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# Placental weight in the first pregnancy and risk for preeclampsia in the second pregnancy: A population-based study of 186 859 women

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## Abstract

**Objective—**To study whether placental weight in the first pregnancy is associated with preeclampsia in the second pregnancy.

**Study design—**In this population-based study, we included all women with two consecutive singleton pregnancies reported to the Medical Birth Registry of Norway during 1999–2012 (n = 186 859). Placental weight in the first pregnancy was calculated as z-scores, and the distribution was divided into five groups of equal size (quintiles). We estimated crude and adjusted odds ratios with 95% confidence intervals for preeclampsia in the second pregnancy according to quintiles of placental weight z-scores in the first pregnancy. The 3rd quintile was used as the reference group.

**Results—**Among women without preeclampsia in the first pregnancy, 1.4% (2507/177 149) developed preeclampsia in the second pregnancy. In these women, the risk for preeclampsia in the second pregnancy was associated with placental weight in the first pregnancy in both lowest (crude odds ratio (cOR) 1.30, 95% confidence interval (CI); 1.14–1.47) and highest quintile (cOR 1.20, 95% CI; 1.06–1.36). The risk associated with the highest quintile of placental weight was confined to term preeclampsia. Among women with preeclampsia in the first pregnancy, 15.7% (1522/9710) developed recurrent preeclampsia, and the risk for recurrent preeclampsia was associated with placental weight in lowest quintile in the first pregnancy (cOR 1.30, 95% CI; 1.10–1.55). Adjustment for interval between pregnancies, maternal diabetes, age, and smoking in the first pregnancy did not alter these estimates notably.



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**Conclusion—**Placental weight in the first pregnancy might help to identify women who could be at risk for developing preeclampsia in a second pregnancy.

### Keywords

Placental weight; Population study; Preeclampsia; Pregnancy

## Introduction

Preeclampsia is a pregnancy complication characterized by high blood pressure and proteinuria. The condition arises in about 3–6% of first pregnancies, and in 1–2% of second pregnancies [1,2] Preeclampsia is associated with increased risk for preterm delivery, intrauterine growth restriction, and perinatal mortality [3]. Despite its clear impact on maternal and infant health, the etiology of this condition is not well understood, and prediction of women who will develop preeclampsia is difficult.

Studies suggest that there is a strong correlation between prepregnancy cardiovascular risk factors and development of preeclampsia [4], and also between preeclampsia and cardiovascular disease later in life [5]. Several of the cardiovascular risk factors associated with preeclampsia such as high body mass index, diabetes and chronic hypertension have also been associated with placental weight [6–8]. Abnormal placental development is considered the prevailing cause of preeclampsia [9], and both small and large placentas are overrepresented in preeclamptic pregnancies [10].

Taken together, these studies suggest that factors that increase cardiovascular disease risk also contribute to the placental pathology that causes both abnormal placental weight and preeclampsia. If this is true, high or low placental weight may be a marker of a woman's underlying risk for preeclampsia. If placental weight is a marker of a woman's risk for preeclampsia, the placental weight from the first pregnancy could possibly predict the risk for preeclampsia in a subsequent pregnancy. If so, placental weight could be routinely measured and used to identify women at higher risk for developing preeclampsia in a future pregnancy. To our knowledge, the possible association of placental weight in the first pregnancy with the risk for preeclampsia in the second pregnancy has not been studied.

Among 186 859 women in Norway with their first and second singleton pregnancy during a 14 year period (1999–2012), we studied the association of placental weight in the first pregnancy with the risk for preeclampsia in the second pregnancy.

## Materials and methods

We performed a population-based study using data from the Medical Birth Registry of Norway. The Medical Birth Registry contains information on all births after the 16th gestational week in Norway since 1967 [11]. The reporting is compulsory by law and is performed by the doctor or the midwife in charge of the delivery. Placental weight has been reported since 1999.

In this study, we included women with a first and second singleton delivery after the 20th gestational week during the period 1999–2012 ($n$ = 193 637). We excluded women with missing information on placental weight ($n$ = 6599), birthweight ($n$ = 170) or offspring sex ($n$ = 9). A total of 6778 women were thus excluded, leaving 186 859 women for statistical analyses.

Preeclampsia in second pregnancy was our outcome variable. Preeclampsia was reported to the Medical Birth Registry. The diagnosis was made by clinical examination in antenatal care and/or at the maternity ward [12] and defined as blood pressure ≥140/90 mmHg combined with proteinuria (protein dipstick 1+ or > 0.3 g/24 h) after the 20th gestational week. Almost all women in Norway attend the public antenatal health care program, and on average, each woman has attended twelve antenatal care visits before delivery, with increasing frequency as the pregnancy proceeds. Preeclampsia with preterm delivery is likely to be an indicator of early onset and severe preeclampsia [13], and we performed sub-analyses using preterm (delivery before pregnancy week 37) and term preeclampsia (delivery in pregnancy week 37 or later) as secondary outcomes.

Our main exposure variable was placental weight in the first pregnancy. The placenta was weighed within one hour after delivery at the obstetric ward, with membranes and umbilical cord according to obstetric standards in Norway.

The following variables from the first pregnancy were included in the data analyses as potentially confounding factors: birth-weight (in grams) [14], preeclampsia (yes/no) [14], maternal diabetes (yes/no) [7], maternal age (in years) [15], maternal smoking (yes/no) [16], and the interval between pregnancies (in years) [17]. Diabetes included; diabetes type-1, type-2, gestational diabetes, non-specified diabetes prior to pregnancy, and use of oral anti-diabetic medication. Gestational diabetes was diagnosed in the antenatal screening program, and was defined as a plasma glucose concentration ≥7.8 – <11.1 mmol/l two hours after 75 mg oral glucose tolerance test. Smoking was reported as daily or occasional smoking at the first antenatal visit, typically pregnancy week 8–12.

Differences in the distribution of study factors in the first pregnancy according to development of preeclampsia in the second pregnancy were tested by using the Student's $t$-test for continuous variables and the Chi-square test for categorical variables.

Placental weight and birthweight are closely linked to gestational age at birth. To adjust for differences in gestational age between pregnancies, we calculated z-scores of placental weight by using means and standard deviations of placental weight for each pregnancy week at birth in the sample as a whole. Z-scores were calculated separately for male and female offspring. Gestational age at birth was estimated on the basis of a routine ultrasonographic fetal examination in pregnancy week 17–19. If ultrasonographic examination had not been performed (for 2.7%), gestational age at birth was based on the first day of the last menstruation. The distribution of placental weight z-scores in the first pregnancy was divided into quintiles. Thus, 20% of the pregnancies were expected to fall into each quintile, assuming normal distribution.

The risks for preeclampsia in the second pregnancy according to quintiles of placental weight z-score in the first pregnancy were estimated as crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) separately for women with and women without preeclampsia in the first pregnancy. Women with placental weight z-scores in the 3rd quintile were used as the reference group. In additional analyses, we estimated the risks for preterm and for term preeclampsia in the second pregnancy. Women who delivered preterm were not included in the analyses of risk for term preeclampsia. All statistical analyses were conducted by using the IBM SPSS Statistics Version 22.0, (IBM Corp., Armonk, NY, USA).

The Medical Birth Registry of Norway is approved by the Norwegian Data Inspectorate. The use of data for this study was approved by the Regional Committee for Ethics in Medical Research (Reference number 2014/131).

## Results

Characteristics of our study sample are presented in Table 1. In total, 5.2% (9710/186 859) of all women had preeclampsia in the first, and 2.2% (4029/186 859) had preeclampsia in the second pregnancy. Of the women with preeclampsia in the first pregnancy, the risk for recurrence was 15.7% (1522/9710), and 0.8% (1522/186 859) of all women had preeclampsia in both pregnancies. The women with recurrent preeclampsia represented 37.8% (1522/4029) of all cases of preeclampsia in the second pregnancy, and 62.2% (2507/4029) of the preeclampsia cases in the second pregnancy had no history of preeclampsia (Fig. 1).

### Women without previous preeclampsia

Among women without preeclampsia in the first pregnancy, mean placental weight in the first pregnancy was 662 g (SD 184 g), and mean birthweight was 3490 g (SD 547 g) (Table 1). The overall absolute risk for preeclampsia in the second pregnancy was 1.4%, and the risk was 1.6% for women with low placental weight (1st quintile) and 1.5% for women with high placental weight (5th quintile) in the first pregnancy (Table 2). The OR for preeclampsia in the second pregnancy was increased for both low (cOR 1.30, 95% CI; 1.14–1.47) and for high placental weight (cOR 1.20, 95% CI; 1.06–1.36) in the first pregnancy as compared to women with placental weight in the 3rd quintile (reference). Low placental weight in the first pregnancy increased the risk both for preterm and for term preeclampsia in second pregnancy (Table 3, Fig. 2a and b). However, the increased risk for preeclampsia associated with high placental weight was confined to term preeclampsia (cOR 1.32, 95% CI; 1.15–1.53) (Table 3, Fig. 2b).

### Women with previous preeclampsia

Among women with preeclampsia in the first pregnancy, mean placental weight in the first pregnancy was 625 g (SD 201 g), and mean birthweight was 3134 g (SD 840 g) (Table 1). The overall recurrence risk for preeclampsia was 15.7%, and the recurrence risk was 18.5% for women with low placental weight in the first pregnancy (Table 2). The OR for preeclampsia in the second pregnancy was increased for low placental weight in the first pregnancy as compared to the reference group (3rd quintile) (cOR 1.30, 95% CI; 1.10–1.55)

(Table 2). Low placental weight increased the risk particularly for preterm preeclampsia in the second pregnancy. The absolute risk for preterm preeclampsia in the second pregnancy was 6.4% in women with low placental weight (cOR 1.58, 95% CI; 1.18–2.12) (Table 3, Fig. 2c). Adjustment for other study factors did not alter any of the above estimated ORs notably (Table 2, Table 3).

## Comment

In this study of 186 859 women with two singleton pregnancies, we found that low placental weight in the first pregnancy increased the risk for preeclampsia in the second pregnancy. Additionally, in women without preeclampsia in the first pregnancy, high placental weight increased the risk for developing term preeclampsia in the second pregnancy.

We used data from the Medical Birth Registry of Norway, and the source population included all women in Norway with two singleton pregnancies during the years 1999–2012. Women with missing information on study variables were excluded (3.5%), of whom the majority (97%) were excluded due to missing information on placental weight in the first pregnancy. In separate analyses of women excluded due to missing placental weight, the prevalences of preeclampsia in first and second pregnancies were similar to the women included in our analyses. Also, mean offspring birthweight was similar, suggesting no selection bias.

Some women with severe preeclampsia in a first pregnancy may not have a second pregnancy. Thus, the women with severe preeclampsia in the first pregnancy may be underrepresented in our study, and it is possible that our estimated association of low placental weight with risk for recurrent preeclampsia represents an underestimate. It is also possible that the interval between pregnancies may be longer for women with previous preeclampsia as compared to women without previous preeclampsia [17]. However, adjustment for interval between pregnancies did not change the associations notably.

The diagnosis of preeclampsia in the Medical Birth Registry has high validity [12]. Also, the prevalence of preeclampsia in the first and in the second pregnancy in our study was similar to other studies [2,18]. Erroneous reporting of placental weight and other study factors in the first pregnancy may have occurred, but it is unlikely that such possible misclassifications differed by occurrence of preeclampsia in the second pregnancy.

Placental weight is strongly influenced by gestational age at birth, and pregnancies with preeclampsia may have shorter duration than pregnancies without preeclampsia. Therefore, we made adjustment for possible differences in gestational age at birth by using z-scores. We also made adjustments for maternal diabetes, age, smoking and interval between pregnancies, since preeclampsia and placental weight previously has been associated with these factors [7,15–17]. However, both in pregnancies with and pregnancies without previous preeclampsia, adjustments for these factors did not alter our estimates notably. Unfortunately, information on changes from first to second pregnancy in maternal body mass index, blood pressure or other risk factors of cardiovascular disease was not available. To study whether placental weight in preterm and in term preeclampsia in the first pregnancy

is associated with preterm or with term preeclampsia in the second pregnancy was beyond the scope of this study.

To our knowledge, the association of placental weight in the first pregnancy with risk for preeclampsia in the second pregnancy has not previously been reported. However, low birthweight in the first pregnancy has been associated with increased risk for preeclampsia in the second pregnancy, independent of previous preeclampsia [14]. This previous finding supports our results since birthweight and placental weight are correlated [19].

We found that low placental weight in the first pregnancy was associated with preeclampsia in the second pregnancy in women without, and in women with previous preeclampsia. The mechanisms underlying this association are unknown, but could involve several pathways. Preeclampsia and cardiovascular disease share several risk factors [4,5]. Our finding may therefore suggest that the biology underlying placental growth is also related to preeclampsia and to cardiovascular disease. For example, prepregnancy hypertension [8] and thrombophilia [20] are associated with low placental weight and also with the development of preeclampsia [20–22]. Arterial stiffness and arteriosclerosis could be other maternal vascular conditions that could possibly restrict placental growth [23]. Thus, low placental weight in the first pregnancy may be an indicator of an underlying increased risk for hypertensive disorders.

Placental development depends on a well-functioning endometrium. Any anatomic, hormonal, or immunological abnormality of the endometrium could possibly cause sub-optimal endometrial function and thereby impair trophoblast proliferation and consequently placental development [24]. Several growth factors and angiogenic factors are synthesized in trophoblastic cells in the placenta. Low levels of placental growth factor, endoglin and human chorionic gonadotropin in early pregnancy are associated with increased risk for preeclampsia [25,26] and for low birthweight [27]. Thus, for some women, underlying factors that caused low placental weight, in the first pregnancy, such as impaired endometrial function or maternal vascular conditions, may still be present or have progressed by the second pregnancy and possibly be a cause of preeclampsia.

Placental growth is regulated by both maternal and paternal genes, and for most women in our study it is likely that both pregnancies have the same father [17]. Thus, both maternal and paternal genes may influence placental growth and also the risk for developing preeclampsia [28].

Among women without previous preeclampsia, both low and high placental weight in the first pregnancy increased the risk for preeclampsia in the second pregnancy. High placental weight was associated with preeclampsia at term only, and term preeclampsia may be less severe than early onset preeclampsia [1]. Our finding may suggest different underlying maternal factors behind the development of preterm and term preeclampsia in a second pregnancy. High maternal body mass index has been associated with both high placental weight and with preeclampsia [6]. Hence, some women with high placental weight in the first pregnancy may have high maternal body mass index, and their body mass index may have increased from the first to the second pregnancy. Also, presence of other maternal

factors associated with high placental weight, such as glucose concentrations [7] and blood pressure, may have increased in the interval between pregnancies. Thereby, their risk for preeclampsia may be higher in the second as compared to their first pregnancy [22,29].

Most cases of preeclampsia in second pregnancies were among women with no history of preeclampsia (62.2%). However, in women with no history of preeclampsia, the absolute risk for preeclampsia in a second pregnancy was low (1.4%), and the risk difference according to placental weight may not be of clinical importance (range 1.2–1.6%). In women with preeclampsia in the first pregnancy, a total of 15.7% developed recurrent preeclampsia, and 4.4% developed preterm preeclampsia. The women with low placental weight were at increased risk for recurrence, particularity for preterm preeclampsia. Such information may help to identify women who could be at risk for developing preeclampsia in a second pregnancy.

In conclusion, we found that low placental weight in the first pregnancy was associated with increased risk for developing preeclampsia in the second pregnancy. Additionally, in women without preeclampsia in the first pregnancy, high placental weight increased the risk for developing term preeclampsia in the second pregnancy.

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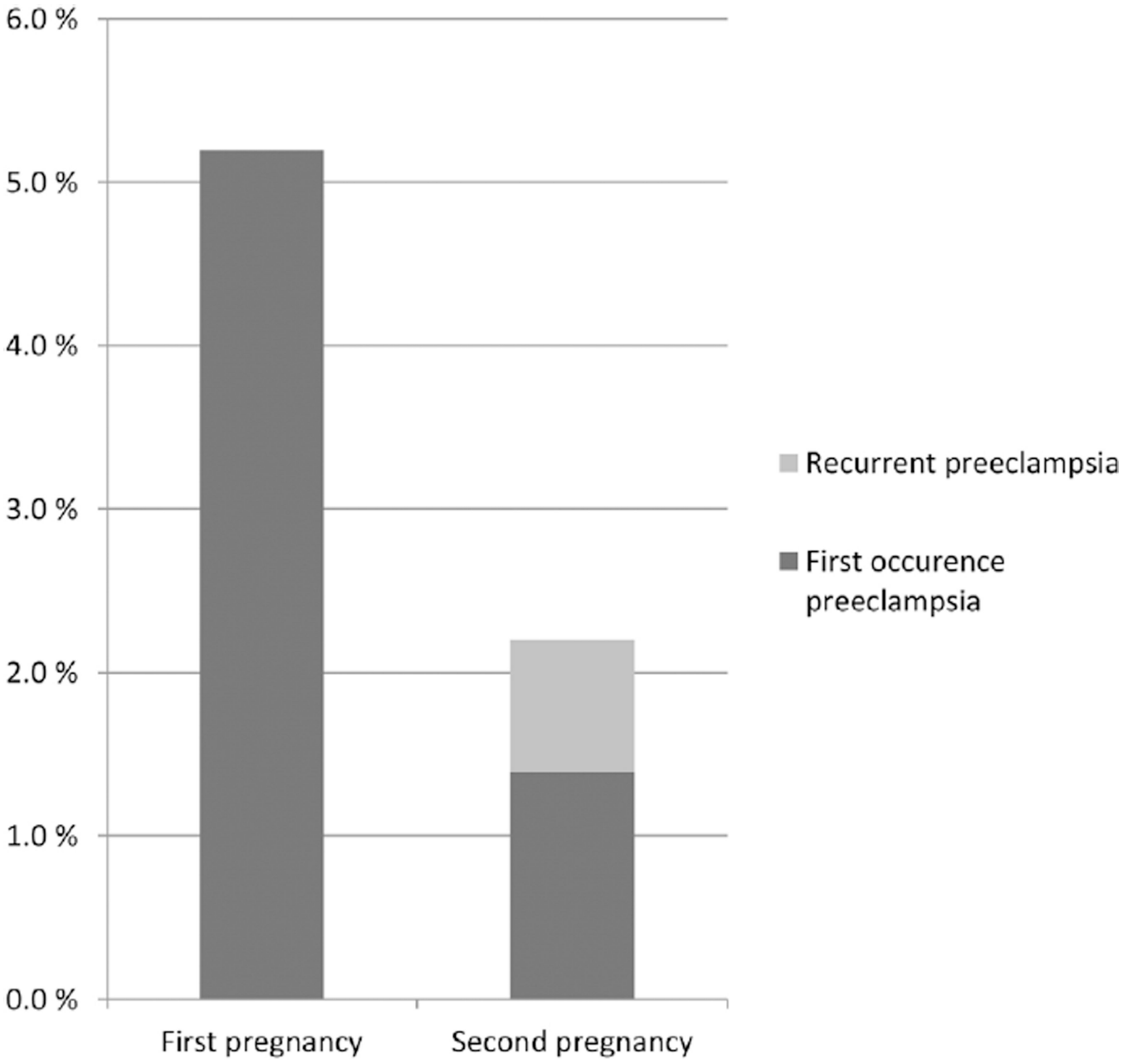


**Fig. 1.**

Prevalence of preeclampsia in first and second pregnancy among 186 859 women in Norway with two consecutive singleton pregnancies during the years 1999–2012.

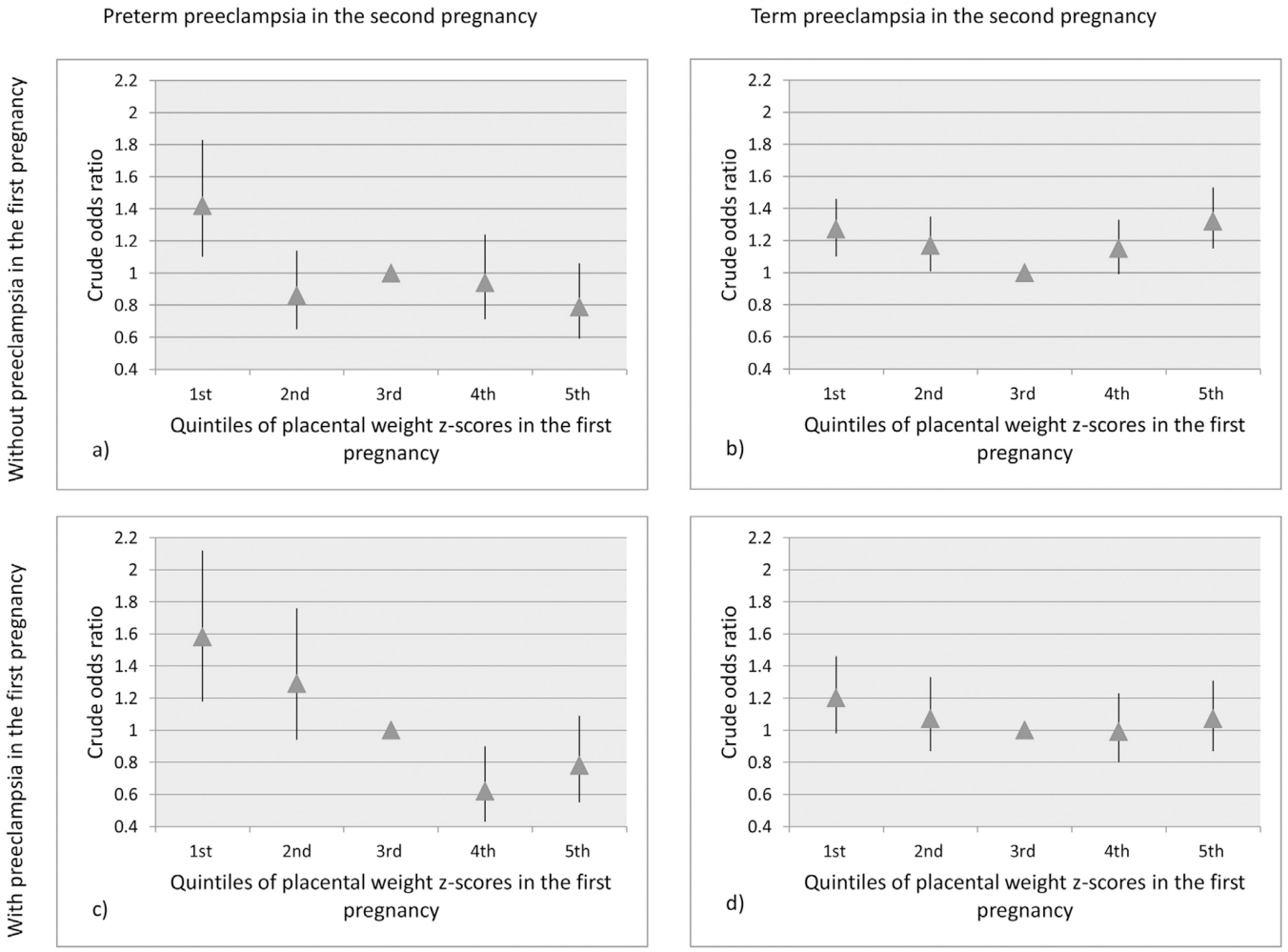


**Fig. 2.**

Crude odds ratios (OR) with 95% confidence intervals for preterm (a, c) and for term (b, d) preeclampsia in the second pregnancy according to quintiles of placental weight z-score in the first pregnancy, among women without preeclampsia in the first pregnancy (n = 177 149) (a, b) and women with preeclampsia in the first pregnancy (n = 9710) (c, d).

## Table 1

Means and proportions of study factors in the first pregnancy among 186 859 women in Norway with their first and second singleton pregnancies during the years 1999–2012.

| Study factors in first pregnancy | Total | Preeclampsia in first pregnancy | | |
|---|---|---|---|---|
| | | Yes | No | p-value |
| Total number (%) | 186 859 (100) | 9710 (5.2) | 177 149 (94.8) | |
| Placental weight in grams (SD) | 660 (185) | 625 (201) | 662 (184) | <0.001† |
| Birthweight in grams (SD) | 3471 (572) | 3134 (840) | 3490 (547) | <0.001† |
| Gestational age in weeks (SD) | 39.5 (2.1) | 38.0 (3.1) | 39.5 (2.0) | <0.001† |
| Maternal age years (SD) | 26.9 (4.5) | 26.7 (4.6) | 26.9 (4.5) | <0.001† |
| Interval between pregnancies in years (SD) | 3.1 (1.7) | 3.2 (1.7) | 3.1 (1.7) | <0.001† |
| Diabetes, number (%) | 2575 (1.4) | 325 (3.3) | 2250 (1.3) | <0.001‡ |
| Smoking, number (%) | 26817 (17.3) | 1230 (15.2) | 25 587 (17.4) | <0.001‡ |

SD, standard deviation.

†Student's *t*-test.

‡Chi-square test.

**Table 2**

Crude and adjusted odds ratios for preeclampsia in the second pregnancy according to quintiles of placental weight z-score in the first pregnancy- among women without preeclampsia ($n$ = 177 149) and women with preeclampsia ($n$ = 9710) in the first pregnancy in Norway during the years 1999–2012.

| Placental weight z-score in first pregnancy | Mean placental weight, g (SD) | Preeclampsia in second pregnancy | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Yes | % | No | % | cOR | 95% CI | aOR | 95% CI |
| **Total** | 660 (185) | 4029 | 2.2 | 182 830 | 97.8 | | | | |
| **Without preeclampsia in first pregnancy** | | | | | | | | | |
| 1st quintile | 482 (66) | 560 | 1.6 | 34 272 | 98.4 | 1.30* | 1.14– 1.47 | 1.28* | 1.12– 1.47 |
| 2nd quintile | 583 (46) | 489 | 1.4 | 35 422 | 98.6 | 1.09 | 0.96– 1.25 | 1.03 | 0.90– 1.19 |
| 3rd quintile | 646 (52) | 444 | 1.2 | 35 184 | 98.8 | Reference | | Reference | |
| 4th quintile | 722 (56) | 487 | 1.4 | 34 934 | 98.6 | 1.11 | 0.97– 1.26 | 1.07 | 0.93– 1.23 |
| 5th quintile | 876 (262) | 527 | 1.5 | 34 830 | 98.5 | 1.20* | 1.06– 1.36 | 1.15 | 1.00– 1.33 |
| Total | 662 (184) | 2507 | 1.4 | 174 642 | 98.5 | | | | |
| **With preeclampsia in first pregnancy** | | | | | | | | | |
| 1st quintile | 431 (95) | 412 | 18.5 | 1816 | 81.5 | 1.30* | 1.10– 1.55 | 1.26* | 1.04– 1.52 |
| 2nd quintile | 535 (96) | 300 | 16.4 | 1531 | 83.6 | 1.13 | 0.94– 1.35 | 1.16 | 0.95– 1.41 |
| 3rd quintile | 606 (87) | 257 | 14.8 | 1476 | 85.2 | Reference | | Reference | |
| 4th quintile | 695 (75) | 242 | 13.5 | 1556 | 86.5 | 0.89 | 0.74– 1.08 | 0.92 | 0.75– 1.13 |
| 5th quintile | 861 (223) | 311 | 14.7 | 1809 | 85.3 | 0.99 | 0.83– 1.18 | 0.93 | 0.77– 1.14 |
| Total | 625 (201) | 1522 | 15.7 | 8188 | 84.3 | | | | |

SD, standard deviation; cOR, crude odds ratios; 95% CI, 95% confidence interval; aOR, odds ratios adjusted for maternal diabetes, age and smoking in the first pregnancy and interval between pregnancies.

*Statistical significant OR.

**Table 3**

Crude and adjusted odds ratios with 95% confidence intervals for preterm and for term preeclampsia in the second pregnancy according to quintiles of placental weight z-score in the first pregnancy, among women without preeclampsia in the first pregnancy (n = 177 149) and women with preeclampsia in the first pregnancy (n = 9710).

| Placental weight z-score in first pregnancy | n | Preterm preeclampsia in second pregnancy | | | | | | Term preeclampsia in second pregnancy | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Yes | % | cOR | 95% CI | aOR | 95% CI | Yes | % | cOR | 95% CI | aOR | 95% CI |
| Total | 186 859 | 945 | 0.5 | | | | | 3084 | 1.7 | | | | |
| **Without preeclampsia in the first pregnancy** | | | | | | | | | | | | | |
| 1 st quintile | 34 832 | 144 | 0.4 | 1.42* | 1.10–1.83 | 1.48* | 1.13–1.95 | 416 | 1.3 | 1.27* | 1.10–1.46 | 1.22* | 1.05–1.43 |
| 2nd quintile | 35 911 | 90 | 0.3 | 0.86 | 0.65–1.14 | 0.81 | 0.59–1.11 | 399 | 1.2 | 1.17* | 1.01–1.35 | 1.10 | 0.93–1.29 |
| 3rd quintile | 35 628 | 104 | 0.3 | Reference | | Reference | | 340 | 1.0 | Reference | | Reference | |
| 4th quintile | 35 421 | 97 | 0.3 | 0.94 | 0.71–1.24 | 0.90 | 0.67–1.23 | 390 | 1.1 | 1.15 | 1.00–1.33 | 1.13 | 0.96–1.32 |
| 5th quintile | 35 357 | 82 | 0.2 | 0.79 | 0.59–1.06 | 0.77 | 0.56–1.05 | 445 | 1.3 | 1.32* | 1.15–1.53 | 1.30* | 1.12–1.52 |
| Total | 177 149 | 517 | 0.3 | | | | 1990 | 1.2 | | | | | |
| **With preeclampsia in the first pregnancy** | | | | | | | | | | | | | |
| 1 st quintile | 2228 | 143 | 6.4 | 1.58* | 1.18–2.12 | 1.62* | 1.17–2.26 | 269 | 13.6 | 1.20 | 0.98–1.46 | 1.12 | 0.90–1.40 |
| 2nd quintile | 1831 | 97 | 5.3 | 1.29 | 0.94–1.76 | 1.42* | 1.01–2.01 | 203 | 12.4 | 1.07 | 0.87–1.33 | 1.08 | 0.86–1.36 |
| 3rd quintile | 1733 | 72 | 4.2 | Reference | | Reference | | 185 | 11.7 | Reference | | Reference | |
| 4th quintile | 1798 | 47 | 2.6 | 0.62* | 0.43–0.90 | 0.71 | 0.47–1.07 | 195 | 11.6 | 0.99 | 0.80–1.23 | 0.96 | 0.79–1.26 |
| 5th quintile | 2120 | 69 | 3.3 | 0.78 | 0.55–1.09 | 0.84 | 0.58–1.22 | 242 | 12.4 | 1.07 | 0.87–1.31 | 1.01 | 0.81–1.26 |
| Total | 9710 | 428 | 4.4 | | | | | 1094 | 12.3 | | | | |

cOR, crude odds ratios; 95% CI, 95% confidence interval; aOR, odds ratios adjusted for maternal diabetes, age and smoking in the first pregnancy and interval between pregnancies.

*Statistical significant OR.