Original Article

OPEN

New theory about the pathophysiology of preeclampsia derived from the paradox of positive effects of maternal smoking

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Objective: The aim of this study was to evaluate if maternal height affects the link between the inverse association on smoking during pregnancy and preeclampsia.

Study design: The study population consisted of all women with singleton pregnancies ($n = 803\,698$) in Finland during the years 2004–2018, excluding women with unknown smoking and diagnosis of prepregnancy chronic hypertension. Information on smoking and background factors were derived from the Finnish Medical Birth Register. Smoking was categorized in three classes: no, quitted in the first trimester and continued throughout the pregnancy. Information on preeclampsia was derived from the Finnish Hospital Discharge Register and the Finnish Medical Birth Register. Multiple logistic regression models were used to estimate first the association between smoking and preeclampsia, and finally whether maternal height modified the association.

Results: In the standard comparison, we found evidence of an association between preeclampsia and continued smoking [adjusted odds ratio = 0.74, 95% confidence interval (95% CI) = 0.67–0.81], but no association was found between quitted smoking and preeclampsia. Thus, the interaction of continued smoking and maternal height by *z*-scores was estimated. Among taller mothers, continued smoking was associated with a higher risk for preeclampsia than in smoking mothers with average height ($\beta = 0.33$, SE = 0.14, $P = 0.02$).

Conclusion: Our results partly challenge the smoking-preeclampsia paradox: smoking seems not to protect tall mothers against preeclampsia. We speculate the findings through a new theory about the pathophysiology of preeclampsia. It seems that tall pregnant smokers must raise their blood pressure aggressively to ensure perfusion in the dysfunctional placenta.

Keywords: body, exposure, height, maternal, population register, preeclampsia, smoking

Abbreviations: BP, blood pressure; ICD, International Classification of Diseases; SDP, smoking during pregnancy

INTRODUCTION

Preeclampsia affects around 5% of all pregnancies and it is associated with a significantly increased risk for both maternal and neonatal morbidity and mortality [1,2]. The presence of elevated blood pressure (BP) and proteinuria are the main diagnostic criteria for preeclampsia [1]. For example, prepregnancy hypertension, type 2 diabetes and overweight predispose to preeclampsia [3–5]. In contrast, maternal smoking throughout pregnancy has paradoxically been associated with a lower risk for preeclampsia [6,7].

Smoking during pregnancy (SDP) has many detrimental effects on maternal and child health, but still on average 6–8% of women continue to SDP in the American and European region [8]. Up to every other young and low educated women continue to SDP [9]. In our previous study, we showed that women who SDP have greater rates of both outpatient and inpatient hospital care during pregnancy for various reasons [10]. SDP has been linked strongly with preterm birth and low birth weight as well as long-term adverse pulmonary and neurodevelopmental outcomes [11–15]. The reason why SDP is inversely associated with preeclampsia is largely unknown.

A previous study by Ness *et al.* [16] found that the inverse association between SDP and preeclampsia was not observed among smoking women who were overweight/obese (BMI $\geq 25\,kg/m^2$). However, previous studies have not considered if maternal height modifies the association between SDP and preeclampsia. It has been shown that low height is associated with higher BP among general

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adult population as well as among pregnant women [17,18]. Thus, a Danish National Birth Cohort study showed that taller individuals have a lower risk for preeclampsia than for shorter women [19]. Bourgeois *et al.* [20] found that even though greater height associated with lower SBP and pulse pressure, it was also associated with higher DBP among USA adult population. In fact, higher baseline DBP has been showed to associate with a higher risk for preeclampsia [21].

The aim of this study was to investigate if maternal height affects the link between SDP and preeclampsia. We hypothesized that maternal height modifies this association, such that SDP does not associate with lower risk for preeclampsia in all height groups of pregnant women. The secondary aim was similarly to investigate the association between SDP and gestational hypertension.

MATERIALS AND METHODS

Data sources

Data from the Finnish Medical Birth Register and the Finnish Hospital Discharge Register were used in this study. The Finnish Institute for Health and Welfare (THL), which is the current register keeper, performed the ethical evaluation and granted the permission to use their confidential health register data, as required by national data-protection legislation. Pregnant mother's unique personal identification number was used to combine all register data. The data linkages were performed by the statistical authorities and only unidentifiable data were provided for the researchers outside the Finnish Institute for Health and Welfare.

The Medical Birth Register includes all live births and stillbirths of foetuses with a gestational age of 22 weeks or more or with a birth weight of 500 g or more. The register keeper collects the data from all delivery hospitals and, in the case of home births, from the assisting healthcare personnel. The register includes information on the mother's and the child's identification numbers; maternal background, healthcare and interventions during pregnancy and delivery; and the newborn's outcome until 7 days of age. The Medical Birth Register is considered to be a complete record of all births and newborns in Finland. Most of the register content corresponds well or satisfactorily with hospital record data according to two data quality studies [22,23].

The Hospital Discharge Register includes information on all episodes of inpatient care (including all hospitalizations requiring an overnight stay) in public and private hospitals since 1969 and outpatient visits in public hospitals since 1998. The register contains information on the patient's background, hospitalization period, procedures and the main diagnosis as well as up to two other diagnoses by International Classification of Diseases (ICD) code (Eight Revision [ICD-8] in 1969–1986, Ninth Revision [ICD-9] in 1987–1995 and Tenth Revision [ICD-10] since 1996). A systematic review showed that the completeness and accuracy of the register range from satisfactory to very good [24].

Study sample

The study population consisted of all pregnant women with singleton pregnancies ($n = 827\,894$) in Finland between the years 2004 and 2018. The follow-up began in year 2004 because the collection of BMI began at that year. ICD-10 classification was used during the whole study period. The information on SDP was missing from 24 196 (2.9%) singleton pregnancies, which were excluded from the statistical analysis. Women with prepregnancy diagnosis of chronic hypertension (ICD-10 codes: O10 and O11) were excluded ($n = 7657$) as was done in a previous Swedish register-based study on SDP and preeclampsia [25]. The final study population consisted of 803 698 pregnant women (97.1% of all singleton pregnancies during the study period).

Information on SDP and other background factors (maternal age, parity, marital status, prepregnancy BMI and duration of pregnancy) were derived from the Finnish Medical Birth Register. Midwives collected smoking information from the mothers during antenatal care. SDP was categorized into three groups: no smoking/smoking during the first trimester (quitted smoking)/ smoking after the first trimester of pregnancy (continued smoking).

The characteristics of the study population by maternal smoking, no smoking/quitted smoking/ continued smoking is presented in Table 1.

Outcome diagnoses

Information on preeclampsia and gestational hypertension without preeclampsia was derived from the Finnish Hospital Discharge Register and the Finnish Medical Birth Register. ICD-10 diagnostic codes O10-O15 regarding oedema, proteinuria and hypertensive disorders in pregnancy, childbirth and the puerperium for each pregnancywere obtained from year 2004 through 2018. In this study, preeclampsia was defined by ICD-10 codes O14 and O15. The national diagnostic criteria of preeclampsia include a rise in BP ($\geq$140/90 mmHg) combined with proteinuria ($\geq$0.5 g/ 24 h) occurring after 20 weeks of gestation. Gestational hypertension was defined by ICD-10 code O13.

Statistics

Logistic regression models were used to estimate the association between SDP and the outcomes. In the unadjusted model (Model 1), preeclampsia/gestational hypertension was added as the independent variable and SDP as the dependent variable. In the adjusted model (Model 2), we added the maternal age and parityas continuous covariates, year ofdeliveryand prepregnancyBMI as a categorical, and preterm birth as a binominal covariate into the model. This model can be thought of as an approximation of the standard comparison seen in the literature.

Finally, SDP $\times$ height was added in the Model 3 to explore whether maternal height modifies the association between SDP and preeclampsia/gestational hypertension. We also performed subgroup analyses by maternal height. Mothers were divided into three groups according to the z-score of height:

1. *Z*-score below −1 ('low height', height below 159 cm, $n = 119\,958$, 14.8%)
2. *Z*-score from −1 to 1 ('average height', height between 159 and 171 cm, $n = 559\,948$, 69.0%), and
3. *Z*-score over 1 ('high height', height over 171 cm, $n = 131\,714$, 16.2%).

TABLE 1. Characteristics of the study population by smoking information

	No smoking, *n* (%)	Quitted smoking, *n* (%)	Continued smoking, *n* (%)	Missing information of smoking, *n* (%)	*P*
All	683 122 (82.51%)	44477 (5.37%)	76 099 (9.19%)	24 196 (2.92%)	
Maternal age (years)					
Less than 20	8919 (1.31%)	2417 (5.43%)	6247 (8.21%)	581 (2.40%)	<0.001
20–34	532 975 (78.02%)	37 373 (84.03%)	60 303 (79.24%)	18 410 (76.09%)	
35–39	114 554 (16.77%)	3934 (8.85%)	7592 (9.98%)	4148 (17.14%)	
40 or more	26 674 (3.90%)	753 (1.69%)	1957 (2.57%)	1057 (4.37%)	
Parity					
0	218 440 (31.98%)	18852 (42.39%)	22 169 (29.13%)	6376 (26.35%)	<0.001
1	208 796 (30.56%)	12 007 (27.00%)	19 420 (25.52%)	7139 (29.50%)	
2–3	184 442 (27.00%)	10222 (22.98%)	22 589 (29.68%)	7152 (29.56%)	
4 or more	71 325 (10.44%)	3393 (7.63%)	11 896 (15.63%)	3182 (13.15%)	
Unknown	119 (0.02%)	3 (0.01%)	25 (0.03%)	347 (1.43%)	
Marital status					
Married/cohabiting	673 630 (98.61%)	43 699 (98.25%)	73 968 (97.20%)	23 366 (96.57%)	<0.001
Single	7147 (1.05%)	595 (1.34%)	1857 (2.44%)	460 (1.90%)	
Unknown	2345 (0.34%)	183 (0.41%)	274 (0.36%)	370 (1.53%)	
BMI (kg/m^2)					
Less than 20	87 957 (12.88%)	6041 (13.58%)	11 773 (15.47%)	2315 (9.57%)	<0.001
20.0–24.9	349863 (51.22%)	20 657 (46.44%)	31 828 (41.82%)	8544 (35.31%)	
25.0–29.9	143 171 (20.96%)	10396 (23.37%)	16 875 (22.18%)	3878 (16.03%)	
30.0–34.9	51 309 (7.51%)	4317 (9.71%)	7833 (10.29%)	1535 (6.34%)	
35.0 or more	24 220 (3.55%)	2270 (5.10%)	4342 (5.71%)	750 (3.10%)	
Unknown	26 602 (3.89%)	796 (1.79%)	3448 (4.53%)	7174 (29.65%)	
Duration of pregnancy					
Preterm delivery (<37 weeks)	28 849 (4.22%)	1985 (4.46%)	4328 (5.69%)	1751 (7.24%)	<0.001
Term delivery (≥37 weeks)	654 273 (95.78%)	42 492 (95.54%)	71 771 (94.31%)	22 445 (92.76%)	

Sensitivity analyses were performed with subgroups of mothers with term delivery ($n = 790\ 981$) and preterm delivery ($n = 36\ 913$).

The data analysis was performed using commercially available software (SAS, version 9.4; SAS Institute Inc., Cary, North Carolina, USA). Differences in the results were evaluated by using 95% confidence intervals (95% CIs) and *P* values. Nonoverlapping CIs and *P* values less than 0.05 were considered to be significant.

RESULTS

The characteristics of the study population by smoking exposure are summarized in Table 1. Majority, 83%, of the mothers did not smoke during pregnancy. A total of 5% of the population quitted smoking during the first trimester of pregnancy and 9% continued to smoke thereafter. Smoking information was missing of 3% of the population.

The association of smoking during pregnancy on preeclampsia

In the unadjusted model (model 1), quitting SDP during the first trimester was associated with an increased risk for preeclampsia, but continued SDP was associated with lower rates of preeclampsia. In the adjusted model (model 2), continued smoking associated with lower risk for preeclampsia ($\beta = -0.30$, SE = 0.05, $P < 0.001$) in the whole population when the analyses were adjusted by maternal age, parity, BMI and duration of pregnancy (Table 2). The odds for preeclampsia were 0.74 (95% CI = 0.67–0.81) for mothers who continued smoking compared with nonsmokers (Table 3). No such association was seen between quitted smoking and preeclampsia. BMI was a significant predictor of preeclampsia, such that women with higher BMI had a higher risk for preeclampsia.

The effect of maternal height on the association between smoking during pregnancy and preeclampsia

In the standard comparison, we found evidence of an association between preeclampsia and continued smoking, but not with quitting smoking. Thus, we estimated only the interaction of continued smoking and maternal height (low, average and high) in model 3. The results show that among taller mothers continued smoking was associated with a higher risk for preeclampsia than smoking mothers with average height ($\beta = 0.33$, SE = 0.14, $P = 0.02$, Table 2). Table 3 summarizes the association between maternal smoking and the risk for preeclampsia within subgroups according to maternal height. Continued smoking associated with lower risk for preeclampsia among low and average height, but not among taller mothers [odds ratio (OR) = 0.98, CI = 0.76–1.28].

Sensitivity analyses according to the duration of pregnancy

The results remained in the sensitivity analyses (model 2) with subgroup of mothers with term and preterm deliveries (Table 4). The analyses (model 3) also showed that among taller mothers with term delivery continued smoking was associated with a higher risk for preeclampsia compared to smoking mothers with average height ($\beta = 0.38$, SE = 0.17, $P = 0.02$). However, in the subgroup of mothers with

TABLE 2. The results from the logistic regression model estimating the association between SDP and the risk for preeclampsia and the interaction effects SDP x maternal height (low, average, high) on preeclampsia

	Model 1			Model 2			Model 3		
	β	SE	*P*	β	SE	*P*	β	SE	*P*
Intercept	−4.88	0.01	<0.001*	−4.88	0.08	<0.001*	−4.93	0.08	<0.001*
Continued smoking	−0.18	0.05	<0.001*	−0.30	0.05	<0.001*	−0.35	0.06	<0.001*
Quitted smoking	0.15	0.05	0.005*	0.02	0.05	0.762	0.02	0.12	0.892
Maternal age				−0.01	<0.01	<0.001*	<−0.01	<0.01	0.004**
Parity				−0.28	0.01	<0.001*	−0.28	0.01	<0.001*
Year of delivery									
2004–2008				0.30	0.03	<0.001*	0.31	0.03	<0.001*
2009–2013				0.08	0.03	0.020**	0.08	0.03	0.020**
2014–2018				ref			ref		
BMI less than 20				−0.24	0.05	<0.001*	0.24	0.05	<0.001*
20–24.9				ref			ref		
25–29.9				0.37	0.03	<0.001*	0.37	0.03	<0.001*
30–34.9				0.71	0.04	<0.001*	0.71	0.04	<0.001*
35 or more				1.02	0.05	<0.001*	1.03	0.05	<0.001*
Preterm delivery				2.40	0.03	<0.001*	2.41	0.03	<0.001*
Continued SDP*Low height							0.02	0.12	0.892
Continued SDP*Average height							ref		
Continued SDP*High height							0.33	0.14	0.019**

SDP, smoking during pregnancy; SE, standard error.
*$P < 0.001$.
**$P < 0.05$.

TABLE 3. The association between maternal smoking and risk for preeclampsia by maternal height

	No smoking		Quitted smoking		Continued smoking	
	n (per 1000)	OR (95% CI)	*n* (per 1000)	OR (95% CI)	*n* (per 1000)	OR (95% CI)A
All	5144 (7.5)	ref	388 (8.7)	1.02 (0.91–1.13))	481 (6.3)	0.74 (0.67–0.81)*
Z-score of height						
<−1	879 (9.1)	ref	61 (9.0)	0.88 (0.68–1.15)	97 (7.3)	0.75 (0.60–0.93)**
−1 to 1	3487 (7.5)	ref	268 (8.7)	1.02 (0.90–1.16)	310 (6.0)	0.70 (0.62–0.79)*
>1	692 (6.2)	ref	57 (8.6)	1.20 (0.91–1.58)	68 (6.9)	0.98 (0.76–1.28)

Adjusted by maternal age, parity, year of delivery, BMI and duration of pregnancy in the logistic regression analyses.
*$P < 0.001$.
**$P < 0.05$.

TABLE 4. Sensitivity analyses according to the duration of pregnancy: association between maternal smoking and risk for preeclampsia by maternal height

	No smoking		Quitted smoking		Continued smoking	
Term delivery	***n* (per 1000)**	**OR (95% CI)**	***n* (per 1000)**	**OR (95% CI)**	***n* (per 1000)**	**OR (95% CI)**
All	3484 (5.3)	ref	269 (6.3)	1.04 (0.92–1.18)	314 (4.4)	0.77 (0.68–0.86)**
Z-score of height						
<−1	579 (6.3)	ref	43 (6.7)	0.97 (0.71–1.33)	65 (5.3)	0.86 (0.66–1.12)
−1 to 1	2339 (5.3)	ref	186 (6.3)	1.05 (0.90–1.22)	196 (4.0)	0.70 (0.60–0.81)**
>1	489 (4.5)	ref	38 (6.0)	1.13 (0.81–1.58)	48 (5.1)	1.04 (0.76–1.41)
Preterm delivery	***n* (per 1000)**	**OR (95% CI)**	***n* (per 1000)**	**OR (95% CI)**	***n* (per 1000)**	**OR (95% CI)**
All	1660 (57.5)	ref	119 (59.9)	0.96 (0.79–1.16)	167 (38.6)	0.69 (0.58–0.81)**
Z-score of height						
<1	300 (60.5)	ref	18 (48.4)	0.72 (0.44–1.18)	32 (35.3)	0.58 (0.39–0.84)**
−1 to 1	1148 (59.8)	ref	82 (61.3)	0.96 (0.76–1.21)	114 (40.4)	0.69 (0.57–0.85)**
>1	203 (49.4)	ref	19 (72.5)	1.42 (0.86–2.33)	20 (41.8)	0.85 (0.52–1.39)

Adjusted by maternal age, parity, year of delivery and BMI in the logistic regression analyses.
*$P < 0.001$.
**$P < 0.05$.

TABLE 5. The results from the logistic regression model estimating the association between SDP and the risk for gestational hypertension and the interaction effects SDP x maternal height (low, average, high) on gestational hypertension

	Model 1			Model 2			Model 3		
	β	SE	*P*	β	SE	*P*	β	SE	*P*
Intercept	−3.57	0.01	<0.001*	−4.22	0.04	<0.001*	−4.23	0.04	<0.001*
Continued smoking	−0.05	0.02	0.03**	−0.08	0.02	0.001**	−0.07	0.03	0.02**
Quitted smoking	0.31	0.03	<0.001*	0.24	0.03	<0.001*	0.23	0.03	<0.001*
Maternal age				0.01	<0.01	<0.001*	0.02	<0.01	<0.001*
Parity				−0.14	<0.01	<0.001*	−0.14	<0.01	<0.001*
Year of delivery									
2004–2008				0.16	0.02	<0.001*	0.19	0.02	<0.001*
2009–2013				0.06	0.02	0.004**	0.06	0.02	0.004
2014–2018				ref			Ref		
BMI									
less than 20				−0.36	0.03	<0.001*	−0.39	0.03	<0.001*
20–24.9				ref					
25–29.9				0.57	0.02	<0.001*	0.54	0.02	<0.001*
30–34.9				1.06	0.02	<0.001*	1.04	0.02	<0.001*
35 or more				1.45	0.02	<0.001*	1.43	0.02	<0.001*
Preterm delivery				0.53	0.03	<0.001*	0.54	0.03	<0.001*
Continued SDP*Low height							−0.05	0.07	0.44
Continued SDP*Average height							Ref		
Continued SDP*High height							0.02	0.07	0.81
Quitted SDP*Low height							−0.06	0.08	0.44
Quitted SDP*Average height							Ref		
Quitted SDP*High height							0.12	0.07	0.09

SDP, smoking during pregnancy; SE, standard error.
*$P < 0.001$.
**$P < 0.05$.

preterm birth, there was no interaction between continued smoking and maternal height on the risk for preeclampsia ($\beta = 0.20$, SE = 0.27, $P = 0.46$).

The association on smoking during pregnancy and gestational hypertension

The results for the association between SDP and gestational hypertension are summarized in Table 5. In the adjusted model (model 2), continued smoking associated with a lower risk for gestational hypertension ($\beta = -0.08$, SE = 0.07, $P = 0.001$). In contrary, quitted smoking associated with a higher risk for gestational hypertension ($\beta = 0.24$, SE = 0.03, $P < 0.001$). Similarly, as with preeclampsia, we estimated the interaction of quitted and continued smoking and maternal height (low, average and high) in model 3. The results show no significant associations between maternal smoking and the risk for gestational hypertension within subgroups according to maternal height (Table 5).

The odds for gestational hypertension were 1.28 (95% CI = 1.21–1.35) for mothers who quitted smoking and 0.92 (95% CI = 0.88–0.97) for mothers who continued smoking compared with nonsmokers (Table 6). No differences were observed between smoking and gestational hypertension according to height groups.

DISCUSSION

To our knowledge, this is the first study that has considered the effect of maternal height on the association between SDP and preeclampsia. Our study showed that maternal height affects the paradoxical link between SDP and lower risk for preeclampsia. SDP seemed to lower risk only among mothers with low or average height, but not among taller mothers. This was also seen in the sensitivity analyses that also considered duration of pregnancy.

The previously observed paradoxical link between continued SDP and lower risk for preeclampsia, as well as

TABLE 6. The association between maternal smoking and risk for gestational hypertension by maternal height

	No smoking		Quitted smoking		Continued smoking	
	n (per 1000)	OR (95% CI)	*n* (per 1000)	OR (95% CI)	*n* (per 1000)	OR (95% CI)
All	18 797 (27.5)	ref	1649 (37.1)	1.28 (1.21–1.35)*	1988 (19.8)	0.92 (0.88–0.97)**
Z-score of height						
<−1	2666 (27.6)	ref	226 (33.5)	1.21 (1.05–1.39)**	322 (24.3)	0.91 (0.81–1.03)
−1 to 1	13 002 (28.1)	ref	1145 (37.1)	1.24 (1.17–1.32)*	1 390 (27.0)	0.94 (0.89–0.99)**
>1	3064 (27.3)	ref	277 (41.7)	1.38 (1.22–1.57)*	270 (27.4)	0.91 (0.80–1.04)

Adjusted by maternal age, parity, year of delivery, BMI and duration of pregnancy.
*$P < 0.001$.
**$P < 0.05$.

gestational hypertension, was also seen in our study. Some previous studies have shown that women who quitted smoking during early pregnancy seem to have, in contrast, an increased risk for preeclampsia [26]. Our results showed similar findings for gestational hypertension but for preeclampsia only in the unadjusted model (Table 2). It has been speculated that carbon monoxide might mediate the inverse association between SDP and preeclampsia by inhibiting placental production of antiangiogenic proteins, placental apoptosis and necrosis [27]. Carbon monoxide is also a known vasodilator [28]. Wikström *et al*. [25] showed that the lower risk for preeclampsia was only seen in smokers, but not among snuff users. Therefore, tobacco combustion products are the probable protective ingredients against preeclampsia in cigarette smoke rather than nicotine.

However, our results imply that SDP does not 'protect' tall smoking mothers against preeclampsia. We speculate this finding with recent study results and basic physiology as follows. The uterine spiral arteries supply oxygenated blood to the placenta and foetus. During a normal pregnancy, the walls of the spiral arteries lose smooth muscle cells and elastic lamina, and are transformed from small, high-resistance muscular arteries into large, high-flow vessels [29]. In pregnancies complicated by preeclampsia, this transformation is not successful. The spiral arteries retain their muscle walls and small diameters, which has been shown to be associated with abnormal uterine and umbilical artery Doppler patterns and adverse pregnancy outcomes [30]. Furthermore, it has been demonstrated that the lumens of the spiral arteries in preeclampsia are narrowed by 'acute atherosis' referring to the fact that atherosis develops rapidly during the few months of pregnancy [31]. Thus, the initiating pathophysiology of preeclampsia may lie in the spiral arteries too narrow to supply enough blood to the growing placenta and foetus. This theory is in line with the older studies implying that decreased uterine placental perfusion has a major role in the development of preeclampsia [32–34].

The law of Poiseuille states that blood flow through a vessel for a given pressure difference increases in proportion to the fourth power of the diameter of the vessel lumen. It is well known that taller individuals have larger arterial lumen diameters than shorter persons [35,36]. Thus, the larger the arterial lumen diameter is, the lower is BP needed to ensure organ perfusion. Indeed, it has been demonstrated that taller women have a lower risk for preeclampsia than for shorter women [19]. But if the remodelling of the spiral arteries fails, BP has to be raised to ensure a sufficient flow through the narrow spiral artery lumens in the early stage of preeclampsia. As a potent vasodilator, carbon monoxide may relax the muscle walls of the spiral arteries and thus promote placental perfusion without the need to raise BP rapidly. For taller women, who physiologically have lower BP, this controversial aid from SDP may not be enough to support placental perfusion, and they have to raise BP more and more quickly than shorter pregnant women. It is known that increased sympathetic tone [37,38] and elevated levels of endothelin 1 [32,34,39] occur at the onset of preeclampsia. Agonistic autoantibodies to the angiotensin II type 1 receptor (AT1-AAs) also develop in women with preeclampsia promoting hypertension by vasoconstriction and renal sodium reabsorption [32,40,41]. It seems logical that these compensatory mechanisms have to be accelerated more aggressively by the taller than shorter smoking mothers. We speculate that this might lead to a vicious cycle of events given that the spiral arteries with muscular walls can maintain their responsiveness to vasoconstrictive substances. The ischemic placenta, in turn, synthesizes and releases vasoactive factors and cytokines into the maternal circulation inducing activation/dysfunction of the vascular endothelium [32,33,42,43]. The finding that maternal height did not affect the association between SDP and gestational hypertension with presumably remodelled, large spiral arteries, supports our theory.

Strengths and limitations

The strength of this study is the use of Finnish health registers, which are shown to be reliable for research purposes [22,23]. Our data cover information of all singleton pregnancies between the years 2004 and 2018. In addition, we were able to adjust for a wide range of maternal background factors, including prepregnancy BMI, and women with prepregnancy hypertension were excluded from the study. Unfortunately, the registers do not contain reliable information on maternal alcohol or illicit drug use.

The main limitation of our study is that SDP was based on maternal self-report, which is known to underestimate the true prevalence of SDP. However, the information on SDP from the medical birth register has been shown to be in excellent agreement with data from a Finnish survey[44]. The data contained information on timing of SDP, which is a significant strength. Another limitation is that preeclampsia diagnoses were set in variety of hospitals, and we lack information on maternal BP values or the amount of proteinuria, which have led to the diagnosis of preeclampsia. The diagnostic criteria of preeclampsia are the same across the country, so there is no reason to assume systematic bias between the groups. Another limitation of this study is that the study period was 15 years. Thus, we were not able to include the concepts of organ damage other than urinary protein and the child's development *in utero* that are included in the concept of preeclampsia in recent guidelines.

Perspectives

Smoking is known to be harmful for the mother-infant dyad. Paradoxically, maternal smoking has previously been associated with a lower risk for preeclampsia. In this study, we showed that this is not the case among tall smoking women. We speculate the findings through a new theory about the pathophysiology of preeclampsia. It seems that pregnancy combined with smoking among tall individuals mayraise their BP levels more and thus swing homeostasis through vicious cycle of events more than in shorter women. This speculation is supported by the previously presented hypothesis that maternal cardiovascular function might play an important role in the pathophysiology of preeclampsia [45]. Further, it has been previously shown that cardiovascular abnormalities are evident in pregnant women several weeks before clinical signs or symptoms of preeclampsia [45].

Another question remains regarding the paradox of positive effects of maternal smoking on preeclampsia. The short-term and long-term adverse effects of preeclampsia for the mother-infant dyad are also well known [46]. Even though there is less preeclampsia in smokers, they might have an increased risk for proteinuria during pregnancy, the other main diagnostic criteria for preeclampsia. It is noteworthy this could also predispose these smoking women to later cardiovascular and renal diseases similarly as preeclampsia does. Thus, the long-term health of smoking individuals, with normal BP but with proteinuria, needs to be investigated in the future.

In conclusion, maternal height affects the paradoxical link between SDP and lower risk or preeclampsia, such that no association was found between continued smoking and preeclampsia among taller mothers. The possibility exists that height should be taken into account when assessing the risk of preeclampsia and a closer attention should be paid to mothers taller than average.

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Conflicts of interest

The authors report no conflict of interest.

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