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## ORIGINAL INVESTIGATION

# Influence of Snuff and Smoking Habits in Early Pregnancy on Risks for Stillbirth and Early Neonatal Mortality

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## ABSTRACT

**Introduction:** Prenatal exposure to Swedish snuff (including nicotine and other components in grinded tobacco) is reported to increase stillbirth risk, but the effect of snuff on early neonatal mortality is unknown. Prenatal smoking exposure is associated with risks for both stillbirth and early neonatal mortality. We aimed to study if women who quit using snuff or quit smoking before first antenatal visit reduce their risks.

**Methods:** In a nationwide study of 851,371 singleton births in Sweden from 1999 to 2010, we used multiple logistic regression models to examine associations between cessation or continuation of snuff use or smoking and risks for stillbirth (at 28 weeks or later) and early neonatal mortality (death during the first week of life).

**Results:** Compared with nontobacco users, snuff users and smokers in early pregnancy had increased risks for stillbirths, and adjusted odds ratios (ORs), with 95% confidence intervals (CI), were 1.43 (1.02–1.99) and 1.59 (1.40–1.80), respectively. Women who stopped using snuff or stopped smoking before first visit to antenatal care had no increased risks. Compared with nontobacco users, smokers had an increased risk for early neonatal mortality (adjusted OR = 1.37 [95% CI 1.11–1.71]). Women who stopped smoking and snuff users in early pregnancy had no increased risks of early neonatal mortality.

**Conclusions:** Both snuff and smoking influence risk for stillbirth, and women who stop using snuff or smoking have a similar stillbirth risk as nontobacco users. Smoking but not snuff use influences risk for early neonatal mortality.

## INTRODUCTION

A dramatic decline in perinatal mortality rates (stillbirths and early neonatal deaths [deaths during the first week of life]) has been reported from several high-income countries (Flenady, Middleton, et al., 2011; World Health Organization, 2006). This decline is mainly explained by reduced early neonatal death rates due to improved obstetrical and neonatal care. Stillbirths now account for the majority of perinatal deaths in most high-income countries, and a reduction in stillbirth rates is both desirable and possible (Flenady, Middleton, et al., 2011; World Health Organization, 2006).

Despite extensive efforts, few new risk factors for stillbirth have been identified (Flenady, Middleton, et al., 2011). Smoking during pregnancy is associated with increased risks of stillbirth and early neonatal mortality (Cnattingius, Haglund, & Meirik, 1988; Kleinman, Pierre, Madans, Land, & Schramm, 1988; Salihu et al., 2008; Salihu & Wilson, 2007). Swedish oral moist snuff (Swedish “snus”), which is a kind of smokeless tobacco, increases the risk of stillbirth (Wikström,

Cnattingius, & Stephansson, 2010), and the association between snuff use and early neonatal mortality has not been investigated. Snuff contains quantities of nicotine comparable with those typically absorbed from cigarette smoking but does not result in exposure to the products of combustion, for example, carbon monoxide (Foulds, Ramstrom, Burke, & Fagerstrom, 2003). However, like smoking, snuff use increases the risk of preterm birth (Baba, Wikström, Stephansson, & Cnattingius, 2012; Wikström, Cnattingius, Galanti, Kieler, & Stephansson, 2010), which is a major risk factor for early neonatal mortality (Goldenberg, Culhane, Iams, & Romero, 2008). The use of oral moist snuff has increased among women in Sweden and in other parts of the world (Gartner et al., 2007). Fetuses prenatally exposed to maternal smoking are exposed to both nicotine and tobacco combustion products, whereas fetuses prenatally exposed to maternal snuff use are essentially only exposed to nicotine. If women who stop smoking or stop using snuff reduced their risks of stillbirth or early neonatal mortality, causality would be supported. Women who stop smoking during pregnancy reduce their stillbirth risk

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(Wisborg, Kesmodel, Henriksen, Olsen, & Secher, 2001), but we are neither aware of any study investigating the association between change of snuff habits and risk of stillbirth nor aware of any study examining if change of snuff or smoking habits influence risk of early neonatal mortality.

The Swedish Medical Birth Register gave access to nationwide information about tobacco habits 3 months before and in early pregnancy for the years 1999–2010. We used this information to perform a large population-based study to evaluate whether cessation of snuff use and smoking in early pregnancy reduce risks of stillbirth and early neonatal mortality.

## METHODS

### Study Population

Information from the Swedish Medical Birth Register was used to define the study population. The Birth Register contains data on more than 98% of all births in Sweden, including demographic data, information on reproductive history, and complications during pregnancy, delivery, and the neonatal period. Information on tobacco habits and body mass index (BMI) was registered at the first prenatal visit, and information on maternal age and parity was registered at delivery. Using the Swedish Personal Identification Number, uniquely assigned to each Swedish resident, the Medical Birth Register can be linked to other Swedish data sources (Ludvigsson, Otterblad-Olausson, Pettersson, & Ekbom, 2009). Information about mother's highest level of formal education was achieved by individual record linkage to the Education Register (December 31, 2010).

At the time of registration for prenatal care, which occurs before the 15th weeks of gestation for more than 95% of the pregnancies, information on tobacco use at 3 months before pregnancy and present tobacco use is collected by midwives (Centre for Epidemiology, Swedish National Board of Health and Welfare, 2003). Information about smoking has been recorded since 1982 and information about snuff use since 1999. Women are, since 1999, categorized as nontobacco users, snuff users, smokers, and combined snuff and cigarette users.

To increase the homogeneity of the study population, we only included women born in the Nordic countries (i.e., women born in Sweden, Denmark, Norway, Iceland, and Finland) with single births during the years 1999–2010 ( $n = 948,137$ ).

We excluded pregnancies with missing information on gestational age ( $n = 707$ ) and maternal age ( $n = 23$ ) at delivery. The stillbirth definition was changed in 2008 in Sweden from fetal death at 28 weeks or later to fetal death at 22 weeks or later. To have a consistent definition of stillbirth during the entire study period (28 weeks or more), we therefore excluded 186 stillbirths with a gestational age from 22 to 27 completed weeks.

Of the remaining 947,221 women, information on both prepregnancy and early pregnancy tobacco habits was available for 857,650 women. Among these women, 667,301 women (78%) were nontobacco users both 3 months before pregnancy and in early pregnancy. Among 23,654 women reporting that they used snuff 3 months before pregnancy, the majority (60%) had stopped using snuff before the first visit to prenatal care. Similarly, among 162,893 prepregnancy smokers, the majority (53%) had stopped smoking at the first visit to prenatal care.

### Smoking During Pregnancy

In order to estimate whether changes between prepregnancy and early pregnancy tobacco habits affect risks of stillbirth or early neonatal mortality, we categorized tobacco habits into five groups: (a) nontobacco users (nonusers of snuff and cigarettes, both before and in early pregnancy); (b) women who stopped using snuff (i.e., used snuff before but not in early pregnancy); (c) current snuff users (used snuff both before and in early pregnancy); (d) women who stopped smoking (smoked before but not in early pregnancy); and (e) current smokers (smoked both before and in early pregnancy). These groups included more than 99% ( $n = 851,371$ ) of women with available information about tobacco habits ( $n = 857,650$ ). Thus, we excluded 6,279 women who were nontobacco users before pregnancy but started to use snuff or smoke in early pregnancy (1,230 and 793, respectively); women who changed from smoking before pregnancy to snuff use in early pregnancy (or vice versa; 769 and 78, respectively); and women who were both smokers and snuff users before and/or in early pregnancy (3,409).

### Outcome Variables

Stillbirths are registered in the Birth Register and information about early neonatal deaths was obtained through linkage of individual records to the population-based Cause of Death Register. In Sweden, gestational age is assessed by ultrasound scans in 97% of women, usually around the 17<sup>th</sup> weeks of gestation (Swedish Council on Technology Assessment in Health Care, 1998). If no early second-trimester ultrasound scan was available, the last menstrual period was used to calculate gestational age at delivery.

Stillbirth was defined as fetal death at 28 weeks of gestation or later, and after excluding 1,589 live births with a gestational age <28 weeks, stillbirth analyses were based on 849,782 births. Early neonatal death was defined as death of a live born infant during the first week of life (Barfield & the Committee of Fetus and Newborn, 2011). Analyses of early neonatal mortality was based on all live birth with a gestational age  $\geq 22$  weeks ( $n = 849,049$ ). The study was approved by one of the Regional Ethical Review Boards in Stockholm, Sweden.

### Statistical Analysis

Multivariable logistic regression analyses were used to estimate associations between tobacco habits and risks of stillbirth and early neonatal mortality. Using nontobacco users as the reference group, we estimated the risk of stillbirth and early neonatal mortality among women who continued to use snuff, stopped using snuff, continued to smoke, and stopped smoking. Maternal age at delivery, parity, early pregnancy BMI, and education were considered to be potential confounders. Odds ratios, presented with 95% CI, were calculated after adjustments for other maternal characteristics, which were categorized according to Table 1. We also wanted to investigate whether a possible effect of snuff use or smoking on early neonatal mortality risk was explained by preterm birth. In a supplementary analysis of risk of early neonatal mortality, we therefore also adjusted for gestational age (categorized as  $\leq 31$  weeks, 32–36 weeks, and  $\geq 37$  weeks). Observations with missing information on covariates were excluded in the multivariable analyses. All analyses were performed using the Statistical Analysis Software version 9.2 (SAS Institute).

## Influence of snuff and smoking habits in early pregnancy

Because observations are not independent in women who delivered more than one infant during the study period, we calculated estimates using clustered data in the generalized estimation equation method (PROC GENMOD).

## RESULTS

Overall stillbirth and early neonatal mortality rates were 2.7 and 1.0 per 1,000, respectively (Table 1). Compared with nontobacco users, women who had stopped using snuff at registration to prenatal care had a slightly lower stillbirth rate, whereas women who had stopped smoking at registration to prenatal care had a slightly higher stillbirth rate than nontobacco users. Current snuff users and current smokers had substantially higher stillbirth rates than nontobacco users. Women who had stopped using snuff or stopped smoking had similar early neonatal mortality rates as nontobacco users. Current smokers, but not current snuff users, had a higher early neonatal mortality rate than nontobacco users.

High stillbirth and early neonatal mortality rates were also found among the youngest ( $\leq 19$  years) and oldest ( $\geq 35$  years)

mothers, primiparous and multiparous ( $\geq 3$ ) women, obese women ( $\text{BMI} \geq 30$ ), and women with lower ( $\leq 9$  years) education.

Compared with nontobacco users, women who stopped using snuff and women who stopped smoking before first visit to prenatal care had no increased risks of stillbirth (Table 2). Women who continued to use snuff and women who continued to smoke had increased risks of stillbirth.

Current snuff use or cessation of snuff use did not influence risk of early neonatal mortality (Table 3). Women who stopped smoking before first visit to prenatal care had a similar risk of early neonatal mortality as nontobacco users. Compared with nontobacco users, women who continued to smoke had an increased risk of early neonatal mortality (Table 3, adjusted model 1). When we also adjusted for gestational age, women who continued to smoke had no increased risk of early neonatal mortality (Table 3, adjusted model 2).

## DISCUSSION

In this nationwide Swedish study, we found that women who continued to use snuff or to smoke in early pregnancy had

**Table 1. Maternal Characteristics and Risks for Stillbirth and Early Neonatal Mortality: Women With Singleton Births in Sweden, 1999–2010**

	Total number of pregnancies	Stillbirths <sup>a</sup>		Early neonatal deaths <sup>b</sup>	
	<i>n</i>	<i>n</i>	Rate/1,000	<i>n</i>	Rate/1,000 live births
Total	8,51,371	2,322	2.7	856	1.0
Maternal characteristic					
Tobacco habits					
Nonuser	6,67,301	1,684	2.5	633	1.0
Stopped using snuff	14,162	27	1.9	15	1.1
Current snuff user	9,198	37	4.0	7	0.8
Stopped smoking	85,712	229	2.7	87	1.0
Current smoker	74,998	345	4.6	114	1.5
Maternal age (years)					
$\leq 19$	13,382	45	3.4	25	1.9
20–24	99,001	271	2.7	95	1.0
25–29	2,60,620	629	2.4	237	0.9
30–34	3,08,560	816	2.6	307	1.0
$\geq 35$	1,69,808	561	3.3	192	1.1
Parity					
1	3,86,709	1,145	3.0	443	1.1
2	3,14,256	732	2.3	247	0.8
$\geq 3$	1,50,406	445	3.0	166	1.1
Body mass index					
$\leq 19.9$	74,368	156	2.1	57	0.8
20.0–24.9	4,30,539	928	2.2	357	0.8
25.0–29.9	1,95,714	611	3.1	224	1.1
$\geq 30$	88,714	461	5.2	154	1.7
Missing	62,036	166	2.7	64	1.0
Education (years)					
$\leq 9$	60,775	217	3.6	90	1.5
10–12	3,66,481	1,160	3.2	394	1.1
13–14	1,17,317	302	2.6	112	1.0
$\geq 15$	3,04,396	639	2.1	259	0.9
Missing	2,402	4	1.7	1	0.4

Note. <sup>a</sup>Stillbirth rates calculated on pregnancies with gestational age  $\geq 28$  weeks ( $n = 849,782$ ).

<sup>b</sup>Rates of early neonatal mortality calculated on liveborn infants at  $\geq 22$  weeks ( $n = 849,049$ ).

increased risks of stillbirth, whereas women who stopped using snuff or to smoke reduced their stillbirth risk to that of nontobacco users. We also found that smoking but not snuff use increased the risk of early neonatal mortality.

Snuff use and smoking have previously been associated with increased stillbirth risk (Flenady, Koopmans, et al., 2011; Raymond, Cnattingius, & Kiely, 1994; Wikström, Cnattingius, & Stephansson, 2010). Few studies have investigated smoking cessation and risk of stillbirth. One Danish study showed that those who stopped smoking before 16 weeks had a similar risk of stillbirth to nonsmokers (Wisborg, Kesmodel, Henriksen, Olsen, & Secher, 2001). We previously reported that compared with women who smoke in both their first and second pregnancies, women who stop smoking after their first pregnancy reduce their risk of stillbirth in the second pregnancy (Högberg & Cnattingius, 2007). In the present investigation, women who stopped using snuff and women who stopped smoking before the first prenatal visit reduced their risk of stillbirth to the same level as nontobacco users. In contrast, both women who continued to use snuff or continued to smoke had increased stillbirth risks. These findings favor the hypothesis that maternal snuff use and smoking may cause a direct toxic exposure during pregnancy, which increases the risk of stillbirth.

Nicotine exposure levels are similar in snuff users and in cigarette smokers. Snuff includes nicotine, whereas smoking also entails a large number of combustion products (Foulds, Ramstrom, Burke, & Fagerström, 2003). Since both smoking and snuff use were associated with increased stillbirth risks, we speculate that prenatal nicotine exposure may cause stillbirth. However, the mechanism by which nicotine may influence stillbirth risk is not clear. Nicotine reduces fetal blood

flow (Lambers & Clark, 1996) and causes contractions of the placental vessels (Romani et al., 2011; Suzuki et al., 1971). As abnormal pattern of uterine artery Doppler flow velocimetry at 22–24 weeks is strongly associated with subsequent stillbirth risk (Smith, Yu, Papageorgiou, Cacho, & Nicolaides, 2007), nicotine may cause stillbirth by affecting placental and fetal blood flow. Nicotine may also influence the immune system and risk of infections, which also is associated with stillbirth risk (McAllister-Sistilli et al., 1998).

Most previous investigations have found that smoking also increases the risk of early neonatal mortality, and a dose–response relationship between amount smoked and risk is generally reported (Cnattingius, Haglund, & Meirik, 1988). Our study supports and extends on these findings, as we were able to show that women who stopped smoking were not at increased risk of early neonatal mortality. We also found that the smoking-related risk of early neonatal death disappeared when we adjusted for gestational age. This finding lends support to the hypothesis that the smoking-related risk of early neonatal mortality is mediated through preterm birth. In contrast to smoking, we found no effect of current snuff use or cessation of snuff use on the risk of early neonatal mortality. However, we have previously reported that both prenatal snuff and smoking exposure increase the risk of preterm birth, suggesting that nicotine, rather than tobacco combustion, affects the risk of preterm birth (Baba, Wikström, Stephansson, & Cnattingius, 2012). Considering the small number of current snuff users whose infants died during their first week of life, we cannot exclude that the negative finding with respect to snuff use and early neonatal mortality was due to low statistical power.

Like snuff, nicotine replacement therapy (NRT) mainly contains nicotine. NRT usually generates lower nicotine levels than smoking and probably also snuff, but nicotine level remains continuously high during use (Benowitz, 1997). One study from Denmark showed no increased stillbirth risk for women using NRT in early pregnancy (Strandberg-Larsen, Tinggaard, Nybo Andersen, Olsen, & Grønbaek, 2008). Considering that more than 50% of the snuff users and smokers in our study quit using tobacco before the first prenatal visit, it is possible that a large proportion of the Danish NRT users only temporarily used NRT.

### Strengths and Limitations

Major strengths of our study include its population-based design, with information on both snuff use and smoking, both before and in early pregnancy of more than 800,000 women.

**Table 2. Tobacco Exposure in Early Pregnancy and Risk for Stillbirth**

	Crude OR (95% CI)	Adjusted <sup>a</sup> OR (95% CI)
Nonuser <sup>b</sup>	1.00	1.00
Stopped using snuff	0.76 (0.52–1.10)	0.73 (0.50–1.06)
Current snuff user	1.56 (1.12–2.17)	1.43 (1.02–1.99)
Stopped smoking	1.06 (0.92–1.22)	0.96 (0.83–1.11)
Current smoker	1.84 (1.64–2.07)	1.59 (1.40–1.80)

Note. OR = odds ratio, CI = confidence intervals.

<sup>a</sup>ORs were adjusted for maternal age, parity, early pregnancy body mass index, and education.

<sup>b</sup>Reference group.

**Table 3. Tobacco Habits in Early Pregnancy and Risk for Early Neonatal Mortality**

	Crude OR (95% CI)	Adjusted models	
		Model 1 <sup>a</sup> OR (95% CI)	Model 2 <sup>b</sup> OR (95% CI)
Nonuser <sup>c</sup>	1.00	1.00	1.00
Stopped using snuff	1.12 (0.67–1.86)	1.06 (0.64–1.78)	1.15 (0.68–1.93)
Current snuff user	0.80 (0.38–1.70)	0.75 (0.35–1.58)	0.64 (0.30–1.37)
Stopped smoking	1.07 (0.86–1.34)	0.96 (0.76–1.21)	1.02 (0.80–1.28)
Current smoker	1.62 (1.33–1.98)	1.37 (1.11–1.71)	1.09 (0.87–1.35)

Note. OR = odds ratio, CI = confidence intervals.

<sup>a</sup>ORs were adjusted for maternal age, parity, early pregnancy body mass index, and education.

<sup>b</sup>ORs were adjusted for maternal age, parity, early pregnancy body mass index, education, and gestational age.

<sup>c</sup>Reference group.



Information on snuff and smoking habits was collected in early pregnancy, which precludes recall bias. We adjusted for maternal characteristics, such as age, parity, BMI, and social factors. Major weaknesses include that information on tobacco exposure 3 months before pregnancy was based on interviews performed by a midwife at the first visit to prenatal care. Information on tobacco exposure in early pregnancy was prospectively collected, but we had no access to biological samples to validate this information. Most women in Sweden are aware of potential adverse effect of tobacco on pregnancy outcomes, and underreporting of tobacco use must be considered. Some women who stopped smoking in early pregnancy later resume smoking (George, Granath, Johansson, & Cnattingius, 2006). Self-reported information on maternal snuff use has not been validated, but the validity of self-reported smoking during pregnancy is acceptable in Sweden (George et al., 2006).

In conclusion, both smoking and use of oral moist snuff in early pregnancy increase risk of stillbirth. Smoking, but not snuff use, increases the risk of early neonatal death. Also, women who stop using snuff or to smoke before or in early pregnancy reduced their stillbirth risk compared with those of nontobacco users. These findings suggest that nicotine (included in both tobacco smoke and snuff) may increase stillbirth risk. We conclude that products containing nicotine should be avoided during pregnancy and educational programs for cessation of tobacco during pregnancy should be promoted.

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## DECLARATION OF INTERESTS

None declared.

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