

Effect of Swedish snuff (*snus*) on preterm birth

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Objective To compare the effects of Swedish snuff and cigarette smoking on risks of preterm birth.

Design Population-based cohort study.

Setting Sweden.

Population All live, singleton births in Sweden 1999–2006.

Methods Odds ratios (OR) with 95% confidence intervals (CI) were used to estimate relative risks for preterm birth in snuff users ($n = 7607$), light smokers (1–9 cigarettes/day; $n = 41\,436$) and heavy smokers (ten or more cigarettes/day; $n = 16\,951$) using non-tobacco users ($n = 503\,957$) as reference.

Main outcome measures Very (<32 weeks) and moderately (32–36 weeks) preterm birth.

Results Compared with non-tobacco users, snuff users had increased risks of both very (adjusted OR 1.38; 95% CI 1.04–1.83) and moderately (adjusted OR 1.25; 95% CI 1.12–1.40) preterm birth. Compared with non-tobacco users, light smokers had increased risks of both very (adjusted OR 1.60; 95% CI 1.42–1.81) and moderately (adjusted OR: 1.18; 95% CI: 1.12–1.24) preterm birth, and heavy smokers had even higher risks. Among smokers, but not among snuff users, the risk was more pronounced for spontaneous than induced preterm birth.

Conclusions The use of Swedish snuff was associated with increased risks of very and moderately preterm birth with both spontaneous and induced onsets. Swedish snuff is not a safe alternative to cigarette smoking during pregnancy.

Keywords Pregnancy, premature birth, smokeless, snuff, tobacco.

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Introduction

Preterm birth is a leading cause of neonatal and infant mortality as well as short- and long-term disability.^{1,2} The preterm birth rate has risen in several industrialised countries, including in the United States where the rate has increased from 9.5% in 1981 to 12.7% in 2005.²

Smoking during pregnancy is associated with an increased risk of preterm birth, especially of spontaneous onset, but the mechanism is unclear.^{3–6} Smokeless tobacco contains and delivers quantities of nicotine comparable to those typically absorbed from cigarette smoking, but does not result in exposure to the products of combustion, for example carbon monoxide.^{7,8} There are two main forms of smokeless tobacco: chewing tobacco and snuff. Among the high-income countries, Sweden has the highest per capita consumption of smokeless tobacco, predominantly in the form of *snus*, which is an oral moist snuff. The Swedish snuff contains lower levels of some harmful substances, for example nitrosamines, than many of the brands available in North

America and some low-income countries.⁷ Globally, the use of smokeless tobacco has increased and the largest increase has occurred in women of childbearing age.^{9,10} Possible effects of smokeless tobacco on risk of preterm birth have been investigated in only a few studies with somewhat ambiguous results, indicating lower,¹¹ unaltered¹² and higher¹³ risks of preterm birth (<37 weeks) in women using smokeless tobacco during pregnancy compared with non-tobacco users. One of these studies was based on the Swedish Medical Birth Register, including the first 2 years of registration of snuff use among pregnant women.¹³

Data from the Birth Register are now available for six additional years, which made it possible to estimate the potential effects of Swedish snuff on preterm birth in greater detail. Specifically, we wanted to investigate snuff use in relation to severity and onset (spontaneous or induced) of preterm birth. We also aimed to compare the effects of snuff and smoking, to disentangle the possible effects of nicotine versus tobacco combustion products on preterm birth.

Methods

Study design

Information from the Swedish Medical Birth Register was used to define the study population. Women born in the Nordic countries (Sweden, Norway, Denmark, Finland or Iceland) who delivered a live, singleton infant between 1999 and 2006 were included in the study ($n = 610\,757$). The Birth Register contains data on more than 99% of all births in Sweden and includes demographic data, information on reproductive history and complications that occur during pregnancy, delivery and the neonatal period.¹⁴ By means of each individual's unique national registration number, the Birth Register can be linked with other Swedish data sources.

In Sweden, gestational age is assessed by ultrasound scans in 95% of women, usually around the 17th week of gestation.¹⁵ If no early second-trimester ultrasound scan was available, the last menstrual period was used to calculate gestational age at delivery. We excluded 558 pregnancies with missing information on gestational age at delivery.

In the Birth Register, information about cigarette smoking has been recorded since 1983 and about snuff use since 1999. The information about tobacco use is collected by midwives at the woman's first antenatal visit, which occurs before the 15th week of gestation in more than 95% of the pregnancies.¹⁶ Tobacco use is categorised, as reported by the women, into: noncurrent tobacco user, current snuff user, current light smoker (one to nine cigarettes per day), and current heavy smoker (at least 10 cigarettes per day). In all, 39 767 pregnancies (6.5%) had complete missing information about current tobacco use. For the purpose of this study, pregnancies where maternal smoking was recorded but with missing information about snuff use ($n = 41\,351$) were considered as exposed to smoking only. Conversely, pregnancies where snuff use was recorded but with missing information about smoking ($n = 2039$) were included as exposed to snuff only. Whenever maternal tobacco use was recorded as absent for one product and information about the other was missing ($n = 673$), the corresponding pregnancies were included as related to non-tobacco users. As a consequence, in this study we analysed the following mutually exclusive categories of exposure for the pregnancies included in the Register (Table 1): non-tobacco users ($n = 503\,957$); exclusive snuff user ($n = 7607$); exclusive light smoking ($n = 41\,436$), exclusive heavy smoking ($n = 16\,951$) and current use of both snuff and cigarettes ($n = 481$).

Births before 37 weeks of gestation were considered preterm and were categorised into very (before 32 weeks) and moderately (32 weeks + 0 days to 36 weeks + 6 days) preterm births. Information about onset of birth is routinely

Table 1. Rates of very (<32 weeks) and moderate (32–36 weeks) preterm birth by maternal characteristics among Nordic women: live single births in Sweden, 1999–2006

Maternal characteristics	No. of births	Very preterm birth (%)	Moderate preterm birth (%)
Tobacco habit			
Non-use	503 957	0.55	4.01
Snuff use	7607	0.74	4.97
Cigarette smoking			
1–9 cigarettes/day	41 436	0.95	4.97
≥10 cigarettes/day	16 951	1.10	6.05
Snuff and cigarette use	481	0.83	4.99
Missing	39 767	1.58	6.39
Maternal age (years)			
≤19	9744	1.19	5.60
20–24	70 051	0.69	4.94
25–29	194 825	0.61	4.41
30–34	221 763	0.61	3.93
≥35	113 816	0.78	4.31
Parity			
0	275 652	0.85	5.33
1–2	304 312	0.49	3.27
≥3	30 235	0.75	5.16
BMI (kg/m²)			
≤19.9	46 639	0.57	4.62
20–24.9	287 478	0.54	3.89
25–29.9	128 801	0.61	4.14
≥30	56 807	0.89	4.95
Missing	90 474	1.01	5.24
Education (years)			
≤9	45 107	0.97	5.37
10–11	110 265	0.77	4.72
12	172 764	0.64	4.37
≥13	280 890	0.58	3.91
Missing	1173	1.02	6.05
Living with infants father			
Yes	547 992	0.59	4.11
No	26 937	0.84	5.06
Missing	35 270	1.68	6.61
Total no. of pregnancies	610 199	4040	26 215

recorded in a standardised manner by the midwife at the delivery ward, and is categorised into spontaneous onset of labour, induced onset of labour, and caesarean birth before the onset of labour. In this study, onset of birth was divided into spontaneous and induced (i.e. induced onset of labour or caesarean birth before onset of labour). All births with a diagnosis of preterm prelabour rupture of the membranes (PPROM, International Classification of Diseases, tenth version [ICD-10] code: O42) were included as a spontaneous onset of birth.

Information on maternal age at birth, early pregnancy body mass index (BMI, categorised into underweight: <20 kg/m², normal weight: 20–24.9 kg/m², overweight:

25–29.9 kg/m² or obese: ≥ 30 kg/m²), parity and whether the woman was living with the infant's father were obtained from the Birth Register. Through linkage with the Education Register, information on the number of years of formal education completed as of 1 January 2008, was obtained and categorised as <9, 10–11, 12, or 13 years or more.

The study was approved by one of the Regional Ethical Review Boards in Stockholm, Sweden. The board did not require the women to provide informed consent.

Statistical analysis

SAS PROC GENMOD (SAS Institute Inc., Cary, NC, USA) was used to estimate the association between tobacco habit and risk of preterm birth and onset of delivery. Odds ratios (OR), presented with 95% confidence intervals (CI), were calculated before and after adjustments for maternal characteristics. Women who reported daily use of both snuff and cigarettes and women with missing information on tobacco consumption were excluded from the analysis. Snuff users, light smokers and heavy smokers were analysed separately and non-tobacco users were used as reference group. We considered as potential confounders: maternal age at delivery, early pregnancy BMI, parity, years of formal education and whether the woman was living with the infant's father. The last variable was not associated with any of the outcomes and was excluded from the final model. All analyses were performed using the STATISTICAL ANALYSIS SOFTWARE version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

In the cohort, 1.2% of the women exclusively used snuff, 6.8% were light smokers, 2.8% were heavy smokers and 0.08% used both snuff and cigarettes in early pregnancy. We had no information on tobacco use in 6.5% of the

cohort. Among 610 199 births, 5.0% were preterm with 0.7% ($n = 4040$) very preterm and 4.3% ($n = 26\,215$) moderately preterm (Table 1). Women who used snuff and women who smoked cigarettes during pregnancy had higher rates of preterm birth than women who did not use tobacco. High rates of preterm birth were also seen in the youngest and in the oldest mothers, in women either expecting their first child or their fourth or higher order child, and in women who were underweight or obese in early pregnancy. Rates of preterm birth increased with decreasing length of formal education and were higher for women who were not living with the infant's father than for women who were living with the infant's father.

Women who used snuff at the first antenatal visit had a higher risk of moderately and very preterm birth than non-tobacco users, also after adjusting for maternal age, parity, BMI and years of formal education (Table 2). Cigarette smokers also had higher risks of preterm birth than non-tobacco users, and risks increased with amount smoked (Table 2).

For snuff use, we found that the overall adjusted OR related to preterm birth was 1.27 (95% CI 1.14–1.41). Data from the Swedish Birth Register between 1999 and 2000 have been used in a previous study.¹³ When we repeated the analysis after restricting the study population to women giving birth in 2001–2006, snuff users had an OR for preterm birth of 1.24 (95% CI: 1.06–1.39).

Of all preterm births, 70% had a spontaneous, 27% had an induced and 3% had an unknown onset of labour. Compared with non-tobacco users, snuff users had increased risks of both spontaneous and induced preterm birth (adjusted ORs 1.25; 95% CI 1.10–1.41 and 1.33; 95% CI 1.10–1.61, respectively). Smokers also had increased risks of both spontaneous and induced onsets of preterm birth compared with non-tobacco users, but the association was stronger to preterm birth with a spontaneous onset, especially for heavy smokers (Table 3).

Table 2. Tobacco exposure status and risks of very (<32 weeks) and moderate (32–36 weeks) preterm birth

Tobacco habit	Very preterm birth ($n = 3408$)			Moderate preterm birth ($n = 23\,648$)		
	No. of women	Odds ratio (95% CI)		No. of women	Odds ratio (95% CI)	
		Crude	Adjusted*		Crude	Adjusted*
Non-use	2772	Reference	Reference	20 184	Reference	Reference
Snuff use	56	1.34 (1.03–1.75)	1.38 (1.04–1.83)	378	1.26 (1.13–1.39)	1.25 (1.12–1.40)
Cigarette smoking						
1–9 cigarette/day	394	1.74 (1.56–1.93)	1.60 (1.42–1.81)	2061	1.26 (1.20–1.32)	1.18 (1.12–1.24)
≥ 10 cigarette/day	186	2.00 (1.73–2.33)	1.90 (1.61–2.25)	1025	1.55 (1.46–1.66)	1.45 (1.35–1.56)

*Adjusted for maternal age, early-pregnancy BMI, parity and years of education.

Table 3. Adjusted odds ratios (OR) for spontaneous and induced onsets of preterm birth (<37 weeks) by tobacco exposure status

Tobacco habit	Preterm birth					
	Spontaneous onset (n = 18 872)			Induced onset (n = 7350)		
	No. of women	Rate(%)	Adjusted OR (95% CI)*	No. of women	Rate (%)	Adjusted OR (95% CI)*
Non use	16 022	3.18	Reference	6260	1.24	Reference
Snuff use	298	3.92	1.25 (1.10–1.41)	125	1.64	1.33 (1.10–1.61)
Cigarette smoking						
1–9 cigarette/day	1713	4.13	1.24 (1.17–1.32)	654	1.58	1.17 (1.06–1.28)
≥10 cigarette/day	839	4.95	1.56 (1.44–1.69)	311	1.83	1.30 (1.14–1.48)

*Adjusted for maternal age, early pregnancy BMI, parity and years of education.

Comment

This large population-based study supports associations between use of Swedish snuff during pregnancy and increased risks of very and moderately preterm birth. We found that snuff was a risk factor for both spontaneous and induced preterm birth. We could also confirm earlier findings of a dose–response association between smoking and preterm birth with a more pronounced smoking-related risk for spontaneous than induced preterm birth.⁵

In contrast to cigarette smoking, which includes nicotine as well as carbon monoxide and a large number of combustion products, Swedish snuff contains nicotine as the sole substance that has been clearly implicated in pregnancy outcome.^{7–9} Our finding that both snuff and cigarette smoking are associated with preterm birth suggests that nicotine plays an important role in tobacco-related preterm births. We had no information about the amount of snuff used, and were therefore unable to study dose–response relationships as we could with cigarette smoking.

Preterm births have either a spontaneous onset, presenting with preterm labour or PPRM, or an induced onset, presenting with elective birth for fetal or maternal indications. To our knowledge, our study is the first to evaluate the association between smokeless tobacco and onset of preterm birth. We found that Swedish snuff use was associated with a similar risk increase for spontaneous and induced preterm births, suggesting that nicotine has an impact both on mechanisms associated with preterm spontaneous onset of labour and on pregnancy complications associated with iatrogenic elective preterm birth. In agreement with previous studies, the smoking-related risk was stronger for spontaneous than for induced preterm birth.⁵

The present study included more than 7600 pregnancies exposed to smokeless tobacco use, which is a considerably larger sample than in the former studies, which included between 100 and 800 users.^{11–13} A South African study

reported a lower risk of preterm birth (<36 weeks) in snuff users compared with non-users, though the mean gestational age for all births was lower in snuff users than in non-users and in smokers.¹¹ The major reason for this discrepancy could be that the women in the South African study were recruited late in pregnancy; therefore earlier preterm birth may have been overlooked. Also, the intensity of snuff consumption is not clear. The snuff used in South Africa is a dry snuff, either commercial or home manufactured. Dry snuff is usually inhaled through the nose or more commonly placed in the lower labial vestibule. In an Indian study, use of smokeless tobacco was investigated in relation to preterm birth by severity.¹² The authors could only report a tendency ($P = 0.06$) for a higher risk (OR 1.4) of preterm birth (36 weeks or earlier) in women who used smokeless tobacco during pregnancy compared with non-tobacco users. When analysing very (<32 weeks) and extremely (<28 weeks) preterm births separately, the reported ORs for smokeless tobacco users were 4.9 and 8.0, respectively. We could not confirm these high risks. In the Indian population, chewing tobacco was used, mostly in the form of *mishri*, which is a pyrolysed and powdered tobacco used as tooth paste. Other usage included locally manufactured traditional products mixing tobacco with *betel quid* (areca nut). Chewing betel nut *per se* has been linked to adverse pregnancy outcomes, probably through fetal exposure to arecoline, an alkaloid with effects on feto–placental circulation similar to those of nicotine.^{17,18} Differences in toxicants between these types of tobacco and Swedish snuff, socio-demographic and anthropometric differences between the populations, and differences in management during pregnancy may therefore explain some of the differences in risks between the reports. However, the studies from South Africa and India also raise concerns about residual confounding.

In a previous study from the Swedish Birth Register that included 789 snuff users giving birth between 1999 and

2000, an odds ratio of 1.98 was found for preterm birth (36 weeks or earlier) for snuff use compared with non-use of tobacco.¹³ When we in the present study assessed 6783 snuff users giving birth between 2001 and 2006, the corresponding association was considerably weaker (OR 1.21). Apart from slight differences in inclusion and exclusion criteria between the two studies, a plausible explanation for this discrepancy between risk estimates is that pregnant snuff users in the most recent years may have decreased their consumption or stopped using snuff in late pregnancy after hearing about the reports on adverse pregnancy outcome among snuff users. However, given the differences in number of exposed individuals between the studies, the previously reported relative risk¹³ may have been overestimated.

A major strength of the present study is the nationwide population-based design with information on current tobacco use at the first antenatal visit in 93.5% of the pregnant population. We adjusted for confounding variables such as maternal age, BMI, parity and socio-economic status measured as years of formal education and whether the woman was living with the infant's father. In addition, the relatively homogeneous population of women born in the Nordic countries, the fact that antenatal and obstetric care is free of charge with standardised management routines and that more than 99% of births are delivered in public hospitals, should minimise, but cannot eliminate, the potential for residual confounding by unmeasured socio-demographic factors or differences in management. Another strength of the study is that information about current tobacco use was collected by interviews in early pregnancy, before the onset of potential adverse pregnancy outcomes, which precludes recall bias. Moreover, gestational age was assessed during the second trimester by ultrasound scans in almost all pregnancies.¹⁵ Self-reported information on smoking during pregnancy is valid in Sweden,¹⁹ but we lack validation studies with respect to snuff use. Another limitation is that categories of tobacco use were based on information only from one time-point in early pregnancy. Some women may have stopped using tobacco later in pregnancy, while about 10% of the women who stop smoking in early pregnancy are estimated to resume later in pregnancy.²⁰

Use of Swedish snuff seems to be less harmful than cigarette smoking concerning risks for cardiovascular disease and cancer, and the role of Swedish snuff in smoking harm reduction has been discussed internationally.²¹ The ban of smoking in public places, a public health measure with known effects on smoking reduction at the population level,²² may be followed by a global increase in Swedish snuff use because of its promotion by international cigarette manufacturers. Promoting snuff use to reduce smoking might have some beneficial effects, but may also lead to

recruitment of new tobacco users, predominantly using snuff.²³ The findings of an association between snuff use and preterm birth plead against promoting snuff as an alternative nicotine source during pregnancy.

In conclusion; the use of Swedish snuff during pregnancy is associated with increased risks of both very and moderately preterm birth. Swedish snuff seems not to be a safe alternative to cigarette smoking during pregnancy.

Disclosure of interests

One coauthor (MR Galanti) has previously worked as epidemiologist at the Centre for Tobacco Prevention of the Stockholm County Council, a governmental unit affiliated to the Department of Public Health Sciences at the Karolinska Institutet. In her role as researcher she has never been involved in any kind of advocacy, policy-making or public statement concerning Swedish snuff (*snus*). All other coauthors report no conflict of interests.

Contribution to authorship

SC had the original idea for the study. All authors contributed to the design of the study. A-KW performed the analyses under supervision of OS. A-KW wrote the first draft of the manuscript. All authors made substantial contribution to the interpretation of results and manuscript revision.

Details of ethics approval

The study was approved by one of the Regional Ethical Review Boards in Stockholm, Sweden: reference number: 2008/1481-31, date of approval: 22 October 2008. The board did not require the women to provide informed consent.

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