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ORIGINAL RESEARCH ARTICLE

Interaction of maternal smoking and gestational diabetes mellitus on newborn head circumference and birthweight

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Abstract

Introduction: Maternal smoking during pregnancy and gestational diabetes mellitus (GDM) have opposite effects on fetal growth during pregnancy. The aim of the study was to evaluate the interaction of smoking during pregnancy and gestational diabetes mellitus on head circumference and birthweight of newborns.

Material and Methods: The study included all primiparous women with singleton pregnancies ($n = 290\,602$) without previously diagnosed diabetes or hypertension in Finland between 2006 and 2018. The information on gestational diabetes mellitus, newborn birthweight and head circumference, and maternal smoking and backgrounds was derived from the Finnish Medical Birth Register. Linear regression models were used in the analyses.

Results: In total 8.0% of parturients quit smoking during the first trimester and 9.9% continued smoking thereafter. The prevalence of GDM was 8.9% ($n = 25\,948$). Newborns of women who continued smoking had a smaller head circumference ($b = -0.24$, SE = 0.01, $p < 0.0001$) and birthweight ($b = -0.28$, SE = 0.01, $p < 0.0001$) compared to newborns of women who did not smoke. Head circumference and birthweight were greater in newborns of women with GDM ($b = 0.09$, SE = 0.01, $p < 0.0001$ and $b = 0.16$, SE = 0.01, $p < 0.0001$, respectively) compared to newborns of women without GDM. In the interaction analyses, head circumference ($b = -0.13$, SE = 0.01, $p < 0.0001$) was smaller and birthweight ($b = -0.13$, SE = 0.02, $p < 0.0001$) was lower in newborns of women with GDM who continued smoking compared to newborns of women without GDM who did not smoke.

Conclusions: Although smoking and GDM have opposite effects on fetal growth, the negative effects of exposure to smoking are also seen in newborns of women with GDM. Compared to smoking after the first trimester of pregnancy, cessation of smoking during the first trimester was associated with greater head circumference and birthweight in newborns.

Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus; ICD, International Classification of Diseases; SDP, smoking during pregnancy.

KEYWORDS
birthweight, gestational diabetes, head circumference, perinatal, pregnancy, tobacco

1 | INTRODUCTION

Smoking during pregnancy (SDP) and gestational diabetes mellitus (GDM) both adversely affect pregnancy with several perinatal consequences. Both of the above can be prevented completely or at least partially by lifestyle choices.[1–3] In Finland, an increasing number of pregnant women are overweight, and GDM has become significantly more common. In 2010, only about 7% were diagnosed with GDM, while 21% of pregnant women were diagnosed in 2019.[4] Smoking appears to increase the risk of GDM.[5–7] Despite the well-known risks, approximately one in every 12 pregnant women continues to smoke during pregnancy in Finland, exposing more than 3500 fetuses to maternal smoking annually.[8] Both SDP and GDM increase the risk of preterm delivery, fetal growth disorders and complications during labor.[9–12] In addition to immediate health effects, SDP and GDM have been estimated to have significant consequences on the child's life course.[13,14]

SDP and GDM have opposite effects on fetal growth during pregnancy. Newborns of women who smoke are on average smaller at birth,[15] while GDM is one of the most significant factors causing fetal macrosomia.[1] The background of macrosomia is most commonly hyperinsulinemia, which especially causes enlargement of fat tissue and internal organs. This results in a larger fetal body circumference relative to head size.[10,16,17] Fetal macrosomia predisposes the parturient to complications during childbirth, such as shoulder dystocia, perineal tears, and caesarean section.[18]

When the fetus is exposed to smoking, the child's head and abdominal circumference, height, weight, and femur length are smaller than fetuses unexposed to smoking.[19–21] Smoking affects fetal head growth and brain development, which may predispose to later psychological and neuropsychiatric challenges.[22] The low birthweight of newborns of women who smoke is thought to be due to insufficient oxygenation of the fetus and impaired transfer of nutrients through the placenta. Nicotine is known to constrict uterine arteries, while carbon monoxide binds to hemoglobin, reducing fetal oxygen supply.[23–25] If smoking is continued despite the pregnancy, the fetuses appear to be small throughout the pregnancy, and the connection has been shown to be stronger the more or longer the fetus is exposed to smoking.[9,15,24]

Masalin et al. ($n=4111$) found that in newborns of women with GDM, smoking did not affect birthweight.[6] However, there is no research on the interaction of GDM and SDP on fetal head circumference. Thus, the aim of this study is to evaluate the interaction between smoking and GDM simultaneously on birthweight and head circumference of newborns. Our hypothesis was that, despite possible similar fetal birthweights between newborns born to women with GDM who smoked and those born to women who did not smoke without GDM, the former group would exhibit a smaller head circumference in their newborns.

Key message

Although smoking and gestational diabetes mellitus (GDM) have opposite effects on fetal growth, in our cohort, in the groups of women with and without GDM, maternal smoking after the first trimester was associated with smaller head circumference and birthweight in newborns compared to newborns of women who did not smoke and quit smoking during the first trimester.

2 | MATERIAL AND METHODS

2.1 | Data sources

The research data on newborn and maternal characteristics were derived from the Finnish Medical Birth Register and the Finnish Hospital Discharge Register, which are currently maintained by the Finnish Institute of Health and Welfare (THL). The THL performed an ethical assessment and granted permission to use its confidential register data. Encrypted personal identifiers of mothers were used to combine all registry data. Data links were performed by the statistical authorities, and only de-identified data were provided to researchers outside the THL.

The Medical Birth Register is considered a complete register of all births and newborns in Finland. The register data include all live and stillborn fetuses with a gestational age of at least 22 weeks or with a birthweight of at least 500 g. Register data are collected from all maternity hospitals (hospital births), auxiliary health care personnel (home births), the Central Population Register (missing live births) and the Cause of Death Register (missing stillbirths and infant deaths). The register contains the mother's and newborn's personal identification number; the mother's personal information, including health care, previous pregnancies and deliveries, and interventions during pregnancy and delivery; and neonatal outcome up to 7 days of age. According to data quality studies, most of the content of the register data corresponds well or satisfactorily to the information in the hospital records.[26]

The Hospital Discharge Register includes information on all episodes of inpatient care, including all inpatient stays in public and private hospitals since 1969 and outpatient visits in public hospitals since 1998. The register contains information on the patient's background, procedures, hospital stays and main diagnosis and secondary diagnoses according to the International Classification of Diseases (ICD) code (Eighth Revision [ICD-8] in 1969–1986, Ninth Revision [ICD-9] in 1987–1995 and Tenth Revision [ICD-10] since 1996). ICD-10 classification was used throughout the study period.

A systematic review revealed that the completeness and accuracy of the register range from satisfactory to very good.[27]

2.2 | Study sample

The study population consisted of 835 551 newborns in Finland during the years 2006–2018. Nulliparous women were included in the study. Multiparous women were excluded ($n=487\,399$). Pregnant women diagnosed with pregestational diabetes (ICD-10 codes: O24.0, O24.1, O24.2, and O24.3) ($n=2691$) and women with chronic hypertension ($n=529$) before pregnancy as well as women without data on maternal weight and height ($n=16\,040$) were excluded from the data. The final study population consisted of newborns born to 290 602 primiparous women, who comprised 83.5% of all women who gave birth for the first time and had a singleton pregnancy during the study period.

The information on newborn and maternal background factors were derived from the Finnish Medical Birth Register. Maternal smoking status was self-reported and documented in a structural form at hospitals at time of delivery. SDP was categorized into three groups: no smoking, smoking during the first trimester only (quit smoking) and smoking after the first trimester of pregnancy (continued smoking). Body mass index (BMI) was categorized into five groups: <20 (underweight), 20.0–24.9 (normal weight), 25.0–29.9 (overweight), 30.0–34.9 (obese, class I), and at least 35.0 (obese class II or III). Information on the newborn was also collected: sex, birthweight, and head circumference. We calculated birthweight *z*-score based on Finnish references. Head circumference was calculated as *z*-scores (according to sex and gestational age) within the study cohort. The GDM diagnoses were obtained from the Finnish Medical Birth Register. GDM was defined by the ICD-10 codes O24.4 and O24.9.

2.3 | Statistical analyses

Linear regression models were used to estimate the association between SDP and GDM and the outcomes. In the first model, SDP, GDM, and the covariates were added as the independent variables and head circumference/birthweight as the dependent variable. We added maternal age as a continuous covariate and pre-pregnancy BMI as a categorical covariate into the model. In the second model, SDP and GDM interaction was added to explore whether maternal GDM modifies the association between SDP and head circumference/birthweight. Normal distribution assumption was checked from studentized residuals.

We also performed subgroup analyses by maternal BMI. Women were divided into five groups according to the BMI:

1. <20 (underweight, $n=45\,607$, 15.69%),
2. 20.0–24.9 (normal weight, $n=159\,440$, 54.87%),
3. 25.0–29.9 (overweight, $n=57\,333$, 19.73%),
4. 30.0–34.9 (obese class I, $n=19\,508$, 6.71%), and
5. 35.0 or more (obese classes II and III, $n=8714$, 3.00%).

Information on socioeconomic status was only known in 53.4%, which is why it was not added to the main analyses as a confounding factor. Sensitivity analyzes were performed similarly to the main analyses, but socioeconomic status was added as a confounding factor.

Differences in the results were evaluated by using 95% confidence intervals and *p*-values. The data analysis was performed with commercially available software (SAS, version 9.4; SAS Institute Inc, Cary, North Carolina).

3 | RESULTS

In the study population, 8.0% of women quit smoking during the first trimester of pregnancy and 9.9% continued smoking thereafter. The majority (82.1%) of pregnant women did not smoke during pregnancy. Table 1 presents the characteristics of the participants according to GDM diagnoses and smoking status. The overall prevalence of GDM in this study cohort was 8.9% ($n=25\,948$). Smoking at any time during pregnancy was slightly higher among women with GDM (19.7%) compared to women without GDM (17.7%). The women with GDM were on average older, and those who smoked or had smoked during pregnancy were on average younger.

3.1 | GDM and SDP—Interaction on newborn head circumference

Head circumference was greater in newborns of women with GDM (mean *z*-score = 0.07, $b=0.09$, SE = 0.01, $p<0.0001$) compared to newborns of women without GDM (mean *z*-score = −0.02). Newborns of women who continued smoking after the first trimester had a smaller head circumference (mean *z*-score = −0.13, $b=-0.24$, SE = 0.01, $p<0.0001$) compared newborns of women who did not smoke (mean *z*-score = 0.11). Head circumference of the newborns of those women who quit smoking during the first trimester was slightly smaller (mean *z*-score = 0.09, $b=0.02$, SE = 0.01, $p=0.02$) compared to newborns of women who did not smoke. The mean z-scores, standard error and confidence intervals for head circumference and birthweight are presented in Table 2.

The results of the interaction analyses by SDP and GDM on head circumference are depicted in Figure 1. The interaction between SDP and GDM was statistically significant ($p=0.02$). GDM was significant predictor in the model ($p<0.0001$), such that the head circumference was greater in newborns of women with GDM compared to newborns of women without GDM. Similarly, SDP was statistically significant predictor in the model ($p<0.0001$). Figure 1 depicts the results from the linear regression model estimating the interaction of SDP and GDM on head circumference. The head circumference was statistically significantly smaller in newborns of women with GDM who continued smoking after the first trimester (mean *z*-score = 0.06, $b=-0.13$, SE = 0.01, $p<0.0001$) compared to newborns of women who did not smoke without GDM (mean *z*-score = 0.07, SE 0.003).

TABLE 1 Background characteristics of the study population by GDM and SDP.

	GDM, *n* (%)[a]			Smoking status, *n* (%)				
	Yes	No	*p*-value	No smoking	Quit smoking	Continued smoking	*p*-value	Total, *n* (%)[a]
Total	25 948 (8.93)	264 654 (91.07)		238 539 (82.08)	23 302 (8.02)	28 761 (9.90)		290 602
Maternal age, mean (SD)	29.36 (5.43)	27.60 (5.16)	<0.0001	28.36 (5.00)	25.77 (5.05)	24.31 (5.22)	<0.0001	
Marital status			<0.0003				<0.0001	
Single	221 (0.85)	1719 (0.65)		1448 (0.61)	188 (0.81)	304 (1.06)		1940 (0.67)
Cohabiting	11 797 (45.46)	118 900 (44.93)		119 743 (50.20)	6042 (25.93)	4912 (17.08)		130 697 (44.97)
Married	13 820 (53.26)	142 969 (54.02)		116 369 (48.78)	16 977 (72.86)	23 443 (81.51)		156 789 (53.95)
Unknown	110 (0.42)	1066 (0.40)		979 (0.41)	95 (0.41)	102 (0.35)		1176 (0.40)
Smoking status			<0.0001					
No smoking	20 846 (80.34)	217 693 (82.26)						238 539 (82.08)
Quit smoking	2543 (9.80)	20 759 (7.84)						23 302 (8.02)
Continued smoking	2559 (9.86)	26 202 (9.90)						28 761 (9.90)
GDM							<0.0001	
Yes				20 846 (8.74)	2543 (10.91)	2559 (8.89)		25 948 (8.93)
No				217 693 (91.26)	20 759 (89.09)	26 202 (91.10)		264 654 (91.07)
BMI			<0.0001				<0.0001	
<20	1649 (6.36)	43 958 (16.61)		36 712 (15.39)	3580 (15.36)	5315 (18.48)		45 607 (15.69)
20–24.9	8704 (33.54)	150 736 (56.96)		134 478 (56.38)	11 468 (49.21)	13 494 (46.92)		159 440 (54.87)
25–29.9	7837 (30.20)	49 496 (18.70)		45 947 (19.26)	5268 (22.61)	6118 (21.27)		57 333 (19.73)
30–34.9	4541 (17.50)	14 967 (5.66)		14 969 (6.28)	2005 (8.60)	2534 (8.81)		19 508 (6.71)
35 or more	3217 (12.40)	5497 (2.08)		6433 (2.70)	981 (4.21)	1300 (4.52)		8714 (3.00)
Sosioeconomic status							<0.0001	
Upper white-collar	3074 (7.11)	40 139 (92.89)		40 715 (94.21)	1539 (3.56)	959 (2.22)		43 213 (14.87)
Lower white-collar	7536 (9.36)	72 980 (90.64)		66 979 (83.19)	6916 (8.59)	6621 (8.22)		80 516 (27.71)
Blue-collar	2990 (9.49)	28 600 (90.51)		22 055 (69.80)	3771 (11.93)	5771 (18.26)		31 597 (10.87)
Other/unknown	12 341 (9.12)	122 935 (90.88)		108 790 (80.42)	11 076 (8.19)	15 410 (11.39)		135 276 (46.55)

Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus; SD, standard deviation; SDP, smoking during pregnancy.

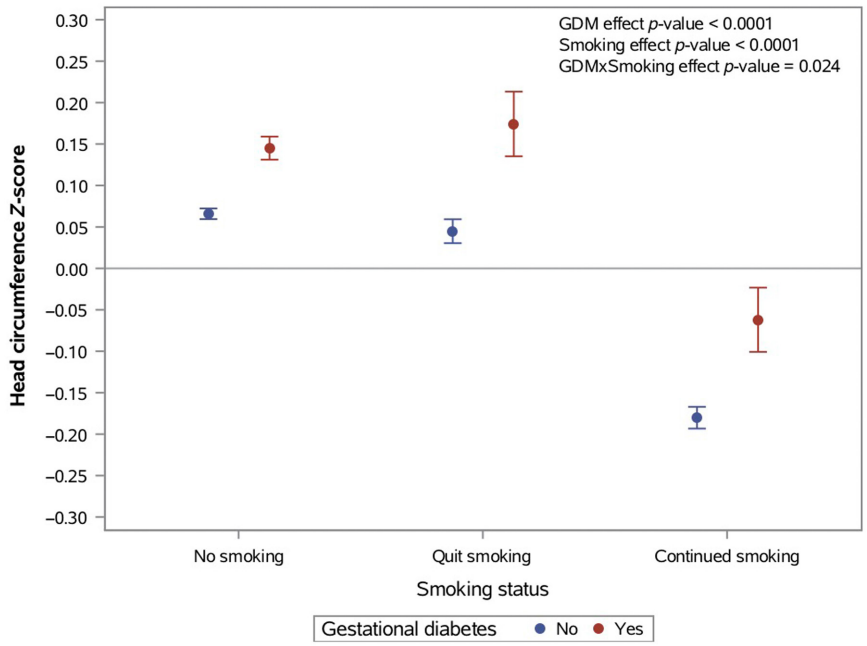
[a]If not stated otherwise.

TABLE 2 Information on the mean *z*-scores, standard error and confidence intervals for head circumference and birthweight by GDM and SDP.

		Head circumference				Birthweight			
SDP	GDM	*n*	Mean *z*-score	SE	95% CI	*n*	Mean *z*-score	SE	95% CI
No	No	214 821	0.066	0.003	0.059 to 0.072	217 649	−0.135	0.003	−0.142 to −0.128
No	Yes	20 518	0.145	0.007	0.131 to 0.159	20 842	−0.029	0.007	−0.043 to −0.015
Quit	No	20 478	0.045	0.007	0.030 to 0.059	20 757	−0.089	0.007	−0.103 to −0.074
Quit	Yes	2498	0.174	0.020	0.135 to 0.213	2543	0.075	0.020	0.035 to 0.115
Continued	No	25 841	−0.180	0.007	−0.193 to −0.167	26 195	−0.463	0.007	−0.476 to −0.450
Continued	Yes	2536	0.062	0.020	−0.101 to 0.023	2558	−0.265	0.020	−0.305 to −0.226

Abbreviations: CI, 95% confidence interval; GDM, gestational diabetes mellitus; SDP, smoking during pregnancy; SE, standard error.

FIGURE 1 The results from the linear regression model estimating the interaction of smoking during pregnancy and gestational diabetes mellitus (GDM) on head circumference.



3.2 | GDM and SDP—Interaction on newborn birthweight

Birthweight was greater in newborns of women with GDM (mean *z*-score = −0.07, *b* = 0.16, SE = 0.01, $p < 0.0001$) compared to newborns of women without GDM (mean *z*-score = −0.23, Table 2). The birthweight of newborns of women who continued smoking after the first trimester was lower (mean *z*-score = −0.36, *b* = −0.28, SE = 0.01, $p < 0.0001$) compared to the newborns of women who did not smoke (mean *z*-score = −0.082). The birthweight of the newborns of those women who quit smoking during the first trimester was higher (mean *z*-score = −0.01, *b* = 0.08, SE = 0.01, $p = 0.53$) compared to newborns of women who did not smoke (mean *z*-score = −0.08) and newborns of women who continued smoking after the first trimester (mean *z*-score = −0.36).

The results of the interaction analyses by SDP and GDM on birthweight are depicted in Figure 2. The interaction between SDP and GDM was statistically significant ($p < 0.0001$). GDM was associated with increased newborn birthweight in all smoking groups ($p < 0.0001$). SDP was statistically significant predictor in the model ($p < 0.0001$). Figure 2 depicts the results from the linear regression model estimating the interaction of SDP and GDM on birthweight. The birthweight of newborns was statistically significantly lower in the group of women with GDM who continued smoking after the first trimester (*b* = −0.13, SE = 0.02, $p < 0.0001$) compared to newborns of women without GDM who did not smoke.

3.3 | Sensitivity analyses

Supporting Information contain information on the interaction of maternal SDP and GDM on head circumference (Figures S1–S5) and on birthweight (Figures S6–S10) according to the BMI categories. In the group of women with normal weight (BMI 20–24.9), the confidence intervals for newborn head circumference overlap between

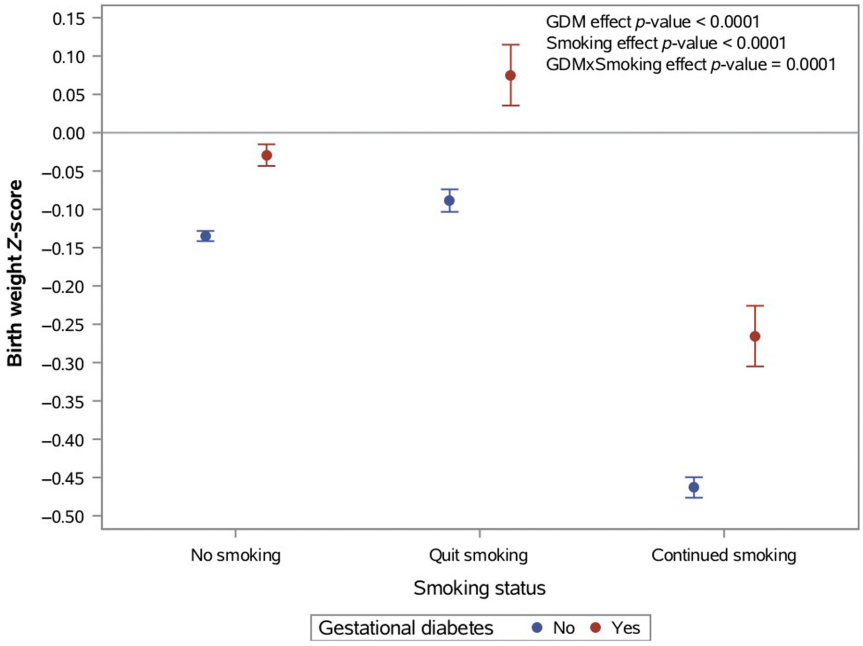


FIGURE 2 The results from the linear regression model estimating the interaction of smoking during pregnancy and gestational diabetes mellitus (GDM) on birthweight.

women who did not smoke without GDM and women who smoked with GDM. The confidence intervals in the latter group are notably wider due to the limited number of normal-weight smokers with GDM. However, the primary observed trend remains statistically significant and valid.

The results remained similar and valid ($n = 155\,326$) when socioeconomic status was added into the model (Figures S11 and S12). The only observed difference was that in interaction between maternal SDP and GDM in relation to head circumference was not significant ($p = 0.0886$).

4 | DISCUSSION

In our national cohort, newborns exposed to smoking after the first trimester had on average smaller head circumference and birthweight among newborns born to both women with GDM and those without GDM. Newborns of women with GDM exposed to smoking after the first trimester had larger head circumference and birthweight compared to newborns of women who smoked after the first trimester without GDM. In contrary to a previous study by Masalin et al.,[6] newborns exposed to smoking after the first trimester were found to have a lower birthweight, as well as a smaller head circumference in newborns born to both women with and without GDM, compared to newborns whose mothers did not smoke or quit smoking during early pregnancy. Thus, the continuation of smoking during pregnancy was associated with reduction in the head growth of newborns and is associated with lower birthweight in both women with and without GDM. The results remained similar in the sensitivity analyses by BMI groups and when adjusted with socioeconomic status.

In our study, newborns exposed to smoking after the first trimester was associated with statistically significant smaller head circumference compared to newborns of women who did not smoke. The same finding is also described in the previous literature.[19,20] A smaller head circumference has been shown to be directly related to a smaller brain volume,[28,29] and differences has also been shown to persist into adulthood.[22,30] Newborns of women with GDM who continued smoking after the first trimester had statistically significant smaller head circumference compared to newborns of women who did not smoke and newborns of women who quit smoking during the first trimester of pregnancy. Thus, quitting smoking during the first trimester may be associated with reduction in adverse association with birthweight and head circumference compared to smoking after the first trimester. If women had GDM but smoked after the first trimester, the newborn head circumference was smaller than the head circumference of newborns of women without GDM who did not smoke.

In this study, women who smoke more often had GDM. The same phenomenon has been reported in earlier studies.[5–7] Our study found that GDM was associated with increased birthweight regardless of maternal smoking status. In addition, the birthweight of the newborns born to women who smoke with GDM was lower compared to the newborns of women who did not smoke and did not have GDM. Contrary to our results, Masalin et al. found in an observational cohort study encompassing 4111 Finnish primiparous women that if pregnancy was complicated by GDM, newborn birthweight was not affected by smoking after the first trimester.[6] Study by Victora et al. ($n = 60\,206$) found that GDM protected the newborns from low birthweight but not from short stature.[31] In our study, we used a larger national register dataset compared to these studies, which may partially explain the differences in the results. Although we observed that newborns born to women with GDM who smoked after the first trimester of pregnancy was associated with lower birthweights than women with GDM who did not smoke, and thus the risk of macrosomia might be lower, we

emphasize the importance of smoking cessation for all women. Continuing to smoke is undeniably harmful for both the mother and offspring.[13,14,32]

We found that smoking was not associated with negative impact the growth of the newborns who were exposed to smoking only during the first trimester of pregnancy. However, within the group of women with GDM, the newborns of women who quit smoking had a higher birthweight compared to the newborns of women who did not smoke. We speculate that this observation could be attributed to differences between these women who successfully quit smoking and women who did not smoke. Factors such as a higher prevalence of overweight and obese among smokers or other lifestyle considerations may contribute to this disparity.

The strength of this study stems from its extensive use of national registry data, encompassing nearly 95% of all first-time mothers with singleton pregnancies over a 14-year period. Our dataset provided comprehensive information on maternal background, so that we could exclude women with pre-pregnancy diabetes and chronic hypertension diagnoses from the analyses.

However, a notable limitation of this research lies in the reliance on self-reported data for smoking habits, potentially introducing inaccuracies. We also lacked data on the quantity of cigarettes smoked, which hindered a comprehensive assessment of fetal exposure to harmful substances. It is worth noting that previous research suggests that individuals tend to underreport their smoking habits,[33–35] which, in turn, may lead to an underestimation of the impact of maternal smoking on fetal growth. In the study data, the prevalence of smoking was 18%. This is higher compared to the average smoking prevalence of 15% among pregnant women in Finland, which is explained by inclusion of only primiparous women who are known to smoke more often during pregnancy.[36] The research material includes only first-time pregnant women, who are younger and known to smoke more than those who gave birth again.[36] Unfortunately, the registry data do not contain information on paternal smoking, thus we could not control for passive smoking exposure during pregnancy.

Another limitation is that there was no specific information on establishing the diagnosis of GDM, whether it was based on an oral glucose tolerance test or abnormal fasting glucose values. In addition, there was no individualized information on the treatment of GDM. There was only information on the treatment of GDM based on a survey by the Finnish Diabetes Association.[37] According to the survey, GDM was found in 59% of pregnant women already during their first pregnancy. 82% of gestational diabetes was treated with diet without medication. In addition to diet therapy, 8% had metformin, 11% insulin and 8% had insulin and metformin combination therapy.[37] Despite potential treatment, women diagnosed with GDM had statistically significant differences in outcomes compared to women without GDM. The prevalence of GDM in our study was 8.9%, which is lower than the current prevalence of 20.6%. This is due to the longitudinal design of this study, as the prevalence of GDM has doubled in the last decade and the proportion of obese (BMI ≥30) women giving birth has increased from 11% to 19.5% from 2005 to 2022.[38] Unfortunately, the Medical Birth Register does not contain information on the women's weight gain during pregnancy, dietary intake or physical activity, which would serve us more detailed information about risk factors for GDM during pregnancy. We performed sensitivity analyses using socioeconomic status as a confounder, which was only available for about half of the data. Unavailability of data on several important confounders suggest that there is a possibility of potential residual confounding in our observation and results should be interpreted with caution.

During pregnancy, women are highly motivated to change their lifestyles.[39,40] Therefore, providing them with research-backed information and education about the potential associations with fetal harms and complications associated with SDP and GDM may support them towards positive lifestyle changes. In the future, there is a need to study the interaction of GDM and SDP on the risk for prematurity and other pregnancy complications.

5 | CONCLUSION

Although smoking and gestational diabetes have opposite effects on fetal growth, our study found that whether the woman had GDM or not, maternal smoking after the first trimester was associated with smaller head circumference and birthweight in newborns compared to newborns of women who did not smoke or quit smoking during the first trimester. Further research is needed in the future to support the findings where confounding factors have been taken into account more comprehensively.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Mikael O. Ekblad and Mika Gissler. The first draft of the manuscript was written by Lotta S. Holopainen. Lotta S. Holopainen and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are not publicly available due to data protection regulations, but similar data can be applied from the Finnish Social and Health Data Permit Authority Findata (https://findata.fi/en/).

ETHICS STATEMENT

Our research does not require a separate permission from the ethics committee, because the material is based on anonymous or

pseudonymised material and data subjects are not contacted. As our study used routinely recorded administrative health records, informed consent was not required. THL Finnish Institute for Health and Welfare performed the ethical review and granted the permission to use its confidential register data.

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SUPPORTING INFORMATION

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

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