

ORIGINAL ARTICLE

WILEY

Epidemiology of Allergic Disease

Smoking and snuff use in pregnancy and the risk of asthma and wheeze in pre-schoolchildren—A population-based register study

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Funding information

Vetenskapsrådet, Grant/Award Number: 340-2013-5867; Stockholms Läns Landsting; Forskningsrådet om Hälsa, Arbetsliv och Välfärd, Grant/Award Number: 2015-00289; Hjärt-Lungfonden

Abstract

Background: Associations between tobacco smoking during pregnancy and offspring asthma have been observed, but the role of nicotine and familial factors remains unclear.

Objective: To estimate the association between tobacco use in pregnancy, both smoking and Swedish oral moist snuff, and asthma/wheeze in the offspring, how it varies by the child's age and explore the influence of measured and unmeasured familial confounding.

Methods: Register-based cohort study with sibling comparisons. The cohort included 788 508 children, born in Sweden 2005-2012 with information on maternal tobacco use in pregnancy, followed until December 2015. Asthma was based on a validated algorithm using asthma diagnoses from hospital visits and prescribed asthma drugs from nation-wide registers, both as incident asthma/wheeze in age 0-8 years and current asthma at ages 2, 3, 4, 5 and 6 years.

Results: For smoking during pregnancy (SDP), we saw a pattern with higher hazard ratios for asthma/wheeze around ages 5 and 18 months. Snuff did not show the same pattern. For current asthma, we saw the strongest association at age 2 years (adjOR = 1.22, 95% CI: 1.17-1.28), for snuff it was weaker (adjOR = 1.06, 95% CI: 0.96-1.18). When using sibling controls, the estimates for SDP were clearly attenuated, albeit with wide confidence intervals.

Conclusion and clinical relevance: We saw an association between SDP and asthma at early age. The association with snuff was clearly weaker. The associations with SDP were attenuated when adjusting for measured and unmeasured familial factors shared by siblings. Based on those results, nicotine seems to have a limited role in the association between SDP and asthma; rather environmental tobacco smoke and other familial factors seem to explain observed associations.

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1 | INTRODUCTION

Maternal smoking is globally one of the most important preventable causes of detrimental effects in pregnancy, delivery and in the neonatal period with increased risk of placental abruption, growth restriction, premature birth and increased risk of sudden infant death.¹ Smoking during pregnancy (SDP) has also been associated with asthma and wheeze in childhood. Meta-analyses and a large pooled study have shown increased risk of asthma and wheeze in children who were exposed to tobacco smoke in utero.²⁻⁴ Those findings are to some extent supported by animal studies,¹ showing differences in lung development in animals exposed to tobacco smoke^{5,6} or nicotine⁷ in utero compared with those unexposed. The available studies also imply that nicotine passes the placenta and interacts with nicotinic receptors in the lungs of monkey fetuses,⁸ which indicates that nicotine could be the causal agent.

However, the associations with SDP could also be due to confounding. In previous studies, confounding adjustments may have been inadequate, with regard to both known measurable confounders and complex confounders, such as lifestyle, genetic and parental behavioural factors. Further, it is difficult to distinguish the effects of SDP from that of environmental tobacco smoke (ETS) exposure in early life.

Besides nicotine, the smoker is exposed to several substances from combustion. Although nicotine exposure in utero has been suggested as a cause of lung changes,^{7,8} it is unclear if that is the case for asthma and wheeze. Swedish oral moist snuff (snus) is a commonly used tobacco product in Sweden, which is placed under the lip. It contains high levels of nicotine, but no combustion products.⁹ Previous studies have found associations between snuff use in pregnancy and negative pregnancy outcomes, such as preterm delivery and pre-eclampsia,¹⁰ neonatal apnoea¹¹ and oral clefts.¹² Studying the use of snuff in pregnancy in relation to asthma and wheeze enables us to shed light on the mechanism behind the association between SDP and asthma. Details regarding timing of asthma and wheeze onset in relation to tobacco exposure could also give important clues, for example regarding potential mediators.

The Swedish Medical Birth Registry (MBR) has recorded maternal smoking during pregnancy since 1982 and snuff use since 1999 and can be linked to registers with information on health and socio-economic factors. Thus, the Swedish national registers are a unique source for studying tobacco exposure in utero and the potential effect on asthma and wheeze in the child. Further, family comparison designs, where we make comparisons between family members who are discordant for exposure, is a way to control for unmeasured lifestyle confounders,¹³ such as ETS and diet, to the extent it is shared by the family members being compared.

Our aim was to advance the understanding of underlying causal processes in the association between SDP and asthma or wheeze in the offspring. By estimating the association between Swedish oral moist snuff use in pregnancy and asthma/wheeze, we may further understand the role of nicotine. We also aimed to investigate how the association with asthma/wheeze incidence and prevalence varies by the age of the child. Finally, the use of sibling comparisons may

elucidate the role of unmeasured familial factors, including genes and lifestyle factors such as ETS and family diet.

2 | METHODS

2.1 | Study population

This cohort study, based on national registry data, included all children born in Sweden 1 July 2005 - 31 December 2012, who were registered in the Medical Birth Register (MBR).¹⁴ The MBR includes information on pregnancies and deliveries for approximately 97% of the children born in Sweden those years, including data on tobacco use in pregnancy, maternal body mass index (BMI), age, family situation (mother living together with the father or not) and birth outcomes. Using the Swedish personal number, which is unique for each resident in Sweden,¹⁵ we linked the MBR data to the Total Population Register (TPR) for information on deaths and emigration.¹⁶ We found 805 679 children registered in the MBR. We excluded children who were stillborn ($n = 2851$), children missing information on mother's identity ($n = 1005$) or migrated to/from Sweden during pregnancy ($n = 13\,356$), children themselves not registered as residents in Sweden ($n = 137$) and those with erroneous migration data ($n = 67$). After exclusions, $N = 788\,508$ children remained the cohort.

The Regional Ethical Review Board in Stockholm, Sweden approved the study (Dnr 2013/862-31/5). Since the study was strictly register-based, the Ethical Review Board did not require informed consent.

2.2 | Exposure variables

We retrieved exposure information on smoking and Swedish oral moist snuff use from the MBR. Information on current tobacco use is recorded by the midwife at the first antenatal care visit (usually in week 5-12), 3 months before the first visit (retrospectively) and in week 30-32. We defined three exposure measures. The main smoke exposure variable was as follows:

- Smoking both 3 months before first antenatal care visit and at the time of the visit vs not smoking at any the those two occasions (smoking in early pregnancy).

Two additional smoke exposure variables were as follows:

- Smoking at all three occasions (ie still smoking in late pregnancy) vs not smoking at all.
- Smoking 3 months before the first visit, but not at the time of the first visit vs not smoking at any the those two occasions (smoking before or in very early pregnancy).

We defined oral moist snuff use as snuff use 3 months before the first visit and at the time of the first visit vs not using snuff at any of those two occasions.

A validation study on smoking information at the first antenatal care visit in MBR has shown a sensitivity of 87% and a specificity of 95% as compared to cotinine levels at childbirth.¹⁷ The information on snuff use at the first antenatal care visit had a sensitivity of 76% and a specificity of 100% when validated against prospectively collected questionnaire data. However, in week 30-32 the sensitivity for snuff use was as low as 51%.⁹ Therefore we only included snuff data from the first antenatal care visit.

2.3 | Outcome variables

We retrieved information regarding asthma outcomes from two national registers—the Swedish Prescribed Drug Register (SPDR) and the National Patient Register (NPR). The SPDR contains information on all prescribed drugs that are dispensed at pharmacies in Sweden, with prescription date, dispense date and drug substance coded according to the Anatomic Therapeutic Chemical (ATC) classification system and started on 1 July 2005. We chose the cohort to ensure availability of data from the SPDR from birth. The NPR was gradually built up starting in 1964 and including all in-patient hospital visits since 1987 as well as approximately 80% of all out-patient visits (not including primary care) since 2001.

We defined *incident asthma/wheeze* in the offspring in accordance with an asthma medication algorithm, which has been validated as a proxy for asthma¹⁸ in combination with asthma diagnosis (International Classification of Diseases, ICD-10: J45-J46) information from the NPR. For children below 4.5 years, we required both an asthma diagnosis and fulfilling the medication algorithm. Children above 4.5 years were classified as having asthma, if having either an asthma diagnosis or fulfilling the asthma medication algorithm. A child fulfilled the asthma medication algorithm if having.

1. At least two dispenses of asthma controller medication, including inhaled corticosteroids (ICS; R03BA) and/or leukotriene receptor antagonist (LRTA; R03DC03) and/or fixed combinations of ICS and β 2-agonists (R03AK06 or R03AK07), independent on time between distributions in children older than 4.5 years and with at least 14 days between the two dispenses for children below 4.5 years.

Or

2. At least one dispensed controller medication and two dispenses of short-acting inhaled β 2-agonists (R03AC02, R03AC03, R03AC12, R03AC13) within 12 months.

Or

3. At least three dispenses of short-acting inhaled β 2-agonists within 12 months.

As asthma/wheeze onset date, we used the date of the prescription of the first asthma medication dispense or the first diagnosis in NPR, whichever came first.

If finding an association between tobacco exposure in utero and incident asthma or wheeze, a natural question would be if the association was driven by transient asthma or if tobacco exposure is also associated with asthma at later age. We therefore also defined *current asthma* at ages 2, 3, 4, 5 and 6 years. This was defined as having incident asthma/wheeze, with the addition of at least one record of dispensed asthma medication in the SPDR or a record of asthma diagnosis in the NPR at that particular age (from the birthday in question until the day before the next birthday).

We had information from the SPDR until 31 December 2015 and from the NPR until 31 December 2013. Due to the differences in the stricter asthma definition depending on the age of the child, children with attained age <4.5 on 31 December 2013 were followed no longer than 31 Dec 2013, while older children were followed until 31 December 2015.

2.4 | Potential confounders

We used a Directed Acyclic Graph (DAG) to identify what variables we needed to adjust for in our analyses. Those variables were birth year, parity, maternal body mass index (BMI), age and family situation, asthma in the mother, asthma in the father, parental education, income and country of birth. The Multi-Generation Register (MGR) was used to identify the fathers. We retrieved birth year, parity (1; 2; 3; $\geq$ 4), maternal age ($\leq$ 19; 20-24; 25-29; 30-34; $\geq$ 35 years at birth), BMI (categorised in accordance with World Health Organization: < 18.5; 18.5-24.9; 25.0-29.9; $\geq$ 30 kg/m²) and family situation (living with the father or not) from the MBR. We defined asthma in the parents in the same way as for the older children with the addition of the earlier ICD version codes (ICD-7:241, ICD-8:493, ICD-9:493) for diagnoses in the NPR. We retrieved parental birth country (Sweden; other Nordic country; Europe except the Nordic countries, North America or Oceania; other country) from the TPR. Parental education (middle school; high school, college/university) and income the year the child was born (in quintiles by birth year) were retrieved from the Longitudinal integration database for health insurance and labour market studies.¹⁹

2.5 | Statistical methods

The association between tobacco use in pregnancy and incident asthma/wheeze in the offspring was analysed as time-to-event, using flexible parametric models with age as time scale (Stata package stpm2).²⁰ The use of such a model may reveal important information about time-varying effects of the exposure. Attained age was the underlying time scale with date of discharge from hospital after birth as the start of follow-up and end of follow-up were defined as the earliest of date of disease onset, date of first emigration,

date of death or 31 December 2013 for children with attained age <4.5 years and 31 December 2015 for older children. With this model, the baseline hazard is modelled using restricted cubic splines, in this case with seven degrees of freedom corresponding to 6 knots. The hazard ratio (HR) for tobacco use was allowed to be time-varying, also using restricted cubic splines with 6 knots. We explored models with both fewer and more knots, to ensure that we had enough knots to capture the variations in the associations over time, but without causing unnecessary instability in the curves. The results are presented as HR curves over age with 95% confidence intervals (CI). We also estimated HRs with cox proportional hazards model with time-varying effects in the age intervals 0-365 days (0-1 year), 366-730 days (1-2 years) and ≥ 731 days (≥ 2 years), for comparison with estimates from the corresponding sibling analyses described below. All models were estimated both without adjustments (crude) and adjusted for birth year, parity, maternal age, BMI and family situation, asthma in the parents, parental birth countries, education and income, allowing all to have time-varying effects.

We used logistic regression to analyse the association between tobacco use and current asthma at the different ages, with results presented as odds ratios (OR) with 95% CI. The logistic regression models were estimated both without adjustments (crude) and adjusted for the same covariates as the flexible parametric models.

We also performed sensitivity analyses for snuff, where we excluded all women who said they had smoked 3 months before the first antenatal care visit or during pregnancy from both the exposed and unexposed group.

In order to adjust for unmeasured familial factors, we also used a sibling comparison approach based on all full sibling pairs in the study population who were discordant on both smoking exposure and asthma. This method accounts for all confounding and mediating factors, whether environmental or genetic, that make siblings similar. It should be noted that this includes ETS to the extent it was shared between the siblings. Here we used conditional logistic regression with sibling pairs as strata. There would be a risk of carry-over effect of non-shared ETS exposure of the older sibling emanating from the exposure in utero of the younger sibling. Therefore, we included an interaction effect for sibling order and exposure, indicating unexposed older sibling (ie risk of ETS since the mother then smoked when expecting the younger sibling) in all sibling analyses.²¹ For analyses of asthma/wheeze incidence, we used Cox proportional hazards model stratified on sibling pairs, with time-varying effects, and for asthma prevalence, we used conditional logistic regression. The sibling comparison analyses were adjusted for all measured covariates that could differ between the siblings (birth year, parity, maternal BMI and maternal age). The sibling comparisons were done only for smoking and not for snuff use, since snuff use was much less common among pregnant women and subsequently the number of exposure discordant sibling pairs was very small. Considering the advice to parents of children diagnosed with asthma is to quit smoking, there could be a second type of carry-over effect such that mothers with a first child with asthma onset before the next pregnancy would be less

likely to smoke in a later pregnancy. We checked this using logistic regression estimating the association between smoking in a pregnancy and asthma in an older sibling before the start of that pregnancy, adjusted for all parental factors and smoking in the previous pregnancy.

Models adjusted for measured covariates included subjects with complete information.

3 | RESULTS

A description of the study population is shown in Table 1. The prevalence of smoking in early pregnancy was 6.2%, while the prevalence of Swedish oral moist snuff use was 0.9%. Maternal tobacco use, both smoking and use of snuff, in pregnancy was more common in younger, under-weight and obese women, in women with asthma and in women with lower socio-economic status (education and income), although the differences were less pronounced regarding snuff use compared with smoking. Smoking was most common in women born in a European country other than the Nordic countries, while snuff use was most common in women born in Sweden. Complete information on all covariates was available for 92% of the study population (SDP $n = 628\,982$; snuff $n = 678\,090$).

The mean follow-up time in the cohort was 6.0 years, corresponding to 4.7 million person-years. There were 73 547 children having *incident asthma/wheeze*.

Figure 1A displays how the crude association between smoking in early pregnancy and offspring *incident asthma/wheeze* varied by age, with hazard ratios increasing from birth up to around 5 months of age. It then decreased and started to increase again around 12 months of age and reached a new peak around 18 months. When adjusting for covariates the HR decreased, but the bimodal pattern was still discernible (Figure 1B). For mothers still smoking in late pregnancy, the pattern was similar, although more pronounced with HR peaks slightly higher (Figure 1C). However, for women smoking before or in very early pregnancy, we did not see elevated HRs around 5 months of age, but the peak around 18 months was there (Figure 1D). The pattern was different for the association between snuff use in early pregnancy and incident asthma/wheeze (Figure 1E-F), with lower HRs, in particular in the first year of life. However, the peak around 18 months was seen also for snuff, although lower and with wider confidence intervals, the latter due to the much smaller number of exposed children (Figure 2F). Figures of HRs for the crude associations with still smoking in late pregnancy and smoking before or in very early pregnancy are found in online supplement Figure S1A-B. Sensitivity analysis regarding snuff use, excluding women who smoked just before or during pregnancy, showed similar results (Figure S2).

Odds ratios for smoking in early pregnancy and *current asthma* at ages 2-6 years are displayed in Figure 2A. In the crude analyses, the odds for asthma were increased for exposed children at all ages. When adjusting for covariates, they were generally lower and close to null from 4 years of age. For snuff use, we saw a similar pattern

TABLE 1 Descriptive statistics of the study population

	Smoking in early pregnancy						Snuff use in pregnancy					
	No			Yes			No			Yes		
	N	%		N	%	Missing	N	%		N	%	Missing
Total	629 881	79.9		50 316	6.4	108 311	726 981	92.2		71 65	0.9	54 362
Child gender												
Boy	323 368	79.8		25 889	6.4	55 857	373 211	92.1		37 34	0.9	28 169
Girl	306 513	79.9		24 427	6.4	52 454	353 770	92.3		34 31	0.9	26 193
Birth year												
2005	35 241	74.6		3527	7.5	8496	42 198	89.3		404	0.9	4662
2006	78 412	77.6		6992	6.9	15 696	92 156	91.2		899	0.9	8045
2007	77 988	76.2		6728	6.6	17 690	91 849	89.7		793	0.8	9764
2008	84 420	80.8		6935	6.6	13 159	98 082	93.8		913	0.9	5519
2009	86 381	81.4		6865	6.5	12 840	99 209	93.5		1141	1.1	5736
2010	91 140	81.9		6968	6.3	13 166	104 058	93.5		1077	1.0	6139
2011	88 179	82.0		6350	5.9	12 975	100 171	93.2		991	0.9	6342
2012	88 120	81.3		5951	5.5	14 289	99 258	91.6		947	0.9	8155
Parity												
1	264 436	76.5		21 412	6.2	59 704	315 423	91.3		2909	0.8	27 220
2	243 453	83.6		15 303	5.3	32 408	270 524	92.9		2464	0.8	18 176
3	86 468	81.4		8108	7.6	11 625	98 543	92.8		1209	1.1	6449
≥4	35 524	77.9		5493	12.0	4574	42 491	93.2		583	1.3	2517
Mother's age, yrs												
≤19	5568	46.4		2879	24.0	3 543	10 923	91.1		173	1.4	894
20-24	64 838	64.8		13 419	13.4	21 844	91 178	91.1		1420	1.4	7503
25-29	177 234	78.5		14 464	6.4	34 020	208 023	92.2		1950	0.9	15 745
30-34	233 314	84.5		11 265	4.1	31 453	255 342	92.5		2052	0.7	18 638
≥35	148 924	85.3		8289	4.7	17 449	161 512	92.5		1570	0.9	11 580
Missing	3	60.0		0	0.0	2	3	60.0		0	0.0	2
Mother's BMI												
<18.5	14 115	81.2		1578	9.1	1696	16 697	96.0		203	1.2	489
18.5-24.9	369 698	85.0		23 888	5.5	41 137	418 061	96.2		3656	0.8	13 006
25-29.9	150 288	82.0		13 181	7.2	19 854	175 900	96.0		1841	1.0	5582

(Continues)

TABLE 1 (Continued)

	Smoking in early pregnancy						Snuff use in pregnancy					
	No			Yes			Missing			No		
	N	%		N	%		N	%		N	%	
≥30	68 363	77.4		9195	10.4		10 712	12.1		84 374	95.6	
Missing	27 417	42.3		2474	3.8		34 912	53.9		31 949	49.3	
Parents cohabiting												
Living together	598 306	84.6		40 451	5.7		68 370	9.7		679 808	96.1	
Not living together	27 484	60.8		9454	20.9		8249	18.3		42 299	93.6	
Missing	4091	11.3		411	1.1		31 692	87.6		4 874	13.5	
Asthma in mother												
No	550 251	80.3		41 211	6.0		93 415	13.6		632 711	92.4	
Yes	79 630	76.8		9105	8.8		14 896	14.4		94 270	91.0	
Asthma in father												
No	563 178	79.9		44 950	6.4		96 950	13.8		650 344	92.2	
Yes	66 703	80.0		5366	6.4		11 361	13.6		76 637	91.9	
Mother's birth place												
Sweden	493 302	79.4		40 173	6.5		87 909	14.1		568 009	91.4	
Nordic country	9011	77.8		959	8.3		1616	13.9		10 638	91.8	
Europe, North America, Oceania	40 636	72.8		5931	10.6		9265	16.6		53 209	95.3	
Other	86 859	87.2		3247	3.3		9514	9.6		95 044	95.4	
Missing	73	84.9		6	7.0		7	8.1		81	94.2	
Father's birth place												
Sweden	489 690	80.1		37 068	6.1		84 698	13.9		559 265	91.5	
Nordic country	9242	76.4		1112	9.2		1745	14.4		11 126	92.0	
Europe, North America, Oceania	43 826	71.8		6755	11.1		10 440	17.1		57 796	94.7	
Other	79 708	84.8		4350	4.6		9962	10.6		89 681	95.4	
Missing	7415	74.8		1031	10.4		1466	14.8		9113	91.9	
Mother's education												
Middle school	50 598	59.6		17 825	21.0		16 506	19.4		78 638	92.6	
High school	222 624	73.7		26 257	8.7		53 084	17.6		276 187	91.5	
College/University	345 963	89.1		5005	1.3		37 241	9.6		359 390	92.6	
Missing	10 696	79.8		1229	9.2		1480	11.0		12 766	95.2	

(Continues)

TABLE 1 (Continued)

	Smoking in early pregnancy						Snuff use in pregnancy					
	No			Yes			Missing			No		
	N	%	N	N	%	N	N	%	N	N	%	N
Father's education												
Middle school	61 432	65.8	14 936	16.0	18.2	16 990	86 437	92.6	1101	1.2	5820	6.2
High school	278 229	76.5	28 068	7.7	15.8	57 620	333 596	91.7	4391	1.2	25 930	7.1
College/Univeristy	272 933	88.8	4623	1.5	9.7	29 820	284 806	92.7	1521	0.5	21 049	6.8
Missing	17 287	72.5	2689	11.3	16.3	3881	22 142	92.8	152	0.6	1563	6.6
Father's disposable income												
1st Quintile	119 327	76.0	16 377	10.4	13.6	21 311	146 809	93.5	1474	0.9	8732	5.6
2nd Quintile	123 405	78.4	12 800	8.1	13.5	21 192	145 535	92.5	1804	1.1	10 058	6.4
3rd Quintile	124 344	79.0	10 304	6.5	14.4	22 718	144 584	91.9	1498	1.0	11 284	7.2
4th Quintile	126 891	80.7	7334	4.7	14.7	23 098	144 195	91.7	1461	0.9	11 667	7.4
5th Quintile	134 239	85.4	3325	2.1	12.5	19 669	143 851	91.5	920	0.6	12 462	7.9
Missing	1675	77.0	176	8.1	14.9	323	2007	92.3	8	0.4	159	7.3
Mother's disposable income												
1st Quintile	116 084	75.6	16 069	10.5	13.9	21 367	142 801	93.0	1480	1.0	9239	6.0
2nd Quintile	119 960	78.1	12 476	8.1	13.8	21 169	141 719	92.3	1674	1.1	10 212	6.6
3rd Quintile	122 665	79.8	9336	6.1	14.1	21 672	141 478	92.1	1641	1.1	10 554	6.9
4th Quintile	125 094	81.4	6905	4.5	14.1	21 669	141 279	91.9	1362	0.9	11 027	7.2
5th Quintile	131 276	85.5	3231	2.1	12.4	19 015	140 655	91.6	881	0.6	11 986	7.8
Missing	14 802	72.1	2299	11.2	16.7	3419	19 049	92.8	127	0.6	1344	6.5

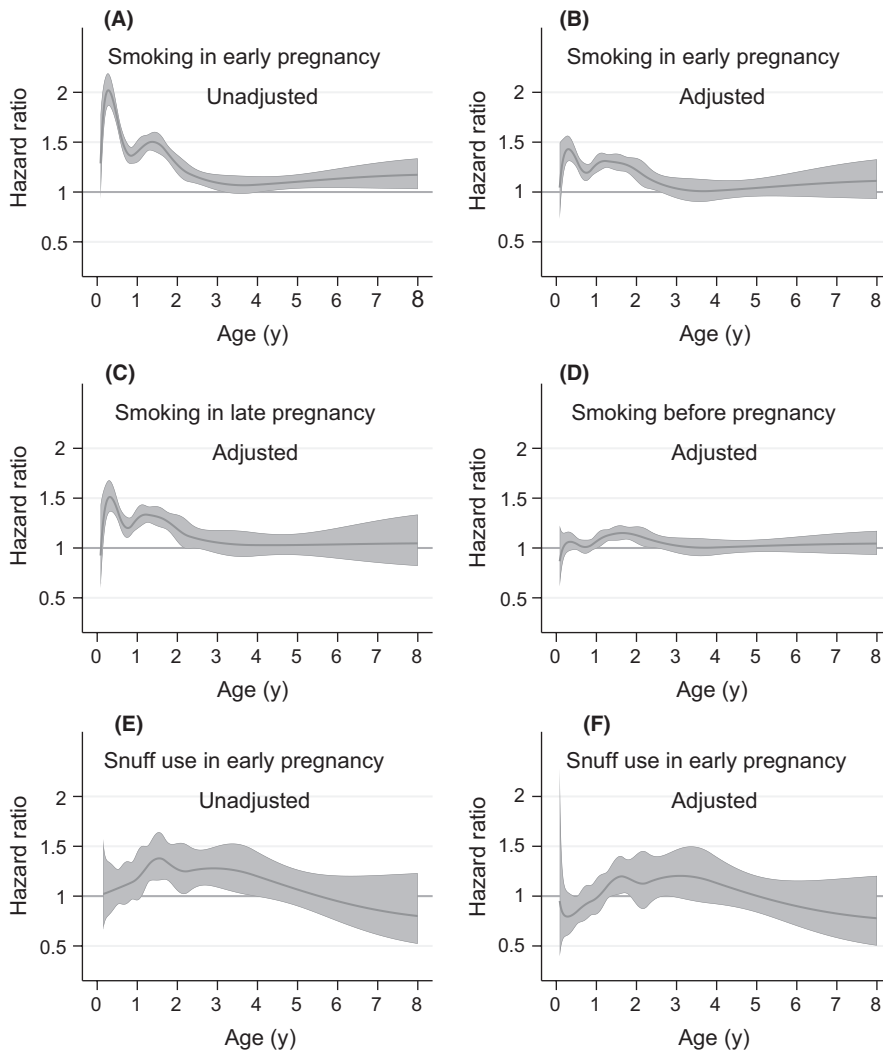


FIGURE 1 Time-varying hazard ratios with 95% confidence intervals (shaded area) from flexible parametric models for the association between incident asthma and smoking early pregnancy in (unadjusted: A, adjusted: B), still smoking in late pregnancy (C), smoking before or in very early pregnancy (D) and oral moist snuff use in early pregnancy (unadjusted: E, adjusted: F), with the adjustments made for birth year, parity, maternal age, BMI and family situation (mother living together with the father or not), asthma in the parents, parental birth country, education and income

with crude ORs around 1.2 at most ages, which were clearly lower when adjusting for covariates (Figure 2B).

To control for life style factors shared within families and genetic factors that make siblings similar, we performed sibling comparisons. Of the 4 633 women who were discordant for smoking in two pregnancies, 74% smoked in the first pregnancy and 26% in the second. Among those women, $n = 272$ women had children who were discordant for current asthma at age 2 years, $n = 210$ for asthma at age 3 years and $n = 104$ for asthma at age 4 years. The decreasing number of discordant siblings was mainly due to fewer families having siblings within the cohort reaching each age, as it would require having children with small age difference. For this reason, we were not able to make sibling comparisons at higher ages. When we controlled for unmeasured confounding by comparing siblings, ORs were lower, compared with the adjusted analyses of the association between SDP and current asthma, although with much wider confidence intervals (Figure 2A).

The sibling comparisons using time-to-event analyses mostly showed similar results as the logistic regressions, with attenuation with higher age of the child and with adjustment for measured confounders and unmeasured familial factors (Table 2).

Evaluation of potential carry-over effects, showed that if a mother had a child with an asthma onset before a subsequent pregnancy, she was possibly slightly more likely to smoke in the subsequent pregnancy (OR = 1.20, 95% CI 0.97-1.48).

4 | DISCUSSION

Our results showed an association between smoking in early pregnancy and increased incidence in asthma and wheeze, while the association with snuff use was close to null. There was also an association between smoking in early pregnancy and current asthma, which decreased with increasing age and was close to the null at 4 years of age. All associations decreased markedly when adjusting for the covariates maternal age, BMI, parity, family situation and parental education, income and asthma. The estimates decreased further in the sibling comparisons, which were controlled for unmeasured family factors shared by siblings, including ETS if shared between the siblings, though with wide confidence intervals.

The association between smoking and offspring asthma was particularly strong around 4-5 and 18 months of age, and it was even

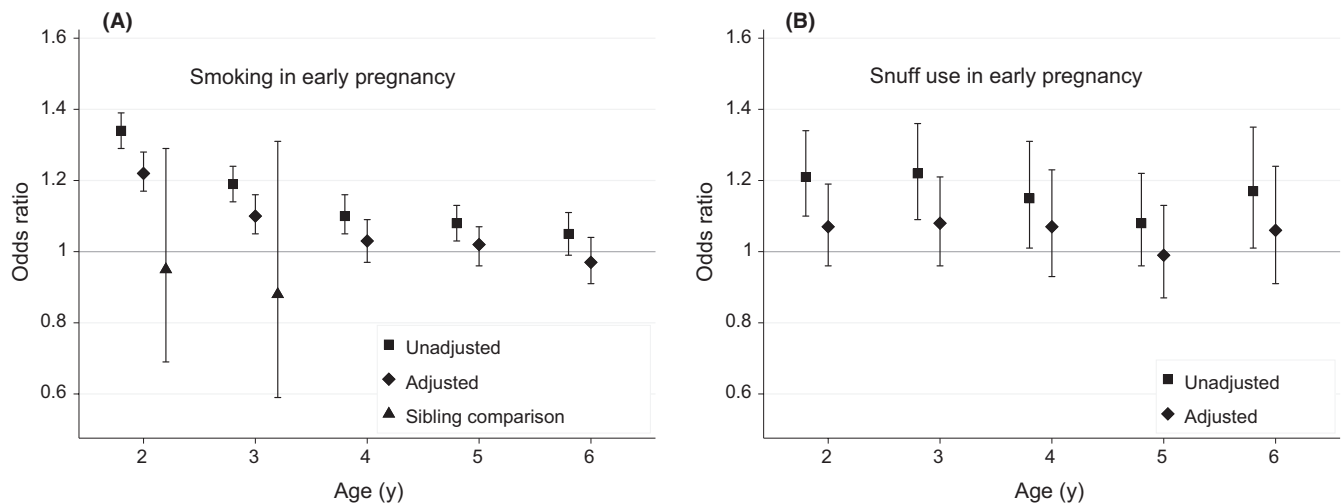


FIGURE 2 Odds ratios with 95% confidence intervals for the association between current asthma at ages 2-6 years and (A) smoking and (B) oral moist snuff use in early pregnancy; unadjusted, adjusted (for birth year, parity, maternal age, BMI and family situation, asthma in the parents, parental birth country, education and income) and sibling comparisons

TABLE 2 Hazard ratios and 95% confidence intervals for the association between incident asthma/wheeze and smoking or snuff use in early pregnancy from Cox regression by age

	HR [95% CI] by age					
	0-365 d		366-730 d		>730 d	
Asthma/wheeze						
Smoking in early pregnancy						
Crude	1.57	[1.50,1.65]	1.44	[1.37,1.51]	1.15	[1.09,1.21]
Adjusted	1.32	[1.25,1.39]	1.28	[1.21,1.36]	1.06	[1.00,1.12]
Sibling	1.20	[0.60,2.40]	1.08	[0.38,3.06]	0.36	[0.06,2.05]
Snuff use in early pregnancy						
Crude	1.06	[0.92,1.21]	1.30	[1.15,1.47]	1.15	[1.02,1.31]
Adjusted	0.86	[0.74,0.99]	1.17	[1.03,1.32]	1.04	[0.91,1.19]

more pronounced for children of women still smoking in late pregnancy. In children of mothers who stopped smoking before the first antenatal visit, there was a slightly increased risk in comparison to non-smokers.

Because snuff is high in nicotine, the modest association between snuff use and asthma suggests that nicotine exposure in utero has a limited role in the association between SDP and asthma or wheeze. This is further supported by the attenuation of the estimates for smoking in the sibling comparison, indicating that the causal factors of the association between SDP and asthma/wheeze are factors shared between siblings, which could be ETS and/or any other familial factors, rather than SDP.

Considering that women who smoke during pregnancy are also more likely to smoke after the pregnancy and potentially more prone to smoke near the child compared with nonusers and to women who stopped smoking before the first antenatal care visit, it is difficult to distinguish between SDP and ETS in early life. Some researchers have distinguished between women smoking only in pregnancy, only after pregnancy and both during and after pregnancy. Some studies have found stronger associations between smoking during pregnancy only and asthma/wheeze, compared with maternal smoking

after the pregnancy only and, more surprising, also compared with smoking both during and after pregnancy.^{4,22,23} Others have estimated the effects of SDP and ETS with or without the other and found stronger associations with ETS compared to SDP,²⁴⁻²⁶ while one study found the opposite.²⁷ The difference in HRs between exposure to smoking in utero and those that stopped smoking early in the pregnancy in our study may be a sign of an effect of smoking in utero. However, it may also be due to differences in postnatal smoking behaviour, that is not all starting to smoke again, after quitting in the early pregnancy, and a higher awareness of the danger of tobacco smoke exposure to children, making those returning to smoking more prone to smoke outdoors. To speculate, the slightly increased HRs at the age 12-24 months also for children of women who quit smoking before the first antenatal care visit may reflect that a proportion of these women pick up smoking when they no longer breast feed their children and consequently expose their children to ETS.

The ages of the children when the rates of asthma and wheeze associated with SDP are increased, correspond to the age when the protection from the maternal immune system fades out at the same time as the mothers and their babies start attending mother-baby

activities (2-6 months) and the age when children in Sweden commonly start day care (12-24 months). Thus, those are periods when the children are at high risk of infections. Previous studies have shown associations between ETS, and to some extent SDP, and respiratory infections.²⁸⁻³⁰ Considering how the hazard ratios varied with age, we speculate that this indicate that SDP (or ETS) makes the child more susceptible to viral respiratory tract infections or that it makes viral infections more likely to affect the bronchi of the exposed child, which in turn increases the risk of asthma and wheeze.

Pooled or meta-analyses on the association between SDP and asthma or wheeze in pre-schoolchildren have all shown estimates in the range $OR = 1.25$ - $OR = 1.85$,^{2,4,31} which is in line with our results for the full cohort. In one study, unmeasured confounding was adjusted for by means of a sibling design. Similar to our results they found ORs for SDP and asthma in the range 1.09-1.19 in the full cohort, which were attenuated in the sibling comparison.³² Thus, although our confidence intervals were wide in the sibling comparisons, our results are supported by the results of this previous sibling comparison.

To our knowledge, this is the first study on Swedish oral moist snuff use in pregnancy and offspring asthma and wheeze. We found only a weak association between snuff use in pregnancy and asthma and wheeze, despite animal studies suggesting that nicotine exposure would affect lung development.^{7,8} Considering we found stronger evidence of an association with SDP, the responsible substance seems more likely to be linked to the combustion of the tobacco. However, given the results from the sibling comparison, we cannot exclude that the association is due to ETS or other familial factors, rather than the smoking during pregnancy.

A strength of this study is that it is built on population-based nation-wide registers, thus making the results generalisable to the general population. Most data are prospectively recorded, including specific dates of first hospital visit and first dispense of asthma drugs, which enables us to have more detailed analyses regarding timing of the association. We also had information on the use of snuff in pregnancy and rich information on potentially confounding parental factors, for example age, education, family situation, birth country, asthma, maternal BMI and parity. Our ability to link siblings made it possible to do sibling comparisons and thereby control for confounding and mediating factors shared by the siblings. The sibling comparisons automatically adjust for all confounding factors and all mediators that the siblings share.³³ In this case, it means that we adjust for confounding from pre-conception parental factors that are constant between the conceptions. We also adjust for mediators that the siblings share, which, for example includes household ETS unless the smoker(s) quit smoking between pregnancies. However, the design does not adjust for factors that are unique for each child, such as the biological effect of smoking exposure in utero.

This study also suffers from some limitations. Due to a high degree of misclassification of snuff use in late pregnancy, we could not use this information.⁹ However, a study on snuff use in pregnancy showed that 87% of the women reporting snuff use in early

pregnancy, reported still doing so in week 32.⁹ Using smoking information from late pregnancy gave very similar results to those only using smoking in early pregnancy. The tobacco-exposure information was self-reported by the mothers. Validation studies using cotinine measurements have indicated high agreement between maternal reports and biomarkers levels.^{9,17,34} We did not have information on ETS, neither from the father nor from the mother after birth. However, the sibling comparisons automatically controlled for this to the extent it was shared by the siblings. Although sibling comparison is a powerful design for reducing confounding from unmeasured factors, it suffers from some limitations.³⁵ A requirement for a sibling pair to be informative in those analyses is that they are discordant on the exposure, which may limit the generalisability of the results. Thus, we need to consider if the effect of SDP may be different in children of women who smoke in one pregnancy but not in the other compared with those whose mothers smoke in both. Further, the design is more sensitive to measurement errors, in particular in the exposure variables, compared with other designs.³⁶ Bias in sibling comparison analyses may also be due to carry-over effects from exposure or outcome in the first sibling to the second.²¹ In this study, the most likely carry-over effects would be that of (a) exposing the firstborn sibling to tobacco smoke if the mother is smoking when expecting the second child or (b) that the mother's decision to smoke in the second pregnancy is influenced by asthma in the first child. In the first case, the issue can be solved by adding an interaction term between sibling order and exposure in those analyses, as we did.²¹ Regarding the second issue, we tested for an association between asthma in the first child and smoking in the second pregnancy. Here, we saw a tendency to increased risk of smoking in the second pregnancy if the first child had asthma before the start of the second pregnancy. This is most likely due to unmeasured confounding rather than mothers deciding to smoke if their child has asthma. Thus, we conclude that this carry-over effect would be negligible. Moreover, we did not have enough sibling pairs that were discordant for both prevalent asthma/wheeze and maternal snuff use in pregnancy to run sibling comparisons for the association between snuff and prevalent asthma/wheeze. Considering that the already weak association between snuff use and asthma/wheeze was clearly reduced when adjusting for parental covariates, it seems unlikely that a sibling comparison for snuff and prevalent asthma/wheeze would have given a different result. We also lacked information from primary care visits, and although we had information on asthma medication dispenses, we have most likely miss-classified some mild cases not needing medication as healthy. As always in observational studies, residual confounding may influence the results.

In conclusion, we found an association between smoking during pregnancy and asthma/wheeze, in particular at the ages when the children are at high risk of respiratory tract infections. The associations with current asthma/wheeze decreased with increasing age and when adjusting for confounders. They were further diluted when controlling for unmeasured familial factors, including ETS

shared by siblings, although with wide confidence intervals. We are also the first to study the association between snuff use in pregnancy and asthma, showing no or a very weak association. Our weak findings for snuff combined with attenuated associations between SDP and asthma in the sibling comparison indicate a limited role of nicotine exposure during pregnancy; rather ETS and other familial factors seem to explain observed associations.

ACKNOWLEDGEMENT

Financial support was provided from the Swedish Research Council through the Swedish Initiative for Research on Microdata in the Social And Medical Sciences (SIMSAM) framework grant no 340-2013-5867, FORTE grant no 2015-00289 grants provided by the Stockholm County Council (ALF-projects), and the Swedish Heart-Lung Foundation.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare, except H Larsson, who has served as a speaker for Evolan Pharma and Shire and has received research grants from Shire; all outside the submitted work.

DATA AVAILABILITY STATEMENT

Original data are held by Swedish National Board of Health and Welfare and Statistics Sweden and because of Swedish data storage laws we cannot make the data publicly available. However, any researcher can access the data by obtaining an ethical approval from a regional ethical review board and thereafter asking the Swedish National Board of Health and Welfare and Statistics Sweden for the original data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

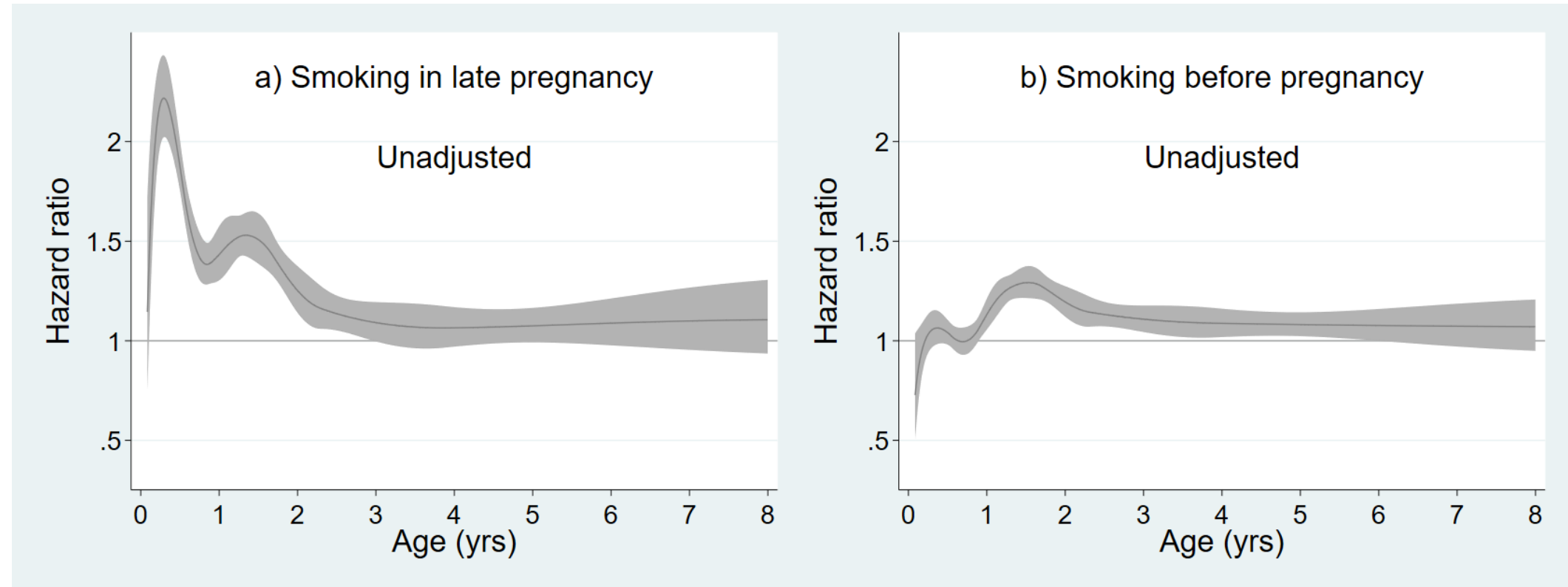
How to cite this article: Lundholm C, Gunnerbeck A, D'Onofrio BM, Larsson H, Pershagen G, Almqvist C. Smoking and snuff use in pregnancy and the risk of asthma and wheeze in pre-schoolchildren—A population-based register study. *Clin Exp Allergy*. 2020;50:597-608. <https://doi.org/10.1111/cea.13593>

Online supplement

Smoking and snuff use in pregnancy and the risk of asthma and wheeze
in pre-school children – a population-based register study

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Göran Pershagen, Catarina Almqvist

eFigure 1. Hazard ratios with 95% confidence intervals (shaded area) from flexible parametric models for the crude association between incident asthma/wheeze and (a) smoking in early pregnancy, (b) still smoking in late pregnancy.



eFigure 2: Sensitivity analysis regarding snuff use, excluding women who smoked three months before the first antenatal care visit, showed similar results. Hazard ratios with 95% confidence intervals (shaded area) from flexible parametric models adjusted for birth year, parity, maternal age, BMI and family situation (mother living together with the father or not), asthma in the parents, parental birth country, education and income.

