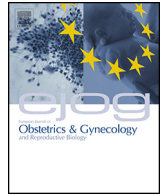




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Smoking cessation in early-pregnancy, gestational weight gain and subsequent risks of pregnancy complications



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ABSTRACT

Objective: Smoking cessation is associated with weight gain. We first examined the associations of smoking cessation in early-pregnancy with gestational weight gain and subsequently evaluated the risks of pregnancy complications among women who quit smoking in early-pregnancy according to their gestational weight gain.

Methods: In a population-based prospective cohort study among 7,389 women, we measured weight in each pregnancy period. Information on smoking and pregnancy complications was obtained from questionnaires and medical records.

Results: As compared to continued smoking during pregnancy, smoking cessation in early-pregnancy was not associated with gestational weight gain. Smoking cessation in early-pregnancy was associated with decreased risks of delivering small-for-gestational-age infants (Odds Ratio (OR) 0.52 (95 % Confidence Interval (CI) 0.37, 0.75)), but with increased risks of pre-eclampsia (OR 2.07 (95 % CI 1.01, 4.27)) and delivering large-for-gestational-age infants (OR 2.11 (95 % CI 1.45, 3.09)). Among women who quit smoking in early-pregnancy with >12 kg weight gain, the risks of pre-eclampsia and delivering large-for-gestational-age infants were slightly increased.

Conclusion: As compared to continued smoking during pregnancy, smoking cessation in early-pregnancy is not associated with increased gestational weight gain. Among women who quit smoking in early-pregnancy, higher gestational weight gain does not strongly affect their risks of pregnancy complications.

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Introduction

Maternal smoking during pregnancy is a major public health problem leading to increased risks of pregnancy complications [1,2]. Despite strong recommendations to quit smoking before pregnancy, approximately 15 % of women smoke at the start of pregnancy and 8% of women continue to smoke during pregnancy [3–5]. Women might be reluctant to quit smoking due to concerns of potential unfavorable effects subsequent to smoking cessation, such as excessive weight gain [6–8]. In general, excessive weight gain is a well-known side effect of smoking cessation, and might discourage women from cessation attempts [9]. During pregnancy, excessive weight gain is a risk

factor for pregnancy complications [10–12]. Thus far, only a few studies assessed the association of smoking cessation in early-pregnancy with total gestational weight gain. These studies suggested that smoking cessation in early-pregnancy might be associated with a moderate increased risk of excessive gestational weight gain, but no information about the pattern of subsequent gestational weight gain throughout pregnancy is available [13–19]. It also remains unknown whether gestational weight gain subsequent to smoking cessation in early-pregnancy affects the well-known benefits of smoking cessation on pregnancy complications.

Therefore, in a population-based prospective cohort study among 7,389 pregnant women, we first examined whether smoking cessation in early-pregnancy is associated with subsequent gestational weight gain. Second, we evaluated the risks of pregnancy complications among women who quit smoking in early-pregnancy according to their subsequent gestational weight gain.

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Methods

Study design and participants

This study was embedded in the Generation R study, a population-based prospective cohort study in Rotterdam, the Netherlands [20]. All pregnant women were enrolled between 2001 and 2005. Response rate at baseline was 61 %, calculated by dividing the number of participating live born children by the total number of live born children born in the study area during the inclusion period. 7,738 women had information on smoking during pregnancy. After excluding women with less than two weight measurements during pregnancy and excluding non-singleton live births, population for analysis included 7,389 women (**Supplemental Fig. S1**).

Smoking during pregnancy

We obtained information on maternal smoking during pregnancy through questionnaires (never smoking during pregnancy, smoking cessation in early-pregnancy or continued smoking during pregnancy), as described previously [21]. We compared the effect of smoking cessation in early-pregnancy to continued smoking during pregnancy, to explore the potential health benefits among women who are motivated to quit smoking once they know they are pregnant.

Weight gain during pregnancy

Maternal weight was repeatedly measured in early- (<18 weeks), mid- (18–25 weeks) and late-pregnancy (>25 weeks) without shoes and heavy clothing [20]. Information about maternal weight before pregnancy was obtained by questionnaire (correlation coefficient with weight at enrolment 0.95). Period specific weight gain was calculated as the difference between two weight measurements divided by difference in gestational age. Information about maximum weight during pregnancy was self-reported 2 months after delivery (correlation coefficient with weight measurement at 30 weeks gestation 0.96). Because of larger numbers of measurements available, we used gestational weight gain until 30 weeks for main analyses [22]. Among women with information on maximum weight available, we defined inadequate and excessive gestational weight gain in relation to maternal pre-pregnancy BMI according to the US Institute of Medicine (IOM) Guidelines [23].

Pregnancy complications

Information on gestational hypertension, pre-eclampsia, gestational diabetes and gestational age and weight at birth was obtained from medical records. Pre-term birth was defined as a gestational age <37 weeks at birth. We defined small- and large-for-gestational-age at birth as a fetal sex and gestational age-adjusted birth weight below the 10th percentile and above the 90th percentile in the study cohort, respectively [24]. We examined the associations with composite outcomes (maternal pregnancy complications and adverse birth outcomes) and with complications separately.

Covariates

Information about maternal age, ethnicity, education level, parity, folic acid supplementation and alcohol consumption was obtained through questionnaires [20].

Statistical analysis

First, we assessed population characteristics according to smoking status. Second, we assessed the associations of smoking cessation with weight gain in each pregnancy period and until 30 weeks of gestation using linear regression models. We constructed standard deviation scores (SDS) of weight gain to compare the effect estimates between different pregnancy periods and used weight gain in kilogram/week for clinical interpretability. We assessed the associations of smoking cessation with the risks of inadequate and excessive gestational weight gain using logistic regression models. Third, with logistic regression models, we assessed the risks of pregnancy complications among women who quit smoking in early-pregnancy according to the amount of weight gain until 30 weeks of gestation in tertiles, compared to women who continued smoking during pregnancy. To further assess whether the combined effects of smoking cessation in early-pregnancy and gestational weight gain were different from the separate effects, we tested for interaction between these exposures on each pregnancy complication. We constructed different models: basic model (adjusted for gestational age at intake and weight measurement), confounder model (basic model additionally adjusted for maternal age, ethnicity, education level, parity, folic acid supplementation, and alcohol consumption during pregnancy), and maternal BMI model (confounder model additionally adjusted for maternal pre-pregnancy BMI). Confounder selection was based on literature and included in the model when associated with both exposure and outcome and changes in effect estimates of >10 % [12,25–30]. To deal with missing data, we performed multiple imputations of covariates. Analyses were performed using

Statistical Package of Social Sciences version 24.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Subject characteristics

Table 1 shows that in our population 1,382 (18.7 %) women continued smoking during pregnancy, 641 (8.7 %) women quit smoking in early-pregnancy and 5,366 (72.6 %) women never smoked during pregnancy. Women who quit smoking in early-pregnancy had a lower pre-pregnancy BMI and higher maximum gestational weight gain, compared to women who continued smoking during pregnancy.

Smoking status and gestational weight gain

Table 2 shows that, as compared to continued smoking during pregnancy, smoking cessation in early-pregnancy was not associated with gestational weight gain per pregnancy period or until 30 weeks gestation. As compared to continued smoking during pregnancy, never smoking during pregnancy was associated with a lower gestational weight gain in each pregnancy period (p-values<0.05). Additional adjustment for maternal pre-pregnancy BMI did not materially affect associations. Associations with gestational weight gain in kilogram/week were similar (**Supplemental Table S1**). As compared to continued smoking during pregnancy, smoking cessation in early-pregnancy was not associated with the risks of inadequate or excessive weight gain, whereas never smoking during pregnancy was associated with decreased risks of excessive gestational weight gain (Odds Ratio (OR) 0.54 (95 % Confidence Interval (CI) 0.42, 0.69)), but not with risks of inadequate gestational weight gain (**Fig. 1**).

Table 1

Characteristics of the study population according to maternal smoking status during pregnancy.

	Maternal smoking status during pregnancy			P-value ¹
	Continued smoking during pregnancy (n = 1,382)	Smoking cessation in early-pregnancy (n = 641)	Never smoking during pregnancy (n = 5,366)	
Maternal characteristics				
Age at enrolment, median (95 %), years	28.4 (19.4, 37.5)	30.1 (20.0, 37.8)	30.6 (20.9, 38.0)	<0.01
Height, mean (SD), cm	166.9 (7.1)	168.2 (7.0)	167.4 (7.4)	<0.01
Gestational age at intake, median (95 %), weeks	14.1 (10.4, 22.2)	13.4 (10.1, 20.9)	13.9 (10.9, 22.4)	<0.01
Ethnicity, no. Dutch (%)	654 (47.3)	332 (51.8)	2,662 (49.6)	<0.01
Education level, no. higher phase (%)	240 (17.4)	265 (41.3)	2,511 (46.8)	<0.01
Pre-pregnancy BMI, median (95 %), kg/m ²	22.5 (18.2, 32.7)	22.3 (18.4, 31.6)	22.7 (18.7, 32.3)	0.31
BMI class overweight/obese, no. (%)	331 (24.0)	140 (21.8)	1,356 (25.3)	0.01
Gestational weight gain ² , mean (SD), kg				
Early-pregnancy weight gain	3.2 (3.6)	2.8 (3.5)	2.0 (3.3)	<0.01
Mid-pregnancy weight gain	3.3 (2.5)	3.7 (2.3)	3.1 (2.3)	<0.01
Late-pregnancy weight gain	5.2 (3.0)	5.6 (2.7)	4.9 (2.7)	<0.01
Maximum gestational weight gain	16.2 (6.5)	17.3 (6.3)	14.4 (5.6)	<0.01
Parity, no. nulliparous (%)	766 (55.4)	438 (68.3)	2,993 (55.8)	<0.01
Alcohol use during pregnancy, no. (%), continued	498 (36.0)	292 (45.6)	1,903 (35.5)	<0.01
Folic acid supplementation during pregnancy, no. (%), never	423 (30.6)	119 (18.6)	1,256 (23.4)	<0.01
Maternal pregnancy complications				
Gestational hypertensive disorder, no. (%)	74 (5.4)	49 (7.6)	302 (5.6)	0.11
Gestational hypertension	54 (3.9)	29 (4.5)	194 (3.6)	0.49
Pre-eclampsia	20 (1.4)	20 (3.1)	108 (2.0)	0.05
Gestational diabetes, no. (%)	15 (1.1)	2 (0.3)	57 (1.1)	0.18
Birth outcomes				
Gestational age at birth, median (95 %), weeks	39.9 (36.4, 42.0)	40.0 (36.9, 42.0)	40.1 (37.1, 42.1)	<0.01
Birth weight, mean (SD), grams	3260.4 (541.2)	3423.5 (559.0)	3458.0 (546.6)	<0.01
Gender, no. girl (%)	634 (45.9)	329 (51.3)	2,703 (50.4)	0.01
Preterm birth, no. (%)	90 (6.5)	32 (5.0)	242 (4.5)	0.01
Small-for-gestational-age infants, no. (%)	218 (15.8)	57 (8.9)	449 (8.4)	<0.01
Large-for-gestational-age infants, no. (%)	71 (5.1)	70 (10.9)	572 (10.7)	<0.01

¹ Differences in subject characteristics between the groups were evaluated using one-way ANOVA tests for continuous variables and chi-square tests for proportions.² Gestational weight gain per pregnancy period was calculated as the difference between the two weight measurements in each trimester. Maximum gestational weight gain was defined as the difference between pre-pregnancy weight and the highest self-reported weight at pregnancy.**Table 2**Associations of maternal smoking status during pregnancy with gestational weight gain¹.

Maternal smoking status during pregnancy	Early-pregnancy weight gain Difference in SDS (95 % CI)	Mid-pregnancy weight gain Difference in SDS (95 % CI)	Late-pregnancy weight gain Difference in SDS (95 % CI)	Total pregnancy weight gain Difference in SDS (95 % CI)
Continued smoking during pregnancy (n = 1,382)	Reference	Reference	Reference	Reference
Smoking cessation in early-pregnancy (n = 641)				
Confounder model ²	-0.08 (-0.19, 0.03)	0.05 (-0.06, 0.15)	0.08 (-0.02, 0.18)	0.04 (-0.06, 0.14)
Maternal BMI model ³	-0.09 (-0.20, 0.02)	0.08 (-0.03, 0.19)	0.08 (-0.02, 0.18)	0.04 (-0.06, 0.14)
Never smoking during pregnancy (n = 5,366)				
Confounder model ²	-0.34 (-0.41, -0.26)*	-0.15 (-0.22, -0.09)*	-0.12 (-0.18, -0.05)*	-0.35 (-0.42, -0.28)*
Maternal BMI model ³	-0.33 (-0.41, -0.26)*	-0.13 (-0.21, -0.06)*	-0.12 (-0.19, -0.05)*	-0.34 (-0.40, -0.27)*

¹ Values represent regression coefficients (95 % confidence interval) from linear regression models that reflect the differences in weight gain per week in standard deviation scores (SDS) in early-, mid- and late-pregnancy and total gestational weight gain until 30 weeks of gestation for women who quit smoking in early-pregnancy and for women who continued smoking during pregnancy, as compared to those who never smoked during pregnancy. Estimates are based on multiple imputed data.² Confounder model includes adjustment for gestational age at enrolment, maternal age, ethnicity, education level, parity, folic acid supplementation and alcohol consumption during pregnancy.³ Maternal BMI model includes the confounder model additionally adjusted for maternal pre-pregnancy body mass index.

* P < 0.01.

Smoking status, gestational weight gain and pregnancy complications

Table 3 shows that, overall, as compared to women who continued smoking during pregnancy, women who quit smoking in early-pregnancy had increased risks of pre-eclampsia (OR 2.07 (95 % CI 1.01, 4.27)), but not of other maternal pregnancy

complications. Their risks were similar to women who never smoked during pregnancy. The amount of gestational weight gain did not have a strong effect on the observed associations (all p-values for interaction >0.05). Among women who quit smoking in early-pregnancy, the risks of pre-eclampsia were highest among women with low or high gestational weight gain, as compared to

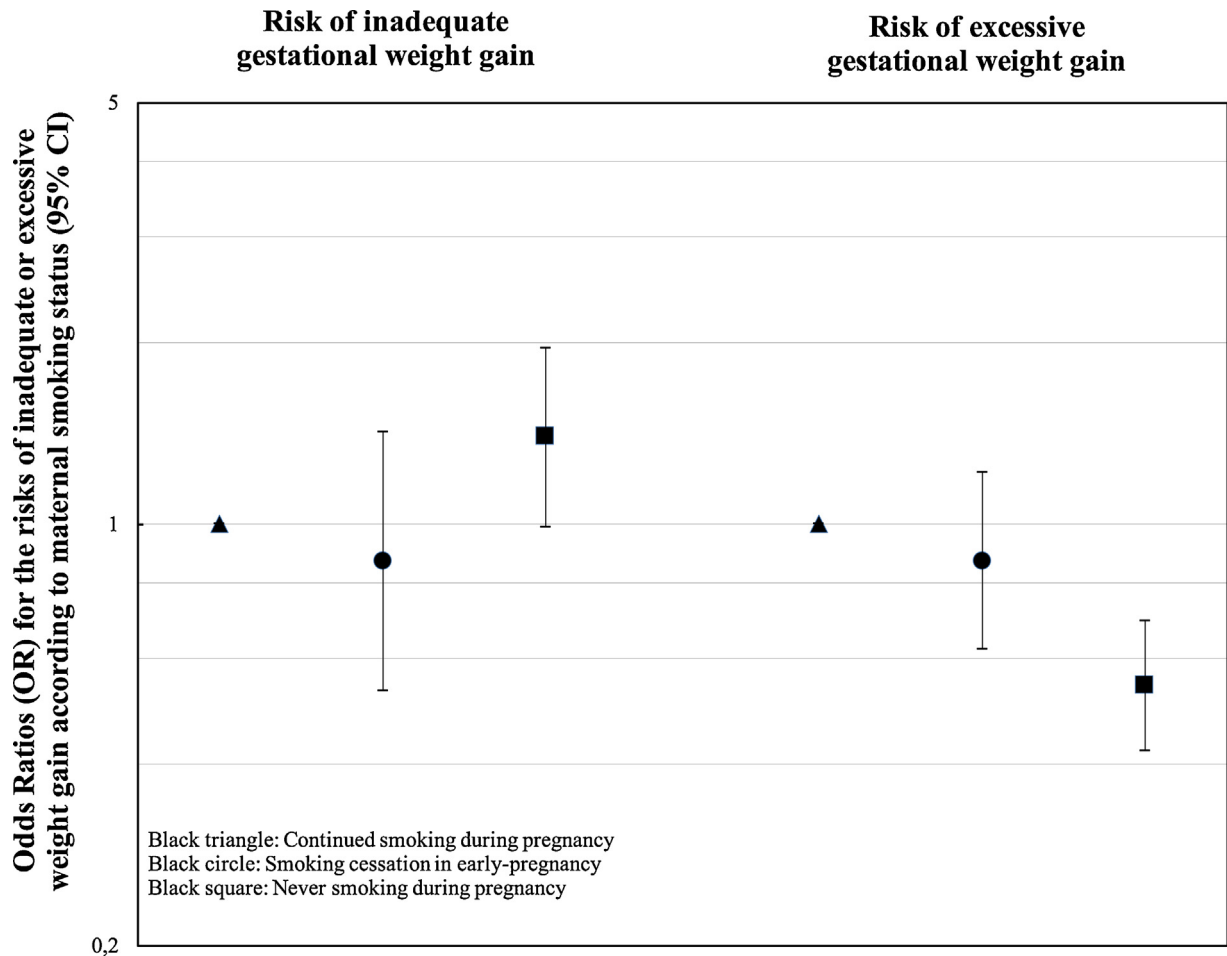


Fig. 1. Association of maternal smoking status during pregnancy with the risks of inadequate or excessive gestational weight gain¹.

¹Values are Odds Ratios (95 % Confidence Intervals) from logistic regression models that reflect the risks of inadequate and excessive gestational weight gain for women who quit smoking in early-pregnancy and for women who never smoked during pregnancy, as compared to those who continued smoking during pregnancy. We assessed these risks among a subgroup of 3,161 women from our main analyses with information on maximum gestational weight gain available. Adjustments were made for gestational age at enrolment, maternal age, ethnicity, education level, parity, folic acid supplementation use, alcohol consumption during pregnancy and gestational age at birth.

women who continued smoking during pregnancy (OR 3.70 (95 % CI 1.39, 9.86), OR 2.36 (95 % CI 1.01, 5.52) respectively). Adjustment for maternal pre-pregnancy BMI did not explain these associations.

Overall, as compared to women who continued smoking in pregnancy, women who quit smoking in early-pregnancy tended to have lower risks of any adverse birth outcome (Table 4). When we explored individual birth outcomes, we observed that women who quit smoking in early-pregnancy had decreased risks of delivering small-for-gestational-age infants (OR 0.52 (95 % CI 0.37, 0.75) and increased risks of delivering large-for-gestational-age infants (OR 2.11 (95 % CI 1.45, 3.09), as compared to women who continued smoking during pregnancy. These risks were comparable to the risks of women who never smoked during pregnancy. We observed a significant interaction between smoking status and total gestational weight gain on the composite of adverse birth outcomes (p-value 0.02), but not on each adverse birth outcome separately (p-value>0.05). When taking gestational weight gain into account, women who quit smoking in early-pregnancy with a gestational weight gain >12 kg had the lowest risks of delivering small-for-gestational-age infants (OR 0.36 (95 % CI 0.21, 0.63), whereas their risks of delivering large-for-gestational-age infants were the highest (OR 2.64 (95 % CI 1.68, 4.14), as compared to women who continued smoking during pregnancy. Additional adjustment for maternal pre-pregnancy BMI did not explain the associations.

Discussion

We observed that smoking cessation in early-pregnancy was not associated with a higher period-specific or total gestational weight gain, as compared to continued smoking during pregnancy. As compared to women who continued smoking during pregnancy, women who quit smoking in early-pregnancy had lower risks of delivering small-for-gestational-age infants, but increased risks of pre-eclampsia and delivering large-for-gestational-age infants. These risks were comparable to women who never smoked during pregnancy. The influence of gestational weight gain on these associations was small.

Interpretation main findings

Benefits of smoking cessation prior to pregnancy are well-known. However, still a substantial amount of pregnant women smoke during pregnancy, which leads to strongly increased risks of adverse pregnancy outcomes [2]. In non-pregnant populations, smoking cessation is associated with weight gain and subsequent adverse health outcomes, including type 2 diabetes [8]. The effects of smoking on weight gain might be caused through increased fat mass levels by altered food satiation and hormone leptin mechanisms [31]. Concerns about weight gain after smoking cessation is commonly cited as a reason to be reluctant to quit

Table 3Associations of maternal smoking status during pregnancy and gestational weight gain with the risk of maternal pregnancy complications¹.

	OR (95 % CI) Confounder model ²	OR (95 % CI) Maternal BMI model ³	P-value Interaction term ⁴
Composite of maternal pregnancy complications (n = 418)			0.70
Continued smoking during pregnancy	Reference	Reference	
Smoking cessation in early-pregnancy	1.16 (0.77, 1.75)	1.18 (0.77, 1.79)	
First tertile of weight gain (<9 kg)	0.95 (0.42, 2.14)	0.70 (0.30, 1.63)	
Second tertile of weight gain (9–12 kg)	0.84 (0.41, 1.72)	0.91 (0.44, 1.90)	
Third tertile of weight gain (>12 kg)	1.47 (0.90, 2.39)	1.61 (0.98, 2.65)	
Never smoking during pregnancy	1.14 (0.86, 1.51)	1.13 (0.84, 1.51)	
Gestational hypertension (n = 238)			0.92
Continued smoking during pregnancy	Reference	Reference	
Smoking cessation in early-pregnancy	1.00 (0.59, 1.67)	1.02 (0.60, 1.73)	
First tertile of weight gain (<9 kg)	0.20 (0.03, 1.46)	0.13 (0.02, 0.96)*	
Second tertile of weight gain (9–12 kg)	0.95 (0.42, 2.18)	1.09 (0.47, 2.52)	
Third tertile of weight gain (>12 kg)	1.37 (0.75, 2.50)	1.57 (0.85, 2.90)	
Never smoking during pregnancy	0.99 (0.69, 1.41)	0.97 (0.67, 1.39)	
Pre-eclampsia (n = 122)			0.33
Continued smoking during pregnancy	Reference	Reference	
Smoking cessation in early-pregnancy	2.07 (1.01, 4.27)*	2.00 (0.97, 4.13)	
First tertile of weight gain (<9 kg)	3.70 (1.39, 9.86)**	3.01 (1.11, 8.17)*	
Second tertile of weight gain (9–12 kg)	0.44 (0.07, 2.88)	0.45 (0.06, 3.43)	
Third tertile of weight gain (>12 kg)	2.36 (1.01, 5.52)*	2.39 (1.02, 5.62)*	
Never smoking during pregnancy	1.57 (0.89, 2.78)	1.54 (0.87, 2.72)	
Gestational diabetes mellitus (n = 65)			0.35
Continued smoking during pregnancy	Reference	Reference	
Smoking cessation in early-pregnancy	0.39 (0.09, 1.78)	0.38 (0.09, 1.74)	
First tertile of weight gain (<9 kg)	NA	NA	
Second tertile of weight gain (9–12 kg)	0.65 (0.08, 5.04)	0.73 (0.09, 5.72)	
Third tertile of weight gain (>12 kg)	0.42 (0.05, 3.26)	0.46 (0.06, 3.61)	
Never smoking during pregnancy	1.02 (0.53, 1.97)	0.97 (0.50, 1.86)	

¹ Values are Odds Ratios (95 % Confidence Intervals) from logistic regression models reflecting the risks of maternal pregnancy complications for women who quit smoking in early-pregnancy (n = 559) and never smoked during pregnancy (n = 4,681), as compared to women who continued smoking during pregnancy (n = 1,129). The composite outcome for maternal pregnancy complications includes: gestational hypertension, pre-eclampsia and gestational diabetes mellitus. Estimates are based on multiple imputed data.

² Confounder model includes adjustment for gestational age at enrolment and at weight measurement, maternal age, ethnicity, education level, parity, folic acid supplementation and alcohol consumption during pregnancy.

³ Maternal BMI model includes the confounder model additionally adjusted for maternal pre-pregnancy body mass index.

⁴ We tested the following interaction term between smoking status*total gestational weight gain.

* P < 0.05.

** P < 0.01.

smoking [32]. In pregnancy, excessive weight gain is a well-known risk factor for pregnancy complications [10,33]. Whether smoking cessation in early-pregnancy is also associated with subsequent higher gestational weight gain and whether this attenuates the positive effects of smoking cessation on pregnancy outcomes remains unclear.

Few studies examined the associations of smoking cessation in pregnancy with gestational weight gain and reported inconsistent findings [13,19,34,35]. A Swedish cohort study among 1,753 pregnant women, reported that smoking cessation in early-pregnancy was associated with a higher amount of gestational weight, as compared to never smoking or continued smoking during pregnancy [14]. A Danish study among 1,774 women showed that women who quit smoking gained more weight during pregnancy than women who never smoked during pregnancy [13]. Contrarily, a study among 357 high risk pregnant women participating in a smoking intervention program, reported no difference in gestational weight gain between women who quit smoking and women who continued smoking during pregnancy [15]. In line with the latter study, we observed no association of smoking cessation in early-pregnancy with gestational weight gain throughout pregnancy, as compared to continued smoking during pregnancy. Women who never smoked during pregnancy had the lowest amount of gestational weight gain, which might reflect an overall healthier lifestyle. Discrepancy between our study and previous observational studies observing an association of smoking cessation in early-pregnancy with higher total gestational weight gain, might be due to the lack

of adjustment for multiple confounders in previous studies, but also to our relatively healthy population. Further studies are needed to replicate our findings among higher risk populations. Findings should be addressed more often in clinical practice to women who hesitate to quit smoking in pregnancy because of weight gain concerns.

Smoking cessation in early-pregnancy is associated with major offspring health benefits. Rates of spontaneous preterm birth and small-for-gestational-age infants become similar to those of women who never smoked during pregnancy [5]. Contrarily, risks of pre-eclampsia and delivering large-for-gestational-age infants have been suggested to be higher among women who quit smoking in early-pregnancy than in those who continued smoking during pregnancy [36,37]. In line with previous studies, we observed that smoking cessation in early-pregnancy was associated with lower risks of delivering small-for-gestational-age infants, whereas the risks of pre-eclampsia and delivering large-for-gestational-age infants were higher, as compared to continued smoking during pregnancy and were largely comparable to never smoking during pregnancy. The effects were only slightly affected by the amount of gestational weight gain, with slightly lower risks of delivering small-for-gestational-age infants and higher risks of pre-eclampsia and delivering large-for-gestational-age infants among women who quit smoking in early-pregnancy and gained high amounts of gestational weight. These findings suggests that other mechanisms than the amount of gestational weight gain, may explain the observed associations. Smoking during pregnancy might influence intrauterine fetal growth directly by toxic effects [38,39].

Table 4Associations of maternal smoking status during pregnancy and gestational weight gain with the risk of adverse birth outcomes¹.

	OR (95 % CI) Confounder model ²	OR (95 % CI) Maternal BMI model ³	P-value Interaction term ⁴
Composite of adverse birth outcomes (n = 1450)			0.02*
Continued smoking during pregnancy	Reference	Reference	
Smoking cessation in early-pregnancy	0.86 (0.68, 1.10)	0.86 (0.68, 1.10)	
First tertile of weight gain (<9 kg)	0.89 (0.58, 1.37)	0.86 (0.56, 1.33)	
Second tertile of weight gain (9–12 kg)	0.93 (0.64, 1.35)	0.93 (0.64, 1.36)	
Third tertile of weight gain (>12 kg)	0.81 (0.59, 1.12)	0.82 (0.59, 1.13)	
Never smoking during pregnancy	0.81 (0.69, 0.95)**	0.81 (0.69, 0.94)**	
Preterm birth (n = 275)			0.56
Continued smoking during pregnancy	Reference	Reference	
Smoking cessation in early-pregnancy	0.74 (0.47, 1.19)	0.74 (0.47, 1.19)	
First tertile of weight gain (<9 kg)	1.13 (0.55, 2.34)	1.12 (0.54, 2.32)	
Second tertile of weight gain (9–12 kg)	0.79 (0.37, 1.68)	0.79 (0.37, 1.68)	
Third tertile of weight gain (>12 kg)	0.53 (0.26, 1.09)	0.54 (0.26, 1.10)	
Never smoking during pregnancy	0.63 (0.46, 0.85)**	0.63 (0.46, 0.85)**	
Small-for-gestational-age infants (n = 602)			0.96
Continued smoking during pregnancy	Reference	Reference	
Smoking cessation in early-pregnancy	0.52 (0.37, 0.75)**	0.52 (0.37, 0.75)**	
First tertile of weight gain (<9 kg)	0.76 (0.43, 1.34)	0.79 (0.44, 1.40)	
Second tertile of weight gain (9–12 kg)	0.60 (0.34, 1.06)	0.59 (0.34, 1.04)	
Third tertile of weight gain (>12 kg)	0.36 (0.21, 0.63)**	0.36 (0.21, 0.63)**	
Never smoking during pregnancy	0.55 (0.44, 0.67)**	0.55 (0.45, 0.68)**	
Large-for-gestational-age infants (n = 621)			0.27
Continued smoking during pregnancy	Reference	Reference	
Smoking cessation in early-pregnancy	2.11 (1.45, 3.09)**	2.13 (1.45, 3.12)**	
First tertile of weight gain (<9 kg)	1.17 (0.55, 2.49)	1.01 (0.48, 2.14)	
Second tertile of weight gain (9–12 kg)	2.07 (1.19, 3.59)*	2.13 (1.22, 3.72)**	
Third tertile of weight gain (>12 kg)	2.64 (1.68, 4.14)**	2.79 (1.77, 4.39)**	
Never smoking during pregnancy	1.85 (1.39, 2.47)**	1.81 (1.36, 2.42)**	

¹ Values are Odds Ratios (95 % Confidence Intervals) from logistic regression models reflecting the risks of adverse birth outcomes for women who quit smoking in early-pregnancy (n = 559) and never smoked during pregnancy (n = 4,681), as compared to women who continued smoking during pregnancy (n = 1,129). The composite outcome for adverse birth outcomes includes: preterm birth, delivering small-for-gestational-age infants and delivering large-for-gestational-age infants. Estimates are based on multiple imputed data.

² Confounder model includes adjustment for gestational age at enrolment and at weight measurement, maternal age, ethnicity, education level, parity, folic acid supplementation and alcohol consumption during pregnancy.

³ Maternal BMI model includes the confounder model additionally adjusted for maternal pre-pregnancy body mass index.

⁴ We tested the following interaction term between smoking status*total gestational weight gain.

* P < 0.05.

** P < 0.01.

Contrarily, the protective role of smoking on pre-eclampsia might be explained by the effects of carbon monoxide on placental growth and nicotine on the antioxidant systems [40]. Thus, our findings suggest that, as compared to continued smoking, smoking cessation in early-pregnancy is associated with lower risks of delivering small-for-gestational-age infants, but higher risks of pre-eclampsia and delivering large-for-gestational-age, comparable to women who never smoked during pregnancy. These effects are not strongly influenced by the amount of gestational weight gain. The benefits of smoking cessation in early-pregnancy on risks of delivering small-for-gestational-age infants clearly outweigh the potential risks of excessive gestational weight gain and its negative effect on pregnancy outcomes. Preventive strategies should actively support smoking cessation in early-pregnancy among women who still smoke at the start of their pregnancy. Since risks of pregnancy complications were slightly higher among those women who quit smoking in early-pregnancy with higher gestational weight gain, future preventive strategies should also consider addressing excessive weight gain among this specific group of women.

Methodological considerations

The most important strength of our study was the prospective data collection from early-pregnancy onwards of a large population with measurements of maternal weight in each pregnancy period. The nonresponse at baseline would have led to biased effect estimates if the associations were different between those

included and not, but this seems unlikely because biased estimates in large cohort studies often arise from loss to follow-up rather than from nonresponse at baseline [41]. We had relatively low numbers of cases of pregnancy complications, which might indicate a selection towards a relatively healthy population and might have affected the generalizability of our findings. Self-reported data might lead to non-differential misclassification bias and an underestimation of our results [42,43]. However, previous studies have shown that self-reported data on smoking status is useful and highly correlated to biomarkers of tobacco exposure. We observed high correlations between weight measured in early- and late-pregnancy with self-reported pre-pregnancy weight and maximum weight, respectively, but self-reported weight might lead to misclassification. We had detailed information about a large number of potential confounders, but residual confounding might still be an issue.

Conclusion

As compared to continued smoking during pregnancy, smoking cessation in early-pregnancy was not associated with increased gestational weight gain. As compared to women who continued smoking during pregnancy, women who quit smoking in early-pregnancy have lower risks of delivering small-for-gestational-age infants, but higher risks of pre-eclampsia and delivering large-for-gestational-age infants. Risks are comparable to women who never smoked during pregnancy and not strongly influenced by the amount of gestational weight gain.

Contribution to authorship

LA, RW, and RG designed and constructed the research, wrote the paper and had primary responsibility for the final content. LA, RW and RG carried out the statistical analysis. VVVJ and EAS coordinated data acquisition and critically reviewed and revised the manuscript. All authors approved the final manuscript and agree to be accountable for all aspects of the work.

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Details of ethical approval

The study protocol was approved by the Medical Ethical Committee of the Erasmus Medical Centre, Rotterdam (MEC 198.782/2001/31, MEC 217.595/2002/202, MEC 2007-413). Written informed consent was obtained from all participating mothers.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ejogrb.2020.07.040>.

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