | 2344 (89.0%)               |
| Nordic country of birth        | 2323 (88.2%)             | 2310 (87.7%)                | 0.011                    | 2310 (87.7%)               |
| Nulliparous                    | 1027 (39.0%)             | 1027 (39.0%)                | 0.000                    | 1027 (39.0%)               |
| History of pre-eclampsia***    | 162 (10.1%)              | 168 (10.5%)                 | 0.009                    | 168 (10.5%)                |
| Previous diseases****          |                          |                            |                          |                            |
| Diabetes                       | 242 (9.2%)               | 244 (9.3%)                  | 0.002                    | 244 (9.3%)                 |
| Cardiovascular disease         | 159 (6.0%)               | 109 (4.1%)                  | 0.061                    | 109 (4.1%)                 |
Pre-surgery BMI matching
Pre-eclampsia was diagnosed in 1.7 per 100 pregnancies in post-gastric bypass pregnancies and in 9.7 per 100 in pre-surgery matched controls (risk difference (RD) −8.0, 95% CI −9.5 to −6.8; Figures 1 and 2). For the general population, pre-eclampsia was diagnosed in 3.0 per 100 pregnancies (Table S4, Figure 1).

A majority of the pre-eclampsia cases were diagnosed at term, with 64% (29/45) in the post-gastric bypass group and 63% (162/256) among matched controls (Figures 1 and 2). 33% (15/45) of women with pre-eclampsia gave birth to an SGA infant in the post-gastric bypass group and 17% (44/256) among matched controls (Figure 2).

Compared with pre-surgery matched controls, post-gastric bypass pregnancies had markedly lower risk of pre-eclampsia (HR 0.19, 95% CI 0.13–0.26; Figure 2). Although the relative risk of pre-eclampsia in post-gastric bypass pregnancies as compared with pre-surgery matched controls was similar for nulliparous versus parous women and preterm versus term onset pre-eclampsia, the absolute risk difference differed significantly (Figure 2). The absolute risk reduction of pre-eclampsia for post-gastric bypass pregnancies versus pre-surgery matched controls was significantly greater for nulliparous women (RD −13.6 per 100 pregnancies, 95% CI −16.1 to −11.2) than parous women (RD −4.4 per 100 pregnancies, 95% CI −5.7 to −3.1) and somewhat larger for term-onset (RD −5.4 per 100 pregnancies, 95% CI −6.5 to −4.3) versus preterm-onset pre-eclampsia (RD −3.0 per 100 pregnancies, 95% CI −3.7 to −2.2; Figures 1 and 2).

Early-pregnancy BMI matching
Pre-eclampsia was diagnosed in 1.9 per 100 pregnancies in post-gastric bypass pregnancies and in 5.0 per 100 in the early-pregnancy BMI-matched controls (RD −3.1, 95% CI −4.1 to −2.1; Figure 2).

Compared with early-pregnancy BMI-matched controls, post-gastric bypass pregnancies had lower risk of pre-eclampsia (HR 0.44, 95% CI 0.33–0.60). As for the pre-surgery matched group, the relative risk of pre-eclampsia in post-gastric bypass pregnancies compared with matched controls was similar for nulliparous and parous women, but the absolute risk difference differed significantly (nulliparous women: RD −4.5 per 100 pregnancies, 95% CI −6.3 to −2.7 versus parous women: RD −2.1 per 100 pregnancies, 95% CI −3.2 to −1.1; Figures 1 and 2). The absolute risk difference was similar for preterm versus term onset pre-eclampsia.

Additionally, post-gastric bypass pregnancies compared with the matched controls had lower risk of pre-eclampsia co-occurring with SGA (HR 0.39, 95% CI 0.24–0.63; Figure 2), although the absolute risk difference was small (0.6 versus 1.7 per 100 pregnancies; RD −1.1, 95% CI −1.7 to −0.5).

Further, there was no difference in risk of pre-eclampsia between those with a surgery-to-conception interval less than 1 year compared with 1 year or more (P interaction = 0.37), or for those with a pre-surgery BMI of 42 kg/m2 or more compared with less than 42 kg/m2 (Figure 3). Weight loss between surgery and early pregnancy modified the effect with those losing 39 kg or more (≥14 kg/m2) having a lower risk of pre-eclampsia compared with those losing less than 39 kg (<14 kg/m2; Figure 3).

Values are n (%) if not otherwise stated.
*Propensity score matching, separately matched for nulliparous and parous deliveries, including pre-surgery BMI and diabetes status (early-pregnancy BMI and pre-conception diabetes used for controls), maternal age, early-pregnancy smoking status, educational level, height, country of birth, delivery year and history of pre-eclampsia using all available data.
**Propensity score matching, separately matched for nulliparous and parous deliveries, including early-pregnancy BMI and pre-conception diabetes status (6 months before), maternal age, early-pregnancy smoking status, educational level, height, country of birth, delivery year and history of pre-eclampsia using all available data.
***Only possible for parous women. Percentages are calculated based on pregnancies to parous women.
****Pre-surgery BMI matching: Ever before surgery for the gastric bypass group and ever before conception for controls.

Early-pregnancy BMI matching: 6 months before conception for the gastric bypass and control group. Note that cardiovascular disease does not include pre-pregnancy hypertension.
There was no difference in pre-eclampsia co-occurring with SGA (HR 0.71, 95% CI 0.45–1.11; Figure 2) between post-gastric bypass pregnancies and early-pregnancy matched controls.

**Discussion**

**Principal findings**

In this large nationwide population-based matched cohort study, we found that the risk of pre-eclampsia was significantly lower in post-gastric bypass pregnancies compared with pre-surgery and early-pregnancy BMI-matched control pregnancies including other similar characteristics. The absolute risk reduction was considerably greater among nulliparous compared with parous women.

**Comparison with other studies**

Few previous studies have included a comparison group matched on pre-surgery BMI. All published studies reported a tendency of lower pre-eclampsia risk, but only...
one study\textsuperscript{15} found a significantly lower risk in the bariatric group compared with the pre-surgery BMI-matched control group (Table S5). These inconsistent findings may be attributed to the small sample sizes (range 70–139 in the post-bariatric surgery group) and the inclusion of various bariatric surgery procedures.

Further, only three previous studies\textsuperscript{9–11} have included a comparison group matched on pre-pregnancy BMI, and of these only one study found a lower risk of pre-eclampsia in the bariatric surgery group compared with the pre-pregnancy BMI-matched group (Table S5). Other studies have used unmatched obese comparison groups,\textsuperscript{6–8,12,14,17,18} which might be problematic and lead to bias of the findings if pre-surgery BMI is not equivalent in the surgery and control groups (Table S5). Four of these studies\textsuperscript{7,8,17,18} included a severely obese comparison group (BMI $\geq$35 kg/m$^2$; i.e. eligible for bariatric surgery) and all but one reported a lower risk of pre-eclampsia,\textsuperscript{7,17,18} whereas the other\textsuperscript{6,12,14} included an obese comparator group (BMI $\geq$30 kg/m$^2$). Risk of pre-eclampsia increases with BMI, so a comparison group with lower median BMI than the bariatric surgery group would most likely lead to bias toward the null of the findings, because the underlying risk of pre-eclampsia will be lower in the controls. Two of the three studies did not report a significantly reduced risk of pre-eclampsia.\textsuperscript{12,14}

### Interpretation

We have previously shown that women with a history of bariatric surgery compared with pre-surgery BMI-matched controls have a decreased risk of gestational diabetes, large-for-gestational-age infants, birth defects and delivery outcomes such as caesarean section, but an increased risk of preterm birth and SGA.\textsuperscript{25–28} Further, in comparison to early-pregnancy BMI-matched controls, we have also found an increased risk of SGA infants and preterm birth and decreased risks of large-for-gestational age infants.\textsuperscript{29}

Gastric bypass results in reduced food intake and altered metabolism causing weight loss and improvements in metabolic co-morbidities such as diabetes, hypertension, dyslipidaemia and most likely involve changes in the gut–brain signalling system.\textsuperscript{30} Our finding of the markedly lower risk of pre-eclampsia after gastric bypass may be attributed to the large weight loss and associated metabolic improvements, as we observed that those losing the most weight had the lowest risk of pre-eclampsia. A lower risk of pre-eclampsia compared with early-pregnancy BMI-matched controls, suggests that the preventive effect, in addition to weight loss, may be explained by the metabolic
and hormonal changes of the procedure itself. Dramatic reduction in diabetes after bariatric surgery has been reported previously, and was also observed in the current study. Furthermore, the incidence of pre-eclampsia in the gastric bypass group was even lower compared with the general population, despite the considerably lower mean early-pregnancy BMI in the general population compared with the gastric bypass group (Table S3).

The majority of the pre-eclampsia events were diagnosed at term (≥37 weeks of gestation). Although the relative risks for preterm and term onset pre-eclampsia among post-gastric bypass pregnancies versus pre-surgery and early matched controls were similar, the absolute risk difference was higher for term onset compared with preterm onset, especially for the pre-surgery matched group. This association was expected as term onset pre-eclampsia, is the type of pre-eclampsia that is associated with pre-pregnancy BMI and linked to maternal metabolic factors affecting endothelial dysfunction in the second half of the pregnancy, whereas early-onset pre-eclampsia appears to be more associated with defective placentation occurring in the first trimester.

Pre-eclampsia is often called the disease of the first pregnancy, and accordingly the majority of the pre-eclampsia events occurred among first-time mothers in the current study, with the highest incidence of 16% in matched pre-surgery BMI controls. Although the relative risk of pre-eclampsia was almost identical for nulliparous and parous women (for both the matched groups), the absolute risk difference was much higher in nulliparous women.

Strengths and limitations
Strengths of this study include the use of multiple linked nationwide registers to create a large population-based cohort with detailed information on both the exposure and the outcome, as well as multiple potential confounders. The exposure, gastric bypass status before pregnancy, was identified by using data from the quality registry SOReg that covers 98% of all bariatric surgery procedures in Sweden. Data in this register are prospectively entered by a nurse and/or the surgeon who performed the procedure, hence the risk of misclassification of the exposure is minimal. Additionally, data on pre-surgery weight and height enabled us to match on pre-surgery BMI.

Information on the outcome, pre-eclampsia, was retrieved by combining data from inpatient and outpatient care recorded in the National Patient Register with data from the Medical Birth Register. This approach enabled us to retrieve information on the date of pre-eclampsia diagnosis, which otherwise is not available from the Medical Birth Register. Access to date of pre-eclampsia diagnosis and our large sample size allowed us, with good precision, to examine pre-eclampsia subtypes. As pre-eclampsia was identified based on ICD-coding there is a potential risk for misclassification. However, our algorithm for identification of pre-eclampsia required either one inpatient care visit, or two outpatient visits, or one outpatient visit following a diagnosis at the delivery admission, or a diagnosis only at the delivery admission (if none of the others occurred). Additionally, Swedish and Scandinavian validation studies have found that the ICD-coding has reasonable accuracy in population databases. 

Further, we used the first date of diagnosis as disease onset. Although this gives us a close approximation, date of diagnosis is not exactly equivalent to disease onset. Also, a limitation is that ultrasound for gestational age assessment was performed early in the second trimester, which is less accurate than first-trimester ultrasound.

We restricted the type of bariatric surgery to gastric bypass in the current study because this procedure constituted more than 90% during the study period. A strength is therefore that we did not include a mixture of procedures. However due to this, our results may not be generalisable to other procedures.

We used detailed propensity score matching and created two comparison groups (matched either for pre-surgery BMI or early-pregnancy BMI) with similar characteristics as the surgery group. We further adjusted for potential confounders. Despite this there may be residual confounding as there could be differences between the gastric bypass and control pregnancies. In the matching procedure, 296 of the gastric bypass pregnancies were excluded because no controls could be identified, with the majority having either BMI ≥50 kg/m² or pre-existing diabetes. For the early-pregnancy BMI matching, 164 observations were excluded, due to lack of available early-pregnancy BMI (Table S6). It is possible that some of the women with a history of gastric bypass could not conceive before surgery, whereas the women with severe obesity without surgery history consisted of a group of potentially healthier obese women who were able to conceive. If true, our pre-surgery matched results would most likely have underestimated the true effect as a comparator group resulting from randomisation would have had an even greater risk of pre-eclampsia.

For the pre-surgery BMI matching, early-pregnancy BMI was used for the controls because BMI at the time of their matched cases’ gastric bypass procedure was not available. However, the median surgery-to-conception interval for the bariatric group was only 1.6 years. We therefore do not believe that this short interval would substantially bias the result.

Conclusions
We found that gastric bypass was associated with a lower risk of pre-eclampsia in post-gastric bypass pregnancies compared with pre-surgery and early-pregnancy BMI-matched control pregnancies including other similar characteristics, with the largest absolute risk reduction among
nulliparous women. Our findings therefore highlight the effectiveness of gastric bypass as a treatment of severe obesity and associated metabolic abnormalities before pregnancy in the prevention of pre-eclampsia. However, when counseling women on the safety of undergoing bariatric surgery before becoming pregnant the benefit–risk balance needs to be discussed, including not only positive effects, such as lower risk for gestational diabetes, delivering large-for-gestational age babies, birth defects and delivery complications,25–27 but also the negative effects including higher risk of nutritional deficiencies, preterm birth and SGA birth.25,28,36

Disclosure of interests
All authors have completed the ICMJE Form for Disclosure of Potential Conflicts of Interest (available on request from the corresponding author) and declare: Dr Neovius has participated as advisory board member for Itrim and Ethicon Johnson & Johnson outside the submitted work. Dr Ottsoson has participated as advisory board member for Ethicon Johnson & Johnson. The other authors have no competing interests to state. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship
KJ, MN, and OS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis and had the final responsibility for the decision to submit for publication. Concept and design were by KJ, MN, OS and A-KW. Data acquisition, analysis, and interpretation were by KJ, MN, IN, JO, JS and OS. KJ drafted the manuscript, and all authors critically revised the manuscript for important intellectual content. Statistical analysis was by JS; funding was obtained by KJ and MN. Administrative, technical, or material support were supplied by KJ, MN and OS.

Details of ethics approval
The study was approved by the regional ethics committee in Stockholm, Sweden (No. 2013/730-31; date of approval 2013-03-04) with amendments (2013/1592-32; 2016/1213-32; 2016/2329-32;2019/05573).

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Data availability
The data included in this study are based on national register data and cannot be made publicly available by us for legal reasons. The data has been exported for this research project by the National Board of Health and Welfare in Sweden, which does not permit data-sharing according to the Swedish Secrecy Act 24:8. Researchers who are interested in obtaining the relevant data, despite the Swedish Secrecy Act, should contact the National Board of Health and Welfare: socialstyrelsen@socialstyrelsen.se.

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

Supplementary Method. Study design.
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