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Full length article

# Use of moist smokeless tobacco (snus) and the risk of development of alcohol dependence: A cohort study in a middle-aged population in Sweden<sup>☆</sup>

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## ABSTRACT

**Background:** Convincing evidence shows that smoking is associated with alcohol dependence (AD) and a positive correlation between snus and alcohol consumption was previously shown in cross-sectional studies. We performed a longitudinal evaluation of the risk of snus users to develop AD.

**Methods:** A cohort study in Västerbotten County, Sweden, linked individual data on socioeconomic situation and health survey data from 21,037 men and women (46.5% men). AD was defined by the CAGE questionnaire and evaluated at baseline 1991–1997 and again after 10 years. The risk of developing AD was assessed using logistic regression analysis and propensity score matching.

**Results:** 2370 men and 430 women used snus and were without AD at baseline. Over the 10-year period, 499 men and 257 women developed AD, among whom 191 and 26, respectively, were baseline snus users. The crude relative risks of AD for male and female snus users compared to non-users were 1.8 with 95% CI (1.5, 2.2) and 2.9 (2.0, 4.3), respectively. Adjusted logistic regression showed a positive dose–response relationship between snus use and risk of AD. Analyses involving propensity score matching revealed 33 and 17 new cases of AD in men and women, respectively, after 10 years given 1000 men and 1000 women without AD had been baseline snus users rather than non-users. Results for current, previous and never smokers were similar.

**Conclusions:** The use of snus is prospectively associated with an increased risk of AD with a dose–response relationship that is independent of smoking status.

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## 1. Introduction

Smoking is a major cause of disease and death globally, and it is the largest single preventable cause of cardiovascular diseases (Boffetta and Straif, 2009) and several cancers, including lung cancer (Lee and Hamling, 2009), and chronic obstructive pulmonary disease. The key driving force for the use of tobacco is nicotine.

In contrast, for non-smoked tobacco in the form of moist oral tobacco, snus, there is little scientific evidence for any risk of cancer,

myocardial infarction, or stroke, although there are some indications of a slightly increased risk of fatal myocardial infarction (Hansson et al., 2012), fatal stroke (Hansson et al., 2012, 2014) and, for pregnant women, of preterm birth and stillbirth (Wikström et al., 2010). Nicotine in itself has previously been claimed by some researchers not to be harmful (Fagerström and Bridgman, 2014), and it has even been suggested to be comparable to coffee with respect to health effects (Phillips and Heavner, 2009). Accordingly, snus as a substitute for smoked tobacco and as a remedy for nicotine delivery, has also previously been claimed to be suitable for tobacco harm reduction (Fagerström and Bridgman, 2014; Le Houezec et al., 2011; Maki, 2014; Rodu and Godshall, 2006). The idea is that snus would compensate for the pleasure related to the nicotine in smoked tobacco, without causing the harm of combusted tobacco. This is also the general opinion in Sweden. However, if there are negative effects on health due to snus use,

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even if the harm is much smaller compared to smoking, this would be of interest for the general public and of importance for public health and tobacco policies in populations with a high prevalence of snus use.

There is strong evidence for the co-occurrence of smoking and alcohol use and of nicotine and alcohol dependence (AD) (Falk et al., 2006; John et al., 2003a). Among adolescents, snus is associated with smoking and alcohol use (Galanti et al., 2001). Among adults, a Swedish cross-sectional study recently also confirmed a link between snus use and risky alcohol consumption (Engström et al., 2010). To the best of our knowledge, reports on the longitudinal association between snus use and the development of alcohol misuse and dependence among adults are lacking.

Snus has been used in Sweden for a long time, and as smoking has declined, the use of snus has increased. In 2013, the prevalence of daily smoking among middle-aged (aged 45–64 years) Swedish men and women was similar at 15% and 14%, respectively, and 9% of men and 5% of women smoked occasionally. Thus, the overall prevalence of current smokers was 24% among men and 19% among women. At the same time, 20% of men and 4% of women used snus daily and 3% and 1% did so occasionally (Folkhälsomyndigheten, 2013). It must be noted that many snus users, particularly those older than 45 years, also have a history of smoking (Boffetta and Straif, 2009; Folkhälsomyndigheten, 2013) and that the combination of smoking and snus use in Sweden is stable or even increasing (Norberg et al., 2011). During 2010–2013, the highest prevalence of daily snus use in Sweden was seen in Västerbotten County along with the lowest prevalence of daily smoking in both genders (Folkhälsomyndigheten, 2013). Thus, the patterns of tobacco use are complicated, and when possible effects from snus on health are investigated, large study populations are needed to be able to account for confounding by smoking.

In the European Union, the manufacturing and selling of snus is prohibited except in Sweden and this ban has been repeatedly challenged. Outside EU, for example in Norway and the US, the use of snus is currently increasing at a significant rate. Therefore, the evidence of possible harmful effects of snus is of importance, and not only in Sweden. We used a large Swedish cohort of middle-aged persons to investigate the longitudinal relationship between the use of snus and alcohol dependence (AD). Our hypothesis was that the use of snus increased the risk of developing AD.

## 2. Methods

### 2.1. Study population

The cohort study was based on the Västerbotten Intervention Programme (VIP) conducted in Västerbotten county. In 2011, the county population was 260,000, about 70% of whom resided in the two major urban areas: The university city of Umeå and the industrial town of Skellefteå. The background, design, and methodology of the VIP has previously been described in detail (Norberg et al., 2010). Since 1990, the VIP has been an integral part of the primary health-care routines, and all residents of Västerbotten county are invited to undergo a health assessment and receive health-promoting counselling in the year in which they turn 40, 50, or 60 years old. Persons aged 30 years were only included until 1996. Thus, participants were again eligible for the VIP after 10 years until the age of 60 years if they still lived in the county. According to the program routine, subjects can participate within a few months before or after the actual year they turn 30, 40, 50, or 60 years, although this happens rarely. As a part of the VIP, cardiovascular risk markers are measured and participants answer a comprehensive questionnaire on their health and lifestyle habits, including tobacco consumption and alcohol-related problems.

**Table 1**

Drop-out analysis at the 10-year follow-up by baseline characteristics among participants in the Västerbotten Intervention Programme from 1991 to 1997. Subjects classified with alcohol dependence at baseline, i.e. answered yes to 2–4 of the CAGE questions, were excluded from further analysis.

	Did not return for follow-up (%)	Returned (%)
Smoker		
Never	23.5	76.5
Previous	23.6	76.4
Current	29.5	70.5
Use of snus		
No	24.8	75.2
Yes	26.3	73.7
Age		
30 yrs	34.3	65.7
40 yrs	24.0	76.0
50 yrs	21.0	79.0
Sex		
Men	26.6	73.4
Women	23.8	76.2
CAGE, number of yes answers		
0*	24.0	76.0
1	27.3	72.7
2	30.6	69.4
3	33.0	67.0
4	43.8	56.2

\* This category includes alcohol abstainers.

We used the Linnaeus database that is maintained by the Ageing and Living Conditions research program at Umeå University. This interdisciplinary research program focuses on the relationship between socioeconomic status (SES) and health in ageing populations (Malmberg et al., 2010). In the Linnaeus database, information from nation-wide administrative registers provided by Statistics Sweden, which contain comprehensive annual data about SES, family situation, and place of residence, and the National Board of Health and Welfare, which contains information on hospitalizations and causes of death, is linked to data from the VIP on an individual level (Norberg et al., 2010). The information obtained is anonymized.

During the time period from 1 January, 1991 to 31 December, 1997, 33,368 persons participated for the first time in the VIP. Annual participation rates increased from 52% in 1991 to 61% in 1997. Of these, 24,972 (74.8%) returned for a second VIP examination (of whom 46.5% were men). The average follow-up time was 10 years  $\pm$  3 months (see above regarding VIP routines). The follow-up time was 9 years for 6.6% of the participants, 10 years for 91.4% of the participants, and 11 years for 2% of the participants. A drop-out analysis revealed that the return rate was 70% or more irrespective of sex and smoking and snus habits (Table 1). The 30-year-olds returned at a rate of 65.9% and subjects with AD returned at a lower rate, especially those who answered yes to all CAGE questions (CAGE is described below).

Individuals with missing values for the CAGE questionnaire and tobacco consumption at baseline were excluded ( $n=1855$ ). Individuals who reported AD according to the CAGE questionnaire at baseline were also excluded from further analysis of the risk of developing AD ( $n=1414$ ). Thus, 21,037 subjects (of whom 44.8% were men) remained in the study population.

The VIP participants provided their informed consent, and the research was approved by the Regional Ethical Committee at Umeå University (Dnr 07-142Ö).

### 2.2. Study exposure

The study exposure was the use of tobacco with focus on the use of snus. Snus use was assessed using the question “Have you

ever used snus?” with five response categories of never used snus, former use, and weekly consumption of fewer than 2 cans, 2–4 cans, and 5 or more cans of snus. All five responses were used in the logistic regression analysis. For propensity score matching analysis, snus use was categorized as “use” or “non-use”, of snus, and former snus users were categorized as non-users. There was no information on occasional versus daily snus use.

### 2.3. Study outcome

The study outcome was alcohol dependence (AD) at follow-up. Alcohol use was screened by means of a question asking if the respondent was a total abstainer from alcohol. The total abstainers (9.2% of men and 13.2% of women) did not answer further questions about alcohol based on the CAGE questionnaire (McIntosh et al., 1994; O'Brien, 2008). The CAGE questionnaire consists of four questions and is designed to identify individuals with alcohol misuse and dependence. The themes of the questions related to alcohol consumption are Cut down, Annoyance, Guilt and Eye-opener. CAGE has been validated in many studies (O'Brien, 2008; Skogen et al., 2011) and is a quick indicator of AD that needs further evaluation in a clinical setting. The amount of alcohol consumed is not evaluated. The number of “Yes” responses to the four questions is tallied. Two or more “Yes” responses are considered indicative of alcohol misuse carrying a risk of AD. Being an alcohol abstainer or giving fewer than two positive answers to the CAGE questionnaire was categorized as not AD.

### 2.4. Study covariates

**Smoking:** Smoking was treated as a confounder and assessed with the question, “Do you currently smoke?” with the following responses: No, I have never smoked, I am smoking cigarettes daily, I am smoking cigars, I am smoking a pipe, I am smoking but only occasionally, I previously smoked daily, and I previously smoked occasionally. This was categorized into “never”, “former” or “current” smoking. The former and current smokers included both daily and occasional smoking.

Additional covariates were chosen based on our previous publication where we reported on the determinants of snus use (Norberg et al., 2011). In addition to age, sex and smoking, the following covariates were chosen.

**Socioeconomic status:** To ensure that SES data were from a time point before the VIP examination, SES data from the year prior to the VIP examinations were used. This was motivated by the facts that only the years of the VIP examinations were available (not exact the dates) and that the official registration from Statistics Sweden is only updated once a year. Married couples and cohabiting couples with children were recorded as cohabiting. All other subjects were recorded as singles. “Living with children aged 18 years or younger” was also used as an indicator of family situation. Education was categorized as nine years or fewer (basic), which is the compulsory level in Sweden, ten to twelve years of schooling (mid-level), and university level (high). Individual yearly income from employment or self-employment was given in SEK 100 per year and adjusted in accordance with the 1990 retail price index to make incomes comparable during the study period. “Unemployed” included full and partial unemployment and was defined as “unemployment allowances exceeding income from employment in a specific year”.

**Place of residency:** A geographical variable was included due to differing patterns of tobacco consumption depending on area of residency (Norberg et al., 2011). Based on where the VIP examination was conducted (which in most cases reflect where an individual lives), this variable was categorized into six categories: Umeå (a university city and the administrative centre of the county), Skellefteå (an industrial town), Lycksele (a small regional

centre), and three different rural areas “Rural east” (the coastal area in the east, rather densely populated with frequent commuting to workplaces in the urbanized areas), “Rural middle” (the middle and less densely populated part of the county), and “Rural west” (the remote mountainous and most sparsely populated area in the west).

### 2.5. Statistical analysis

The distributions of baseline characteristics for SES and smoking are presented for users and non-users of snus by gender. Income data are presented as the median and interquartile range. The crude relative risk (RR) of developing AD is calculated as the ratio of the 10-year cumulative incidence of AD between non-users and users of snus.

In a standard setup, we used simple logistic regression, followed by multiple logistic regression analysis, to estimate associations between baseline use versus non-use of snus and the outcome of AD according to CAGE at the 10-year follow-up, controlling for confounders.

Due to the large sample and the availability of a large variety of variables in our data set, we had excellent opportunities to control for confounders. Therefore, we also used the statistical technique of propensity score matching (Rubin, 1974) to further overcome the problem of confounding between snus use and other lifestyle and socioeconomic factors. For each individual, one of the two potential outcomes was assumed (AD at follow-up; No or Yes),  $Y_0$  and  $Y_1$ , where  $Y_0$  was the outcome if not exposed to snus use and  $Y_1$  if exposed. The individual outcome effect was defined by  $Y_1 - Y_0$ , and our goal was to estimate the average outcome effect for the population. In a randomized study, this is simply calculated by the average observed outcome among the exposed minus the average observed outcome among the non-exposed. However, in an observational study, the potential of self-selection to the exposure would lead to a biased result. This was resolved by reconstruction of the missing  $Y$  value for each person through matching by propensity scores, which refers to the probability of being a snus user, given the chosen explanatory variables. Based on our previous studies on determinants of snus use (Norberg et al., 2011), the following variables were included: age, snus use, smoking, education, income, unemployment, civil status, living with children, year of VIP examination, and place of residence. The propensity scores were estimated through logistic regression with snus use as the outcome and with the fitted values being the individual estimates. One snus user was matched to one non-user based on the minimum distance in the propensity scores. Similarly, one non-user was matched with one snus user. The matching was performed with replacement. In this way, a pseudo-population was created that was twice as large as the original one. The average effect of the exposure was calculated as the average of all individual (paired) outcomes. Estimates of the standard error (SE) and 95% confidence interval (95% CI) were calculated and used as uncertainty measures for the estimates.

The analyses were performed in the statistical computing environment R (R Core Team, 2014), and the propensity score matching used the R package Matching (Sekhon and Grieve, 2012).

## 3. Results

Age, smoking, and SES characteristics at baseline for snus users and non-users by gender are summarized in Table 2. Snus use was more frequent in the younger groups. The majority of non-users had never smoked, whereas the majority of snus users were previous smokers. A higher proportion of female snus users lived as singles compared to non-users, but for men this difference was negligible.

**Table 2**  
Characteristics of participants who did not report alcohol dependence according to the CAGE questionnaire at the baseline examination in the Västerbotten Intervention Programme during 1991–1997. Numbers are given and the percent is in parentheses.

	Men		Women	
	Not using snus (n = 7046)	Using snus (n = 2370)	Not using snus (n = 11,191)	Using snus (n = 430)
Age group				
30years old*	1334(18.9)	585(24.7)	2071(18.5)	199(46.3)
40years old	2664(37.8)	1032(43.5)	4499(40.2)	185(43.0)
50years old	3048(43.3)	753(31.8)	4621(41.3)	46(10.7)
Smoker				
Never	3846(54.6)	729(30.8)	5352(47.8)	92(21.4)
Former	1784(25.3)	1085(45.8)	2875(25.7)	242(56.3)
Present	1416(20.1)	556(23.4)	2964(26.5)	96(22.3)
Income, SEK100/year**	2177(1698–2637)	2089(1597–2512)	1492(921–1895)	1354(659–1769)
Cohabiting				
Yes	5417(76.9)	1842(77.7)	8904(79.6)	316(73.5)
No	1629(23.1)	528(22.3)	2287(20.4)	114(26.5)
Living with children				
Yes	5115(72.6)	1751(73.9)	8442(75.4)	341(79.3)
No	1931(27.4)	619(26.1)	2749(24.6)	89(20.7)
Education				
Basic	1425(20.2)	480(20.3)	1644(14.7)	36(8.4)
Mid-level	4240(60.2)	1541(65.0)	6496(58.0)	265(61.6)
High	1381(19.6)	349(14.7)	3051(27.3)	129(30.0)
Unemployed				
Yes	381(5.4)	157(6.6)	478(4.3)	39(9.1)
No	6665(94.6)	2213(93.4)	10713(95.7)	391(90.9)
Place of residence***				
Umeå	1910(27.1)	584(24.6)	3082(27.5)	137(31.9)
Skellefteå	1086(15.4)	312(13.2)	1852(16.5)	46(10.7)
Lycksele	473(6.7)	179(7.6)	694(6.2)	37(8.6)
Rural east	1944(27.6)	639(27.0)	3115(27.8)	108(25.1)
Rural middle	895(12.7)	332(14.0)	1299(11.6)	53(12.3)
Rural west	738(10.5)	324(13.7)	1149(10.3)	49(11.4)
Year of examination				
1991	734(10.4)	239(10.1)	1133(10.1)	24(5.6)
1992	1024(14.5)	323(13.6)	1647(14.7)	48(11.2)
1993	1203(17.1)	366(15.4)	1874(16.7)	57(13.3)
1994	1037(14.7)	367(15.5)	1692(15.1)	87(20.2)
1995	1141(16.2)	398(16.8)	1850(16.5)	72(16.7)
1996	942(13.4)	322(13.6)	1438(12.8)	53(12.3)
1997	963(13.7)	355(15.0)	1557(13.9)	89(20.7)

\* Thirty year olds were included only up to 1996.

\*\* Income is given in 100 SEK/year as the median and interquartile range. SEK = Swedish crowns. The amounts are adjusted to the 1990 retail price index.

\*\*\* The numbers are lower than the total number due to migration out of the county between the second health survey and registration of the migration by authorities.

The education level was lower among male snus users compared to non-users, and the opposite was observed among women.

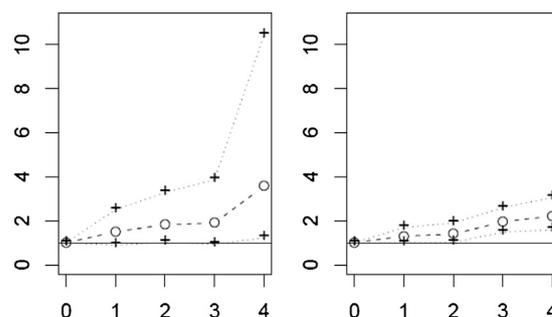
There were 21,037 individuals (9416 men and 11,621 women) included in this study, and among them 499 and 257 new cases of AD appeared among men and women, respectively. There were 2370 men (25.2%) and 430 women (3.7%) who used snus at baseline.

Overall, the 10-year cumulative incidence of developing AD was 7.8% among snus users and 3.0% among non-users. The corresponding numbers were 8.1% and 4.4% for men and 6.0% and 2.1% for women, respectively (Table 3). The crude 10-year RR of AD among snus users compared to non-users was 1.8 with 95% CI (1.5, 2.2) for men, 2.9 (2.0, 4.3) for women, and 2.6 (2.3, 3.1) for both genders together.

The odds ratios (OR) calculated by simple and multiple logistic regression of AD at follow-up are shown in Table 4. Both snus use and smoking were significantly associated with the 10-year development of AD. The clear dose–response relationship between snus use and the risk of AD is also illustrated in Fig. 1. For both men and women, the risk of AD increased over time and also with higher education level. Being 50 years old at baseline was associated with a lower risk of AD than being 30 years old at baseline. For men, being married/cohabiting and living in the central rural part of the county was also related to a lower risk of AD as shown in Table 4. These analyses were repeated after exclusion of the baseline abstainers and the results are essentially the same. If anything, the

results were slightly stronger for both men and women (data not shown).

Next, we performed a propensity score matching for men and women separately. The average outcome among men was 0.033, SE



**Fig. 1.** The result of a logistic regression with odds ratios (ORs, dashed line) showing the development of alcohol dependence from baseline to 10-year follow-up by weekly dose of snus consumption at baseline from 1991 to 1997 among women (to the left) and men (to the right) in the Västerbotten Intervention Programme. The 95% confidence intervals are indicated by the dotted lines, and the outcome is adjusted for smoking, socioeconomic situation, age, and year of examination. The x-axis denotes the use of snus and the reference category is 0 = “never used snus”. The other categories are 1 = “former use”, 2 = “consumption of fewer than 2 cans of snus per week”, 3 = “2–4 cans per week”, and 4 = “5 or more cans per week”. The ORs are plotted on a log scale on the y-axis.

**Table 3**

Snus use at first visit from 1991 to 1997 by gender and alcohol dependence at 10-year follow-up among participants in the Västerbotten Intervention Programme\*. Numbers in each group are given in parenthesis.

	Men		Women		All	
	Not using snus (7046)	Using snus (2370)	Not using snus (11,191)	Using snus (430)	Not using snus (18,237)	Using snus (2800)
No alcohol dependence	6738	2179	10960	404	17698	2583
Alcohol dependence	308	191	231	26	539	217
Ten-year cumulative incidence	4.4%	8.1%	2.1%	6.0%	3.0%	7.8%
Relative risk and 95% CI for snus users	1.8 (1.5, 2.2)		2.9 (2.0, 4.3)		2.6 (2.3, 3.1)	
10-Year cumulative incidence in the population					3.6%	

\* Only individuals without alcohol dependence at baseline were included. Ten-year cumulative incidence, and crude relative risks with 95% confidence intervals (95% CI), for alcohol dependence among snus users versus non-users.

**Table 4**

Simple and multivariable logistic regression analyses with odds ratios (OR) and 95% confidence intervals (95% CI) for development of alcohol dependence at follow-up at 10 years after the first health examination among participants in the Västerbotten Intervention Programme 1991–1997.

	Men		Women	
	Simple OR(95% CI)	Multivariable OR(95% CI)	Simple OR(95% CI)	Multivariable OR(95% CI)
Use of snus				
Never	1.0		1.0	
Previous	1.6(1.2, 2.0)	1.3(1.01, 1.7)	2.5(1.5, 4.0)	1.5(0.9, 2.5)
≤1 can/week	1.7(1.3, 2.3)	1.4(1.02, 1.9)	2.8(1.6, 5.0)	1.8(1.01, 3.3)
2–4 cans/week	2.3(1.8, 3.0)	2.0(1.5, 2.6)	3.2(1.6, 6.3)	1.9(0.9, 3.9)
≥5 cans/week	2.6(1.9, 3.6)	2.2(1.6, 3.1)	5.7(2.0, 16.1)	3.6(1.2, 10.4)
Smoking				
Never	1.0		1.0	
Previous	1.6(1.3, 2.0)	1.5(1.2, 1.9)	2.1(1.5, 2.8)	1.9(1.4, 2.6)
Currently smoking	1.9(1.5, 2.4)	2.0(1.6, 2.5)	2.0(1.5, 2.8)	2.1(1.5, 2.8)
Education				
Basic	1.0		1.0	
Middle	1.0(0.8, 1.3)	0.9(0.7, 1.2)	2.2(1.4, 3.6)	1.8(1.1, 3.0)
High	1.4(1.1, 1.9)	1.4(1.1, 2.0)	2.4(1.4, 4.0)	2.1(1.2, 3.5)
Civil status				
Single	1.0		1.0	
Married/cohabiting	0.8(0.7, 1.0)	0.7(0.5, 0.9)	0.7(0.5, 0.9)	0.8(0.6, 1.1)
Children at home				
No	1.0		1.0	
Yes	1.0(0.8, 1.3)	1.3(0.98, 1.8)	1.1(0.8, 1.5)	1.0(0.7, 1.4)
Unemployed				
No	1.0		1.0	
Yes	1.4(1.1, 1.7)	1.2(0.9, 1.5)	1.5(1.1, 2.1)	1.3(0.9, 1.8)
Age at baseline				
30 years	1.0		1.0	
40 years	1.0(0.8, 1.3)	0.9(0.7, 1.2)	1.0(0.8, 1.6)	1.0(0.7, 1.4)
50 years	0.7(0.5, 0.9)	0.6(0.5, 0.8)	0.4(0.3, 1.7)	0.4(0.3, 0.6)
Residence				
Umeå	1.0		1.0	
Skellefteå	0.7(0.5, 0.9)	0.7(0.5, 1.0)	0.7(0.5, 1.0)	0.8(0.5, 1.2)
Lycksele	1.1(0.8, 1.5)	1.1(0.7, 1.5)	0.7(0.4, 1.3)	0.8(0.5, 1.4)
Rural east	0.8(0.6, 1.0)	0.9(0.7, 1.1)	0.7(0.5, 1.0)	0.9(0.6, 1.2)
Rural middle	0.6(0.4, 0.8)	0.6(0.4, 0.8)	0.7(0.4, 1.1)	0.8(0.6, 1.2)
Rural west	1.0(0.8, 1.4)	1.0(0.7, 1.3)	0.9(0.6, 1.4)	0.9(0.6, 1.5)
Income, SEK 100,000/year	1.0(0.9, 1.0)	1.0(0.9, 1.1)	1.1(0.9, 1.2)	1.1(0.9, 1.3)
Year of examination (continuous)	1.1(1.0, 1.1)	1.1(1.06, 1.2)	1.1(1.0, 1.2)	1.1(1.03, 1.2)

0.007 and 95% CI (0.019, 0.047). The interpretation is that we would expect 33 new cases of AD after ten years of follow-up per 1000 men who did not have AD at baseline, if they had been baseline snus users instead of non-users. For women the average outcome was 0.017, SE 0.027 and 95% CI (–0.035, 0.069), that is 17 new cases per 1000 women would be attributed to snus, when all SES and other characteristics were controlled for (not statistically significant).

In addition, we conducted separate analyses for never-smokers, previous smokers and current smokers. The 10-year cumulative incidence and relative risk were similar compared to the evaluation of the whole population, although these were attenuated among current and previous smokers and somewhat enhanced among

never-smokers (see Supplementary material, Tables 1–3<sup>1</sup>). Similarly, in an adjusted logistic analysis, a dose–response relationship between snus use and the risk of AD was seen in all categories of smoking (see Supplementary material, Tables 4–6<sup>2</sup>). Among smokers, this was significant only at higher doses of 2 or more cans/week among men and 5 or more cans/week among women. Among

<sup>1</sup> Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:10.1016/j.drugalcdep.2015.01.042.

<sup>2</sup> Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi: 10.1016/j.drugalcdep.2015.01.042.

previous smokers, the association was significant at 2–4 cans/week among men, while in women there was a dose–response relationship, which did not reach any statistical significance. Among never-smokers, ORs were significant and showed dose–response patterns among men. Among never-smokers women, the ORs were also significant for previous snus use. However, the dose–response curve collapsed at doses over 4 cans/week due to the fact that very few female never-smokers consumed larger amounts of snus. Calculations after propensity score matching resulted in 20 and 64 new cases of AD after ten years of follow up if 1000 smoking and never smoking men, respectively, had been baseline snus users instead of non-users (Supplementary material, Table 7<sup>3</sup>). For women, the study has low power due to small numbers of snus users in each group after stratification by smoking. However the trend was similar compared to for men.

#### 4. Discussion

For the first time, data from an adult population have shown that compared to non-users, snus users are at increased risk of developing alcohol dependence over a 10-year period. In addition to conventional regression analysis, the propensity score technique was used to balance the distribution of potential confounders for individuals with and without snus use at baseline, and to calculate the hypothetical extra risk of developing AD for the non-snus users, had they been snus-users at baseline instead. The results from the SES-adjusted prospective cohort model and the matched design model were concordant and independent of smoking. Evaluations of health effects due to snus are always rendered difficult to interpret due to the interrelation between snus use and smoking. Therefore, results based on subjects without any smoking history are important. We found increased risk of AD with a clear dose–response relationship between snus use and risk of AD in this group. This is in line with previous cross-sectional results (Engström et al., 2010; Galanti et al., 2001). However, the statistical power among women who never smoked was low because only few women in this age group used snus and in particular at higher doses. Our interpretation is that these results indicate an association between the use of snus and the risk of developing AD. Such a risk would be harmful and not negligible from a population perspective if the prevalence of snus use is high.

The combined use of smoking and alcohol is well documented (John et al., 2003a), and underlying behavioural (Little, 2000) and biological mechanisms have been described in human and animal studies (Burns and Proctor, 2012; Funk et al., 2006) along with the dose–response relationship between smoking and alcohol use (Falk et al., 2006; John et al., 2003b). Both nicotine and alcohol act on the mesolimbic dopamine rewarding pathway that is responsible for reinforcing effects and drug-seeking behaviour. Family studies, genetic linkage analyses, and candidate gene association studies, have revealed that both common and drug-specific genetic factors influence the development of alcohol and nicotine dependence and that environmental factors are less influential (Funk et al., 2006). This study cannot reveal the underlying causal mechanisms between snus use and AD, but our results on the association between snus use and development of AD, irrespective of smoking, are in agreement with the large body of evidence on concurrent nicotine and alcohol dependency.

Nicotine absorption from Swedish snus is somewhat slower than from smoking, but the maximum blood nicotine level after single doses of snus is similar to the level resulting from smoking one cigarette. The elevated nicotine level during snus use is

of longer duration, and the total nicotine exposure is somewhat larger compared to smoking (Holm et al., 1992). In addition, the subjective level of dependence is also similar for snus users and smokers (Holm et al., 1992). A review also concluded that the addictive capacity of nicotine in snus, is comparable to that of smoked tobacco (Henningfield and Fant, 1999). Therefore, in addition to the acknowledged association between smoked tobacco and AD, a link between snus and AD is also plausible. In view of the economic burden to society, the harmful use of alcohol and nicotine addiction should also be included in the overall evaluation of snus (Effertz and Mann, 2012). Moreover, our results could also be relevant for the evolving global spread of e-cigarettes with resulting nicotine dependence.

Some strengths and limitations of this study should be noted. Its longitudinal design and the fact that it is performed in a setting where population-based health surveys have been on-going in a standardized manner for over 20 years is a strength. The availability of this longitudinal and large population register data allowed us to confirm the temporality and dose–response relationship in the association between snus use and AD that could not be shown in many cross-sectional studies. The study population is large and the study has sufficient power to show the association between the use of snus and AD, adjusted for smoking and socioeconomic determinants. Among women, results were in the same direction as among men, but the power of the study was lower due to considerably lower numbers of women using snus. It is also a strength that the study was performed in a context where the use of snus has a long history, our conclusions should not be sensitive to changing or temporary trends.

Despite this, we cannot exclude residual confounding due to self-selection, for example a lower response rate to follow-up among those with AD. However, this would lead to underestimation of the risk of AD and would make our results conservative. It should also be acknowledged that our results refer only to 40–60 years old men and women. We used the CAGE questionnaire as an indicator of AD, and thus we cannot draw conclusions regarding the amount of consumed alcohol. CAGE is considered less sensitive for AD among women and also for less severe forms of alcohol abuse by some researchers (McIntosh et al., 1994), whereas others found good validity for both previous and current excessive alcohol consumption and even stronger validity among women than men (Skogen et al., 2011). Our results should be interpreted with this in mind.

In conclusion, the use of snus is prospectively associated with an increased risk of AD that is independent of smoking status. We observe a positive dose–response relationship, i.e., the larger the amount of snus consumed, the higher the risk of AD. Our results are supported by previous findings on the addictive capacity of snus, the high and prolonged nicotine levels from snus, and underlying behavioural and biological mechanisms that link nicotine and alcohol. These results are important from a public health viewpoint.

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<sup>3</sup> Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi: 10.1016/j.drugalcdep.2015.01.042.

## Contributors

All authors designed the study. Author MN managed the literature searches and summaries of previous related work and wrote the first draft of the manuscript. Author GB undertook the statistical analysis. All authors contributed to and have approved the final manuscript.

## Conflict of interest statement

All other authors declare that they have no conflicts of interest.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.drugalcdep.2015.01.042>.

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