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Original article

Tobacco

Placental weight and birthweight: the relations with number of daily cigarettes and smoking cessation in pregnancy. A population study

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Abstract

Background: We studied associations of number of daily cigarettes in the first trimester with placental weight and birthweight in women who smoked throughout pregnancy, and in women who stopped smoking after the first trimester.

Methods: We included all women with delivery of a singleton in Norway ($n = 698\,891$) during 1999–2014, by using data from the Medical Birth Registry of Norway. We assessed dose-response associations by applying linear regression with restricted cubic splines.

Results: In total, 12.6% smoked daily in the first trimester, and 3.7% stopped daily smoking. In women who smoked throughout pregnancy, placental weight and birthweight decreased by number of cigarettes; however, above 11–12 cigarettes we estimated no further decrease ($P_{\text{non-linearity}} < 0.001$). Maximum decrease in placental weight in smokers compared with non-smokers was 18.2 g [95% confidence interval (CI): 16.6 to 19.7], and for birthweight the maximum decrease was 261.9 g (95% CI: 256.1 to 267.7). In women who stopped smoking, placental weight was higher than in non-smokers and increased by number of cigarettes to a maximum of 16.2 g (95% CI: 9.9 to 22.6). Birthweight was similar in women who stopped smoking and non-smokers, and we found no change by number of cigarettes ($P_{\text{non-linearity}} < 0.001$).

Conclusions: In women who smoked throughout pregnancy, placental weight and birthweight decreased non-linearly by number of cigarettes in the first trimester. In women who stopped smoking, placental weight was higher than in non-smokers and increased linearly by number of cigarettes; birthweight was almost similar to that of non-smokers.

Key words: Birthweight, cigarette smoking, placenta, population study, pregnancy

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Key Messages

- In women who smoked daily throughout pregnancy, placental weight and birthweight decreased by number of daily cigarettes; however, above 11–12 cigarettes we estimated no further decrease in weights.
- Different patterns were observed in women who stopped smoking after the first trimester. In these women, placental weight increased by increasing number of daily cigarettes, whereas birthweight was non-different from non-smokers.
- Smoking in pregnancy had stronger relation with birthweight than with placental weight, thus placental to birthweight ratio was increased in women who smoked at any time in pregnancy.

Introduction

Low birthweight has been associated with increased perinatal mortality[1] and increased mortality later in life.[2] Women who smoke in pregnancy give birth to infants with lower birthweight than non-smokers.[3,4] It is assumed that the more cigarettes a pregnant woman smokes, the lower is the birthweight of her newborn infant.[5,6] However, a non-linear dose-relationship of number of daily cigarettes and birthweight has also been suggested.[7,8] Reliable knowledge of the dose-relationship may increase our understanding of the biological mechanisms of impaired fetal growth in pregnant women who smoke, and may also be important for counselling women who find it difficult to stop smoking.

Growth of the fetus depends on a well-functioning placenta,[9] and in normal pregnancies birthweight and placental weight are highly correlated.[10] One previous study has investigated the relation of number of daily cigarettes with placental weight, and that study of 2507 pregnant women reported no association.[11] The effect of cigarette smoking on placental weight may not be as pronounced as for birthweight.[11–17] Consequently, the placental weight relative to birthweight seems to be increased in smokers compared with non-smokers. Both small and large placentas relative to birthweight have been associated with adverse outcome for the offspring, such as fetal death, low Apgar score at birth and admission to a neonatal intensive care unit.[18–20]

It has been suggested that women who stop smoking during pregnancy, give birth to infants with similar birthweight as non-smokers.[7,21] The association of smoking cessation with placental weight has, to our knowledge, not been studied. Also, the relations of occasional smoking with placental weight or with birthweight remain unknown.

Among 698 891 pregnant women, we compared placental weight, birthweight and placental to birthweight ratio in non-smokers, occasional smokers and daily smokers throughout pregnancy. We also studied the dose-response associations of number of daily cigarettes with placental weight, birthweight and placental to birthweight ratio. Women who stopped daily smoking after the first trimester were studied separately.

Methods

Study population

We performed a population-based registry study by using data from the Medical Birth Registry of Norway. This registry contains information about all births after the 16th week of pregnancy in Norway since 1967, and the reporting of births is mandatory by law.[22] Information about placental weight and cigarette smoking in pregnancy has been reported to the Medical Birth Registry since 1999.[23]

Eligible for our study were all women in Norway with a singleton delivery during the years 1999–2014 ($n = 922\,945$) (Figure 1). We excluded 8810 women with missing information about gestational age of the offspring at delivery, or with delivery before 22 weeks or after 45 weeks of pregnancy. Subsequently, women with missing or incomplete information about smoking in the first trimester ($n = 151\,996$) or in the third trimester ($n = 43\,070$) were excluded. Additionally, we excluded 19 734 women with missing or outlying values on placental weight [less than 25 g or more than 2500 g]. Similarly, we excluded 395 women with missing or outlying values on birthweight (less than 250 g or more than 6500 g) or missing information about maternal age or offspring sex ($n = 49$). Thus, a total of 698 891 women were available for our data analyses (Figure 1).

Study factors

Placental weight and birthweight were measured in grams, and the placental to birthweight ratio was calculated as placental weight divided by birthweight. Thus, a high placental to birthweight ratio indicates high placental weight relative to the weight of the newborn infant. The placenta and the

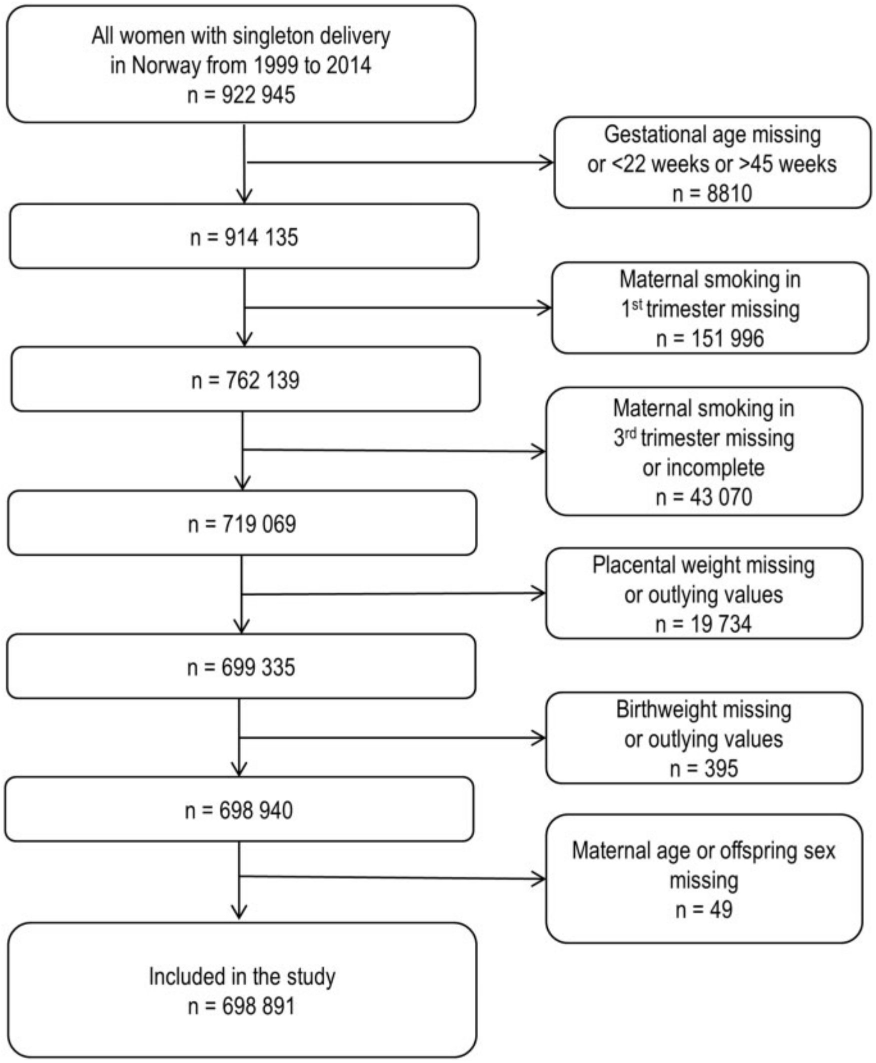

Figure 1. Flow chart of study sample.

newborn infant were weighed within 1 h after delivery, according to Norwegian guidelines.[24] The placenta was weighed with membranes and umbilical cord attached.

Information about cigarette smoking in pregnancy was obtained in a clinical interview by the woman's antenatal care doctor and recorded in the standardized Norwegian antenatal patient record.[25,26] The public antenatal care programme in Norway is free of charge and includes almost all women who give birth. On average, a woman has 10 visits to her antenatal care doctor during pregnancy. From the first and the third trimester of pregnancy, we had information about smoking habits coded as: no smoking, occasional smoking or daily smoking. Among daily smokers in the first trimester, also the number of daily cigarettes was available.

Statistical analyses

We calculated mean placental weight, birthweight and placental to birthweight ratio with standard deviations (SD) in non-smokers, occasional smokers and daily smokers. Differences in means were tested by applying one-way analysis of variance (ANOVA) with Bonferroni-correction.

We assessed the dose-response associations of number of daily cigarettes in the first trimester with placental weight, birthweight and placental to birthweight ratio by applying linear regression analyses with restricted cubic splines with three knots, at the 10th, 50th and 90th percentile of the distribution (at 3, 7 and 15 daily cigarettes).[27] Non-smokers were used as the reference category and occasional smokers were excluded in these analyses. Tests for non-linearity were conducted by testing the coefficient of the second spline transformation equal to zero. Women who smoked daily throughout pregnancy were studied separately from women who stopped daily smoking after the first trimester.

In additional analyses, we used z-scores for placental weight and birthweight to adjust for differences in gestational age at birth between offspring. We calculated z-scores in the sample as a whole by using means and SD of placental weight

Table 1. Descriptives of the study sample according to maternal smoking habits

	Total	Non-smokers	Smokers throughout pregnancy		Smokers who stopped after the first trimester	
			Occasional smokers	Daily smokers	Occasional smokers	Daily smokers
No. women, *n* (%)	698 891 (100.0)	597 957 (85.6)	3922 (0.6)	62 197 (8.9)	8607 (1.2)	26 208 (3.7)
Mean number of daily cigarettes (SD)	–	–	–	9.0 (5.1)	–	7.2 (4.8)
Mean gestational age at birth, weeks (SD)	39.4 (1.9)	39.4 (1.8)	39.3 (2.1)	39.2 (2.0)	39.5 (1.9)	39.5 (2.0)
Mean maternal age, years (SD)	29.5 (5.1)	29.8 (5.0)	28.3 (5.5)	28.2 (5.7)	28.2 (5.4)	27.4 (5.5)
Nulliparous, *n* (%)	288 837 (41.3)	244 197 (40.8)	1629 (41.5)	23 604 (38.0)	4543 (52.8)	14 864 (56.7)
Maternal diabetes, *n* (%)	16 239 (2.3)	14 143 (2.4)	77 (2.0)	1257 (2.0)	167 (1.9)	595 (2.3)
Preeclampsia, *n* (%)	24 054 (3.4)	20 983 (3.5)	104 (2.7)	1524 (2.5)	104 (2.7)	115 (4.4)

and birthweight for each gestational age. Z-scores were calculated separately for male and female offspring. Gestational age at birth was calculated from expected date of delivery, and such date was based on fetal size at routine ultrasonographical examination in pregnancy week 17–19. Antenatal care is free of charge in Norway, and virtually all pregnant women follow the standardized antenatal care programme. If fetal ultrasonographical examination was not performed, gestational age at birth (in weeks) was based on the last menstrual period (for 2.7% of the women). As a general rule, the expected date of delivery based on fetal ultrasonographical examination was used, if the dates by these two methods differed.

The proportion of pregnant smokers in Norway declined from 25% to 8% during the years 1999 to 2014.[28] Also mean placental weight and birthweight changed.[29] We therefore present associations after adjustment for year of delivery, and in additional analyses we also made adjustment for maternal age (in years),[30] parity,[31] preeclampsia[32,33] and maternal diabetes.[34] Parity was defined as the number of previous deliveries after the 16th week of pregnancy (coded: 0 or $\geq$1). Preeclampsia (yes/no) was defined as blood pressure $\geq$140/90 mm Hg and proteinuria (protein dipstick 1+ or >0.3 g/24 h) after the 20th week of pregnancy. Maternal diabetes (yes/no) included diabetes type 1, diabetes type 2, gestational diabetes, non-specified diabetes preceding pregnancy and use of anti-diabetic medication during pregnancy, as reported to the Medical Birth Registry.

We repeated the above analyses among nulliparous women. We used the statistical software packages IBM SPSS Statistics Version 22.0 (IBM Corp., Armonk, NY, USA) and Stata 14.2 SE (StataCorp, College Station, TX, USA).

Ethical considerations

The Medical Birth Registry of Norway is approved by the Norwegian Data Inspectorate. The advisory committee for the Medical Birth Registry of Norway has recommended this study [reference number 07/944/236].

Results

In our study sample of 698 891 women, mean age was 29.5 years (SD 5.1 years) and 41.3% of the women were nulliparous (Table 1). In total, 88 405 women (12.6%) smoked daily in the first trimester. Among these, 26 208 women (29.6%) stopped daily smoking after the first trimester and 62 197 women (70.4%) smoked daily throughout pregnancy. Among the 12 529 women (1.8%) who smoked occasionally in the first trimester 8607 women (68.7%) stopped occasional smoking after the first trimester (Table 1). In our sample, the proportion of women who smoked in pregnancy decreased during the study period (Supplementary Figure 1, available as Supplementary data at *IJE* online).

Placental weight and birthweight in women who smoked throughout pregnancy

In women who smoked throughout pregnancy, mean placental weight did not differ between daily smokers [659.8 g (SD 152.1 g)] and occasional smokers [665.0 g (SD 151.8 g)] (ANOVA, $P = 0.398$), but the placental weight was lower than in non-smokers [673.8 g (SD 150.6 g)] (ANOVA, $P < 0.001$) (Table 2). In daily smokers throughout pregnancy, placental weight adjusted for year of delivery decreased by increasing number of cigarettes in first trimester (Figure 2A). The maximum decrease in placental weight in daily smokers as compared with non-smokers was estimated at 11 daily cigarettes, and was 18.2 g [95% confidence interval (CI): 16.6 to 19.7g]. Above 11 cigarettes, we estimated no further decrease in placental weight. In fact, we observed a slight increase in placental weight above 11 daily cigarettes ($P_{\text{non-linearity}} < 0.001$).

Table 2. Mean placental weight, placental weight z-score, birthweight, birthweight z-score and placental to birthweight ratio according to maternal smoking habits

	n (%)	Placental weight, g (mean, SD)	Placental weight z-score[a] (mean, SD)	Birthweight, g (mean, SD)	Birthweight z-score[a] (mean, SD)	Placental weight to birthweight ratio[b] (mean, SD)
Non-smokers	597 957 (85.6)	673.8 (150.6)	−0.004 (1.001)	3571.0 (568.1)	0.025 (0.989)	0.190 (0.037)
Smokers throughout pregnancy						
Occasional smokers	3922 (0.6)	665.0 (151.8)	−0.043 (0.999)	3478.6 (594.8)	−0.116 (0.998)	0.193 (0.040)
Daily smokers	62 197 (8.9)	659.8 (152.1)	−0.070 (0.997)	3373.0 (584.2)	−0.331 (0.991)	0.197 (0.040)
Smokers who stopped after the first trimester						
Occasional smokers	8607 (1.2)	680.6 (152.4)	0.029 (1.016)	3596.6 (568.1)	0.046 (1.002)	0.190 (0.036)
Daily smokers	26 208 (3.7)	677.8 (154.2)	0.019 (1.018)	3569.1 (593.7)	0.012 (1.025)	0.191 (0.037)
Total	698 891 (100.0)					

[a]Z-scores were calculated in the sample as a whole by using means and standard deviations (SD) of placental weight and birthweight (in grams) for each gestational age birth. Z-scores were calculated separately for male and female offspring.
[b]Placental to birthweight ratio was calculated by dividing placental weight by birthweight (in grams).

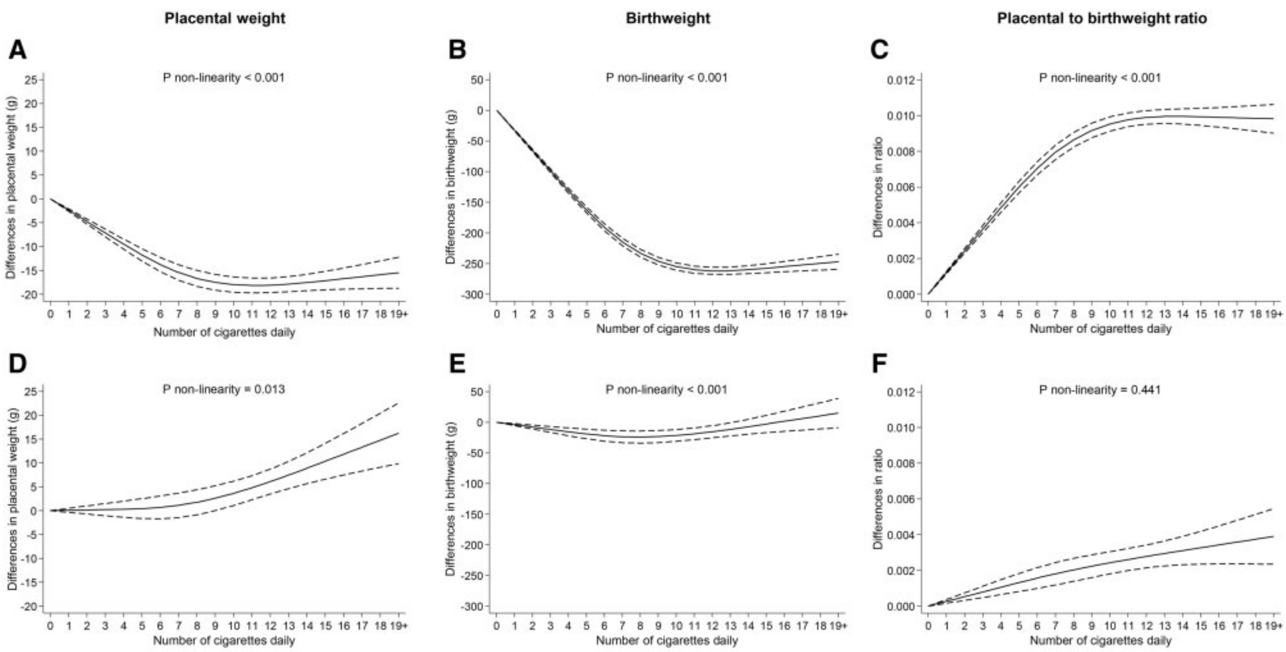

Figure 2. Estimated differences in placental weight, birthweight and placental to birthweight ratio according to number of daily cigarettes in the first trimester of pregnancy. Adjusted for year of delivery. (A-C) Non-smokers and daily smokers throughout pregnancy were included in the analyses ($n = 660\,154$); (D-F) Non-smokers and women who stopped daily smoking after the first trimester were included in the analyses ($n = 624\,165$). Non-smokers were used as the reference category. Data were fitted by the use of a linear regression model with restricted cubic splines with three knots (3, 7 and 15 daily cigarettes). Dashed lines represent 95% confidence intervals.

Unlike the results for placental weight, we found lower birthweight in daily smokers compared with occasional smokers throughout pregnancy [3373.0 g (SD 584.2 g) versus 3478.6 g (SD 594.8 g), ANOVA, $P < 0.001$] (Table 2). Birthweight was highest in non-smokers [3571.0 g (SD 568.1 g)]. As for placental weight, birthweight adjusted for year of delivery decreased by increasing number of daily cigarettes in the first trimester. The maximum estimated decrease in birthweight was 261.9 g (95% CI: 256.1 to 267.7 g), estimated at 12 daily cigarettes (Figure 2B). Above 12 daily cigarettes, we estimated no further decrease in birthweight ($P_{\text{non-linearity}} < 0.001$).

Mean placental to birthweight ratio was highest in women who smoked daily throughout pregnancy, followed by occasional smokers and non-smokers (ANOVA, $P < 0.001$) (Table 2). Placental to birthweight ratio adjusted for year of delivery increased by number of daily cigarettes in the first trimester, but above 12 cigarettes we

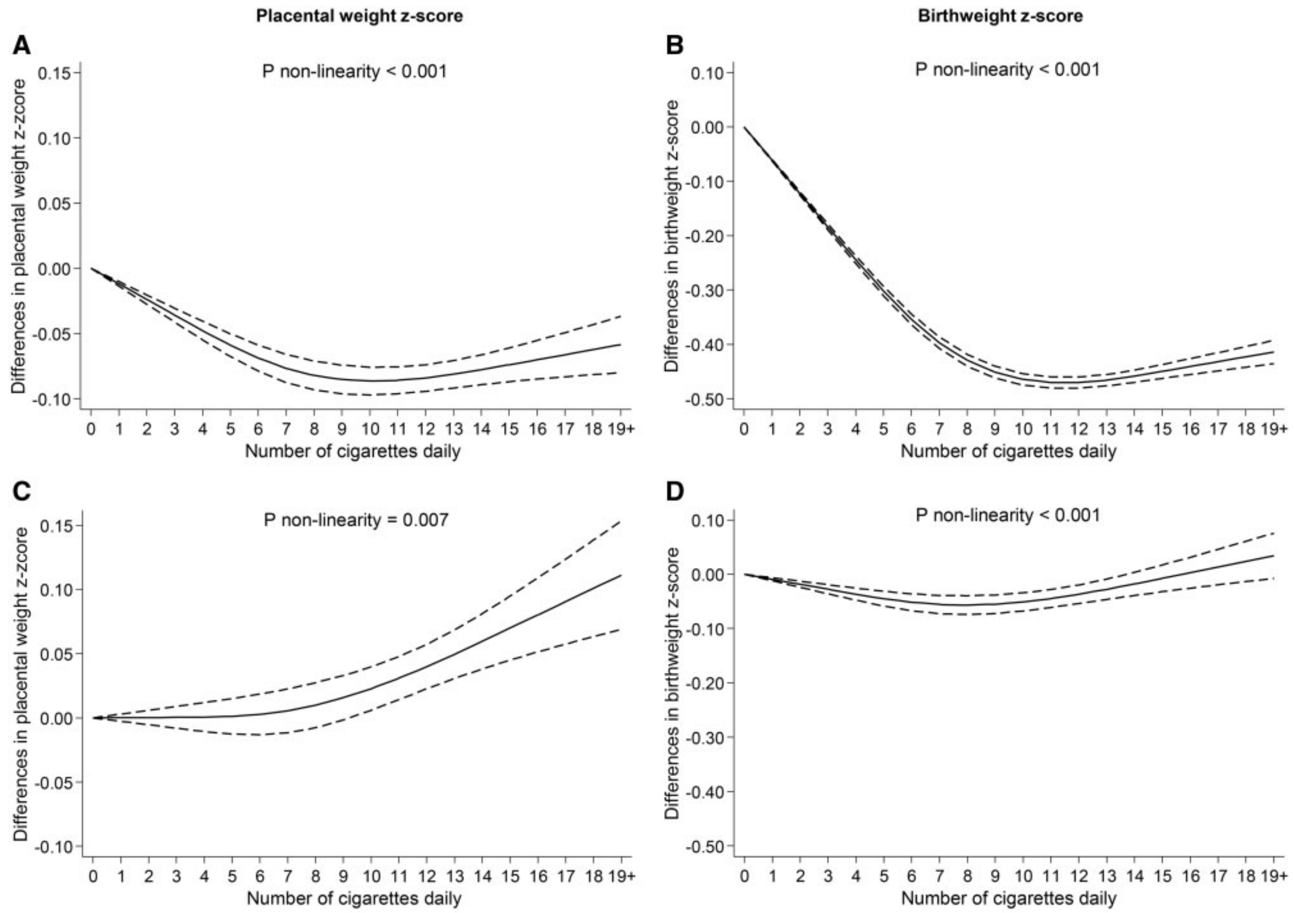

Figure 3. Estimated differences in placental weight z-scores and birthweight z-scores according to number of daily cigarettes in the first trimester of pregnancy. Adjusted for year of delivery. (A, B) Non-smokers and daily smokers throughout pregnancy were included in the analyses ($n = 660\,154$). (C, D) Non-smokers and daily smokers who stopped after the first trimester ($n = 624\,165$) were included in the analyses. Non-smokers were used as the reference category. Data were fitted by the use of a linear regression model with restricted cubic splines with three knots (3, 7 and 15 daily cigarettes). Dashed lines represent 95% confidence intervals.

estimated no further increase ($P_{\text{non-linearity}} < 0.001$) (Figure 2C).

Placental weight and birthweight in women who stopped smoking after the first trimester

In women who stopped occasional or daily smoking after the first trimester, we observed a different pattern; mean placental weight was higher than in non-smokers (Table 2). In women who stopped daily smoking, placental weight adjusted for year of delivery increased by increasing number of daily cigarettes in the first trimester (Figure 2D). Compared with non-smokers, the maximum estimated increase in placental weight for women who stopped daily smoking was 16.2 g (95% CI: 9.9 to 22.6 g), estimated at 19 cigarettes or more.

In women who stopped daily smoking after the first trimester, birthweight was not different from in non-smokers (Table 2), and the dose-response relationship of number of daily cigarettes with birthweight far less pronounced (Figure 2E). Thus, the placental to birthweight ratio increased by increasing number of daily cigarettes for women who stopped smoking after the first trimester (Figure 2F).

Additional analyses

Further adjustment for maternal age, parity, preeclampsia and maternal diabetes did not alter any of the above estimated associations notably (data not shown). We repeated all the above analyses by using z-scores for placental weight and birthweight, and we found similar associations (Figure 3).

In nulliparous women, the overall patterns were similar to all women (Supplementary Figure 2, available as Supplementary data at *IJE* online). However, birthweight increased linearly by number of daily cigarettes in the first trimester in the nulliparous women who smoked throughout pregnancy ($P_{\text{non-linearity}} = 0.464$). We include supplementary tables with the distribution of study factors among the women included in our sample and those who were excluded (Supplementary Tables 1 and 2, available as Supplementary data at *IJE* online).

Discussion

We found that in women who smoked throughout pregnancy, placental weight and birthweight decreased by number of daily cigarettes. However, above 11–12 cigarettes we estimated no further decrease in weights. In women who stopped smoking in pregnancy, we observed different dose-response associations. In these women, placental weight increased whereas birthweight was almost similar across number of cigarettes in the first trimester. Thus, the placental to birthweight ratio increased by number of cigarettes, independent of smoking status in the third trimester.

We aimed to include all women with a singleton delivery during the years 1999–2014, as reported to the Medical Birth Registry of Norway. For 21.4% of all women, we lacked information about smoking habits in the first and/or third trimester, and the proportion with lacking information about smoking habits decreased during our study period from 26.7% to 16.7%. Birthweight was 63 g lower in excluded women, but the means of other study factors were similar to those of included women (Supplementary Table 1, available as Supplementary data at *IJE* online). The difference in birthweight could suggest that women who smoked throughout pregnancy were underrepresented in our study sample. Women from non-Western countries give birth to infants with lower birthweight,[35] and they may be overrepresented among women without information about smoking habits. We made adjustment for year of delivery to account for changes in reporting or in the composition of the study sample that may have occurred during our study period. A few women were excluded due to missing information about gestational age at delivery (0.9%), placental weight (3.3%) or birthweight (0.3%). In these excluded women, smoking habits were similar to the women included (Supplementary Table 2, available as Supplementary data at *IJE* online).

Information about smoking habits was collected in a clinical interview by the antenatal care doctor in the first and in the third trimester. Number of daily cigarettes such as 5, 10, 15 and 20 were overrepresented. Smoking habits may have been erroneously reported by some women.[36] However, a previous study from Norway suggested high correlation of self-reported number of cigarettes with nicotine concentrations in hair,[37] suggesting high validity for self-reported smoking habits. If the number of cigarettes was generally underreported during pregnancy, our associations may represent overestimates. Also, number of daily cigarettes may have decreased during pregnancy. If so, our results may represent underestimates. Unfortunately, we lacked information about number of daily cigarettes in the third trimester for most women. We made adjustment for gestational age at birth by using z-scores for placental weight and birthweight. All analyses were adjusted for year of delivery, and we made further adjustments for maternal age, parity, preeclampsia and maternal diabetes in additional analyses. Adjustment for these study factors did not alter our results notably. Unfortunately, information about maternal body mass index, socioeconomic status or nutritional intake was not available.

It is well known that offspring of smokers have lower birthweight than offspring of non-smokers,[3,4] and it has been suggested that birthweight decreases by number of daily cigarettes in a linear pattern.[6,11] A few previous studies have allowed for a non-linear association of number of daily cigarettes with birthweight in their data analytical strategy,[7,8] and they reported no further decrease in birthweight above 5–8 daily cigarettes. We are aware of one previous study only that has assessed the association of number of daily cigarettes with placental weight.[11] This study included 2507 women in Australia in 1989, and 26.5% of the women were daily smokers. No association with placental weight was found, but birthweight was reported to decrease linearly with number of daily cigarettes. To our knowledge, our study is the first to assess the dose-response association of number of daily cigarettes with placental weight allowing for a non-linear association, and to study the effect of smoking cessation on placental weight.

In our study, placental weight and birthweight were lower in women who smoked throughout pregnancy than in non-smokers. One explanation for this finding is that the nicotine in cigarettes may lead to vasoconstriction in the maternal circulation with subsequent reduced blood flow to the uteroplacental unit.[38] Also, smoking reduces the oxygen binding capacity[39] and oxygen supply is essential for placental and fetal growth.[40] Additionally, nicotine and other components of cigarettes may impair trophoblast proliferation and differentiation, and thereby impair placental development and growth.[41]

Our results show that smoking throughout pregnancy reduces fetal growth relatively more than placental growth, as illustrated by the higher placental to birthweight ratio in smokers compared with non-smokers. High placental weight relative to birthweight has been associated with adverse pregnancy outcomes[18–20] and may therefore be an indicator of unfavourable intrauterine environment. It is possible that the hypoxia caused by cigarette smoking enhances placental angiogenesis as a compensatory response.[42] Increased placental angiogenesis and development of new vessels could possibly explain the large placenta relative to birthweight in smokers.

Surprisingly, we observed that in women who stopped smoking after the first trimester, placental weight increased by number of daily cigarettes. To stop smoking in pregnancy is unlikely to occur at random. In our study, women who stopped smoking after first trimester, smoked on average fewer daily cigarettes than women who continued smoking [7.2 (SD 4.8) versus 9.0 (SD 5.1)], and few women smoked more than 10 daily cigarettes (36% versus 51%). However, these differences in smoking habits cannot explain the differences in the dose-response patterns of number of cigarettes with placental weight and birthweight between women who stopped smoking and women who smoked throughout pregnancy.

Women may stop smoking if pregnancy pathology associated with fetal or placental size is diagnosed. However, after pregnancy week 17–19, fetal ultrasonographical examinations are not routinely performed in Norway. Thus, most small for gestational age fetuses are not diagnosed as such before birth.

In women who stop smoking after the first trimester, the oxygen binding capacity of haemoglobin may be restored. Consequently, smoking cessation may enhance catch-up growth of the placenta and fetus. Such catch-up growth may be most pronounced in the pregnancies exposed to the highest number of cigarettes in the first trimester, since these pregnancies may have been most deprived of oxygen.

The high placental weight in women who stopped smoking could be a consequence of biological selection to successful pregnancy. It is plausible that mainly pregnancies with optimal early placental development continue after exposure to cigarette smoking in the first trimester. It is also plausible that the higher the number of daily cigarettes, the better must the early development of the placenta be to overcome adverse effects of smoking. Most miscarriages occur in the first trimester, and the risk of first trimester miscarriage increases by number of cigarettes.[43] Hence, the increasing placental weight by number of daily cigarettes among women who stop heavy smoking may be the result of strong positive selection in the first trimester to successful pregnancy.

In women who smoked throughout pregnancy, we observed no further decrease in placental weight or in birthweight beyond 11–12 daily cigarettes. This deviance from a linear trend could possibly also be explained by a positive selection of pregnancies with a well-functioning placenta among heavy smokers. Previously it has been shown that in offspring with low birthweight, smoking is associated with lower infant mortality.[44] This paradox has partly, but not fully, been explained by methodological shortcomings.[45–47] Our findings could suggest that a stronger biological selection to pregnancy success in smokers compared with non-smokers explains lower infant mortality in offspring of smokers. Also the reduced risk of preeclampsia associated with cigarette smoking[32] could possibly be explained by selection to pregnancy success of smokers with optimal placentation in first trimester.

Weight gain in pregnancy has been positively associated with birthweight.[48] Women who stop smoking during pregnancy reportedly have higher weight gain compared with women who continue smoking.[49] It is possible that maternal weight in pregnancy increases by number of previous cigarettes. Thus, the increase in placental weight according to number of daily cigarettes could possibly be mediated through increased weight gain among women who stop smoking.

It is known that low oxygen concentration in the decidua is a driver of trophoblast differentiation and early placentation.[50] Hence hypoxia, caused by cigarette smoking in the first trimester, could possibly enhance placentation in early pregnancy.[51] Enhanced early placental development in smokers could therefore be an alternative explanation for the large placentas in women who stop smoking. If such explanation is true, our findings could suggest that the growth-reducing effect of cigarette smoking occurs mainly after the first trimester.

In conclusion, we found that in women who smoked throughout pregnancy, placental weight and birthweight decreased by increasing number of daily cigarettes, but above 11–12 daily cigarettes we found no further decrease. In women who stopped smoking after the first trimester, we found different patterns; placental weight was higher than in non-smokers and increased by number of cigarettes, and birthweight was almost similar to that of non-smokers.

Supplementary data

Supplementary data are available at *IJE* online.

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Conflict of interest: The authors report no conflict of interest.

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