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

Cecilia Lundholm1 | Anna Gunnerbeck1,2,3 | Brian M D’Onofrio1,4 | Henrik Larsson1,5 | Göran Pershagen6 | Catarina Almqvist1,7

1Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
2Neuropediatric Unit, Department of Women’s and Children’s Health, Karolinska Institutet, Stockholm, Sweden
3Pediatric Endocrinology Unit, Astrid Lindgren Children’s Hospital, Karolinska University Hospital, Stockholm, Sweden
4Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN, USA
5School of Medical Sciences, Örebro University, Örebro, Sweden
6Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
7Lung and Allergy Unit, Astrid Lindgren Children’s Hospital, Karolinska University Hospital, Stockholm, Sweden

Correspondence
Cecilia Lundholm, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Box 281, 171 77 Stockholm, Sweden.
Email: cecilia.lundholm@ki.se

Funding information
Vetenskapsrådet, Grant/Award Number: 340-2013-5867; Stockholm’s 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.
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,\(^5\) showing differences in lung development in animals exposed to tobacco smoke\(^5\)\(^-\)\(^6\) or nicotine\(^7\) 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 foetuses,\(^8\) 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 apnoea\(^11\) 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. The information on smoking 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 smoke data was as low as 51%. Therefore we only included smoke 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 includes 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 asthma 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 β2-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 β2-agonists (R03AC02, R03AC03, R03AC12, R03AC13) within 12 months.

Or

3. At least three dispenses of short-acting inhaled β2-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; ≥ 4), maternal age (≤19; 20-24; 25-29; 30-34; ≥35 years at birth), BMI (categorised in accordance with World Health Organization: < 18.5; 18.5-24.9; 25.0-29.9; ≥ 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) from the Longitudinal integration database for health insurance and labour market studies.

### 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). 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. 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** |
| No | Yes | Missing |
| N | % | N | % | N | % |
| Total | 629 881 | 79.9 | 50 316 | 6.4 | 108 311 | 13.7 |
| Child gender |
| Boy | 323 368 | 79.8 | 25 889 | 6.4 | 55 857 | 13.8 |
| Girl | 306 513 | 79.9 | 24 427 | 6.4 | 52 454 | 13.7 |
| Birth year |
| 2005 | 35 241 | 74.6 | 3 527 | 7.5 | 8496 | 18.0 |
| 2006 | 78 412 | 77.6 | 69 922 | 6.9 | 15 696 | 15.5 |
| 2007 | 77 988 | 76.2 | 67 288 | 6.6 | 17 690 | 17.3 |
| 2008 | 84 420 | 80.8 | 69 352 | 6.6 | 13 159 | 12.6 |
| 2009 | 86 381 | 81.4 | 68 653 | 6.5 | 12 840 | 12.1 |
| 2010 | 91 140 | 81.9 | 69 689 | 6.3 | 13 166 | 11.8 |
| 2011 | 88 179 | 82.0 | 63 509 | 5.9 | 12 975 | 12.1 |
| 2012 | 88 120 | 81.3 | 59 511 | 5.5 | 14 289 | 13.2 |
| Parity |
| 1 | 264 436 | 76.5 | 21 414 | 6.2 | 59 704 | 17.3 |
| 2 | 243 453 | 83.6 | 15 303 | 5.3 | 32 408 | 11.1 |
| 3 | 86 468 | 81.4 | 81 086 | 7.6 | 11 625 | 10.9 |
| ≥4 | 35 524 | 77.9 | 54 941 | 12.0 | 45 744 | 10.0 |
| Mother’s age, yrs |
| ≤19 | 5568 | 46.4 | 2879 | 24.0 | 3543 | 29.5 |
| 20-24 | 64 838 | 64.8 | 13 419 | 13.4 | 21 844 | 21.8 |
| 25-29 | 177 234 | 78.5 | 14 464 | 6.4 | 34 020 | 15.1 |
| 30-34 | 233 314 | 84.5 | 11 266 | 4.1 | 31 453 | 11.4 |
| ≥35 | 148 924 | 85.3 | 82 829 | 4.7 | 17 449 | 10.0 |
| Missing | 3 | 60.0 | 0 | 0.0 | 2 | 40.0 |
| Mother's BMI |
| <18.5 | 14 115 | 81.2 | 15 789 | 9.1 | 16 969 | 9.8 |
| 18.5-24.9 | 369 698 | 85.0 | 23 888 | 5.5 | 41 137 | 9.5 |
| 25-29.9 | 150 288 | 82.0 | 13 181 | 7.2 | 19 854 | 10.8 |
| Snuff use in pregnancy |
| No | Yes | Missing |
| N | % | N | % | N | % |
| Total | 726 981 | 92.2 | 71 654 | 9.9 | 54 362 | 7.0 |
| Child gender |
| Boy | 373 211 | 92.1 | 37 324 | 9.9 | 28 169 | 7.0 |
| Girl | 353 770 | 92.3 | 34 331 | 9.9 | 26 193 | 6.8 |
| Birth year |
| 2005 | 42 198 | 89.3 | 40 424 | 9.9 | 46 620 | 9.9 |
| 2006 | 92 156 | 91.2 | 89 999 | 9.1 | 80 455 | 8.0 |
| 2007 | 91 849 | 89.7 | 79 943 | 8.0 | 97 664 | 9.5 |
| 2008 | 98 082 | 93.8 | 91 543 | 9.3 | 55 199 | 5.3 |
| 2009 | 99 209 | 93.5 | 11 141 | 1.1 | 57 365 | 5.4 |
| 2010 | 104 058 | 93.5 | 10 777 | 1.0 | 61 395 | 5.5 |
| 2011 | 100 171 | 93.2 | 9 991 | 0.9 | 63 426 | 5.9 |
| 2012 | 99 258 | 91.6 | 9 477 | 0.9 | 81 505 | 7.5 |
| Parity |
| 1 | 315 423 | 91.3 | 29 009 | 8.8 | 27 220 | 7.9 |
| 2 | 270 524 | 92.9 | 24 644 | 8.8 | 18 176 | 6.2 |
| 3 | 98 543 | 92.8 | 12 090 | 1.1 | 64 449 | 6.1 |
| ≥4 | 42 491 | 93.2 | 58 536 | 1.3 | 25 175 | 5.5 |
| Mother’s age, yrs |
| ≤19 | 10 923 | 91.1 | 17 34 | 1.4 | 894 | 7.5 |
| 20-24 | 91 178 | 91.1 | 14 204 | 1.4 | 75 035 | 7.5 |
| 25-29 | 208 023 | 92.2 | 19 500 | 0.9 | 15 745 | 7.0 |
| 30-34 | 255 342 | 92.5 | 20 527 | 0.7 | 18 638 | 6.8 |
| ≥35 | 161 512 | 92.5 | 15 709 | 0.9 | 11 583 | 6.6 |
| Missing | 3 | 60.0 | 0 | 0.0 | 2 | 40.0 |
| Mother’s BMI |
| <18.5 | 16 697 | 96.0 | 20 3 | 1.2 | 489 | 2.8 |
| 18.5-24.9 | 418 061 | 96.2 | 36 562 | 0.8 | 13 006 | 3.0 |
| 25-29.9 | 175 900 | 96.0 | 18 411 | 1.0 | 55 824 | 3.0 | (Continues)
**TABLE 1** (Continued)

| Smoking in early pregnancy | Missing | Snuff use in pregnancy | Missing |
|---------------------------|---------|-------------------------|---------|
|                           | N       | %                      | N       | %                      |
|                           | No      | Yes                    | No      | Yes                    |
|                           | N       | %                      | N       | %                      |
| ≥30                       | 68 363  | 77.4                   | 9195    | 10.4                   | 10 712   | 12.1                   | 84 374   | 95.6                   | 1113     | 1.3                    | 2783     | 3.2                    |
| Missing                   | 27 417  | 42.3                   | 2474    | 3.8                    | 34 912   | 53.9                   | 31 949   | 49.3                   | 352      | 0.5                    | 32 502   | 50.2                   |
| Parents cohabiting        |         |                        |         |                        |         |                        |         |                        |         |                        |         |                        |
| Living together           | 598 306 | 84.6                   | 40 451  | 5.7                    | 68 370   | 9.7                    | 679 808  | 96.1                   | 6423     | 0.9                    | 20 896   | 3.0                    |
| Not living together       | 27 484  | 60.8                   | 94 545  | 20.9                   | 82 499   | 18.3                   | 42 299   | 93.6                   | 694      | 1.5                    | 2194     | 4.9                    |
| Missing                   | 4091    | 11.3                   | 411     | 1.1                    | 31 692   | 87.6                   | 4 874    | 13.5                   | 48       | 0.1                    | 31 272   | 86.4                   |
| Asthma in mother          |         |                        |         |                        |         |                        |         |                        |         |                        |         |                        |
| No                        | 550 251 | 80.3                   | 41 211  | 6.0                    | 93 415   | 13.6                   | 632 711  | 92.4                   | 5881     | 0.9                    | 46 285   | 6.8                    |
| Yes                       | 79 630  | 76.8                   | 91 05   | 8.8                    | 14 896   | 14.4                   | 94 270   | 91.0                   | 1284     | 1.2                    | 8077     | 7.8                    |
| Asthma in father          |         |                        |         |                        |         |                        |         |                        |         |                        |         |                        |
| No                        | 563 178 | 79.9                   | 44 950  | 6.4                    | 96 950   | 13.8                   | 650 344  | 92.2                   | 6337     | 0.9                    | 48 397   | 6.9                    |
| Yes                       | 66 703  | 80.0                   | 53 66   | 6.4                    | 11 361   | 13.6                   | 76 637   | 91.9                   | 828      | 1.0                    | 5965     | 7.1                    |
| Mother’s birth place      |         |                        |         |                        |         |                        |         |                        |         |                        |         |                        |
| Sweden                    | 493 302 | 79.4                   | 40 173  | 6.5                    | 87 909   | 14.1                   | 568 009  | 91.4                   | 6651     | 1.1                    | 46 724   | 7.5                    |
| Nordic country            | 9011    | 77.8                   | 95 95   | 8.3                    | 1616     | 13.9                   | 10 638   | 91.8                   | 93       | 0.8                    | 855      | 7.4                    |
| Europe, North America, Oceania | 40 636 | 72.8                   | 59 31   | 10.6                   | 92 65    | 16.6                   | 53 209   | 95.3                   | 131      | 0.2                    | 2492     | 4.5                    |
| Other                     | 86 859  | 87.2                   | 32 47   | 3.3                    | 95 14    | 9.6                    | 95 044   | 95.4                   | 289      | 0.3                    | 4287     | 4.3                    |
| Missing                   | 73      | 84.9                   | 6       | 7.0                    | 7        | 8.1                    | 81       | 94.2                   | 1        | 1.2                    | 4        | 4.7                    |
| Father’s birth place      |         |                        |         |                        |         |                        |         |                        |         |                        |         |                        |
| Sweden                    | 489 690 | 80.1                   | 37 068  | 6.1                    | 84 698   | 13.9                   | 559 265  | 91.5                   | 6419     | 1.0                    | 45 772   | 7.5                    |
| Nordic country            | 9242    | 76.4                   | 111 2   | 11.2                   | 1745     | 14.4                   | 11 126   | 92.0                   | 139      | 1.1                    | 834      | 6.9                    |
| Europe, North America, Oceania | 43 826 | 71.8                   | 67 55   | 11.1                   | 10 440   | 17.1                   | 57 796   | 94.7                   | 220      | 0.4                    | 3005     | 4.9                    |
| Other                     | 79 708  | 84.8                   | 43 50   | 4.6                    | 99 62    | 10.6                   | 89 681   | 95.4                   | 315      | 0.3                    | 4024     | 4.3                    |
| Missing                   | 7415    | 74.8                   | 1031    | 10.4                   | 1466     | 14.8                   | 9113     | 91.9                   | 72       | 0.7                    | 727      | 7.3                    |
| Mother’s education        |         |                        |         |                        |         |                        |         |                        |         |                        |         |                        |
| Middle school             | 50 598  | 59.6                   | 17 825  | 21.0                   | 16 506   | 19.4                   | 78 638   | 92.6                   | 1126     | 1.3                    | 5165     | 6.1                    |
| High school               | 222 624 | 73.7                   | 26 257  | 8.7                    | 53 084   | 17.6                   | 276 187  | 91.5                   | 3933     | 1.3                    | 21 845   | 7.2                    |
| College/Univeristy        | 345 963 | 89.1                   | 50 005  | 1.3                    | 37 241   | 9.6                    | 359 390  | 92.6                   | 2057     | 0.5                    | 26 762   | 6.9                    |
| Missing                   | 10 696  | 79.8                   | 12 299  | 9.2                    | 14 80    | 11.0                   | 12 766   | 95.2                   | 49       | 0.4                    | 590      | 4.4                    |
## TABLE 1 (Continued)

| | Smoking in early pregnancy | | Snuff use in pregnancy | |
|---|---|---|---|---|
| | No | % | Yes | % | No | % | Yes | % | N | % | N | % | N | % |
| **Father’s education** | | | | | | | | | | | | | | |
| Middle school | 61 432 | 65.8 | 14 936 | 16.0 | 16 990 | 18.2 | 86 437 | 92.6 | 1101 | 1.2 | 5820 | 6.2 | |
| High school | 278 229 | 76.5 | 28 068 | 7.7 | 57 620 | 15.8 | 333 596 | 91.7 | 4391 | 1.2 | 25 930 | 7.1 | |
| College/University | 272 933 | 88.8 | 4623 | 1.5 | 29 820 | 9.7 | 284 806 | 92.7 | 1521 | 0.5 | 21 049 | 6.8 | |
| Missing | 17 287 | 72.5 | 2689 | 11.3 | 3881 | 16.3 | 22 142 | 92.8 | 152 | 0.6 | 1563 | 6.6 | |
| **Father’s disposable income** | | | | | | | | | | | | | | |
| 1st Quintile | 119 327 | 76.0 | 16 377 | 10.4 | 21 311 | 13.6 | 146 809 | 93.5 | 1474 | 0.9 | 8732 | 5.6 | |
| 2nd Quintile | 123 405 | 78.4 | 12 800 | 8.1 | 21 192 | 13.5 | 145 535 | 92.5 | 1804 | 1.1 | 10 058 | 6.4 | |
| 3rd Quintile | 124 344 | 79.0 | 10 304 | 6.5 | 22 718 | 14.4 | 144 584 | 91.9 | 1498 | 1.0 | 11 284 | 7.2 | |
| 4th Quintile | 126 891 | 80.7 | 7 334 | 4.7 | 23 098 | 14.7 | 144 195 | 91.7 | 1461 | 0.9 | 11 667 | 7.4 | |
| 5th Quintile | 134 239 | 85.4 | 3 325 | 2.1 | 19 669 | 12.5 | 143 851 | 91.5 | 920 | 0.6 | 12 462 | 7.9 | |
| Missing | 1675 | 77.0 | 176 | 8.1 | 323 | 14.9 | 2007 | 92.3 | 8 | 0.4 | 159 | 7.3 | |
| **Mother’s disposable income** | | | | | | | | | | | | | | |
| 1st Quintile | 116 084 | 75.6 | 16 069 | 10.5 | 21 367 | 13.9 | 142 801 | 93.0 | 1480 | 1.0 | 9239 | 6.0 | |
| 2nd Quintile | 119 960 | 78.1 | 12 476 | 8.1 | 21 169 | 13.8 | 141 719 | 92.3 | 1674 | 1.1 | 10 212 | 6.6 | |
| 3rd Quintile | 122 665 | 79.8 | 9 336 | 6.1 | 21 672 | 14.1 | 141 478 | 92.1 | 1641 | 1.1 | 10 554 | 6.9 | |
| 4th Quintile | 125 094 | 81.4 | 6 905 | 4.5 | 21 669 | 14.1 | 141 279 | 91.9 | 1362 | 0.9 | 11 027 | 7.2 | |
| 5th Quintile | 131 276 | 85.5 | 3 231 | 2.1 | 19 015 | 12.4 | 140 655 | 91.6 | 881 | 0.6 | 11 986 | 7.8 | |
| Missing | 14 802 | 72.1 | 2 299 | 11.2 | 3 419 | 16.7 | 19 049 | 92.8 | 127 | 0.6 | 1344 | 6.5 | |
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 children 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 (mother living together with the father or not), asthma in the parents, parental birth country, education and income.
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 surprisingly, also compared with smoking both during and after pregnancy. Others have estimated the effects of SDP and ETS with or without the other and found stronger associations with ETS compared to SDP, while one study found the opposite. 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 quitted 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 visits.

**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.
The siblings share, which, for example includes household ETS and asthma, maternal BMI and parity. Our ability to link siblings is smoking during pregnancy. 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. A requirement for a sibling pair to be informative 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. Bias in sibling comparison analyses may also be due to carry-over effects from exposure or outcome in the first sibling to the second. 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. 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 thereby asking the Swedish National Board of Health and Welfare and Statistics Sweden for the original data.

ORCID
Cecilia Lundholm https://orcid.org/0000-0002-6546-3650
Catarina Almqvist https://orcid.org/0000-0002-1045-1898

REFERENCES
1. Centers for Disease Control and Prevention (US); National Center for Chronic Disease Prevention and Health Promotion (US); Office on Smoking and Health (US). How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease: a report of the surgeon general. Atlanta, GA, USA: U.S. Department of Health and Human Services, Public Health Service, Office of the Surgeon General; 2010.
2. Silvestri M, Franchi S, Pistorio A, et al. Smoke exposure, wheezing, and asthma development: a systematic review and meta-analysis in unselected birth cohorts. Pediatr Pulmonol. 2015;50(4):353-362.
3. Thacher JD, Gehring U, Gruzieva O, et al. Maternal smoking during pregnancy and early childhood development of asthma and rhinoconjunctivitis - a MeDALL project. Environ Health Perspect. 2018;126(4):047005.
4. Neuman A, Hofmann C, Orsini N, et al. Maternal smoking in pregnancy and asthma in preschool children: a pooled analysis of eight birth cohorts. Am J Respir Crit Care Med. 2012;186(10):1037-1043.
5. Nelson E, Jodscheit K, Guo Y. Maternal passive smoking during pregnancy and fetal developmental toxicity. Part 1: gross morphological effects. Hum Exp Toxicol. 1999;18(4):252-256.
6. Subramaniam S, Srinivasan S, Bummer PM, et al. Perinatal side-stream cigarette smoke exposure and the developing pulmonary surfactant system in rats. Hum Exp Toxicol. 1999;18(4):206-211.
7. Sekhon HS, Keller JA, Benowitz NL, et al. Prenatal nicotine exposure alters pulmonary function in newborn rhesus monkeys. Am J Respir Crit Care Med. 2001;164(6):989-994.
8. Sekhon HS, Jia Y, Raab R, et al. Prenatal nicotine increases pulmonary alpha7 nicotinic receptor expression and alters fetal lung development in monkeys. J Clin Invest. 1999;103(5):637-647.
9. Gunnerbeck A, Raaschou P, Cnattingius S, et al. Maternal snuff use and cotinine in late pregnancy-a validation study. Acta Obstet Gynecol Scand. 2018;97(11):1373-1380.
10. England LJ, Levine RJ, Mills JL, et al. Adverse pregnancy outcomes in snuff users. Am J Obstet Gynecol. 2003;189(4):939-943.
11. Gunnerbeck A, Wikstrom AK, Bonamy AK, et al. Relationship of maternal snuff use and cigarette smoking with neonatal apnea. Pediatrics. 2011;128(3):503-509.
12. Gunnerbeck A, Edstedt Bonamy AK, Wikstrom AK, et al. Maternal snuff use and smoking and the risk of oral cleft malformations—a population-based cohort study. PLoS ONE. 2014;9(1):e84715.
13. D’Onofrio BM, Class QA, Rickert ME, et al. Translational epidemiologic approaches to understanding the consequences of early-life exposures. Behav Genet. 2016;46(3):315-328.
14. The Swedish medical birth register - a summary of content and quality. Stockholm: Swedish National Board of Health and Welfare, Center of Epidemiology; 2003.
15. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, et al. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009;24(11):659-667.
16. Ludvigsson JF, Almqvist C, Bonamy AK, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016;31(2):125-136.
17. Mattsson K, Kallen K, Rignell-Hydbom A, et al. Cotinine validation of self-reported smoking during pregnancy in the Swedish medical birth register. Nicotine Tob Res. 2016;18(1):79-83.
18. Ortvist AK, Lundholm C, Wettermark B, et al. Validation of asthma and eczema in population-based Swedish drug and patient registers. Pharmacoepidemiol Drug Saf. 2013;22(8):850-860.
19. Ludvigsson JF, Sedberg P, Olen O, et al. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. Eur J Epidemiol. 2019;34(4):423-437.
20. Lambert PC, Royston P. Further development of flexible parametric models for survival analysis. Stata J. 2009;9(2):265-290.
21. Sjolander A, Frisell T, Kuja-Halkola R, et al. Carryover effects in sibling comparison designs. Epidemiology. 2016;27(6):852-858.
22. Gilliland FD, Li YF, Peters JM. Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. J Allergy Clin Immunol. 2001;108(2):429-436.
23. Sherriff A, Peters TJ, Henderson J, et al. Risk factor associations with wheezing patterns in children followed longitudinally from birth to 3(1/2) years. Int J Epidemiol. 2001;30(6):1473-1484.
24. Hagendorens MM, Bridts CH, Lauwers K, et al. Perinatal risk factors for sensitization, atopic dermatitis and wheezing during the first year of life (PIPO study). Clin Exp Allergy. 2005;35(6):733-740.
25. Hallit S, Raherison C, Waked M, et al. Association between caregiver exposure to toxics during pregnancy and childhood-onset asthma: a case-control study. Iran J Allergy Asthma Immunol. 2017;16(6):488-500.
26. Tanaka K, Miyake Y, Sasaki S, et al. Maternal smoking and environmental tobacco smoke exposure and the risk of allergic diseases in Japanese infants: the Osaka maternal and child health study. J Asthma. 2008;45(9):833-838.
27. Lannero E, Wickman M, Pershagen G, et al. Maternal smoking during pregnancy increases the risk of recurrent wheezing during the first years of life (BAMSE). Respir Res. 2006;7:3.
28. Haberg SE, Stigum H, Nystad W, et al. Effects of pre- and postnatal exposure to parental smoking on early childhood respiratory health. Am J Epidemiol. 2007;166(6):679-686.

29. Molero Y, Zetterqvist J, Lichtenstein P, et al. Parental nicotine replacement therapy and offspring bronchitis/bronchiolitis and asthma - a nationwide population-based cohort study. Clin Epidemiol. 2018;10:1339-1347.

30. Vanker A, Gie RP, Zar HJ. The association between environmental tobacco smoke exposure and childhood respiratory disease: a review. Expert Rev Respir Med. 2017;11(8):661-673.

31. Burke H, Leonardi-Bee J, Hashim A, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. Pediatrics. 2012;129(4):735-744.

32. Gilman SE, Gardener H, Buka SL. Maternal smoking during pregnancy and children’s cognitive and physical development: a causal risk factor? Am J Epidemiol. 2008;168(5):522-531.

33. Sjolander A, Zetterqvist J. Confounders, mediators, or colliders: what types of shared covariates does a sibling comparison design control for? Epidemiology. 2017;28(4):540-547.

34. George L, Granath F, Johansson AL, et al. Self-reported nicotine exposure and plasma levels of cotinine in early and late pregnancy. Acta Obstet Gynecol Scand. 2006;85(11):1331-1337.

35. D’Onofrio BM, Lahey BB, Turkheimer E, et al. Critical need for family-based, quasi-experimental designs in integrating genetic and social science research. Am J Public Health. 2013;103(Suppl 1):S46-S55.

36. Frisell T, Öberg S, Kuja-Halkola R, et al. Sibling comparison designs: bias from non-shared confounders and measurement error. Epidemiology. 2012;23(5):713-720.

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