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REVIEW

ADDICTION SSA

Use of Swedish smokeless tobacco during pregnancy: A systematic review of pregnancy and early life health risk

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Abstract

Background and Aims: Smokeless tobacco is a heterogeneous product group with diverse composition and prevalence globally. Tobacco use during pregnancy is concerning due to the risk of adverse pregnancy outcomes and effects on child health. Nicotine may mediate several of these effects. This systematic review measured health outcomes from Swedish smokeless tobacco (snus) use during pregnancy.

Method: Literature search was conducted by an information specialist in May 2022. We included human studies of snus use during pregnancy compared with no tobacco use, assessed risk of bias, conducted a meta-analysis and assessed confidence in effect-estimates using Grading of Recommendations, Assessment, Development and Evaluations (GRADE).

Results: We included 18 cohort studies (42 to 1 006 398 participants). Snus use during pregnancy probably (moderate confidence in risk estimates) increase the risk of neonatal apnea, adjusted odds ratio 95% confidence interval [aOR (95% CI)] 1.96 (1.30 to 2.96). Snus use during pregnancy possibly (low confidence in risk estimates) increase the risk of stillbirths aOR 1.43 (1.02 to 1.99), extremely premature births aOR 1.69 (1.17 to 2.45), moderately premature birth aOR 1.26 (1.15 to 1.38), SGA aOR 1.26 (1.09 to 1.46), reduced birth weight mean difference of 72.47 g (110.58 g to 34.35 g reduction) and oral cleft malformations aOR 1.48 (1.00 to 2.21). It is uncertain (low confidence in risk estimates, CI crossing 1) whether snus use during pregnancy affects risk of preeclampsia aOR 1.11 (0.97 to 1.28), antenatal bleeding aOR 1.15 (0.92 to 1.44) and very premature birth aOR 1.26 (0.95 to 1.66). Risk of early neonatal mortality and altered heart rate variability is uncertain, very low confidence. Snus using mothers had increased prevalence of caesarean sections, low confidence.

† Deceased.

Conclusions: This systematic review reveals that use of smokeless tobacco (snus) during pregnancy may adversely impact the developing child.

KEYWORDS
Child health, epidemiology, pregnancy, public health, smokeless tobacco, snus

INTRODUCTION

Several alternative nicotine products, such as e-cigarettes, heated tobacco products, tobacco-free nicotine pouches and smokeless tobacco products such as snus, a Swedish moist tobacco product, are available on the market. Snus comes loose or in portion bags (pouches) to be placed under the upper lip and is available in a range of different flavors. Like other tobacco products, snus contains hazardous constituents such as nicotine, tobacco-specific nitrosamines (TSNA), heavy metals and polycyclic aromatic hydrocarbons (PAHs) [1].

Except for Sweden, a country with a long tradition for use of snus, there is a ban on snus retail in the European Union (EU). In Sweden, the prevalence of daily use 3 months before pregnancy has risen from approximately 2% in 2000 to approximately 5% in 2019 [2], and the prevalence of snus use in early pregnancy was 1.2% (2020), self-reported by pregnant women [3]. In Norway, daily use of snus among young women (aged 25–34 years) increased from 1 to 17% during the period 2005–21 [4]. Snus use among pregnant women was not recorded in the Norwegian Birth Registry until 2021. At the beginning of pregnancy 4.7% of Norwegian women used snus, whereas 1.8% used snus at the end of pregnancy [5]. In the United States, 2–3% of the population report use of smokeless tobacco products, with a market share of more than 90% for moist snuff [6–8].

In 2014, the US Surgeon General reported that nicotine may mediate several of the adverse effects associated with use of tobacco during pregnancy [9]. Adverse effects of nicotine on the mother, placenta, fetus and developing child are supported by animal studies. Many of nicotine's effects are mediated through binding and activation of widely distributed nicotinic cholinergic receptors important for fetal development [10]. *In-utero* interference with signaling functions mediated by these receptors has been shown to affect development of several organ systems, e.g. brain and lung [11–14]. Furthermore, animal studies suggest that nicotine may harm the fetus via its effects on placenta development/function [15, 16]. When using information from animal studies, it is important to consider the internal dose/concentration of harmful substances. It is likely that nicotine concentrations in placenta, amniotic fluid and fetal serum exceed those of maternal serum after snus use, as reported for smoking mothers [17]. In addition, the infant may be exposed to nicotine through breast milk if nicotine products are used after birth [18–20].

Nicotine absorption from smokeless tobacco products have the same peak concentration as that from smoking, although the absorption occurs at a slower rate [21]. However, the total amount of nicotine absorbed may be higher with use of smokeless tobacco than from smoking. Snus, as well as other nicotine-containing products, comes with a variety of nicotine contents. In recent years, pouched smokeless tobacco products with increased nicotine content have been introduced onto the market. This is likely to result in elevated user exposure to nicotine.

The use of snus by women at fertile age should be a matter of concern, as several animal experiments and the report from the US Surgeon General have indicated adverse effects both on pregnancy outcomes and the health of the newborn associated with use of snus during pregnancy. In the present review, we summarize the human studies on adverse pregnancy outcomes and child health associated with use of snus during pregnancy.

OBJECTIVES

The aim of this systematic review was to summarize the epidemiological evidence on health outcomes associated with use of snus during pregnancy compared with no use of tobacco.

METHODS

Protocol

The present systematic review on health risks from use of snus during pregnancy [International Prospective Register of Systematic Reviews (PROSPERO) CRD42021290767] was conducted in accordance with the Cochrane Handbook [22].

Search strategy

The literature search was conducted by a head librarian in May 2022. The search was built on previous searches conducted in 2004, updated in 2013 and 2018 (Fig. 1) [23–25]. The following electronic databases were searched: MEDLINE (Ovid), Embase (Ovid), PsycInfo, Cochrane Database of Systematic Reviews, Cochrane Central register of controlled trials and Web of Science. Terms related to geographical regions were used to restrict the search to the use of Swedish snus. In the Nordic countries, this is the predominant smokeless tobacco used. However, we did not exclude studies from other regions. The search strategies are presented in the Supporting information, Appendix S1.

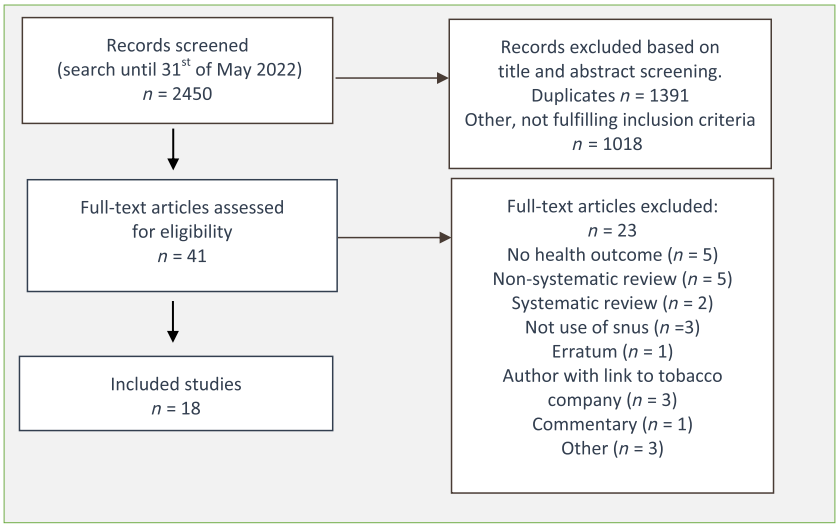

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram illustrating inclusion of publications. In total, 18 studies on adverse pregnancy outcomes and child health of using snus during pregnancy were included from the systematic literature search (May 2022)

Study eligibility criteria

We included human studies, with no restrictions on study design, that reported on health consequences from snus use compared with no use of tobacco during pregnancy and limited to publications in English, Norwegian, Swedish or Danish. Studies sponsored by producers or conducted by researchers with a link to the tobacco industry were excluded [26].

Study selection

The identified titles and abstracts were screened against the inclusion criteria by two researchers independently of each other; discrepancies were resolved by discussion. Relevant papers were assessed in full text by two researchers independently and discrepancies resolved by discussion.

Data extraction

One author collected information from the included studies and another author controlled that the information was extracted correctly. We extracted data on the full reference, study design, data collection period, information about participants (both on mother and fetus), number of participants, outcomes reported, time of reporting and adjusted confounders, as well as information on snus use including quitting information. The majority of relevant studies on use of snus during pregnancy were based on the Swedish Medical Birth Register (SMBR). When an overlap in time of data collection occurred, we used the study with the highest number of included births to avoid double-counting of pregnant women and infants. Hence, for all outcomes apart from birth weight, these were collected from single studies and reported narratively in this review. For all studies reporting on snus use only, these data were collected.

Study quality

Risk of bias in the included studies was assessed and discussed by two researchers. We used the checklist for cohort studies by The Joanna Briggs Institute [27]. All studies reporting effects from snus use during pregnancy on pregnancy outcomes and outcomes in infants and children are presented in the text and Table 1. We used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach to evaluate our confidence in effect estimates on adverse pregnancy outcomes and outcomes at birth and in newborns [28]. Studies with a high risk of bias or where absolute risk estimates could not be determined based on the number of events were not included in the GRADE approach. Graded outcomes are presented in our GRADE table (Table 2). Visualization of graded risk estimates was made using GraphPad Prism version 8 software (GraphPad Software, Inc., San Diego, CA, USA).

Meta-analysis

We conducted a meta-analysis on birth weight based on four studies with a random-effects model using RevMan5, and results are presented as mean difference with 95% confidence interval (CI). We extracted data on the groups with the longest reported periods of snus use during pregnancy. From the studies based on SMBR, we used birth weight of children from women using snus both in early and late pregnancy, and from the study by Kreyberg and co-workers [29] we used birth weight for women using snus up to week 34. For Rygh and co-workers [30] we used birth weight from pregnancies of women reporting use of snus in the third trimester.

RESULTS

The systematic search identified 2450 articles; 1391 were duplicates, while 1018 did not fulfill our inclusion criteria. Forty-one studies were

TABLE 1 Results for use of Swedish snus and adverse pregnancy outcomes and child health

Study	Origin of information on tobacco use	Use of snus during pregnancy	Quit using snus before, in early or during pregnancy	Raw data *a: Adjusted data*
Stillbirths at 28 weeks or later				
Baba 2014 1999–2009	Swedish Medical Birth Registry (SMBR); recorded by midwife at first antenatal visit, before 15 weeks of gestation	OR = 1.56 (1.12–2.17) ***aOR = 1.43 (1.02–1.99)***	OR = 0.76 (0.52–1.10) *aOR = 0.73 (0.50–1.06)*	Raw data *Adjusted for maternal age, parity, BMI and education*
Wikström 2010 1999–2006	SMBR; recorded by midwife: at first antenatal visit, before 15 weeks of gestation	Crude OR not presented *aOR = 1.6 (1.13–2.29)*	Not presented	Raw data *Adjusted for maternal age, BMI, parity, education, chronic hypertension and pre-pregnancy diabetes*
Early neonatal death (1 week after live birth)				
Baba 2014 1999–2009	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation	OR = 0.80 (0.38–1.70) ***aOR = 0.75 (0.35–1.58)*** ***aOR = 0.64 (0.30–1.37)***[a]	OR = 1.12 (0.67–1.86) *aOR = 1.06 (0.64–1. 78)*	Raw data *Adjusted for maternal age, parity, BMI and education (gestational age[a])*
Extremely preterm (< 28 weeks)				
Dahlin 2016 1999–2012	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation	OR = 1.66 (1.15–2.40) ***aOR = 1.69 (1.17–2.45)***	OR = 0.78 (0.52–1.17) *aOR = 0.78 (0.52–1.16)*	Raw data *Adjusted for mother's age, parity, BMI, family situation, education and mother's country of birth*
Very preterm (< 32 weeks)				
Dahlin 2016 1999–2012	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation	OR = 1.28 (0.97–1.69) ***aOR = 1.26 (0.95–1.66)***	OR = 0.96 (0.75–1.22) *aOR = 0.90 (0.71–1.15)*	Raw data *Adjusted for mother's age, parity, BMI, family situation, education and mother's country of birth*
Baba 2012 1999–2009	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation	OR = 1.50 (1.17–1.93) *aOR = 1.44 (1.12–1.86)*	OR = 0.97 (0.75–1.25) *aOR = 0.88 (0.68–1.14)*	Raw data *Adjusted for mother's age, parity, BMI, education and family situation*
Wikström 2010 1999–2006	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation	OR = 1.34 (1.03–1.75) *aOR = 1.38 (1.04–1.83)*	Not presented	Raw data *Adjusted for maternal age, BMI, parity and education*
Moderately preterm (32–36 weeks)				
Dahlin 2016 1999–2012	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation	OR = 1.30 (1.19–1.43) ***aOR = 1.26 (1.15–1.38)***	OR = 1.02 (0.95–1.10) *aOR = 0.95 (0.88–1.02)*	Raw data *Adjusted for mother's age, parity, BMI, family situation, education and mother's country of birth*
Baba 2012 1999–2009	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation	OR = 1.32 (1.19–1.46) aOR = 1.27 (1.15–1.41)	OR = 1.01 (0.92–1.11) *aOR = 0.93 (0.84–1.02)*	Raw data *Adjusted for mother's age, parity, BMI, education and cohabitation*
Wikström 2010 1999–2006	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation	OR = 1.26 (1.13–1.39) *aOR = 1.25 (1.12–1.40)*	Not presented	Raw data *Adjusted for maternal age, BMI, parity and education*
Preterm (< 37 weeks)				
England 2003 1999–2000	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation	Crude OR not presented, *aOR = 1.98 (1.46–2.68)*	Not presented	Raw data *Adjusted for maternal age, BMI, height, parity and fetal sex*
Baba 2012 1999–2009		OR = 1.34 (1.22–1.48) *aOR = 1.29 (1.17–1.43)*	OR = 1.01 (0.92–1.10) *aOR = 0.92 (0.84–1.01)*	Raw data

(Continues)

TABLE 1 (Continued)

Study	Origin of information on tobacco use	Use of snus during pregnancy	Quit using snus before, in early or during pregnancy	Raw data *a: Adjusted data*
	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation			*Adjusted for mother's age, parity, BMI, education and cohabitation*
Wikström 2010 1999–2006	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation	Crude OR not presented *Spontaneous birth:* *aOR = 1.25 (1.10–1.41)* *Induced birth:* *aOR = 1.33 (1.10–1.61)*	Not presented	Raw data *Adjusted for maternal age, BMI, parity and education*
Pre-eclampsia				
Wikström 2010 1999–2006	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation	Crude OR not presented, ***aOR = 1.11 (0.97–1.28)***	Not presented	Raw data *Adjusted for maternal age, BMI, parity and education*
England 2003 1999–2000	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation	Crude OR not presented, *aOR = 1.58 (1.09–2.27)*	Not presented	Raw data *Adjusted for maternal age, BMI and height*
Antenatal bleeding				
Wikström 1999–2006	SMBR; recorded by midwife: at first antenatal visit, before 15 weeks of gestation	Crude OR not presented, ***aOR = 1.5 (0.92–1.44)***	Not presented	Raw data *Adjusted for maternal age, BMI, parity, education, chronic hypertension and pre-pregnancy diabetes*
Small for gestational age (SGA)				
Baba 2013 1999–2010	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation and from gestational week 30 to 32	OR = 1.31 (1.13–1.51) ***aOR = 1.26 (1.09–1.46)*** *Term SGA* *aOR = 1.50 (1.13–1.98)* *Preterm SGA* *aOR = 1.21 (1.02–1.43)* Term SGA:[b] OR = 1.31 (0.96–1.78) *aOR = 1.38 (1.01–1.88)* Preterm SGA:[b]*aOR = 1.50 (1.13–1.98)*	*OR = 0.97 (0.85–1.11)* Term SGA:[b] OR = 1.10 (0.88–1.38) *aOR = 1.08 (0.86–1.35)* Preterm SGA:[b] *aOR = 0.80 (0.60–1.08)*	Raw data *Adjusted for maternal age, parity, BMI, maternal height, family situation, education, and pre-pregnancy diabetes and hypertension*
England 2003 1999–2000	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation	Crude OR not presented, *aOR = 1.25 (0.72–2.17)*	Not presented	Raw data *Adjusted for maternal age, BMI, height and parity*
Birth weight (g)				
Juárez and Merlo 2013 2002–10	SMBR: Questionnaire administered by midwife first antenatal visit (weeks 10–12) and in the third trimester (weeks 30–32)	Crude OR not presented ***A −47 g (−66 to −28)***[b] *Sibling analysis:* *A −20 g (−52 to 12)*[b]	Not presented *A −6 g (−17 to 4)* *Sibling analysis:* *A −14 g (−14 to 3)* *(snus until 10–12 weeks)*	Mean value, crude *Adjusted for mother's age, whether mother is married, sibling order and fetal sex*
England 2003 1999–2000	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation. For 278 births early and late tobacco exposure was known	**−93 g (−147 *to* −39)**[b] A −39 g (−72 *to* −6)	Not presented	Mean value, crude *Adjusted for maternal age, parity, BMI, height, gestational age at birth and fetal sex*
Kreyberg 2019 2014–16	Electronic questionnaires at 18 and 34 weeks of pregnancy	−36 g (−319 to 246)[b] ***A −183 g (−436 to 70)***[b]	102 g (18 to 186) *A 100 g (24 to 176)* *(snus until 18 weeks)*	Univariable *Adjusted for parity, gestational age at birth, fetal sex, pre-pregnancy BMI and maternal age*
Rygh 2019 2012–17	Health personnel at the first antenatal, midwifes at	**−106 g (−186 to −26)**[b]	Not presented	Mean value, crude

(Continues)

TABLE 1 (Continued)

Study	Origin of information on tobacco use	Use of snus during pregnancy	Quit using snus before, in early or during pregnancy	Raw data *a: Adjusted data*
	ultrasound week 18 and at admission in the maternity ward			
Cesarean section				
Gunnerbeck 2011 1999–2006	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation	***18.2%***	Not presented	Raw data: proportion
Neonatal apnea				
Gunnerbeck 2011 1999–2006	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation	OR = 2.24 (1.52–3.32) ***aOR = 1.96 (1.30–2.96)***	Not presented	Raw data *Adjusted for maternal age, height, parity, education, tobacco use, cesarean section, fetal sex, gestational age and SGA*
Oral cleft malformations				
Gunnerbeck 2014 1999–2009	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation	OR = 1.59 (1.07–2.37) ***aOR = 1.48 (1.00–2.21)***	OR = 0.75 (0.46–1.21) *aOR = 0.71 (0.44–1.14)*	Raw data *Adjusted for maternal age, parity, education, cohabitation with father, blood pressure, diabetes, pre-eclampsia, fetal sex, multiple births, maternal country of birth*
Heart rate variability low−/high-frequency ratio				
Nordenstam 2017 2006–11	Questionnaires at 4 time-points pre- and post-natally	LF/HF ratio: **Total snus group: 3.31 (2.78–3.83).** Prenatal-continued exposure (smokers and snus users combined): **4.40 (3.38–5.42)** **Control = 2.15 (1.76–2.54)**	*LF/HF ratio*: Prenatal early exposure until gestational week 6–26 (smokers and snus users combined) 3.19 (2.55–3.84) Control = 2.15 (1.76–2.54)	*Not adjusted*
Nordenstam 2019 2011–17	Questionnaires at 4 time-points pre- and post-natally Questionnaire at follow-up when child was 5–6 years	BP increase: 5.4 mmHg ***BP = 4.2 mmHg (95% CI = 0.2–8.1)*** *LF/HF ratio median*: *Snus 0.69 (0.45–1.21 IQR)* *Control = 0.49 (0.32–0.57 IQR)*	Not presented	Raw data *Adjusted for the child's sex, age, and height*
Intellectual disability				
Madley-Dowd 2021 1999–2012	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation and from gestational week 30 to 32	OR = 1.46 (1.22–1.75) ***aOR = 1.31 (1.10 to 1.57)*** (retrieved from Supporting information)		Raw data *Adjusted for year of birth, sex, parity, highest parental education, income, parental psychiatric history, maternal country of origin and maternal age at birth*
Incident asthma and wheeze				
Lundholm 2020 2005–12	SMBR; recorded by midwife at first antenatal visit, before 15 weeks of gestation	*First year*: *HR = 1.06 (0.92, 1.21)* ***aHR = 0.86 (0.74 to 0.99)*** *Second year*: *HR = 1.30 (1.15, 1.47)* ***aHR = 1.17 (1.03 to 1.32*** *Third year*: *HR = 1.15 (1.02, 1.31)* ***aHR = 1.04 (0.91 to 1.19)***		Raw data *Adjusted for birth year, parity, maternal BMI, age and family situation, asthma in the mother, asthma in the father, parental education, income and country of birth*

(Continues)

TABLE 1 (Continued)

Study	Origin of information on tobacco use	Use of snus during pregnancy	Quit using snus before, in early or during pregnancy	Raw data *a: Adjusted data*
Perinatal depression trajectories				
Wikman 2020	Biology, stress, imaging and cognition (BASIC cohort) recorded at gestational weeks 17 and 32, and 6 weeks and 6 months postpartum	***Pregnancy depression*** ***OR = 2.4 (1.4 –to 3.9)*** *Early postpartum onset* *OR = 1.2 (0.7 to 2.2)* *Late postpartum onset* *OR = 1.6 (0.8 to 3.3)* ***Chronic depression*** ***OR = 2.1 (1.4 to 3.3)***		

All results are presented with 95% confidence intervals (CIs). The first column gives information on where data on tobacco use originated. The light gray column presents risk estimates for women who continued to use snus throughout pregnancy compared with pregnant women who had never used tobacco products. For each outcome we have shown both raw data and adjusted data. We have used the adjusted results when available and marked in bold type those we have used for the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) evaluation. At some points, the table shows risk estimates for women who stopped using snus before or early in pregnancy, compared to those who never used tobacco products. The last column shows which factors have been adjusted for in the analysis. Bold-type letters = estimates presented in text. Where several studies were available for these estimates, results represent the largest cohort. OR = odds ratio; aHR = adjusted odds ratio; LF/HF = low-frequency/high-frequency; IQR = interquartile range; BMI = body mass index.

[a]Adjusted for gestational age.

[b]Effect-estimate based on snus use in both early and late pregnancy.

potentially relevant for pregnancy outcomes and assessed in full text; 18 studies were included [29–46]. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow-chart. Studies excluded after full text assessment are presented with the reason for exclusion in the Supporting information, Table S1.

Effects of snus use on pregnancy outcomes and child health from the individual studies are summarized in Table 1. Table 1 also presents variables included in adjusted analyses, as well as risk estimates from the same studies related to quitting snus use before pregnancy or before the first antenatal visit. Of the participants in the SMBR, approximately 90% had made a visit to the antenatal clinic before week 12 [47]. Supporting information, Fig. S1 presents an overview of size and time-period of cohorts.

Effects on pregnancy outcomes from use of snus during pregnancy compared with no use of tobacco were investigated in 18 studies. Stillbirth was reported in two studies [36, 44] and early neonatal deaths in one study [36]. Premature births were reported in four studies [34, 37, 38, 43], pre-eclampsia in two [38, 45] and antenatal bleeding in one study [44]. Small for gestational age (SGA) was reported in three studies [32, 35, 38], and birth weight was reported in four studies [29, 30, 38, 41]. One study reported on cesarean section and neonatal apnea [39] and one study reported on oral cleft malformations (OCM) [40]. Two studies reported on heart rate variability (HRV), one on infants [42] and the second on HRV and blood pressure of children at age 5–6 years [33]. One study reported on snus use during pregnancy and the child's later risk of asthma and wheeze [31] and one study reported on the risk of intellectual disability [32]. Furthermore, the associated risk of several adverse pregnancy outcomes was reduced among mothers quitting snus before or early in pregnancy (Fig. S2).

Most of these studies collected information from the Swedish Medical Birth Register (SMBR) during overlapping time periods (Supporting information, Fig. S1). SMBR includes several maternal characteristics, including reproductive history and demographic data, as well as tobacco habits, including snus use from 1999. The registry is population-based and includes more than 98% of all births in Sweden. Data are collected by health personnel at ante- and postnatal consultations. For outcomes reported in more than one study we included the study with highest number of births in the GRADE evaluation, in order to avoid double-counting of participants (Table 2). One exception was the study by Madley-Dowd and co-workers, which had the largest number of participants regarding SGA, but we were not able to identify the number of events. For birth weight, the two studies conducted in Sweden [38, 41] did not overlap in time (Supporting information, Fig. S1), and the two Norwegian studies were from different geographical areas [29, 30]. We judged the internal validity of included studies according to The Joanna Briggs Institute Critical Appraisal Tools for Cohorts Study, to have risk of bias ranging from low to high (Supporting information, Table S2).

Stillbirths and early neonatal death

The study by Baba and co-workers (2014) [36] reported on the risk of stillbirth (birth at 28 weeks or later) and early neonatal death (death within 1 week after delivery of live-born infants), using data from SMBR (1999–2010). Current and earlier use of snus was reported at

TABLE 2 Grading of Recommendations, Assessment, Development and Evaluations (GRADE) summary of findings table of use of snus compared with no use of tobacco in pregnancy

Use of snus compared with no use of tobacco in pregnancy

Patient or population: pregnancy
Setting: Swedish snus
Intervention: snus
Comparison: no use of tobacco

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with no snus	Risk difference with snus
Stillbirth	676 499 (1 observational study)	⨁⨁◯◯ Low	**aOR = 1.43** (1.02–1.99)	252 per 100 000	**108 more per 100 000** (5 more to 249 more)
Early neonatal mortality	676 499 (1 observational study)	⨁◯◯◯ Very low[a]	**aOR = 0.75** (0.35–1.58)	95 per 100 000	62 fewer to 55 more per 100 000
Extremely preterm, < 28 weeks	1 006 398 (1 observational study)	⨁⨁◯◯ Low	**aOR = 1.69** (1.17–2.45)	174 per 100 000	**120 more per 100 000** (30 more to 251 more)
Very preterm, weeks 28–31	1 006 398 (1 observational study)	⨁⨁◯◯ Low	**aOR = 1.26** (0.95–1.66)	399 per 100 000	**103 more per 100 000** (20 fewer to 262 more)
Moderately preterm, weeks 32–36	1 006 398 (1 observational study)	⨁⨁◯◯ Low	**aOR = 1.26** (1.15–1.38)	3995 per 100 000	**987 more per 100 000** (572 more to 1436 more)
Pre-eclampsia	506 798 (1 observational study)	⨁⨁◯◯ Low	**aOR = 1.11** (0.97–1.28)	3010 per 100 000	**320 more per 100 000** (88 fewer to 811 more)
Antenatal bleeding	512 160 (1 observational study)	⨁⨁◯◯ Low	**aOR = 1.15** (0.92–1.44)	10 per 1000	**1 more per 1000** (1 fewer to 4 more)
Small for gestational age	672 778 (1 observational study)	⨁⨁◯◯ Low	**aOR = 1.26** (1.09–1.46)	1763 per 100 000	**448 more per 100 000** (156 more to 790 more)
Birth weight (g)	6 16 948 (4 observational studies)	⨁⨁◯◯ Low	–	Mean birth weight was **3570** g	**72.5 g lower** (34 lower to 111 lower)
Cesarean section	511 059 (1 observational study)	⨁⨁◯◯ Low	–	15.4%	18.2%
Neonatal apnea	511 059 (1 observational study)	⨁⨁⨁◯ Moderate[b]	**aOR = 1.96** (1.30–2.96)	153 per 100 000	**147 more per 100 000** (46 more to 299 more)
Oral cleft malformations	774 004 (1 observational study)	⨁⨁◯◯ Low	**aOR = 1.48** (1.00–2.21)	177 per 100 000	**85 more per 100 000** (0 fewer to 214 more)
Heart rate variability (LF/HF ratio)	42 (1 observational study)	⨁◯◯◯ Very low[c]	–	Mean LF/HF 2.15	0.29 higher to 2.02 higher

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). LG/HF = low-frequency/high-frequency; aOR = adjusted odds ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect-estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect-estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect-estimate: the true effect is likely to be substantially different from the estimate of effect.

This table presents the effects on adverse pregnancy outcomes and child health associated with use of snus during pregnancy compared with not using tobacco. Size of the study population, our confidence in effect-estimates evaluated by GRADE and risk estimates are presented. Assumed absolute effect is calculated based on the estimates and incidence of the adverse outcomes in the general population.
CI = confidence interval; OR = odds ratio.
[a]Downgraded due to very wide confidence interval.
[b]Upgraded due to large effect size.
[c]Downgraded due to few participants in the study.

the women's first antenatal visit to the midwife, before 15 weeks of gestation. The study included 9 198 singleton births of pregnant women who used snus both before and in early pregnancy and 14 162 singleton births of pregnant women who stopped using snus before or in early pregnancy (before first antenatal visit), and 667 301 births of pregnant women who did not use tobacco. Pregnant women who used snus had an increased risk of stillbirth compared with those who neither used snus nor smoked; adjusted odds ratio (aOR) with 95% CI (aOR = 1.43, 95% CI = 1.0–1.99), based on 37 stillbirths among the exposed cases. Regarding early neonatal death among offspring of women reporting use of snus during pregnancy, CI for the OR was wide and the result was uncertain (aOR = 0.75, 95% CI = 0.35–1.58, seven exposed cases).

Premature births

The largest cohort study on premature births was by Dahlin and co-workers (2016) [37], also based on information from SMBR (1999–2012). The cohort included 11 167 singleton births of women who used snus both before and in early pregnancy and 995 231 singleton births of women who did not use tobacco. Compared with no tobacco, women using snus before and in early pregnancy had increased risks of extremely preterm birth (before 28 weeks) (aOR = 1.69, 95% CI = 1.17–2.45, 30 exposed cases); very preterm birth (weeks 28–31) (aOR = 1.26, 95% CI = 0.95–1.66, 55 exposed cases); and moderate preterm birth (weeks 32–36) (aOR = 1.26, 95% CI = 1.15 = 1.38, 568 exposed cases). Data were largely consistent among medically induced and spontaneous births [37].

Pre-eclampsia

Wikstrøm and co-workers (2010) [45] obtained information on pre-eclampsia from 499 243 singleton births of non-users of tobacco and 7555 singleton births of snus-using mothers, with data from SMBR (1999–2006). Among women using snus, 3.41% had pre-eclampsia (aOR = 1.11, 95% CI = 0.97–1.28, 258 exposed cases). For women using snus at first antenatal visit and with preterm delivery, risk of pre-eclampsia was aOR = 1.30, 95% CI = 1.00–1.70 (60 exposed cases). However, use of snus recorded at gestational weeks 30–32 did not appear to influence the risk of developing term pre-eclampsia or gestational hypertension.

Antenatal bleeding

The study by Wikström and co-workers [44] reported on antenatal bleeding (placenta previa, placental abruption or other reasons for antenatal bleeding) using data from SMBR. The data included 504 531 women not using any tobacco product and 7629 women using snus. Based on 90 cases among snus-using women, the authors reported an aOR = 1.15, 95% CI = 0.92–1.44.

SGA and birth weight

SGA was examined by Baba and co-workers (2013) [35] using data from SMBR (1999–2010). Based on 9129 singleton births of pregnant women using snus both before and in early pregnancy, the authors reported increased risks for SGA (aOR = 1.26, 95% CI = 1.09–1.46, 207 exposed cases), pre-term SGA (aOR = 1.50, 95% CI = 1.13–1.98, 53 exposed cases); and for term birth SGA (aOR = 1.21, 95% CI = 1.02–1.43, 154 exposed cases) compared to 663 649 singleton births of women not using tobacco. In addition, an increased risk for term birth SGA among pregnant women using snus throughout pregnancy (aOR = 1.38, 95% CI = 1.01–1.88, 46 exposed cases) was reported.

Using data from SMBR (1999–2011), with a 1-year longer data collection than Baba *et al.* [35], Madley-Dowd and co-workers (2021) reported an aOR = 1.22, 95% CI = 1.09–1.37 for SGA among women using snus at any time-point during pregnancy (sensitivity analysis, snus compared with no tobacco) [32]. The number of exposed cases was not reported, and this study was thus not included in the GRADE table. They also performed a within-family analysis for siblings with the same mother, and reported an aOR of 1.06, 95% CI = 0.81–1.38 for snus use during pregnancy compared with no tobacco.

Juárez & Merlo (2013) [41] recorded birth weight of newborns using SMBR data (2002–10), with 2298 singleton births of women using snus throughout pregnancy compared with 591 690 singleton births of women who had never used tobacco, adjusted estimate −46.9 g (95% CI = −66.0 to −27.9). Among 4934 women reporting to quit snus early in pregnancy, adjusted estimate was −6 g (95% CI = −17 to 4). Birth weight after use of snus in late pregnancy, adjusted estimate −93 g (95% CI = −38 to −147), was reported by England and co-workers (2003) [38] using data from SMBR (1999). Two Nordic cohort studies by Kreyberg and co-workers (2019) [29] and Rygh and co-workers (2019) [30] also investigated the effects of snus on birth weight. Kreyberg and co-workers studied 2313 singleton pregnancies from the PreventADALL cohort, a population-based, prospective mother–child birth cohort including infants born at a gestational age of ≥ 35.0 weeks without serious neonatal disease (Oslo and Fredrikstad, Norway and Stockholm, Sweden; 2014–16) [29, 30]. Rygh and co-workers retrieved data from the electronic birth registry for all women aged 16–44 years who gave birth in the years 2012–17 at three different hospitals located in southern Norway. Tobacco information was registered at the first antenatal check-up.

Most women reporting snus use in the study by Kreyberg and co-workers had quit before trying to become pregnant or when knowing that they were pregnant, and birth weight among these 132 participants was somewhat higher than among controls, adjusted estimate 100.0 g (95% CI = 23.9–176.1). Conversely, among 11 mothers reporting continued use of snus at 34 weeks of pregnancy, the adjusted estimate was −183.1 g (95% CI = −436.5 to 70.3).

Rygh and co-workers (2019) [30] compared birth weight for 201 pregnancies of snus-using mothers to that of 9213 non-users of tobacco (2015–17) based on snus information recorded in the third trimester, unadjusted estimate −106 g (95 CI = −186 to −26). Results

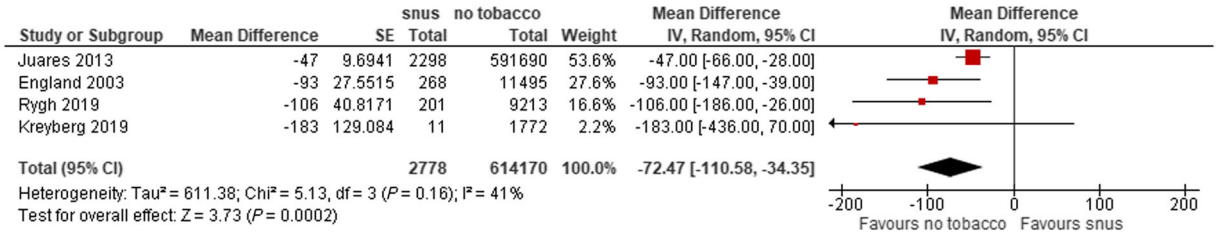

FIGURE 2 Meta-analysis on effects on birth weight from maternal snus use. Based on data from four cohort studies, with a total of 2788 mothers using snus throughout their pregnancies and 614 459 controls, we found an average reduction in birth weight of 72.47 g (95% confidence interval (CI) = −110.58 to −34.35) among children of mothers using snus. We included data on participants reporting snus use throughout pregnancy when possible. IV = inverse variance; SE = standard estimates

were based on crude unadjusted data. Furthermore, they studied birth weight in subgroups stratified on maternal age, parity and education. Birth weight differed most between children of snus users and non-tobacco users among mothers aged 16–24 years and among those with upper secondary education, and first-born children of snus users had the most markedly reduced birth weight.

We conducted a meta-analysis based on data from these four cohort studies on snus and birth weight [29, 30, 38, 41], including 2778 mothers using snus throughout pregnancy and 614 459 non-users of tobacco. We observed a mean reduction in birth weight of 72.5 g (95% CI = −34.4 to −110.6) among newborns of mothers using snus, compared with controls (Fig. 2). We observed consistency in the direction of effect. However, not surprisingly, due to the relatively low number of cases in three of four studies, there was some heterogeneity (I^2 = 41%).

As the study by Rygh and co-workers (2019) was based on unadjusted data, we conducted a sensitivity analysis excluding this study and present this in Supporting information, Fig. S3. The sensitivity analysis showed reduced birth weight of 65.8 g (95% CI = −24.0 to −107.6), thus the conclusion did not change.

Cesarean section

Cesarean section was reported by Gunnerbeck and co-workers (2011) [39], who compared 7599 deliveries of mothers using snus at first antenatal visit with 503 460 deliveries of mothers not using tobacco. Data was obtained from SMBR (1999–2006). There was an increased proportion of cesarean section for snus-using mothers of 18.2% compared to 15.4% among controls.

Neonatal apnea

The main aim of the study by Gunnerbeck and co-workers (2011) [39] described in the previous paragraph was to investigate effects of snus use on neonatal apnea. They found increased risk of neonatal apnea among children of mothers reporting use of snus adjusted for maternal characteristics (aOR = 2.15, 95% CI = 1.44–3.20, 26 exposed cases). In a second analysis adjusted for SGA, gestational age, cesarean section and gender they also found an increased risk of neonatal apnea (aOR = 1.96, 95% CI = 1.30–2.96, 26 exposed cases).

OCM

OCM were investigated by Gunnerbeck and co-workers (2014) [40], who obtained information on 1 086 213 births, including both single and multiple births, from SMBR (1999–2009). For 8859 births of pregnant women using snus both before and in early pregnancy, the authors reported a rate for OCM of 0.28%, whereas the rate among 765 145 births of mothers who did not use tobacco was 0.18%. Risk of OCM for children of mothers reporting use of snus was aOR = 1.48 (95% CI = 1.00–2.21, 25 exposed cases), compared with no use of tobacco.

HRV and blood pressure

HRV, a measure of sympathetic/parasympathetic imbalance, was studied by Nordenstam and co-workers (2017) [42]. They registered HRV among 23 newborns of mothers who had used snus, one twin pregnancy and 19 newborns of mothers who had not used tobacco 4–10 weeks after delivery. The HRV variable low-frequency/high-frequency (LF/HF) ratio was higher among 23 children of mothers using snus (mean = 3.31, 95% CI = 2.78–3.83) compared with 19 controls (mean = 2.15, 95% CI = 1.76–2.54). In a follow-up study, Nordenstam and co-workers (2019) measured the blood pressure of 21 children at age 5–6 years, with mothers who used snus during the entire pregnancy (nicotine dose ≥ 48 mg per day) compared with 19 children of mothers who had never used tobacco [33], and reported higher systolic blood pressure among children exposed during pregnancy (mean difference = 4.2 mmHg, 0.2–8.1 mmHg). Further, HRV was measured among 30 of the 40 children showing that LF/HF ratio was higher in children of mothers using snus during pregnancy [median = 0.69; interquartile range (IQR) = 0.45–1.21; 16 exposed children] than in controls (median = 0.49; IQR = 0.32–0.57; 14 cases).

Risk for intellectual disability

Using the same study populations as previously reported for SGA [32], Madley-Dowd and co-workers (2021) investigated the effect of snus use during pregnancy on the risk for intellectual disability in offspring, with a follow-up time of a minimum 4 years (age range of participants = 4–14 years). Diagnosis was retrieved from the National Patient Register; intellectual disability was defined as having a diagnosis with ICD-10 code F70–F79. They reported a risk of intellectual disability for children whose mother used snus during pregnancy compared to no use of tobacco (aOR = 1.31, 95% CI = 1.10–1.57), and by using a within-family analysis (aOR = 0.92, 95% CI = 0.60–1.42) we could not identify the number of exposed cases for these estimates.

Risk of asthma and wheeze

Lundholm and co-workers included all children in SMBR from July 2005 to December 2012 [31]. Data on asthma medication and diagnosis for 678 090 children was retrieved from the Swedish Prescribed Drug Register and the National Patient Register, respectively. Mean follow-up time was 6 years. During the first year after birth, the risk of incident asthma/wheeze for children of mothers using snus before and in early pregnancy was adjusted hazard ratio (aHR) = 0.86 (95% CI = 0.74–0.99, number of exposed cases not presented); during the second year after birth, aHR = 1.17 (95% CI = 1.03–1.32, number of exposed cases not presented); and during the third year after birth aHR = 1.04 (95% CI = 0.91–1.19, number of exposed cases not presented). The results were reported as hazard plots with time-varying hazard ratios.

Perinatal depression

In a study with a total of 2466 pregnant responders, Wikman and co-workers (2020) [46] explored different characteristics associated with perinatal depression trajectories. One of these characteristics were the use of snus. The authors reported that snus use prior to pregnancy was associated with depression during pregnancy and chronic depression [depression during pregnancy and up to 6 months postpartum (unadjusted analysis), OR = 2.4, 95% CI = 1.4–3.9 and OR = 2.1, 95% CI = 1.4–3.3, respectively].

Grading of our confidence in the effect-estimates

Our GRADE assessments are presented in Table 2 and the risk estimates are visualized in Fig. 3. Confidence in the estimates was moderate to very low. All included cohorts relied their exposure information on self-reported tobacco habits. In our assessment, self-reporting of exposure is a potential risk of bias from misclassification, implying the results to confer moderate risk of bias. However, as this self-reporting would be expected to bias estimates towards unity or null, our confidence in these effect estimates was not downgraded. The studies on stillbirths, early neonatal death, extremely, very and moderately preterm delivery, pre-eclampsia, SGA, cesarean section, neonatal apnea and OCM were all based on data from SMBR [32, 34–37, 39, 40, 43–45]. Because this registry is a national cohort that collects data on virtually all pregnancies and children born in Sweden, we have not downgraded confidence in the risk estimates for outcomes related directly to exposure during pregnancy due to use of only one source. Because the heterogeneity observed in the analysis of birth weight pertains to size of effect with all the studies showing the same direction, we do not downgrade this outcome. Due to a virtual doubling of risk for neonatal apnea, and a more than twofold risk when not adjusted for gestational age, we upgraded our confidence in the risk estimate to moderate. For very preterm birth and pre-eclampsia, the lower end of the confidence intervals just crossed the line of no effects; however, as the upper limits suggested a possible considerably increased risk, we did not downgrade our confidence in the risk estimates to 'very low' for these outcomes.

With moderate confidence in the risk estimate, implying that the true effect is likely to be close to the estimate, use of snus during pregnancy compared to no use of tobacco probably leads to:

- increased risk of neonatal apnea

With low confidence in the risk estimates or result, which implies that the true effect may be substantially different from the estimates, use of snus during pregnancy compared to no use of tobacco may lead to:

- increased risk of stillbirth
- increased risk of extreme preterm birth (< 28 weeks)
- increased risk of moderately preterm birth
- increased risk of small for gestational age
- decreased birth weight
- increased risk of oral cleft malformations
- increased proportion of cesarean sections

There is uncertainty about the effect from use of snus during pregnancy compared to no use of tobacco (low confidence in the risk estimates) for:

- very premature birth (28–31 weeks)
- pre-eclampsia
- antenatal bleeding

With very low confidence in the risk estimate or result, which implies that the true effect might be substantially different from the estimates, there is uncertainty regarding the effect from use of snus during pregnancy compared to no use of tobacco for:

- early neonatal mortality
- altered HRV (LF/HF ratio)

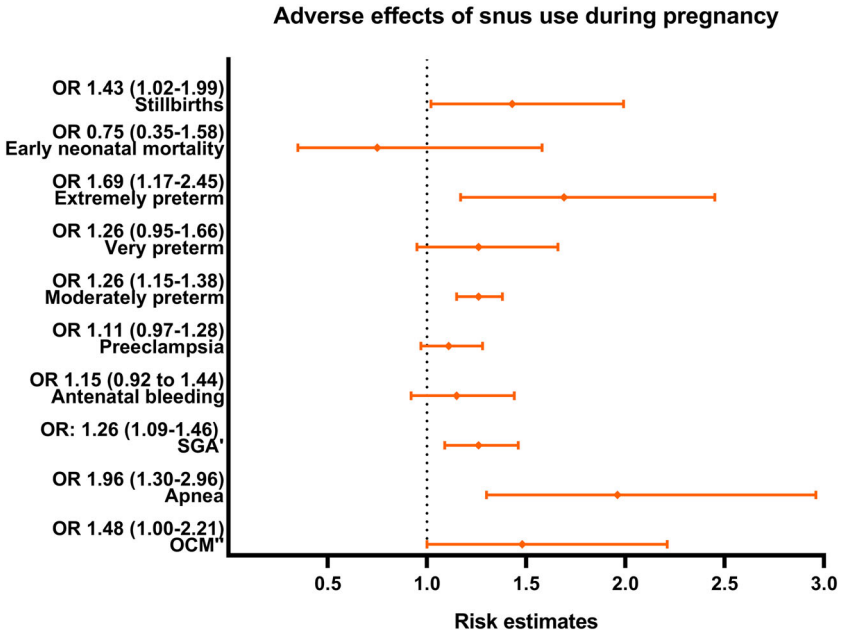

FIGURE 3 Risk estimates of adverse pregnancy outcomes and child health associated with use of snus in pregnancy. Effect of using snus throughout pregnancies on risk estimates for stillbirths, early neonatal mortality, extremely, very and moderately preterm, pre-eclampsia, antenatal bleeding, small for gestational age, apnea and oral cleft malformation are visualized. OCM″ = oral cleft malformation; SGA′ = small for gestational age

DISCUSSION

The present systematic review reported associations between the use of Swedish smokeless tobacco, snus, during pregnancy and various adverse pregnancy outcomes and adverse effects on early child health.

Evidence from randomized controlled trials is evaluated as a high certainty of evidence using the GRADE approach, which may be downgraded if weaknesses are identified. The certainty of evidence from observational studies is evaluated as having low certainty. The certainty of evidence from observational studies may be upgraded if large effect, a dose–response relationship or if all plausible biases would reduce an apparent treatment effect are identified or downgraded if limitations such as imprecision of estimates (wide CIs) are identified. Except for neonatal apnea, which was graded to moderate certainty, our certainty of the evidence for the included health outcomes reported in the present study was graded low to very low.

Experimental studies support the notion that tobacco components, including nicotine, have deleterious effects on the development of fetus and placenta [16, 48]. The combined knowledge of epidemiological findings and developmental toxicity in animals, and reduced risk of adverse pregnancy outcomes among mothers quitting before or early in pregnancy (Supporting information, Fig. S2), support a causal relationship between fetal exposure to constituents from snus and adverse health consequences in the child.

The effects of nicotine replacement therapy on pregnancy outcomes and child health may constitute important information regarding nicotine's potential teratogenicity. Two randomized controlled trials (RCTs) with the ideal of substituting smoking with nicotine patches have shown an increased prevalence of caesarean section, non-gynecological obstetric adverse health outcomes and increased diastolic blood pressure compared to placebo [49, 50]. However, the authors were careful about drawing strong conclusions regarding safety assessments of nicotine from these studies, due to compliance challenges and relatively small study size. These two studies were included in a Cochrane Review. For miscarriage, spontaneous abortion and stillbirth, the review reported the risk estimates 1.6 (95% CI = 0.53–4.83) and 1.24 (95% CI = 0.54–2.84), respectively, but the CIs included considerable harm and considerable benefits [51].

To our knowledge, the previous systematic review on the current topic was based on a search up to 2013 [52], thus an updated review was appropriate. A strength of the present review is its systematic and transparent approach. Considering included studies, most studies collected information from SMBR during overlapping time-periods (Supporting information, Fig. S1). For outcomes reported in more than one study we included the study with highest number of births, as a larger sample size may generally contribute to more accurate risk estimates. By so doing, we also avoided double-counting of births. However, as seen in Table 1, most additional studies (not shown in the GRADE evaluation) reported similar results to those included, consolidating the conclusions of this systematic review.

Small-study-related publication bias and possible publication bias analysis is an integral part of the GRADE evaluation. One outcome (HRV) was downgraded for possible small-study bias. Publication bias was considered as not identified. Snus is mainly used in the Nordic countries, and the Swedish Medical Birth Register is fairly complete. We cannot completely rule out publication bias, but have no reason to suspect such bias here.

Concerning birth weight, Juárez & Merlo's study (2013) included the highest number of pregnancies and infants. Additionally, information on birth weight was available in England and co-workers (2003), using data from SMBR prior to Juárez & Merlo, as well as in the Nordic cohorts reported by Kreyberg *et al.* and Rygh *et al.* [29, 30, 41], thus birth weight was eligible for meta-analysis. We used birth weight reported for newborns of mothers where the snus habits were registered late in pregnancy. A weakness of our meta-analysis was that

birth weight was not adjusted for the same potentially confounding factors in the original studies, and one study reported crude estimates only.

A main challenge with many studies is the uncertainty inherent in self-reporting of maternal snus use, such as amount, frequency of use and different composition of products including nicotine levels. A recent study reported that almost 45% of snus users in SMBR were misclassified as non-users in late pregnancy [53]. We note that the potential consequence of the under-reporting of tobacco use would be an underestimation of the harmful effects identified in this systematic review. Potential confounders such as alcohol, drug use and underlying medical conditions of the mother were rarely reported on, but may not be widespread enough to explain the effects ascribed to snus.

Nordenstam and co-workers reported effects of snus use during pregnancy on infant HRV as well as HRV and blood pressure at the age of 5–6 years [33, 42]. Reported acute effects of nicotine, either administered by oral lozenges or by e-cigarettes, on HRV support these results [33, 42, 54–56]. However, the children may have been exposed to tobacco constituents not just during pregnancy, but even after birth from breastfeeding, second-hand or third-hand smoke. These study populations were small, and the results should be verified in larger populations.

Higher nicotine concentrations have been reported in the placenta, amniotic fluid and fetal serum, compared to serum in mothers who smoke during pregnancy [17]. A higher median cotinine level has been reported in urine from mothers using snus (third trimester) with a nicotine content of ≥ 8 mg per pouch, 768.2 ng/ml compared to snus with ≤ 4 mg per pouch, 576.6 ng/ml [53]. In addition, high concentrations of nicotine, cotinine and 3-hydroxycotinine in breast milk of snus-using mothers have been reported with concomitant identification of cotinine and 3-hydroxycotinine in urine of infants. Nicotine was not identified in breast milk 4 hours after smoking, but still detected after 12.5 hours' abstinence for snus users [19]. Furthermore, considering stillbirth, preterm delivery and OCM, the increased risk of adverse outcome was of similar size for snus as those reported for smoking [36, 37, 40]. For apnea, the risk was markedly higher for snus use compared with that reported for smoking [39]. For adverse health outcomes reported after birth, such as HRV, asthma and wheeze, as well as intellectual disability, exposure to nicotine through breast-feeding may contribute to these outcomes. Of concern, products with markedly higher nicotine levels have become available in recent years [57], which may lead to an increased nicotine exposure from snus. This potential increase in risk of adverse events may not have been captured in previously published data.

Other recognized hazardous constituents in snus, such as tobacco-specific nitrosamines (TSNAs) and polycyclic aromatic hydrocarbons (PAHs), may also have an adverse impact on the fetus. However, lower levels of PAH in snus compared to tobacco smoke may explain different ratios of adverse pregnancy outcomes associated with the two tobacco products [58].

The potential obstetric and child health consequences of snus reported here raise concern regarding the increasing trend in use of smokeless tobacco among young women globally. The tobacco and nicotine market are constantly evolving, and ever more nicotine delivery devices with or without tobacco are available. As most modern nicotine delivery products, such as e-cigarettes/vaping, are not yet well studied in longitudinal cohorts or among pregnant women [14, 59], we believe that the currently reviewed effects of snus on pregnancy and early life health may be the most valid pre-estimates of expected consequences that new nicotine delivery products may have if used during pregnancy.

In conclusion, this systematic review reveals that use of Swedish smokeless tobacco (snus) during pregnancy may have an adverse impact on the developing child. Pregnant women and those planning to become pregnant should be advised to refrain from using snus.

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DECLARATION OF INTERESTS

The authors report no competing interests. The authors alone are responsible for the content and writing of the paper.

AUTHOR CONTRIBUTIONS

Bendik Christian Brinchmann: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing-original draft; writing-review and editing. **Gunn E Vist:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing-original draft; writing-review and editing. **Rune Becher:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing-original draft; writing-review and editing. **Tom K Grimsrud:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing-original draft; writing-review and editing. **Ida Kristin Ørjaseter Elvsaas:** Conceptualization; data curation; investigation; methodology; writing-review and editing. **Vigdis Underland:** Data curation; formal analysis; methodology; writing-review and editing. **Jørn A Holme:** Investigation; validation; writing-review and editing. **Karin C. Lødrup Carlsen:** Conceptualization; data curation; formal analysis; investigation; methodology; supervision; writing-review and editing. **Ina Kreyberg:** Conceptualization; data curation; investigation; writing-review and editing. **Live S. Nordhagen:** Conceptualization; investigation; writing-review and editing. **Karen Eline Stensby Bains:** Investigation; writing-review and editing. **Kai-Håkon Carlsen:** Conceptualization; investigation. **Jan Alexander:** Conceptualization; data curation; investigation; methodology; project administration; resources; supervision; writing-original draft; writing-review and editing. **Håkon Valen:** Conceptualization; data curation; formal analysis; investigation;

methodology; project administration; resources; software; supervision; validation; visualization; writing-original draft; writing-review and editing.

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REFERENCES

1. International Agency for Research on Cancer (IARC) Working Group on the Evaluation of Carcinogenic Risks to Humans. Smokeless Tobacco and Some Tobacco-Specific n-Nitrosamines, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, no. 89 Lyon, France: IARC; 2007.
2. The Public Health Agency of Sweden. Public Health Data. Solna, Sweden: The Public Health Agency of Sweden; 2021.
3. The Swedish National Board of Health and Welfare. Statistics on Pregnancies, Deliveries and Newborn Infants. 2020. Available at: http://sdb.socialstyrelsen.se/if_mfr_004/val.aspx. Accessed 2022.
4. Statistics Norway. Table 07692: Daily snus users and occasional snus users (per cent), by sex, age, statistical variable and year. Oslo, Norway: Statistics Norway; 2021. Available at: https://www.ssb.no/statbank/table/07692/tableViewLayout1/. Accessed 2022.
5. Norwegian Public Health Institute; Norwegian Medical Birth Register. Maternal snus habits in the beginning and end of pregnancy. 2021. Available at: http://statistikkbank.fhi.no/mfr/. Accessed 2022.
6. Cheng YC, Rostron BL, Day HR, Stanton CA, Hull LC, Persoskie A, et al. Patterns of use of smokeless tobacco in US adults, 2013–2014. Am J Public Health. 2017;107:1508–14.
7. Delnevo CD, Wackowski OA, Giovenco DP, Manderski MT, Hrywna M, Ling PM. Examining market trends in the United States smokeless tobacco use: 2005–2011. Tob Control. 2014;23:107–12.
8. Cornelius ME, Loretan CG, Wang TW, Jamal A, Homa DM. Tobacco product use among adults—United States, 2020. Morb Mortal Wkly Rep. 2022;71:397–405.
9. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. The Health Consequences of Smoking—50 years of Progress: a Report of the Surgeon General. Atlanta, GA: Centers for Disease Control and Prevention; 2014.
10. Lambers DS, Clark KE. The maternal and fetal physiologic effects of nicotine. Semin Perinatol. 1996;20:115–26.
11. Lauterstein DE, Tijerina PB, Corbett K, Akgol OB, Shen SS, Gordon T, et al. Frontal cortex transcriptome analysis of mice exposed to electronic cigarettes during early life stages. Int J Environ Res Public Health. 2016;13:417.
12. McGrath-Morrow SA, Hayashi M, Aherrera A, Lopez A, Malinina A, Collaco JM, et al. The effects of electronic cigarette emissions on systemic cotinine levels, weight and postnatal lung growth in neonatal mice. PLOS ONE. 2015;10:e0118344.
13. Zelikoff JT, Parmalee NL, Corbett K, Gordon T, Klein CB, Aschner M. Microglia activation and gene expression alteration of neurotrophins in the hippocampus following early-life exposure to E-cigarette aerosols in a murine model. Toxicol Sci. 2018;162:276–86.
14. National Center for Chronic Disease Prevention, Health Promotion Office on Smoking and Health. Publications and Reports of the Surgeon General. E-cigarette use Among Youth and Young Adults: A Report of The Surgeon General Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2016.
15. Holloway AC, Salomon A, Soares MJ, Garnier V, Raha S, Sergent F, et al. Characterization of the adverse effects of nicotine on placental development: *in vivo* and *in vitro* studies. Am J Physiol Endocrinol Metab. 2014;306:E443–56.
16. Suter MA, Aagaard KM. The impact of tobacco chemicals and nicotine on placental development. Prenat Diagn. 2020;40:1193–200.
17. Luck W, Nau H. Exposure of the fetus, neonate, and nursed infant to nicotine and cotinine from maternal smoking. N Engl J Med. 1984;311:672.
18. Dahlström A, Ebersjö C, Lundell B. Nicotine exposure in breastfed infants. Acta Paediatr. 2004;93:810–6.
19. Nordenstam F, Lundell B, Edstedt Bonamy A-K, Raaschou P, Wickström R. Snus users had high levels of nicotine, cotinine and 3-hydroxycotinine in their breastmilk, and the clearance was slower than in smoking mothers. Acta Paediatr. 2019;108:1250–5.
20. Nordhagen LS, Kreyberg I, Bains KES, Carlsen KH, Glavin K, Skjerven HO, et al. Maternal use of nicotine products and breastfeeding 3 months postpartum. Acta Paediatr. 2020;109:2594–603.
21. Hukkanen J, Jacob P III, Benowitz NL. Metabolism and disposition kinetics of nicotine. Pharmacol Rev. 2005;57:79–115.
22. Furlan AD, Pennick V, Bombardier C, van Tulder M. 2009 updated method guidelines for Systematic Reviews in the Cochrane Back Review Group. Spine (Phila PA 1976). 2009;34:929–1941.
23. Folkehelseinstituttet. Helserisiko ved snusbruk [Health risks From Snus Use. Norwegian Institute of Public Health. Report 2019], versjon 2. Folkehelseinstituttet Rapport 2019. Oslo, Norway: Folkehelseinstituttet; 2019.
24. Folkehelseinstituttet. Helserisiko ved snusbruk [Health risks from Snus Use. Norwegian Institute of Public Health. Report 2014]. Folkehelseinstituttet Rapport 2014. Oslo, Norway: Folkehelseinstituttet; 2014.
25. Natvig NI, Dybing E, Gilljam H, Lind PO, Lund KE, Mørland J, et al. NIPH systematic reviews: Executive Summaries. Health Effects and Dependency Associated With Snuff Consumption Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH); 2005.
26. Godlee F, Malone R, Timmis A, Otto C, Bush A, Pavord I, et al. Journal policy on research funded by the tobacco industry. BMJ. 2013;347:f5193.
27. The Joanna Briggs Institute (JBI). Critical Appraisal Tools for Cohort Studies. Adelaide, Australia: JBI, Faculty of Health Sciences, University of Adelaide; 2020.
28. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. What is 'quality of evidence' and why is it important to clinicians? BMJ. 2008;336:995–8.
29. Kreyberg I, Hilde K, Bains KES, Carlsen K-H, Granum B, Haugen G, et al. Snus in pregnancy and infant birth size: a mother–child birth cohort study. ERJ Open Res. 2019;5:00255–02019.
30. Rygh E, Gallefoss F, Grøtvedt L. Trends in maternal use of snus and smoking tobacco in pregnancy. A register study in southern Norway. BMC Pregnancy Childbirth. 2019;19:500–0.
31. Lundholm C, Gunnerbeck A, D'Onofrio BM, Larsson H, Pershagen G, Almqvist C. Smoking and snuff use in pregnancy and the risk of asthma and wheeze in pre-schoolchildren—a population-based register study. Clin Exp Allergy. 2020;50:597–608.
32. Madley-Dowd P, Lundberg M, Heron J, Zammit S, Ahlqvist VH, Magnusson C, et al. Maternal smoking and smokeless tobacco use during pregnancy and offspring development: sibling analysis in an intergenerational Swedish cohort. Int J Epidemiol. 2022;50:1840–51.
33. Nordenstam F, Norman M, Wickström R. Blood pressure and heart rate variability in preschool children exposed to smokeless tobacco in fetal life. J Am Heart Assoc. 2019;8:e012629.
34. Baba S, Wikström AK, Stephansson O, Cnattingius S. Influence of smoking and snuff cessation on risk of preterm birth. Eur J Epidemiol. 2012;27:297–304.
35. Baba S, Wikström AK, Stephansson O, Cnattingius S. Changes in snuff and smoking habits in Swedish pregnant women and risk for

small for gestational age births. Br J Obstet Gynaecol. 2013;120:456–62.
36. Baba S, Wikström AK, Stephansson O, Cnattingius S. Influence of snuff and smoking habits in early pregnancy on risks for stillbirth and early neonatal mortality. Nicotine Tob Res. 2014;16:78–83.
37. Dahlin S, Gunnerbeck A, Wikström AK, Cnattingius S, Edstedt Bonamy AK. Maternal tobacco use and extremely premature birth—a population-based cohort study. Br J Obstet Gynaecol. 2016;123:1938–46.
38. England LJ, Levine RJ, Mills JL, Klebanoff MA, Yu KF, Cnattingius S. Adverse pregnancy outcomes in snuff users. Am J Obstet Gynecol. 2003;189:939–43.
39. Gunnerbeck A, Wikström AK, Bonamy AK, Wickström R, Cnattingius S. Relationship of maternal snuff use and cigarette smoking with neonatal apnea. Pediatrics. 2011;128:503–9.
40. Gunnerbeck A, Edstedt Bonamy AK, Wikström AK, Granath F, Wickström R, Cnattingius S. Maternal snuff use and smoking and the risk of oral cleft malformations—a population-based cohort study. PLOS ONE. 2014;9:e84715.
41. Juárez SP, Merlo J. The effect of Swedish snuff (snus) on offspring birthweight: a sibling analysis. PLOS ONE. 2013;8:e65611.
42. Nordenstam F, Lundell B, Cohen G, Tessma MK, Raaschou P, Wickström R. Prenatal exposure to snus alters heart rate variability in the infant. Nicotine Tob Res. 2017;19:797–803.
43. Wikström AK, Cnattingius S, Galanti MR, Kieler H, Stephansson O. Effect of Swedish snuff (snus) on preterm birth. Br J Obstet Gynaecol. 2010;117:1005–10.
44. Wikström AK, Cnattingius S, Stephansson O. Maternal use of Swedish snuff (snus) and risk of stillbirth. Epidemiology. 2010;21:772–8.
45. Wikström AK, Stephansson O, Cnattingius S. Tobacco use during pregnancy and preeclampsia risk: effects of cigarette smoking and snuff. Hypertension. 2010;55:1254–9.
46. Wikman A, Axfors C, Iliadis SI, Cox J, Fransson E, Skalkidou A. Characteristics of women with different perinatal depression trajectories. J Neurosci Res. 2020;98:1268–82.
47. Källén B, Källén K. The Swedish Medical Birth Register—a summary of content and quality Stockholm, Sweden: Socialstyrelsen [Swedish National Board of Health and Welfare]; 2003.
48. England LJ, Aagaard K, Bloch M, Conway K, Cosgrove K, Grana R, et al. Developmental toxicity of nicotine: a transdisciplinary synthesis and implications for emerging tobacco products. Neurosci Biobehav Rev. 2017;72:176–89.
49. Coleman T, Cooper S, Thornton JG, Grainge MJ, Watts K, Britton J, et al. A randomized trial of nicotine-replacement therapy patches in pregnancy. N Engl J Med. 2012;366:808–18.
50. Berlin I, Grangé G, Jacob N, Tanguy ML. Nicotine patches in pregnant smokers: randomised, placebo controlled, multicentre trial of efficacy. BMJ. 2014;348:g1622.
51. Claire R, Chamberlain C, Davey MA, Cooper SE, Berlin I, Leonardi-Bee J, et al. Pharmacological interventions for promoting smoking cessation during pregnancy. Cochrane Database Syst Rev. 2020;3:CD010078.
52. Inamdar AS, Croucher RE, Chokhandre MK, Mashyakhy MH, Marinho VC. Maternal smokeless tobacco use in pregnancy and adverse health outcomes in newborns: a systematic review. Nicotine Tob Res. 2015;17:1058–66.
53. Gunnerbeck A, Raaschou P, Cnattingius S, Edstedt Bonamy AK, Wickström R. Maternal snuff use and cotinine in late pregnancy—a validation study. Acta Obstet Gynecol Scand. 2018;97:1373–80.
54. Benowitz NL, Gourlay SG. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. J Am Coll Cardiol. 1997;29:1422–31.
55. Sjoberg N, Saint DA. A single 4 mg dose of nicotine decreases heart rate variability in healthy nonsmokers: implications for smoking cessation programs. Nicotine Tob Res. 2011;13:369–72.
56. Moheimani RS, Bhetraratana M, Peters KM, Yang BK, Yin F, Gornbein J, et al. Sympathomimetic effects of acute E-cigarette use: role of nicotine and non-nicotine constituents. J Am Heart Assoc. 2017;6:e006579.
57. Lawler TS, Stanfill SB, Tran HT, Lee GE, Chen PX, Kimbrell JB, et al. Chemical analysis of snus products from the United States and northern Europe. PLOS ONE. 2020;15:e0227837.
58. Holme JA, Valen H, Brinchmann BC, Vist GE, Grimsrud TK, Becher R, et al. Polycyclic aromatic hydrocarbons (PAHs) may explain the paradoxical effects of cigarette use on preeclampsia (PE). Toxicology. 2022;473:153206.
59. Becher R, Valen H, Vist GE, Brinchmann BC, Holme JA, Grimsrud TK, et al. Adverse health effects of electronic cigarette use: an umbrella review and toxicological evaluation. Norwegian Institute of Public Health; 2022. Available at: https://www.fhi.no/publ/2022/adverse-health-effects-of-electronic-cigarette-use-an-umbrella-review-and-t/. Accessed 2022.

SUPPORTING INFORMATION

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

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