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ORIGINAL RESEARCH ARTICLE

The association of smoking, use of snuff, and preconception alcohol consumption with spontaneous abortion: A population-based cohort study

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Abstract

Introduction: It is unclear whether tobacco in early pregnancy and alcohol use preceding pregnancy are associated with spontaneous abortion. The purpose was to investigate if use of tobacco and/or alcohol is associated with spontaneous abortion among women attending antenatal care, and if age and body mass index (BMI) attenuate the risk.

Material and Methods: A population-based cohort study based on data from the Swedish Pregnancy Register. All pregnant women having had the first antenatal visit from January 2014 to July 2018 were included (n = 525 604). The register had information about smoking and use of snuff before and in early pregnancy, as well as data on alcohol habits before pregnancy, measured by the Alcohol Use Disorders Identification Test (AUDIT), a validated questionnaire. Logistic regression analysis was used to estimate the association between lifestyle factors and spontaneous abortion, and multiple imputation was used to impute missing data.

Results: In total, 34 867 (6.6%) pregnancies ended in a spontaneous abortion after the first visit to maternal health care. At the first maternal healthcare visit, daily smoking was reported by 24 214 (5.1%), and 6403 (1.2%) used snuff. For 19 837 (4.2%) women, a high alcohol score was reported for the year preceding pregnancy. After adjusting for potential confounders and multiple imputation, use of tobacco was associated with spontaneous abortion; smoking 1–9 cigarettes/day (adjusted odds ratio [aOR] 1.11, 95% confidence interval [CI] 1.04–1.18), smoking 10 or more cigarettes/day (aOR 1.12, 95% CI 1.–1.26), and use of snuff (aOR 1.20, 95% CI 1.06–1.37). Higher AUDIT scores were not significantly associated with spontaneous abortion (AUDIT 6–9: aOR 1.03, 95% CI 0.97–1.10 and AUDIT 10 or more: aOR 1.07, 95% CI 0.94–1.22). Increasing maternal age showed the highest risk of spontaneous abortion from the age of 35, and BMI of 30 kg/m^2 or more increased the risk. There were interactions

Abbreviations: aOR, adjusted odds ratio; AUDIT, Alcohol Use Disorders Identification Test; BMI, body mass index; CI, confidence interval; MHC, maternal health care; OR, odds ratio; SA, spontaneous abortion; SPR, Swedish Pregnancy Register.

between different lifestyle factors associated with spontaneous abortion that could either increase or decrease the risk of spontaneous abortion.

Conclusions: Smoking and use of snuff were associated with an increased risk of spontaneous abortion. The AUDIT scores preceding pregnancy were not associated with an increased risk of spontaneous abortion, which contradicts the results from previous studies.

KEYWORDS
alcohol, AUDIT, lifestyle factors, oral tobacco, pregnancy, smoking, snuff, spontaneous abortion

1 | INTRODUCTION

Spontaneous abortion (SA) is common, and it is estimated that 25% of all women younger than 40 years who have been pregnant have experienced an SA. Possible consequences after a SA include depression, anxiety, and post-traumatic stress symptoms in both the woman and her partner.[1] It is a challenge to study risk factors for SA, because early SA is under-reported and unrecognized, and the etiology is multifactorial. Preconception health and care have received more attention, as women's lifestyle during the preconception period affects pregnancy outcome. Women are recommended to stop smoking, not consume alcohol during pregnancy, start taking folic acid, and reduce their pre-pregnancy weight if overweight/obese.

Smoking during pregnancy has been shown to be associated with SA in most studies, as well as in a meta-analysis, although some studies lack information on confounding factors.[2–6] Snuff use (oral tobacco) has increased in Sweden in recent years,[7] but no study has analyzed the possible risk of SA for snuff users.

Alcohol use in early pregnancy indicates a higher risk of SA,[8–10] but the evidence is conflicting.[11] The screening tool, the Alcohol Use Disorders Identification Test (AUDIT),[12] was introduced in Swedish maternal health care (MHC) from 2004 to 2009. AUDIT scores in MHC reflect the extent of alcohol use (abuse) during the year preceding pregnancy[13] and help midwives in MHC to identify women with possible risk behaviors. To our knowledge, no study has analyzed the relation between AUDIT scores and the risk of SA. Furthermore, little is known about pregnancy outcomes for individuals with several risk factors (obesity, age), which makes it difficult to provide adequate information to women who are planning a pregnancy.

The primary aim of the study was to investigate if smoking or use of snuff 3 months before pregnancy or during the time of the first MHC visit or high AUDIT scores during the year preceding pregnancy were associated with SA. The secondary aim was to investigate if maternal characteristics (age, BMI) influence the risk of SA.

> **Key message**
>
> Smoking and use of snuff in early pregnancy are associated with spontaneous abortion. The AUDIT scores preceding pregnancy were not associated with an increased risk of spontaneous abortion.

2 | MATERIAL AND METHODS

This is a population-based cohort study using data from the national Swedish Pregnancy Register (SPR). The SPR contains information about pregnancies and childbirth and covers 92% of all births in Sweden. Data in SPR are mainly based on electronic transfer from the medical records (four maternity clinics did not have technical possibilities to send information to the register), but midwives also record data manually; moreover the data have a coverage rate of 76%–85%, due to different work routines among midwives. The data collection starts at the first MHC visit, which, on average, takes place at gestational week 8 (interquartile range 3). SPR was validated in 2011, and the register data showed good agreement with data in the medical records.[14]

The study population (Supporting Information Figure S1) comprised women who had their first antenatal visit registered in SPR from January 1, 2014 to July 31, 2018. Criteria for inclusion were singleton pregnancies that ended in SA or childbirth. In total, 525 604 pregnancies were included in the analysis.

The SPR includes variables about background, diseases, pregnancy, and childbirth outcome. In this study, we analyzed the following variables:

Smoking 3 months preceding pregnancy and at the time of the first visit at the MHC. Smoking was categorized as: no smoking, 1–9 cigarettes/day, or ≥10 cigarettes/day.

Using Swedish snuff (smokeless tobacco) 3 months preceding pregnancy and at the time of the first visit to the MHC. The snuff was categorized as non-users or users.

Alcohol Use Disorders Identification (AUDIT) is a 10-item questionnaire about alcohol habits. The answers are summed up to a total score that ranges between 0 and 40.[15] In Sweden, AUDIT is used in the MHC at the pregnant woman's first visit, and the questions concern alcohol habits during the year preceding pregnancy. The use of AUDIT in MHC in Sweden has been evaluated.[16] The interpretation of AUDIT scores is based on the MHC guidelines in Sweden: 0 points indicate no use of alcohol, 1–5 points indicate use of alcohol, 6–9 points suggest a risky use of alcohol, and 10–40 points suggest risk of abuse or alcohol addiction.

Age at the first MHC visit. Age was categorized into five subgroups: 13–24, 25–34, 35–39, 40–45, and 45–55 years. Extreme values (<13 and >55 years) were excluded.

Body mass index. Body weight was measured at the first visit to the MHC, and the height was self-reported by the women. Extreme values for weight (<35 kg or >200 kg) and height (<130 cm and >199 cm) were excluded. BMI was calculated as weight in kilograms, divided by height in meters squared. BMI was categorized according to the World Health Organization definition: underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), obesity (BMI 30.0–34.9 kg/m^2), and severe obesity (BMI ≥35 kg/m^2).

Country of birth was self-reported by the women and categorized as born in the Nordic countries or born in other countries.

Education level was self-reported by the women and categorized as: up to high school (12 years), or college/university (>12 years).

Self-rated health was categorized on a three-point scale: poor, neither good nor poor, and good.

The midwife records the information in the medical record or directly into SPR. Data on SA were manually documented by midwives directly in SPR, whereas data on birth were electronically transmitted from the medical record. Data on education, country of birth, and self-rated health were manually documented.

2.1 | Statistical analyses

The distribution of risk behaviors, such as use of snuff and smoking, as well as sociodemographic characteristics, are described with absolute numbers and percentages. Missing data in any variables were excluded from the analysis. To estimate the association between risk behaviors (smoking, use of snuff, preconception alcohol use) and SA, logistic regression analysis was used. Unadjusted and adjusted odds ratio with 95% confidence intervals was estimated before and after adjustment of potential confounders (age, BMI, education level, country of birth, and self-rated health). Risk of SA was stratified based on tobacco use (3 months before pregnancy and at first visit at MHC), AUDIT scores (the year preceding pregnancy), BMI, and the woman's age. A p value less than 0.05 was considered statistically significant. We analyzed missing/non-missing data for the variable smoking, in combination with the following variables: age, BMI, education level, Nordic/non-Nordic born, self-rated health, AUDIT score, and SA/childbirth.

To analyze how and if missing data had an effect on the study results, multiple imputation by chained equation (MICE) imputation was used to impute missing data. We imputed 10 complete data sets and used pooled estimates for the results. The analysis was performed using both SPSS version 25 (IBM Corp.) and STATA 16 (StataCorp LP).

2.2 | Ethics statement

When pregnant women come to MHC, they are informed about the quality register called SPR, as well as their possibility to opt out, under Swedish law. All collected data in this study are coded, and all results are published on a group level. This study was approved on December 9, 2015 by the Regional Ethical Board in Uppsala, with ref. number 2015/484. An additional application was made and approved on April 2, 2019, ref. number 2015/484 (2019–01851).

3 | RESULTS

A total of 525 604 pregnancies were included in the study, of which 34 867 (6.6%) were registered as SA and 490 737 (93.4%) as childbirth. The percentage of missing data is presented in Supporting Information Tables S1–S3. At the first antenatal visit, 1.2% (n = 5962) of the women stated that they used snuff and 5.1% (n = 23 242) that they were smokers; however, there were large differences depending on age, where the youngest were more often smokers (Table S1). Both smoking and use of snuff were more common among women with obesity, being of Nordic origin, having lower levels of education (less than 12 years education), and reporting worse health (Supporting Information Table S4).

According to AUDIT, about one-third of the women reported no alcohol use during the year preceding pregnancy. The most common AUDIT score was between 1 and 5 points (63.3%), indicating use of alcohol, whereas 3.5% reported risky use of alcohol (6–9 points), and 0.7% reported risk of abuse or alcohol addiction (≥10 points). Women with both high and low BMI were more often non-users of alcohol (Supporting Information Tables S2 and S5). No difference was found in the distribution of missing data when data for smoking were combined with age, BMI, education level, born in Nordic/non-Nordic country, AUDIT score, or self-rated health. The analyses showed that there was a higher percentage of missing data in the smoking variable in the SA group, compared with those who had given birth to a child. As a result of the large extent of missing data for certain variables, an imputation analysis was performed.

The association between tobacco exposure before/in early pregnancy and SA is shown in Table 1. Both smoking and use of snuff at the time of first visit to the MHC were associated with an increased risk of SA; adjusted odds ratio (aOR) 1.11 (95% CI 1.04–1.20) for smoking 1–9/day group vs aOR 1.38 (95% CI 1.20–1.38) for smoking 10 or more/day group, and aOR 1.28 (95% CI 1.09–1.49) for snuff users. Smoking and use of snuff 3 months preceding pregnancy showed a decreased risk or no risk difference. An AUDIT score between 6 and 9 points the year preceding pregnancy (OR 1.13, 95% CI 1.04–1.21) and a score of 10 or more (aOR 1.21, 95% CI 1.03–1.43) was associated with SA.

The risk of SA in relation to the AUDIT score is shown in Figure 1. BMI 30 kg/m^2 or more cand increasing maternal age affected the risk of SA (see Table 1).

TABLE 1 Tobacco, AUDIT and other lifestyle/social factors and the risk of spontaneous abortion shown as crude and adjusted odds ratio with and without multiple imputation (MICE)

	Total pregnancies *n*	Spontaneous abortion, *n* (%)	Delivery, *n* (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Snuff at first MHC visit[a]					
Complete case analysis					
No	393 256	23 537 (6.0)	369 719 (94.0)	Ref	Ref
Yes	3491	266 (7.6)	3225 (92.4)	1.29 (1.14–1.46)	1.28 (1.09–1.49)[c]
Multiple imputation					
No	408 825	24 558 (6.0)	384 267 (94.0)	Ref	Ref
Yes	3695	288 (7.8)	3407 (92.2)	1.30 (1.15–1.48)	1.20 (1.06–1.37)[c]
Snuff use 3 months before pregnancy					
Complete case analysis					
No	382 237	23 154 (6.1)	359 083 (93.9)	Ref	Ref
Yes	14 577	713 (4.9)	13 864 (95.1)	0.79 (0.73–0.86)	0.86 (0.78–0.94)
Multiple imputation					
No	397 119	24 175 (6.1)	372 944 (93.9)	Ref	Ref
Yes	15 401	738 (4.8)	14 663 (95.2)	0.79 (0.73–0.86)	0.78 (0.72–0.84)[c]
Smoking at first MHC visit[b]					
Complete case analysis					
No	416 164	24 759 (5.9)	391 405 (94.1)	Ref	Ref
Yes, 1–9/day	17 650	1156 (6.5)	16 494 (93.5)	1.10 (1.04–1.17)	1.11 (1.04–1.20)[c]
Yes, ≥10/day	4352	352 (8.1)	4000 (91.9) (92.8)	1.39 (1.24–1.55)	1.38 (1.20–1.57)[c]
Multiple imputation					
No	490 998	32 341 (6.6)	458 657 (93.4)	Ref	Ref
Yes, 1–9/day	21 600	1562 (7.2)	20 038 (92.8)	1.12 (1.05–1.19)	1.11 (1.04–1.18)[c]
Yes, ≥10/day	4502	370 (8,2)	4132 (91.8)	1.25 (1.05–1.19)	1.12 (1.00–1.26)[c]
Smoking 3 months before pregnancy[b]					
Complete case analysis					
No	386 017	23 481 (6.1)	362 536 (93.9)	Ref	Ref
Yes, 1–9/day	30 624	1870 (6.1)	28 754 (93.9)	1.00 (0.95–1.05)	1.00 (0.94–1.06)[c]
Yes, ≥10/day	26 604	1440 (5.4)	25 164 (94.6)	0.88 (0.83–0.93)	0.90 (0.84–0.96)[c]
Multiple imputation					
No	450 203	30 140 (6.7)	420 063 (93.3)	Ref	Ref
Yes, 1–9/day	39 632	2726 (6.9)	36 906 (93.1)	1.01 (0.96–1.06)	1.03 (0.98–1.08)[c]
Yes, ≥10/day	27 402	1487 (5.4)	25 915 (94.6)	0.80 (0.75–0.84)	0.78 (0.73–0.82)[c]
Some kind of tobacco at first MHC visit					
Complete case analysis					
No	432 164	25 360 (6.2)	406 804 (94.1)	Ref	Ref
Yes	26 699	1859 (7.0)	24 840 (93.0)	1.20 (1.14–1.26)	1.21 (1.13–1.28)[c]
Multiple imputation					
No	532 922	34 951 (6.6)	497 971 (93.4)	Ref	Ref
Yes	33 571	2604 (7.8)	30 967 (92.2)	1.18 (1.13–1.24)	1.14 (1.09–1.20)[c]
Both snuff and smoking at MHC visit					
Complete case analysis					
No	458 479	27 183 (5.9)	431 296 (94.1)	Ref	Ref
Yes	384	36 (9.4)	348 (90.6)	1.64 (1.16–2.31)	1.12 (0.70–1.79)[c]

TABLE 1 (Continued)

	Total pregnancies *n*	Spontaneous abortion, *n* (%)	Delivery, *n* (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Multiple imputation					
No	565 998	37 570 (6.6)	528 428 (93.4)	Ref	Ref
Yes	495	46 (9.3)	449 (90.7)	1.62 (1.11–2.36)	1.43 (0.98–2.08)[c]
Alcohol AUDIT					
Complete case analysis					
0	141 713	10 101 (7.1)	131 612 (92.9)	Ref	Ref
1–5	276 791	19 923 (7.2)	256 868 (92.8)	1.01 (0.98–1.03)	0.96 (0.93–1.03)[d]
6–9	15 428	1205 (7.8)	14 223 (92.2)	1.10 (1.03–1.17)	1.13 (1.04–1.21)[d]
10–40	3241	268 (8.3)	2973 (91.7)	1.17 (1.03–1.33)	1.21 (1.03–1.43)[d]
Multiple imputation					
0	185 643	12 096 (6.5)	173 547 (93.5)	Ref	Ref
1–5	356 630	23 752 (6.7)	332 878 (93.3)	1.02 (1.00–1.05)	0.91(0.88–0.94)[d]
6–9	19 938	1424 (7.1)	18 514 (92.9)	1.11 (1.05–1.18)	1.03 (0.97–1.10)[d]
10–40	4282	320 (7.5)	3962 (92.5)	1.17(1.03–1.33)	1.07(0.94–1.22)[d]
BMI (kg/m^2)					
Complete case analysis					
12–18.49	12 718	728 (5.7)	11 990 (94.3)	0.94 (0.87–1.01)	1.00 (0.91–1.10)[e]
18.5–24.99	279 019	16 884 (6.1)	262 135 (93.9)	Ref	Ref
25–29.99	128 345	8216 (6.4)	120 129 (93.6)	1.06 (1.03–1.09)	1.03 (0.99–1.06)[e]
30–34.99	49 347	3405 (6.9)	45 942 (93.1)	1.15 (1.10–1.19)	1.10 (1.05–1.16)[e]
35–75	21 524	1703 (7.9)	19 821 (92.1)	1.33 (1.26–1.40)	1.27(1.19–1.36)[e]
Multiple imputation					
12–18.49	14 781	875 (5.9)	13 906 (94.1)	0.93 (0.86–1.01)	1.02 (0.94–1.10)[e]
18.5–24.99	321 790	20 453 (6.4)	301 337 (93.6)	Ref	Ref
25–29.99	147 982	10 033 (6.8)	137 949 (93.2)	1.06 (1.03–1.08)	1.02 (0.99–1.05)[e]
30–34.99	57 006	4160 (7.3)	52 846 (92.7)	1.15 (1.11–1.20)	1.08 (1.04–1.12)[e]
35–75	24 934	2071 (8.3)	22 863 (91.7)	1.33 (1.26–1.41)	1.23(1.16–1.30)[e]
Age (years)					
Complete case analysis					
13–24	79 800	4326 (5.4)	75 474 (94.6)	0.95 (0.92–0.98)	0.92 (0.87–0.96)[f]
25–34	342 448	19 413 (5.7)	323 035 (4.3)	Ref	Ref
35–39	83 792	7650 (9.1)	76 142 (90.9)	1.67 (1.62–1.71)	1.64 (1.58–1.70)[f]
40–44	18 308	3201 (17.5)	15 107 (82.5)	3.52 (3.38–3.67)	3.58 (3.39–3.78)[f]
45–55	1130	275 (24.3)	855 (75.7)	5.35 (4.66–6.13)	5.55 (4.59–6.71)[f]
Multiple imputation					
13–24	87 522	4738 (5.4)	82 784 (94.6)	0.95 (0.91–0.98)	0.91 (0.88–0.94)[f]
25–34	367 807	20 872 (5.7)	346 935 (94.3)	Ref	Ref
35–39	90 015	8197 (9.1)	81 818 (90.9)	1.66 (1.62–1.71)	1.70 (1.66–1.75)[f]
40–44	19 919	3485 (17.5)	16 434 (82.5)	3.52 (3.38–3.67)	3.59 (3.45–3.75)[f]
45–55	1230	300 (24.4)	930 (75.6)	5.31(4.62–6.10)	5.49 (4.78–6.31)[f]
Birth					
Complete case analysis					
Nordic countries	351 518	24 997 (7.1)	326 521 (92.9)	Ref	Ref
Other countries	174 086	9870 (5.7)	164 216 (94.3)	0.78 (0.76–0.80)	1.06 (1.01–1.09)[g]

(Continues)

TABLE 1 (Continued)

	Total pregnancies *n*	Spontaneous abortion, *n* (%)	Delivery, *n* (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Multiple imputation					
Nordic countries	377 997	26 886 (7.1)	351 111 (92.9)	Ref	Ref
Other countries	188 496	10 706 (5.7)	177 790 (94.3)	0.78 (0.76–0.80)	0.72 (0.70–0.74)[g]
Education					
Complete case analysis					
Lower education	211 541	15 187 (7.2)	196 354 (92.8)	Ref	Ref
Higher education	228 604	16 097 (7.0)	212 507 (93.0)	0.97 (0.95–1.00)	0.88 (0.86–0.91)[h]
Multiple imputation					
Lower education	281 537	18 532 (6.6)	263 005 (93.4)	Ref	Ref
Higher education	284 956	19 060 (6.7)	265 896 (93.3)	1.01 (0.99–1.039)	0.91 (0.88–0.93)[h]
Self-rated health					
Complete case analysis					
Good	401 422	27 956 (7.0)	373 466 (93.0)	Ref	Ref
Neither good nor poor	30 846	2434 (7.9)	28 412 (92.1)	1.14 (1.09–1.19)	1.04 (0.98–1.10)[i]
Poor	13 031	997 (7.7)	12 034 (92.3)	1.10 (1.03–1.18)	1.02 (0.93–1.11)[i]
Multiple imputation					
Good	508 914	33 435 (6.6)	475 479 (93.4)	Ref	Ref
Neither good nor poor	40 339	2935 (7.3)	37 404 (92.7)	1.12 (1.07–1.18)	1.07 (1.01–1.12)[i]
Poor	17 240	1222 (7.1)	16 018 (92.9)	1.08 (1.01–1.15)	1.03 (0.96–1.09)[i]

[a]Only non-smokers 3 months before pregnancy and at first visit.

[b]Only non-snuff users 3 months before pregnancy and at first visit *A *p* value <0.05 is considered significant.

[c]Adjusted for age, Alcohol-AUDIT, born in Nordic/non-Nordic countries, BMI, education level, and self-rated health.

[d]Adjusted for age, born in Nordic/non-Nordic countries, BMI, education level, smoking at first antenatal visit, use of snuff at first visit, and self-rated health.

[e]Adjusted for age, Alcohol-AUDIT, born in Nordic/non Nordic countries, education level, smoking at first antenatal visit, use of snuff at first visit, and self-rated health.

[f]Adjusted for alcohol-AUDIT, born in Nordic/non-Nordic countries, BMI, education level, smoking at first antenatal visit, use of snuff at first visit, and self-rated health.

[g]Adjusted for age Alcohol-AUDIT, BMI, education level, smoking at first antenatal visit use, of snuff at first visit, and self-rated health.

[h]Adjusted for age Alcohol-AUDIT, born in Nordic/non-Nordic countries, BMI, smoking at first antenatal visit, use of snuff at first visit, and self-rated health.

[i]Adjusted for age Alcohol-AUDIT, born in Nordic/non-Nordic countries, BMI, education, smoking at first antenatal visit, use of snuff at first visit.

3.1 | Results after imputation

After multiple imputation, the results for smoking did not change, except that the dose-dependent difference in the adjusted model was no longer significant. In the analysis of AUDIT scores, there were no differences in the results after the multiple imputation before adjustment for confounders; however, after the adjustment, high AUDIT scores no longer presented a significant risk for SA. After multiple imputation, aOR changed with a decreased risk for SA in women born outside the Nordic countries (Table 1).

There were no significant interactions between tobacco (at first visit to the MHC) and BMI, or between tobacco, BMI, and AUDIT score. There was a significant positive interaction between tobacco, AUDIT score, and age (p = 0.002), and a negative interaction between AUDIT score and BMI (p = 0.017); AUDIT score and age (p = <0.001); and tobacco and age (p = 0.041). The stratification analysis showed that each risk factor contributed independently to the total risk (Figure 2).

4 | DISCUSSION

In this population-based study, we found that smoking, use of snuff, and high AUDIT scores at the first MHC visit (median 8 weeks of gestation) were associated with a higher risk of SA. Missing data for smoking and use of snuff 3 months before pregnancy were 11.9% and 2.3%, respectively; at the first visit to the MHC, the respective numbers were 12.5% and 2.5%. Missing data for AUDIT was 16.8%. After the imputation analysis, the dose-dependent risk of having an SA among smokers and those with high AUDIT scores at the first visit at the MHC disappeared. Our results regarding AUDIT and risk for SA are contradictory to previous studies, which have shown that

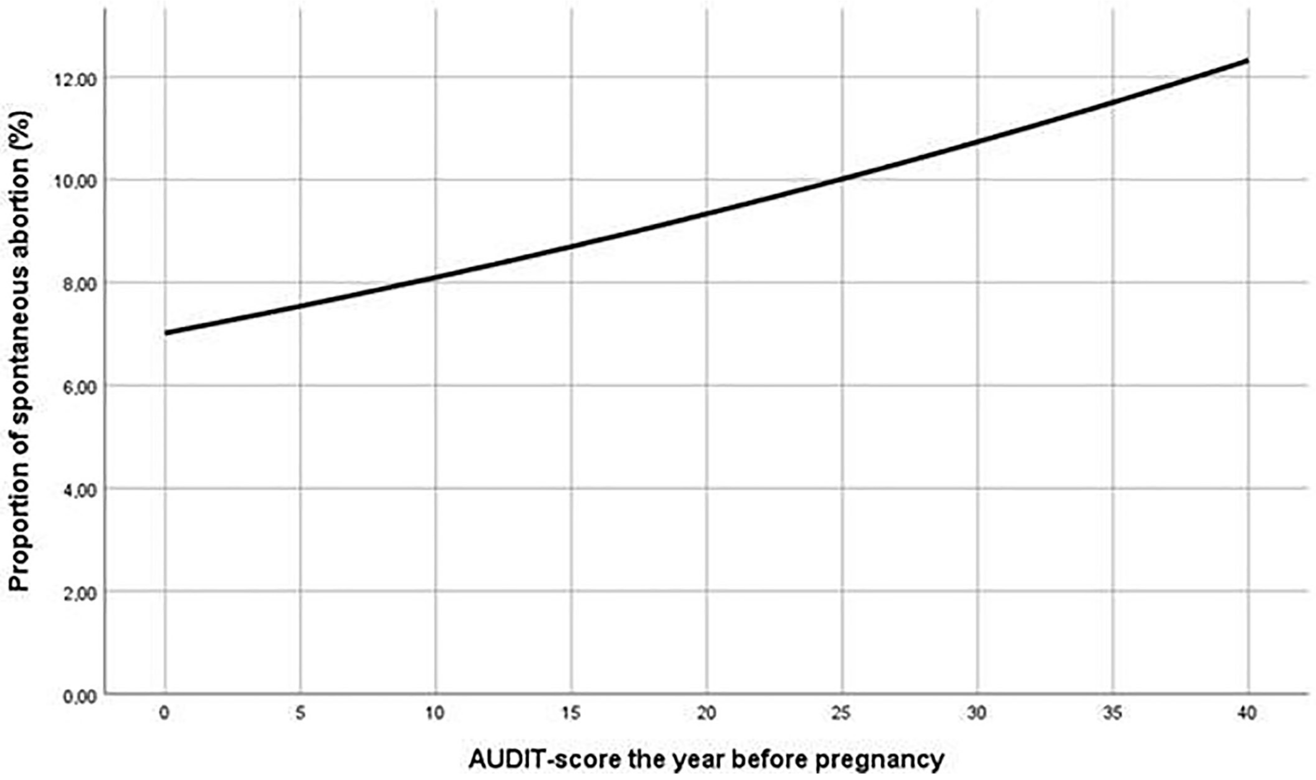


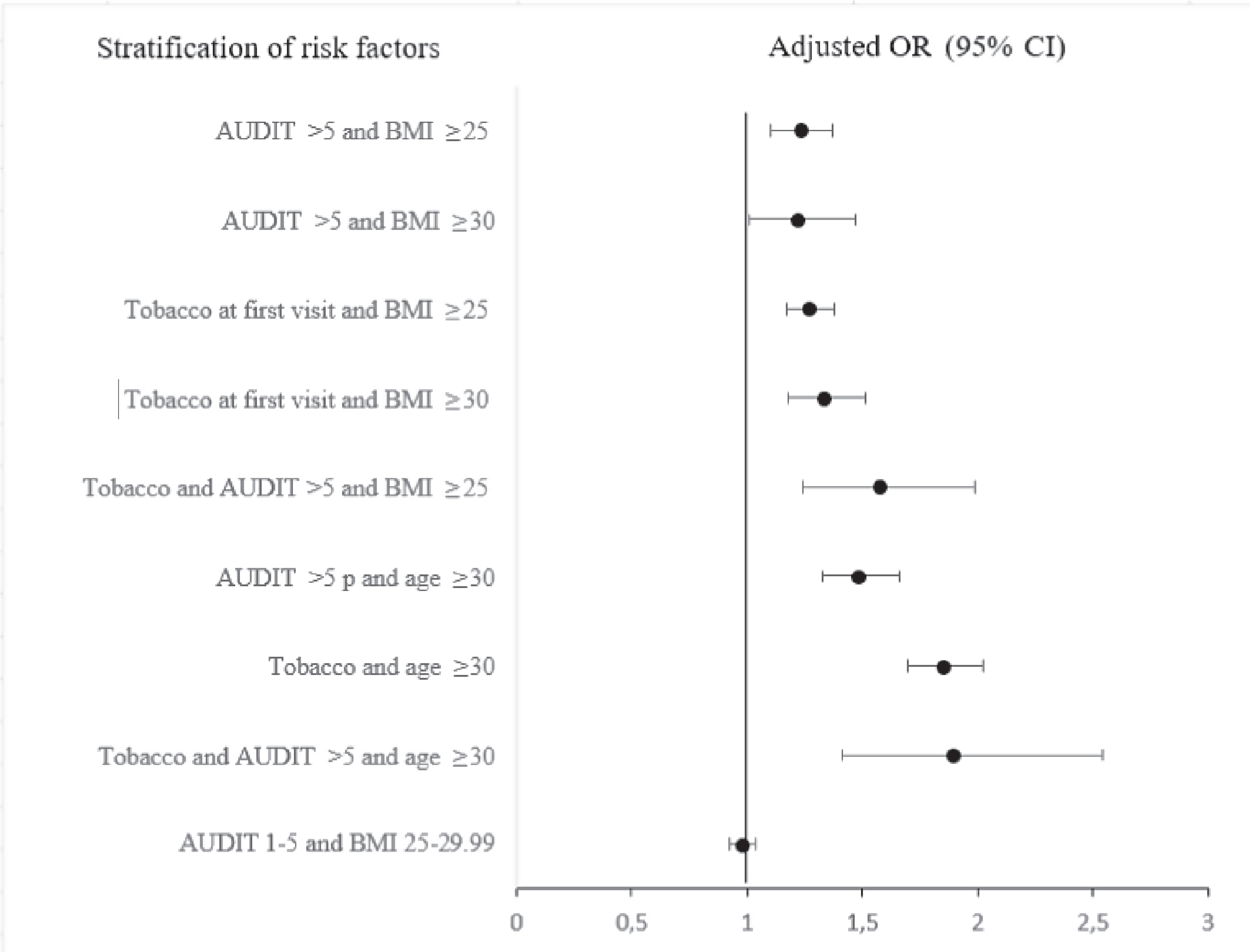
FIGURE 1 The proportions of spontaneous abortion related to AUDIT-score.

high AUDIT scores preceding pregnancy are associated with risk of SA.[10,13] Correct self-reporting of AUDIT scores can be a concern, as it has been shown that pregnant women report a higher AUDIT score when answering anonymously compared with what they do at the MHC.[17] This could explain the divergent results in our study. In addition, there seems to be an interaction effect between tobacco, AUDIT score, BMI, and age, indicating that the presence of several risk factors can both increase and decrease the overall risk.

To our knowledge, this is the first study that analyses whether there is an association between Swedish snuff or alcohol habits according to AUDIT before pregnancy, and the risk of SA. Our findings are important because use of snuff is increasing among young Swedish women,[7] and alcohol consumption in fertile women is common.[18] We found an association between smoking and SA, congruent with other studies.[2,3] However, the expected prevalence of SA can be up to 50% among women of fertile age,[19] and the observed prevalence of 6.6% in our study is substantially lower. This can be explained by the fact that SAs registered in SPR occur during the period after the first MHC visit around gestational week 8, and that most SAs occur earlier in pregnancy. Our findings on the association between SA and older age and higher BMI correspond with other studies.[20,21]

A strength of this study is that we used high-quality data from the population-based pregnancy register, covering information on 92% of all pregnancies in Sweden during a period of 4½ years.[22] Although the validity of data in the registry is generally good, the quality of some variables is uncertain because of problems with patient reporting (eg, AUDIT scores). We have been able to analyze a large number of pregnancies, which made it possible to perform stratification analysis and analyze the possible effects of several confounding factors that might often be difficult to retrieve.

To study SA is generally difficult, and a limitation of the study is that the gestational week (or exact pregnancy length) is unknown in SPR. Unfortunately, data on timing of visits are not routinely registered in the SPR for those who experience an SA; such information is only available for women who have completed a pregnancy with a birth. Therefore, the number of "early" miscarriages is unknown. The use of tobacco and AUDIT is self-reported, (and under-reported, to some extent) with a possible underestimation of the risk numbers. It is also possible that women who refrain from alcohol consumption 1–3 months preceding the pregnancy answer the AUDIT questionnaire based on their habits before they stopped drinking alcohol. There are missing data in all parameters, possibly because not all women want to talk about their lifestyle factors or the midwife forgot to document this information. However, according to the analyses of missing data in the study, there were no differences in the outcomes when comparing the groups with complete or missing data. The possibility of unknown systematic errors or bias always exists and cannot be excluded. Smoking status was incorrectly registered in a few regions during the first years of the register being used (no smoking was recorded in the SPR as a missing value); therefore, these regions had more missing cases for smoking than other regions. Another way to screen for tobacco or alcohol habits could be biological testing; however such testing is not carried out in routine MHC in Sweden. Despite a large number of pregnancies,



1. Adjusted for age, born in Nordic/non-Nordic countries, education level, tobacco at first antenatal visit, and self-reported health
2. Adjusted for age, born in Nordic/non-Nordic countries, education level, tobacco at first antenatal visit, and self-reported health
3. Adjusted for age, Alcohol-AUDIT, born in Nordic/non-Nordic countries, education level, and self-reported health
4. Adjusted for age, Alcohol-AUDIT, born in Nordic/non-Nordic countries, education level, and self-reported health
5. Adjusted for age, born in Nordic/non-Nordic countries, education level, and self-reported health
6. Adjusted born in Nordic/non-Nordic countries, BMI, education level, tobacco at first antenatal visit, and self-reported health
7. Adjusted for in Nordic/non-Nordic countries, BMI, education level, alcohol-AUDIT, and self-reported health
8. Adjusted for born in Nordic/non-Nordic countries, BMI, education level, and self-reported health
9. Adjusted for age, born in Nordic/non-Nordic countries, education level, tobacco at first antenatal visit, and self-reported health

FIGURE 2 Forest plot for combination of lifestyle factors and risk of spontaneous abortion shown as crude and adjusted odds ratio.

the sample sizes were too small in some of the analyses, when we adjusted for confounders.

The interaction effects found between AUDIT and BMI; AUDIT and age; tobacco and age; and tobacco, AUDIT, and age have not previously been reported, to our knowledge. The interaction effects can possibly be explained by the fact that negative lifestyle risk factors often co-exist in an individual.

The finding that both smoking and use of snuff 3 months preceding pregnancy are associated with lower risk of SA is difficult to explain. It may be that women who stopped using tobacco also made other changes in lifestyle factors to optimize the pregnancy. Another explanation could be that many women who were smokers or snuff users experienced an early SA; so they never visited the MHC. This argument is supported by proposed biological mechanisms for an effect from tobacco smoke including fetal hypoxia, vasoconstrictive and antimetabolic effects resulting in placental insufficiency and the subsequent death of the embryo or fetus.[23] The possible effects of smoke could result in a higher proportion of very early SA, resulting in fewer SA in later pregnancy. After imputation, the results changed the risk of SA depending on one's birthplace. An explanation can be that people of non-Nordic origin have a lower education level than their Nordic counterparts but have lower use of snuff. There might also be other external factors such as health-seeking behaviors or barriers to an early visit.

Studies on the use of Swedish snuff are problematic; it is difficult to know the exact dose because snuff is purchased in loose form or in a single-dose packaging and contains different amounts of nicotine and other hazardous substances. Users can also keep a portion of snuff in their mouths for a short time, while others can use many and large portions each day, potentially having various effects on the pregnancy and its outcome.

It is important to communicate with women of fertile age about the possible effects of unhealthy lifestyle factors, especially with those women who are planning a pregnancy. To use the Reproductive Life Plan, a tool for people to reflect on their reproductive intentions, can be an option for a better communication between midwifes and women before pregnancy.[24] The Reproductive Life Plan concept, including counseling on preconception health, has been used in intervention studies in Sweden[25,26] with positive results. This study adds knowledge that can be used by healthcare providers who meet women of fertile age in preconception care in order to increase knowledge of risk factors for SA.

5 | CONCLUSION

In this study, we showed that tobacco use (smoking and snuff) was associated with an increased risk of SA among women who have attended the maternal health care. There was no significant increased risk of SA among pregnant women with high AUDIT-score that is contradictory to other studies. However, more studies on alcohol habits related to risks during pregnancy are needed. To improve pregnancy outcomes and reduce the prevalence of SA, knowledge of how lifestyle factors affect pregnancy must be improved among women and health care providers.

AUTHOR CONTRIBUTION

YS, TT, HB, and JK contributed to the study design. HB ordered data from SPR. YS, HB, and SP undertook the analysis and interpretation. YS wrote the first draft of the manuscript. All authors critically reviewed the manuscript and subsequent drafts. All authors approved the final draft for submission.

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CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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SUPPORTING INFORMATION

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

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