

Maternal tobacco use and extremely premature birth – a population-based cohort study

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Objective To study the associations of maternal tobacco use (smoking or use of snuff) and risk of extremely preterm birth, and if tobacco cessation before antenatal booking influences this risk. To study the association between tobacco use and spontaneous or medically indicated onset of delivery.

Design Population-based cohort study.

Setting Sweden.

Population All live singleton births, registered in the Swedish Medical Birth Register, 1999–2012.

Methods Odds ratios (OR) with 95% confidence intervals (CI) were calculated using multiple logistic regression analysis.

Main outcome measures Extremely preterm birth (<28 weeks of gestation), very preterm birth (28–31 weeks), moderately preterm birth (32–36 weeks).

Results Maternal snuff use (OR 1.58; 95% CI: 1.14–2.21) and smoking (OR 1.61; 95% CI: 1.39–1.87 and OR 1.91; 95% CI: 1.53–2.39 for moderate and heavy smoking, respectively) were

associated with an increased risk of extremely preterm birth.

When cessation of tobacco use was obtained there was no increased risk of preterm birth. Snuff use was associated with a twofold risk increase of medically indicated extremely preterm birth, whereas smoking was associated with increased risks of both medically indicated and spontaneous extremely preterm birth.

Conclusions Snuff use and smoking in pregnancy were associated with increased risks of extremely preterm birth. Women who stopped using tobacco before the antenatal booking had no increased risk. These findings indicate that nicotine, the common substance in cigarettes and snuff, is involved in the mechanisms behind preterm birth. The use of nicotine should be minimized in pregnancy.

Keywords Maternal tobacco use, nicotine, preterm birth, smoking, snuff.

Tweetable abstract Tobacco use increases risk of extremely preterm birth. Cessation is preventive. Avoid nicotine in pregnancy.

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Introduction

Preterm birth is a leading cause of neonatal mortality and a significant contributor to short and long term morbidity.¹ The incidence of preterm birth varies between 5–13% globally, resulting in 15 million preterm deliveries worldwide each year. The preterm birth rate in Europe ranges from 5 to 10%. More than 40% of the preterm births in developed countries occur in the US, where the preterm birth rate is 10%.^{2,3} The risks of mortality and morbidity are strongly

correlated to the degree of prematurity, affecting extremely preterm (<28 weeks) infants most.⁴ Extremely preterm birth is the major contributor to neonatal deaths in most developed countries.^{5,6}

Smoking during pregnancy is one of the most important preventable risk factors for preterm birth in developed countries.^{7,8} Maternal smoking is <6% in Sweden⁶; in Europe and the US maternal smoking ranges from 5 to 20%.^{9,10} In 2002, maternal smoking was attributable to 5–8% of very and moderately preterm births in the US.³ There is a dose-response relationship between smoking and risk of preterm birth,^{11–13} and the risk seems to increase

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with decreasing gestational age.⁷ However, few studies have investigated the association between smoking and extremely preterm birth.^{14,15}

Internationally, Swedish snuff (oral moist powder to be put under the lip) has been promoted as a means for smoke-cessation, since it contains high levels of nicotine and no combustion products.^{16–18} The number of women using snuff has tripled the last decade, and snuff is used during pregnancy in Sweden. The use of nicotine substitution in pregnancy is questioned.^{19,20}

Whether it is nicotine or combustion products in smoke that influence the risk of preterm birth is discussed. Swedish snuff, provides a means of studying the effects of prenatal nicotine exposure.

Previous studies indicate that women who use snuff during pregnancy are at increased risk of preterm birth.^{21–23} The association between maternal snuff use and risk of extremely preterm birth has not been investigated previously, nor has the effect of tobacco cessation before antenatal booking and risk of extremely preterm birth.

Using nation-wide prospectively collected data, the main objective was to investigate the association between maternal tobacco use and risk of extremely preterm birth, and if tobacco cessation in early pregnancy influenced this risk. The second objective was to study the association between tobacco use and mode of onset of delivery.

Material and methods

Study population

The Swedish Medical Birth Register (MBR) is a national registry that contains information on the demography, maternal reproductive history, pregnancy, delivery, and neonatal period for 98% of all births in Sweden.²⁴ This information is reported to the MBR by the delivery hospital. From 1999 to 2012 there were 1 379 482 live singleton births registered in the MBR. After excluding births with missing data on gestational age, birth weight and the mother's personal identification number, a total of 1 371 274 births (99.4%) were included.

Exposures

Information about present tobacco habits, as well as tobacco habits 3 months before pregnancy is routinely collected by midwives at the antenatal booking, which usually occurs at 8–12 gestational weeks. It is also collected in late pregnancy, after gestational week 32. Since the objective of the current study was to study tobacco use as a risk factor for extremely preterm birth (<28 weeks), the information about tobacco exposure at 32 weeks of gestation could not be used. Tobacco use is registered in the MBR as nonuser, smoker 1–9 cigarettes/day, smoker ≥ 10 cigarettes/day, snuff user, or dual user. Information on amount of snuff used per day is

not obtained. Data on maternal smoking in pregnancy is registered in the MBR since 1982, and data on maternal use of snuff is available from 1999. It is exclusively self-reported data without verification by cotinine levels.

A total of 1 270 161 births (92% of the cohort) had available information about tobacco habits both 3 months before pregnancy and at the antenatal booking.

We categorised maternal tobacco habits at the first antenatal visit into five groups: “nonusers” (defined as no use of snuff or cigarettes), “snuff users”, “moderate smokers” (defined as women who smoked 1–9 cigarettes/day), “heavy smokers” (defined as women who smoked 10 or more cigarettes/day) and “dual users” (defined as women who both used snuff and smoked cigarettes). Mothers recorded as smokers, but for whom there was no information about snuff use, were categorised as smokers. Similarly, mothers recorded as snuff users, but for whom there was no information about smoking were categorised as snuff users.

Cessation of tobacco use was defined as women using snuff or smoking 3 months before pregnancy, but who had stopped before the antenatal booking. There is no information on the exact time at which mothers using tobacco 3 months before pregnancy, but not at the antenatal booking, stopped doing so.

To investigate if cessation of tobacco use influenced the risk of extremely preterm birth, we combined information about tobacco use 3 months before pregnancy and in early pregnancy into five categories. Women who used snuff before pregnancy, and who continued using snuff during pregnancy, were categorised as snuff keepers. Smoking women who continued to smoke were categorised as smoke keepers. Women who had stopped using snuff or quit smoking, before the antenatal booking, were categorised as snuff quitters or smoke quitters, respectively.

Outcomes

The MBR contains information about gestational age at parturition, based on ultrasound dating of pregnancy performed during the early second trimester, which more than 96% of pregnant women in Sweden undergo.²⁵ If no information on ultrasound dating was available, the date of the first day of the last menstrual period (LMP) was used to calculate gestational age at delivery. Preterm birth was categorised into extremely preterm (defined as birth before 28 completed weeks of gestation), very preterm (birth between 28 and 31 weeks), and moderately preterm birth (birth between 32 and 36 weeks).

Induced preterm labour or a preterm caesarean delivery before onset of labour, were categorised as medically indicated preterm delivery. Spontaneous preterm labour (SPTL) and preterm premature rupture of membranes (PPROM) were categorised as spontaneous onset of preterm labour.

Covariates

Information about parity, prepregnancy body mass index (BMI) and family situation is routinely collected at the antenatal booking and registered in the MBR. Maternal age is recorded at delivery and registered in the MBR. Maternal country of birth was categorised as Nordic (i.e. Denmark, Finland, Iceland, Norway, and Sweden) or non-Nordic, and this information was obtained through linkage to Statistics Sweden.²⁶ Information on highest level of formal maternal education was included through linkage to the Education Register, also held at Statistics Sweden.

Statistical analysis

Univariate logistic regression analyses were used to estimate crude odds ratios (OR) (95% confidence intervals, CI) for the association between tobacco habits at antenatal booking and preterm birth (extremely, very, moderately), as well as for the association between cessation of tobacco use during pregnancy and preterm birth.

Univariate logistic regression analyses were also used to calculate crude ORs for the association between tobacco habits and spontaneous and medically indicated preterm births. Crude odds ratios were calculated on births with complete data on the covariates used in the adjusted model. We excluded infants of mothers who had missing information on tobacco habits ($n = 114\,884$), were dual users ($n = 4552$), changed substance of tobacco or started to use tobacco during pregnancy ($n = 4001$). Infants with missing information on spontaneous or medically indicated onset of delivery were excluded ($n = 11\,588$) from the analysis of tobacco use and mode of onset of delivery. The non-tobacco users were used as reference group in all analyses.

Multivariate logistic regression analyses were used to estimate adjusted ORs (CI 95%) for the associations described above. Maternal age, parity, BMI, family situation, level of education and maternal country of birth were considered as confounders. In analyses of the association between cessation of tobacco use and risk of preterm birth, as well as for spontaneous or indicated onset of delivery and preterm birth, the groups of moderate and heavy smokers were merged into one group, smokers.

When analysing the risk of very preterm birth (28–31 weeks), we excluded women who gave birth extremely preterm (<28 weeks), since they were no longer at risk of giving birth. Likewise, when analysing the moderately preterm births, women giving birth before 32 weeks of gestation were excluded.

The population attributable fraction (PAF) of maternal smoking and snuff use for premature birth across different gestational ages was estimated by using the equation $\Sigma (AF_i \times P_i)$, where AF_i is the attributable fraction for exposure and P_i represents the proportion of all cases in the exposure category i .²⁷ Since the prevalence of each outcome was

<10%, the odds ratio was presumed to estimate the relative risk.

In order to adjust for the dependence introduced by the fact that mothers may contribute with more than one child, the Generalised Estimation Equation method was applied. All analyses were performed using the procedure PROC GENMOD in SAS version 9.2 (Statistical Analysis Software version 9.2, SAS Institute, Inc., Cary, NC, USA).

Results

Maternal characteristics and tobacco habits

2.2% of the women used snuff 3 months before pregnancy, but as many as 60% had stopped before the antenatal booking. In early pregnancy 1.1% were using snuff. More than 16% of the women smoked 3 months before pregnancy, 7.9% of whom were moderate smokers and 8.4% heavy smokers. However, in early pregnancy only 7.5% were smokers, 5.6% of whom were moderate smokers and 1.9% heavy smokers. More than 70% of the moderate smokers and 36% of the heavy smokers had stopped, whereas 40% had reduced their smoking to moderate smoking before the antenatal booking (Table S1).

Women using tobacco were to a greater extent teenage mothers, had higher BMI, and had lower level of formal education than non-tobacco users. This was most pronounced among smokers, and especially among heavy smokers. Maternal characteristics are shown in Table 1.

Preterm birth

Of the 1 371 274 births included in the cohort, 4.9% were preterm (<37 weeks), 4.26% of whom were moderately preterm (32–36 weeks), 0.45% very preterm (28–31 weeks), and 0.23% were extremely preterm (<28 weeks).

Snuff users in early pregnancy had almost 60% higher risks of extremely preterm birth (adjusted ORs = 1.58, 95% CI 1.14–2.21), compared to that of non-tobacco users. The increased risk of very preterm birth was of borderline significance (adjusted ORs = 1.25, 95% CI 0.98–1.59). The risk of moderately preterm birth (adjusted OR was 1.21, 95% CI 1.11–1.31) was significant among snuff users. Maternal smoking in early pregnancy was associated with increased risk of all categories of preterm birth, with higher risks with decreasing gestational ages. The association was dose-dependent. For moderate smoking and the association with extremely, very and moderate preterm birth the adjusted ORs was 1.61, 95% CI 1.39–1.87, 1.48, 95% CI 1.33–1.64 and 1.20, 95% CI 1.16–1.24, respectively. The adjusted ORs for the association between heavy smoking and extremely, very and moderate preterm birth were ORs = 1.91, 95% CI 1.53–2.39, 1.81, 95% CI 1.56–2.10 and 1.49, 95% CI 1.41–1.58, respectively (Table 2).

Table 1. Maternal characteristics at the antenatal booking. *Total births $n = 1\,301\,377$

	Nonuser $n = 1\,177\,464$ Rate %	Snuff user $n = 14\,671$ Rate %	Moderate smoker** $n = 79\,783$ Rate %	Heavy smoker** $n = 28\,459$ Rate %	Dual user*** $n = 1000$ Rate %
Maternal age (years)					
≤19	1.4	2.0	6.2	3.8	4.9
20–24	12.1	16.2	26.4	19.6	24.7
25–29	30.7	29.1	29.6	27.4	23.2
30–34	35.6	31.4	22.8	26.8	26.1
≥35	20.3	21.3	15.0	22.4	21.1
Parity					
1	44.7	42.8	46.1	31.0	44.8
2	36.9	34.6	30.8	29.7	28.5
≥3	18.4	22.6	23.1	39.2	26.7
BMI (kg/m²)					
≤18.4	2.3	2.6	3.4	2.9	2.8
18.5–24.9	61.6	56.3	53.6	49.1	52.4
25.0–29.9	25.1	27.1	27.0	28.1	26.5
≥30	11.0	14.0	16.0	20.0	18.3
Cohabitant with father					
Yes	95.2	92.4	84.2	80.3	79.1
No	4.8	7.6	15.8	19.7	20.9
Education (years)					
≤9	8.0	11.3	26.1	33.0	27.2
10–12	39.2	52.9	58.5	56.0	56.3
≥13	52.8	35.8	15.4	11.1	16.5
Country of birth					
Nordic	80.1	94.0	82.4	85.3	95.5
Non Nordic	19.9	6.0	17.6	14.7	4.5

*Excluded missing for tobacco use in early pregnancy, $n = 69\,897$.

**Moderate smoker = 1–9 cigarettes/day and heavy smoker ≥10 cigarettes/day.

***Dual users were excluded in further analyses.

Women who used snuff before pregnancy and continued to use snuff at the antenatal booking had increased risk of extremely and moderately preterm birth (adjusted ORs = 1.69, 95% CI 1.17–2.45 and 1.26, 95% CI 1.15–1.38, respectively). The risk of very preterm birth was of borderline significance (adjusted ORs = 1.26, 95% CI 0.95–1.66). Mothers who smoked before pregnancy and continued to smoke at the antenatal booking had increased risk of all categories of preterm birth (adjusted ORs = 1.74, 95% CI 1.51–1.99, 1.52, 95% CI 1.38–1.67, and 1.27, 95% CI 1.23–1.31, for extremely, very and moderate preterm birth, respectively) (Table 3). In contrast, women who used tobacco (snuff use or smoking) before pregnancy, but had stopped before the antenatal booking, were not at increased risk of preterm birth compared to that of nonusers (Table 3).

Maternal tobacco use (smoking and snuff use) was attributable for 6.5% of extremely premature births, 4.5% and 2.2% for very and moderately premature births, respectively. The same PAF was obtained when the

unexposed group used in the calculation was either nonusers or quitters.

Tobacco use, preterm birth and mode of onset of delivery

Women who continued to use snuff had a more than two-fold increase in risk of medically indicated extremely preterm birth (adjusted ORs = 2.16, 95% CI 1.18–3.94) and an almost 50% increased risk of spontaneous extremely preterm birth of borderline significance (adjusted ORs = 1.49, 95% CI 0.92–2.40). There was no increased risk of either spontaneous (adjusted ORs = 1.34, 95% CI 0.92–1.95) or medically indicated very preterm birth (adjusted ORs = 1.19, 95% CI 0.78–1.82). Increased risks for both spontaneous (adjusted ORs = 1.23, 95% CI 1.10–1.37) and medically indicated (adjusted ORs = 1.30, 95% CI 1.09–1.54) moderately preterm birth were observed among snuff users. Compared to non-tobacco users, women who continued to smoke had increased risks of both spontaneous (adjusted ORs = 1.83, 95% CI

Table 2. Crude and adjusted odds ratios for preterm birth and maternal tobacco use in early pregnancy. *Total births $n = 1\,300\,377$

	<i>n</i>	Rate %	Odds ratios (95% CI)			
			Crude ***		Adjusted***	
Extremely preterm (<i>n</i> = 2420)						
Nonuser	2042	0.17	1.00	Reference	1.00	Reference
Snuff user	37	0.25	1.56	1.12–2.18	1.58	1.14–2.21
Moderate smoker	238	0.30	1.73	1.50–1.99	1.61	1.39–1.87
Heavy smoker	103	0.36	2.02	1.62–2.50	1.91	1.53–2.39
Missing	690	0.99				
Very preterm (<i>n</i> = 5453)						
Nonuser	4652	0.40	1.00	Reference	1.00	Reference
Snuff user	72	0.49	1.27	1.00–1.62	1.25	0.98–1.59
Moderate smoker	507	0.64	1.60	1.45–1.76	1.48	1.33–1.64
Heavy smoker	222	0.78	1.96	1.69–2.27	1.81	1.56–2.10
Missing	752	1.09				
Moderately preterm (<i>n</i> = 53 630)						
Nonuser	47 038	4.02	1.00	Reference	1.00	Reference
Snuff user	712	4.89	1.25	1.15–1.35	1.21	1.11–1.31
Moderate smoker	4097	5.18	1.30	1.25–1.35	1.20	1.16–1.24
Heavy smoker	1783	6.34	1.58	1.49–1.66	1.49	1.41–1.58
Missing	4710	6.9				

*Missing for tobacco in early pregnancy and dual users excluded, $n = 70\,897$.

**Only subjects with complete data on covariates in the adjusted model included. Population with complete data $n = 1\,174\,455$.

***Adjusted for maternal age, parity, cohabitant with father, country of birth, level of education and BMI.

Table 3. Crude and adjusted odds ratios for preterm birth by cessation of tobacco use before and in early pregnancy. *Total births $n = 1\,247\,837$

	<i>n</i>	Rate %	Odds ratios (95% CI)			
			Crude **		Adjusted***	
Extremely preterm (<i>n</i> = 2346)						
Nonuser	1732	0.17	1.00	Reference	1.00	Reference
Snuff keeper	30	0.27	1.66	1.15–2.40	1.69	1.17–2.45
Snuff quitter	26	0.14	0.78	0.52–1.17	0.78	0.52–1.16
Smoke keeper	329	0.33	1.87	1.64–2.12	1.74	1.51–1.99
Smoke quitter	229	0.19	1.12	0.97–1.29	1.02	0.88–1.18
Very preterm (<i>n</i> = 5276)						
Nonuser	3975	0.40	1.00	Reference	1.00	Reference
Snuff keeper	55	0.49	1.28	0.97–1.69	1.26	0.95–1.66
Snuff quitter	69	0.36	0.96	0.75–1.22	0.90	0.71–1.15
Smoke keeper	680	0.68	1.68	1.54–1.83	1.52	1.38–1.67
Smoke quitter	497	0.41	1.03	0.93–1.13	0.92	0.83–1.02
Moderately preterm (<i>n</i> = 51 714)						
Nonuser	39 764	4.02	1.00	Reference	1.00	Reference
Snuff keeper	568	5.13	1.30	1.19–1.43	1.26	1.15–1.38
Snuff quitter	775	4.06	1.02	0.95–1.10	0.95	0.88–1.02
Smoke keeper	5555	5.56	1.39	1.34–1.43	1.27	1.23–1.31
Smoke quitter	5052	4.19	1.05	1.02–1.08	0.94	0.91–1.01

*Missing for tobacco before/during pregnancy, dual users, change of tobacco substance excluded, $n = 123\,437$.

**Only subjects with complete data on covariates in the adjusted model included. Total population with complete data in crude and adjusted model $n = 1\,127\,706$.

***Adjusted for maternal age, parity, cohabitant with father, country of birth, level of education and BMI.

1.56–2.14, 1.70, 95% CI 1.50–1.93, and 1.30, 95% CI 1.25–1.35, for extremely, very and moderate preterm birth, respectively) and medically indicated preterm birth (adjusted ORs = 1.50, 95% CI 1.15–1.97, 1.26, 95% CI 1.08–1.47, and 1.17, 95% CI 1.09–1.25, for extremely, very and moderate preterm birth, respectively), across all categories of preterm birth (Table 4). The risk of spontaneous preterm birth was slightly higher than that of medically

indicated preterm birth across all gestational age categories for smokers (Table 4).

Discussion

Main findings

In this large Swedish national cohort study, including more than 1.3 million births, we add to the current literature by

Table 4. Crude and adjusted odds ratios for preterm birth by mode of onset of delivery, spontaneous or medically indicated preterm birth.
*Total births $n = 1\,238\,328$

	<i>n</i>	Rate %	Odds ratios (95% CI)			
				Crude **		Adjusted***
Spontaneous extremely preterm birth (<i>n</i> = 1670)						
Nonuser	1173	0.12	1.00	Reference	1.00	Reference
Snuff keeper	17	0.15	1.43	0.89–2.31	1.49	0.92–2.40
Snuff quitter	16	0.08	0.76	0.47–1.25	0.79	0.48–1.29
Smoke keeper	238	0.24	1.99	1.72–2.31	1.83	1.56–2.14
Smoke quitter	149	0.12	1.06	0.89–1.27	0.97	0.81–1.16
Medically indicated extremely preterm birth (<i>n</i> = 676)						
Nonuser	503	0.05	1.00	Reference	1.00	Reference
Snuff keeper	12	0.11	2.21	1.22–4.03	2.16	1.18–3.94
Snuff quitter	9	0.05	0.80	0.38–1.68	0.73	0.35–1.54
Smoke keeper	79	0.08	1.58	1.23–2.04	1.50	1.15–1.97
Smoke quitter	73	0.06	1.26	0.97–1.62	1.14	0.87–1.48
Spontaneous very preterm birth (<i>n</i> = 2790)						
Nonuser	2061	0.21	1.00	Reference	1.00	Reference
Snuff keeper	30	0.27	1.37	0.95–2.00	1.34	0.92–1.95
Snuff quitter	34	0.18	0.89	0.63–1.26	0.84	0.59–1.20
Smoke keeper	401	0.40	1.92	1.71–2.15	1.70	1.50–1.93
Smoke quitter	264	0.22	1.07	0.94–1.23	0.96	0.83–1.10
Medically indicated very preterm birth (<i>n</i> = 2319)						
Nonuser	1793	0.18	1.00	Reference	1.00	Reference
Snuff keeper	24	0.22	1.22	0.80–1.87	1.19	0.78–1.82
Snuff quitter	31	0.16	0.97	0.68–1.39	0.91	0.64–1.30
Smoke keeper	250	0.25	1.36	1.18–1.57	1.26	1.08–1.47
Smoke quitter	221	0.18	1.00	0.86–1.16	0.90	0.78–1.05
Spontaneous moderately preterm birth (<i>n</i> = 38 081)						
Nonuser	29 214	3.00	1.00	Reference	1.00	Reference
Snuff keeper	405	3.74	1.26	1.13–1.39	1.23	1.10–1.37
Snuff quitter	580	3.09	1.03	0.95–1.13	0.94	0.87–1.03
Smoke keeper	4082	4.18	1.39	1.34–1.44	1.30	1.25–1.35
Smoke quitter	3800	3.21	1.08	1.04–1.16	0.95	0.91–0.99
Medically indicated moderately preterm birth (<i>n</i> = 12 962)						
Nonuser	10 067	1.06	1.00	Reference	1.00	Reference
Snuff keeper	154	1.46	1.43	1.21–1.68	1.30	1.09–1.54
Snuff quitter	187	1.02	0.98	0.84–1.14	0.94	0.81–1.09
Smoke keeper	1372	1.45	1.37	1.29–1.46	1.17	1.09–1.25
Smoke quitter	1182	1.02	0.97	0.91–1.03	0.89	0.84–0.96

*Missing for tobacco before/during pregnancy, duals, change of tobacco substance, and missing for type of delivery excluded, $n = 132\,946$.

**Only subjects with complete data on covariates in the adjusted model included. Total population with complete data in crude and adjusted model $n = 1\,119\,530$.

***Adjusted for maternal age, parity, cohabitant with father, country of birth, level of education and BMI.

showing that both maternal snuff use and smoking are associated with increased risks of extremely preterm birth (<28 weeks). Women who stopped using tobacco in early pregnancy did not have an increased risk of preterm birth. Maternal tobacco use was attributable for 6.5% of extremely preterm births, 4.5% and 2.2% of very and moderately preterm births, respectively. Snuff users had a twofold increased risk of medically indicated extremely preterm birth, while the 50% increased risk of spontaneous extremely preterm birth was of borderline significance. Smokers had increased risk of both spontaneous and medically indicated extremely preterm birth.

Strengths and limitations

A major strength of the current study is the large cohort, based on a nation-wide population. Other strengths are the use of standardised records and the coverage of a long time period, reducing the impact of fluctuations in preterm birth rates. Information on tobacco use was prospectively collected before birth, which precludes recall bias.

A limitation is that the study is based on self-reported tobacco habits, without cotinine levels to confirm the information. However, self-reported data on smoking in the MBR has been found to be valid.²⁸ The risk of misclassification was higher among those who reported that they had stopped smoking.²⁹ Self-reported data regarding the use of snuff, has not been validated in the MBR.

There is no information in MBR on the use of nicotine substitution in pregnancy, a much debated question.²⁰ Studies of nicotine substitution in pregnancy are inconclusive and due to low compliance safety was difficult to study.^{30,31} That maternal snuff use increases the risk of preterm birth suggests that nicotine is not safe to use in pregnancy.

More than 20% of the women who delivered extremely preterm had missing information on tobacco habits. The centralisation of the neonatal care of extremely preterm infants can result in loss of data, since women may give birth in a different region than their antenatal care unit is located.

Conducting a register study, information about mental health, alcohol use, medication and exposure to second-hand smoking in pregnancy was not possible to obtain. Due to limited power, we could not disentangle the associations between tobacco use and underlying pregnancy complications leading to extremely preterm birth.

Interpretation

This is the first study of snuff use and risk of extremely preterm birth, but two previous Swedish studies have found an increased risk of preterm birth (<32 weeks) among snuff-users.^{21,22} In agreement with previous studies,^{21,22} when cessation of tobacco use was obtained before

antenatal booking, there was no increased risk of preterm birth. This is important, since preterm birth, and especially extremely preterm birth, is associated with very high morbidity and mortality.^{1,5}

That maternal smoking is an important risk factor for preterm birth (<37 weeks) and that cessation of smoking reduces this risk is well known.^{12,32} There are, however, few earlier studies of maternal smoking and extremely preterm birth. A study based on the Finnish Medical Birth Register showed considerably lower risks associated with smoking than did the current study.¹⁵ This might be attributed to the fact that the associations were adjusted for factors that are part of the causal pathway between smoking and preterm birth, such as placental abruption and small-for-gestational-age infants, thereby underestimating the risk.¹⁵ A smaller, retrospective Dutch study reported that smoking during pregnancy was associated with a sevenfold increased risk of extremely preterm birth, but found no significant association between smoking and very or moderately preterm birth.¹⁴ That study was restricted to women smoking throughout the entire pregnancy, and the very high relative risk of extremely preterm births in the study might have been due to unmeasured confounding and recall bias. Information on tobacco use during pregnancy, as well as on socioeconomic and neonatal factors such as gestational age and birth weight, was obtained by retrospectively recorded data from the mothers by questionnaires.

When stratifying by mode of onset of delivery as either spontaneous or medically indicated, we found that maternal snuff use was associated with medically indicated extremely preterm birth. In the group of very preterm births there was, if anything, a tendency towards spontaneous onset of delivery, although it was not significant. Maternal snuff use was associated with both spontaneous and medically indicated moderately preterm birth.

Maternal smoking was associated with increased risks of primarily spontaneous, but also medically indicated preterm birth across all preterm categories. These findings are consistent with previous studies.^{21,22,32} We add to these studies by analysing the associations between smoking and preterm birth across all gestational age strata.

Major indications for medically indicated extremely preterm birth are preeclampsia, placental abruption and intrauterine growth restriction. Snuff use is a risk factor for early-onset preeclampsia, intrauterine growth restriction and stillbirth,^{33–36} but is not, in contrast to smoking, associated with increased risk of placental abruption.³⁵ Maternal smoking is a strong risk factor of intrauterine growth restriction, stillbirth and placental abruption, but protects against preeclampsia.^{33–36}

The mechanisms by which maternal smoking or use of snuff increases the risk of preterm birth have not been clarified.^{1,22} Swedish snuff lacks combustion products, and the

common substance in cigarettes and snuff is nicotine, which implies that nicotine is involved in the mechanisms.

Preeclampsia, preterm birth, intrauterine growth restriction, and stillbirth are associated with abnormal placentation.^{37–39} This could indicate that nicotine affects the placentation, and thereby the development of the early stages of preeclampsia. Nicotine seems to affect early preeclampsia but does not seem to be involved in mechanisms behind the late, clinical phase of preeclampsia.³³ It might explain why snuff users run an increased risk of preterm preeclampsia, but not of term preeclampsia.³³ Compared to nonusers, smokers have a reduced risk of preeclampsia, except for preeclampsia with concurrent growth restriction or stillbirth.³³ In contrast to maternal snuff use, maternal smoking is associated with increased risks of other pregnancy complications caused by abnormal placentation, such as placenta previa and placental abruption.³⁵ In addition to nicotine, cigarettes contain combustion products like carbon monoxide, which also affect the placenta but have a protective effect on developing preeclampsia.^{40,41} Carbon monoxide binds to hemoglobin, forming carboxyhemoglobin, which decreases the fetal oxygen delivery.⁴² Both carbon monoxide and nicotine affect the placenta and may also have synergistic effects, resulting in premature birth and fetal growth restriction.³⁶ This may explain why these effects are most pronounced in smokers.

In addition, infection and/or inflammation are associated with risk of preterm birth.⁴³ Smoking and nicotine affect the immune system^{1,13,44,45} which could be part of the mechanisms behind the increased risk of spontaneous preterm birth among tobacco users.²¹

Conclusion

The use of Swedish snuff or smoking in pregnancy was associated with an increased risk of extremely preterm birth. The similar risks between snuff users and smokers, and the fact that cessation reduces those risks, implies that nicotine is associated with risk of preterm birth, and that the use of products containing nicotine should be minimized in pregnancy. Health care providers should educate women by emphasising the major health benefits with early cessation of tobacco use in pregnancy.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

SD analysed and interpreted the data as well as wrote the first draft of the manuscript under supervision of AKEB and AG analysed and interpreted the data, provided statistical expertise and critically revised the manuscript. SC,

AKEB and AKW conceived and designed the study, interpreted the data and critically revised the manuscript. AKEB, AKW and SC also contributed with obstetric, pediatric, and epidemiological expertise.

Details of ethics approval

The study was approved by the Ethical Review Board in Stockholm, Sweden (registration number 02-405, approval date October 24 2002 and amendment 2009/1726-32, approval date November 23 2009).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Change of tobacco use based on tobacco habits 3 months before pregnancy and at the antenatal booking ■

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