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Snus has an adverse impact on asthma, respiratory symptoms and snoring: A cross sectional population study.

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Abstract

Introduction: Studies of the health effects of moist oral tobacco - snus have produced inconsistent results. The main objective of this study is to examine the health effects of snus use on asthma, respiratory symptoms and sleep-related problems, a field that has not been investigated before.

Methods and material: This cross-sectional study was based on a postal questionnaire completed by 26,697 (59.3%) participants aged 16-75 and living in Sweden. The questionnaire included questions on tobacco use, asthma, respiratory symptoms and sleeping problems. The association of snus use with asthma, respiratory symptoms and sleep-related symptoms was mainly tested in never-smokers (n=16,082).

Results: The current use of snus in never-smokers was associated with an increased risk of asthma (OR [95% CI] = 1.51 [1.28-1.77]), asthmatic symptoms, chronic bronchitis and chronic rhinosinusitis. This association was not present among ex-snus users. Snoring was independently related to both the former and current use of snus ((OR [95% CI] = 1.37 [1.12-1.68]) and (OR [95% CI] = 1.59 [1.34-1.89] respectively)). A higher risk of difficulty inducing sleep was seen among snus users.

Conclusion: Snus use was associated with a higher prevalence of asthma, respiratory symptoms and snoring. Health-care professionals should be aware of these possible adverse effects of snus use.

Keywords: snus, tobacco, asthma, chronic bronchitis, snoring, sleep disturbances

Strengths and limitations of the study

- This is one of the first studies to investigate the association between the use of snus and respiratory and sleep related symptoms
- The population is large which enables us to investigate subgroups such as never-smokers
- The data is self-reported
- The study is cross-sectional

Introduction

Snus is a smokeless, moist tobacco product consisting mainly of tobacco, salt, water, humectants and flavouring [1]. The tobacco in snus contains a number of harmful substances, including nicotine and tobacco-specific nitrosamines (TSNAs)[2]. In Sweden, where it is a very popular tobacco alternative, with 18% males and 4% females being current users, snus is regulated under food legislation [3 4]. The highest proportion of snus users is found among men aged 40 [5]. In the mid-1990s, the prevalence of snus use among Swedish men surpassed the prevalence of smoking. The proportion of female snus users is rising, but it has still not reached the prevalence for women smokers [5]. Compared with smoking, it has been suggested that the addiction to snus use is stronger, due to a lower cessation rate [6] and reports of greater experience of nicotine dependence [7]. In spite of this, snus has been reported as a good alternative for smoking cessation, due to the beneficial health effects compared with cigarettes [8].

Studies aiming to identify the risk of health effects as a result of snus use have not reported consistent results. A significant increase in pancreatic cancer has been observed [9 10], but reports regarding the association between snus use and oral and pharyngeal cancer are inconclusive. [9-11]. Snus use appears to increase the risk of short-term case fatality after suffering from acute myocardial infarction [12] and stroke [13]. An increased risk of heart failure among snus users has been reported, with a particularly high risk of non-ischaemic heart failure among elderly men [14].

There is only sparse evidence regarding the potential effect of snus on respiratory health and sleep. An association between snus and asthma has been reported in one study [15] and an elevated risk of insufficient sleep was found among smokeless tobacco users in another [16]. The main objective of this paper was to investigate the health effects of snus use on asthma, respiratory symptoms and sleep-related problems in a large general population sample.

Methods

Study design and participants

This cross-sectional study is based on observations from a postal questionnaire sent to 45,000 randomly selected subjects as part of the the Global Allergy and Asthma European Network (GA^{2}LEN) survey in 2008 [17]. In Sweden 26,697 (59.3%) participants responded. The subjects were aged 16-75 and lived in four Swedish cities (Uppsala, Stockholm, Umeå and Gothenburg) [15].

Ethical approval was granted by the Regional Ethical Review Board in Uppsala, Sweden.

GA^{2}LEN questionnaire

The questionnaire included questions on respiratory symptoms, asthma and smoking. The questions also covered gender, age, weight and height. Body mass index (BMI) was calculated using the values of weight and height. In Sweden, the questionnaire also included questions on the use of snus and sleep-related symptoms. Listed below are definitions relevant to this paper.

Snus *users* were defined as those giving a positive answer to both the questions ''Have you ever used snus every day for at least six months?'' and ''Do you currently use snus?''.

Smokers were defined as those giving a positive answer to the questions ''Have you ever smoked at least one cigarette a day for at least one year?'' and ''Have you smoked at all during the last month?''. Based on the answers to questions on snus use and smoking, the participants were divided into four groups: tobacco free, snus users, smokers and dual users.

Based on answers to the questions on snus use and smoking, the subjects were further divided into never-, ex- and current snus users, as well as into never-, ex- and current smokers.

Asthma was defined as a positive answer to either of the questions ''Have you had an asthma attack during the last 12 months?'' or ''Are you currently taking any asthma medication including inhalers, sprays or tablets?''.

Questions regarding a*sthmatic symptoms* during the last 12 months included: (i) wheezing in the chest; (ii) wheezing together with breathlessness; (iii) wheezing without having a cold; (iv) waking up with tightness in the chest; (v) waking up with shortness of breath and (vi) waking up with a coughing attack.

Chronic bronchitis was defined as a positive answer to the question: ''Are you used to having a cough almost every day with sputum production that lasts for at least three months every year during the winter?''.

Allergic rhinitis was defined as a positive answer to the question ''Have you had hay fever or a runny nose because of other allergies during the last twelve months?''.

Chronic rhinosinusitis was defined as suggested by the EP^{3}OS criteria 2007 [18]. It was considered to be present if participants stated that the following symptoms had been present for more than 12 weeks during the last 12 months: (i) nasal blockage, as well as one of the subsequent symptoms: (ii) facial pain or pressure, (iii) discoloured snot or expectoration or (iv) reduction or loss of smell. The disease was also considered to be present if both symptoms (ii) and (iii) were reported.

Sleep-related problems examined in this study were (i) snoring that is loud and interrupting, (ii) difficulty inducing sleep (DIS), as in having a hard time falling asleep at night, (iii) difficulty maintaining sleep (DMS), as in repeatedly waking up during the night, (iv) being sleepy during the day (EDS) and (v) early morning awakening (EMA), as in waking up too early and

having a hard time falling asleep again [19]. Each group included subjects who claimed they had the problem at least three to five times a week. The use of hypnotics was defined as a positive answer to the question ''Do you take medication for sleeping problems?''.

Educational level was divided into three categories. (i) College was defined as having attended college/university for more than two and a half years. (ii) High school was defined as having attended high school or vocational school for more than two years. (iii) Elementary school was defined as any education below the level of high school.

Activity level was divided into three categories depending on hours spent on intensive exercising per week. (i) Physically inactive was defined as zero hours a week. (ii) Moderately physically active was defined as half an hour up to three hours a week. (iii) Vigorously physically active was defined as four up to seven hours a week.

Data analysis

For statistical analyses, Stata version 12 was used. When comparing the characteristics of the study population, univariate analyses using the chi square test were used. Multivariate logistic regression models were used to study independent associations between various symptoms and different groups of tobacco use after adjusting for potential confounders; gender, age, BMI, centre, educational level and physical activity. Sub-analyses were performed in never-smokers and in never-smokers with reported asthma. A p-value of < 0.05 was regarded as statistically significant.

Results

The frequency of snus use among men was highest in the 25-35 age group. The number of snus-using women was highest in the 45-55 age group, with a steep decrease thereafter. In overall terms, 18.0% of men and 4.7% of women in the study population used snus (Figure 1).

In the whole population, snus use and dual use were highest in the 25-35 age group, while smoking was most prevalent at the ages of 55-65. The group of snus users had a higher BMI than the other groups. They were also more likely to be ex-smokers than persons in the tobacco-free group. Educational level and physical activity level were higher among snus users compared with smokers and dual users but lower compared with those who were tobacco free (Table 1).

Table 1: Characteristics of the study population (%).

		Tobacco users			
	Tobacco free (n=20,699)	Snus (n=2,265)	Smokers (n=3,136)	Smokers and snus (n=597)	*p*-value
Women	57.7	23.5	62.9	25.0	<0.001
Age (years)					<0.001
16-25	15.4	12.8	12.4	15.2	
25-35	21.4	23.2	17.4	26.7	
35-45	17.6	21.5	16.7	16.8	
45-55	15.4	19.7	20.0	21.5	
55-65	17.7	16.5	23.2	14.9	
>65	12.4	7.2	10.1	6.7	
Body mass index					<0.001
<20	8.6	4.7	9.9	5.8	
20-25	51.9	46.6	48.9	48.1	
25-30	30.1	36.2	30.9	35.3	
>30	9.5	12.4	10.3	10.9	
Ex-smokers	26.8	48.1	-	-	<0.001
Educational level					<0.001
Elementary school	15.0	12.5	23.6	18.6	
High school	31.6	42.9	40.7	45.8	
College	53.5	44.7	35.7	35.6	
Activity level					<0.001
Physically inactive	18.1	19.3	32.8	27.8	
Moderately physically active	62.8	62.0	55.1	58.7	
Vigorously physically active	19.0	18.7	12.1	13.5	

Tobacco use and symptoms

In Table 2, we examined the association between tobacco use and symptoms after adjusting for likely confounders. Having asthma was independently related to using snus but not to smoking or the dual use of snus and cigarettes. Although the strongest associations with

respiratory symptoms were found among smokers and dual users, snus users were more likely to suffer from wheezing and night-time chest tightness, as well as chronic bronchitis, allergic rhinitis and chronic rhinosinusitis, compared with the tobacco-free group. Snoring, DIS, EDS and the use of hypnotics were associated with all three groups of tobacco use. Snus users had a decreased risk of DMS (Table 2).

Table 2: The independent association between tobacco use and respiratory health and sleep-related symptoms (adjusted odds ratio (95% CI)).

	Tobacco users		
	Snus users (*n* =2,265)	Smokers (*n*= 3,136)	Smokers and snus users (*n*=597)
Asthma	**1.51 (1.28-1.77)**	0.96 (0.82-1.13)	0.93 (0.65-1.33)
Asthmatic symptoms			
Wheezing	**1.50 (1.33-1.69)**	**2.89 (2.64-3.17)**	**2.09 (1.71-2.55)**
Wheezing and breathlessness	**1.42 (1.23-1.65)**	**2.11 (1.89-2.37)**	**1.46 (1.12-1.90)**
Wheezing without having a cold	**1.50 (1.30-1.73)**	**2.67 (2.40-2.98)**	**2.17 (1.73-2.73)**
Night-time chest tightness	**1.21 (1.05-1.40)**	**1.57 (1.40-1.75)**	**1.43 (1.12-1.82)**
Night-time attacks of breathlessness	1.02 (0.83-1.24)	**1.44 (1.24-1.67)**	**1.58 (1.16-2.13)**
Night-time coughing	1.10 (0.99-1.23)	**1.79 (1.64-1.94)**	**1.79 (1.49-2.15)**
Chronic bronchitis	**1.19 (1.03-1.37)**	**2.39 (2.16-2.65)**	**1.85 (1.48-2.31)**
Allergic rhinitis	**1.17 (1.05-1.30)**	1.01 (0.91-1.11)	0.92 (0.75-1.13)
Chronic rhinosinusitis	**1.28 (1.09-1.50)**	**1.78 (1.57-2.02)**	**1.78 (1.38-2.29)**
Sleeping problems			
Snoring	**1.41 (1.25-1.58)**	**1.78 (1.60-1.97)**	**2.16 (1.77-2.63)**
DIS[a]	**1.76 (1.56-1.99)**	**1.98 (1.79-2.19)**	**2.95 (2.43-3.58)**
DMS[b]	**0.74 (0.66-0.83)**	0.97 (0.88-1.06)	0.91 (0.75-1.12)
EDS[c]	**1.18 (1.07-1.31)**	**1.29 (1.19-1.41)**	**1.38 (1.16-1.65)**
EMA[d]	0.87 (0.76-1.00)	**1.14 (1.03-1.27)**	0.91 (0.70-1.17)
Use of hypnotics	**1.33 (1.07-1.65)**	**2.08 (1.81-2.39)**	**2.77 (2.05-3.74)**

. [a]DIS, difficulty initiating sleep; [b]DMS, difficulty maintaining sleep; [c]EDS, excessive day sleepiness; [d]EMA, early morning awakening at least three to five nights/week

[e]Associations with a *p*-value of < 0.05 are marked as bold

[f]Adjusted for gender, age, BMI, centre, educational level and physical activity

Snus use in never-smokers

In never-smokers, there was an association between snus use and asthma, all the asthmatic symptoms, chronic bronchitis and chronic rhinosinusitis. Sleeping problems with an increased risk among snus users were snoring and DIS. Also among never-smokers, snus users had a decreased risk of DMS (Table 3).

Table 3: Association between snus and respiratory health and sleep-related symptoms in never-smokers (%) and adjusted odds ratio (OR).

	Never smoked			
	Tobacco free (*n* =14,914)	Snus users (*n* =1,168)	*p*-Value	OR (95% CI)
Asthma	6.9	10.1	<0.001	**1.49 (1.20-1.85)**
Asthmatic symptoms				
Wheezing	12.9	18.8	<0.001	**1.56 (1.32-1.84)**
Wheezing and breathlessness	8.2	10.9	0.002	**1.38 (1.12-1.69)**
Wheezing without having a cold	8.0	11.8	<0.001	**1.48 (1.21-1.80)**
Night-time chest tightness	9.4	12.0	0.004	**1.41 (1.16-1.71)**
Night-time attacks of breathlessness	4.8	6.1	0.045	**1.39 (1.07-1.82)**
Night-time coughing	23.1	23.1	0.987	**1.27 (1.09-1.47)**
Chronic bronchitis	9.0	12.5	<0.001	**1.47 (1.21-1.78)**
Allergic rhinitis	24.7	28.0	0.012	1.14 (0.99-1.31)
Chronic rhinosinusitis	7.1	9.3	0.005	**1.37 (1.11-1.70)**
Sleeping problems				
Snoring	11.7	19.0	<0.001	**1.53 (1.29-1.82)**
DIS[a]	11.1	16.5	<0.001	**1.71 (1.44-2.03)**
DMS[b]	25.3	15.8	<0.001	**0.71 (0.59-0.84)**
EDS[c]	28.7	29.8	0.433	1.08 (0.94-1.24)
EMA[d]	12.7	9.0	<0.001	0.83 (0.67-1.04)
Use of hypnotics	4.0	3.1	0.143	1.24 (0.85-1.80)

DIS[a], difficulty inducing sleep; DMS[b], difficulty maintaining sleep; EDS[c], excessive daytime sleepiness; EMA[d], early morning awakening at least three to five nights/week

[e]Associations with a *p*-value of < 0.05 are marked as bold

[f]Adjusted for gender, age, BMI, centre, educational level and physical activity

When snus users among asthma patients who had never smoked were examined, the only symptom with a significantly elevated risk was snoring (OR [95% CI] = 2.68 [1.58-4.55]).

History of snus use in never-smokers

Current snus use was an independent risk factor for having asthma, asthmatic symptoms, chronic bronchitis and chronic rhinosinusitis, while being an ex-snus user was not (Table 4). Snoring was independently related to both the former and the current use of snus. A higher risk of DIS was seen among current snus users. Current snus users had a decreased risk of DMS, whereas ex-snus use was an independent risk factor for the problem. Being an ex-snus user was also an independent risk factor for EMA (Table 4).

Table 4: Association between a history of snus use and respiratory health and sleep-related symptoms among never-smokers (adjusted odds ratio (95% CI).

	Ex-snus users (*n*=832)	Snus users (*n*=1,169)
Asthma	1.06 (0.79-1.40)	1.50 (1.21-1.86)
Asthmatic symptoms		
Wheezing	1.10 (0.89-1.36)	1.56 (1.32-1.84)
Wheezing and breathlessness	1.00 (0.76-1.31)	1.37 (1.12-1.69)
Wheezing without having a cold	1.24 (0.97-1.59)	1.51 (1.23-1.84)
Night-time chest tightness	1.01 (0.78-1.30)	1.41 (1.16-1.71)
Night-time attacks of breathlessness	1.27 (0.92-1.76)	1.42 (1.09-1.86)
Night-time coughing	1.14 (0.96-1.37)	1.29 (1.11-1.50)
Chronic bronchitis	0.91 (0.70-1.19)	1.45 (1.20-1.76)
Allergic rhinitis	0.95 (0.80-1.12)	1.13 (0.98-1.30)
Chronic rhinosinusitis	0.95 (0.71-1.28)	1.36 (1.10-1.70)
Sleeping problems		
Snoring	1.37 (1.12-1.68)	1.59 (1.34-1.89)
DIS[a]	0.81 (0.62-1.05)	1.68 (1.41-2.00)
DMS[b]	1.20 (1.01-1.42)	0.72 (0.60-0.85)
EDS[c]	1.00 (0.85 -1.18)	1.08 (0.94-1.24)
EMA[d]	1.28 (1.03-1.59)	0.85 (0.69-1.06)
Use of hypnotics	1.32 (0.87-2.01)	1.26 (0.87-1.84)

. [a]DIS, difficulty initiating sleep; [b]DMS, difficulty maintaining sleep; [c]EDS, excessive day sleepiness; [d]EMA, early morning awakening at least three to five nights/week

[e]Associations with a *p*-value of < 0.05 are marked as bold

[f]Adjusted for gender, age, BMI, centre, educational level and physical activity

Discussion

Our results reveal a previously unknown association between snus use and negative health effects on the respiratory tract. An increased risk of asthma, asthmatic and other respiratory symptoms was observed among snus users. An association between snus use and sleep-related problems was mixed with an increased risk of snoring and DIS but a decreased risk of DMS.

In the present study, 18% of men and 4.7% of women use snus either exclusively or in combination with smoking. This is similar to the prevalence of snus use reported in a Swedish official statistics [4]. According to our findings, snus use is proportionally higher in younger age groups and among men than women, indicating an earlier initiation.

When compared with the tobacco-free group, a significant risk of asthma was observed among snus users but not among smokers and dual users. As smoking is known to cause retrograde effects on asthma [20], the switch from smoking to snus use among asthmatic patients could possibly serve as a distracting agent. However, the fact that snus users who had never smoked also had an elevated risk of asthma and asthmatic symptoms excludes this possibility. This difference between snus users and smokers also raised concerns about whether asthmatic patients could be more prone to initiating snus use than cigarette smoking. Because the association with asthma and asthmatic symptoms was only present among current snus users but not ex-users of snus, this seems an unlikely explanation. These findings suggest that snus causes an alteration in the lower respiratory tract, resulting in an increased likelihood of suffering from asthma and asthmatic symptoms. As asthmatic patients are a growing challenge among health professionals today [21], these results deserve attention and further investigation. Similarly, to asthma and asthmatic symptoms, the risk of chronic bronchitis and chronic rhinosinusitis was only elevated among current snus users but not ex-snus users.

Current snus use was associated with snoring and, as the association remained present among ex-snus users, this suggests a partly irreversible effect from snus use on factors

leading to snoring. Snoring is caused by high frequency oscillation of the soft palate, pharyngeal wall, epiglottis and tongue during sleep, due to the limited flow of air through the upper airways [22]. The causes of limited airflow among patients who snore are diverse [23] [24]. There are data indicating that, once snoring occurs, it causes progressive irreversible local neurogenic lesions, caused by the trauma of snoring [25]. In former studies, hypnotics [26] and alcohol consumption [27] have been associated with snoring. Adjustment for the use of hypnotics did not have any impact on the risk (results not shown), excluding it as an interfering factor in this study. However, we were not able to adjust for alcohol consumption, as the GA^{2}LEN questionnaire did not include any questions about alcohol. It could thus serve as a confounder in our results. Obesity, gender, age and cigarette smoking are also possible confounders [26], all of which were adjusted for in our analyses.

In the group of snus users who had never smoked, being an asthma patient elevated the risk of snoring from 1.53 to 2.68. This implies that being an asthmatic patient increases the sensitivity to possible effects of snus use contributing to snoring. A deterioration in health-related quality of life in asthmatic patients suffering from snoring has been reported [28]. The possible prevention of snoring by reducing snus initiation among those suffering from asthma should therefore be prioritised.

The risk of DMS was decreased among current snus users but increased among ex-snus users. Ex-snus users also ran an increased risk of EMA. These results suggest that snus use improves sleep and that a cessation leads to exacerbation. In spite of this, current snus users had an increased risk of DIS, but ex-snus users did not, which indicates mixed effects on the quality of sleep.

The main strength of this study is the use of a large database from a random general population sample. The response rate was lowest in Gothenburg, or 54.9%, and highest in Uppsala, or 59.1% [19]. This response rate is somewhat lower than that previous epidemiological studies of the Swedish population have achieved [29 30], which is a limitation. In addition, the fact that this is a cross-sectional study makes it difficult to distinguish

between causes and outcomes. A follow-up study would be beneficial in order to conclude whether causation is present between snus use and these symptoms or only a connection. The fact that participants reported their history of snus use was, however, a great advantage, which helped us to draw conclusions about associations. It would have been beneficial to include questions on the amount of snus used, as well as alcohol consumption, in order to exclude it as an interfering factor. Another limitation is the fact that the answers to the questionnaire are self-reported which might lead to under- or overestimation in some categories, especially those demanding more than a yes or no answer [15]. It is, however, unlikely that the degree of under- or overestimation would differ between groups of tobacco use.

To the best of the authors' knowledge, this field of effects has not been examined before. Further investigations will be needed to draw conclusions on possible reasons for limited airflow in the upper airways, an inflamed/mucus-secreting respiratory tract and a mixed impact on the quality of sleep among snus users. Moreover, these results should be supported by further studies. Our results are important when considering tobacco control policies and can provide input to the discussion of why snus is not a good alternative for smoking cessation. Health-care professionals should be aware of these possible adverse health effects when treating patients dependent on snus and campaigns against snus use should be even more vigorous than before.

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Conflicts of interest

None of the authors have declared any conflicts of interest

Authors' contributions

AG and CJ analysed the data and wrote the first draft of the manuscript. ISO, RM, LE, BF, EL, KF and CJ supervised the study and contributed to the design of present data analyses. All co-authors revised critically the manuscript.

Data sharing

Data sharing: The dataset is still subject to further analyses, but will continue to be held and managed by the Department of Medical Sciences, Uppsala University, Uppsala, Sweden. Relevant anonymised data are available on reasonable request from the authors.

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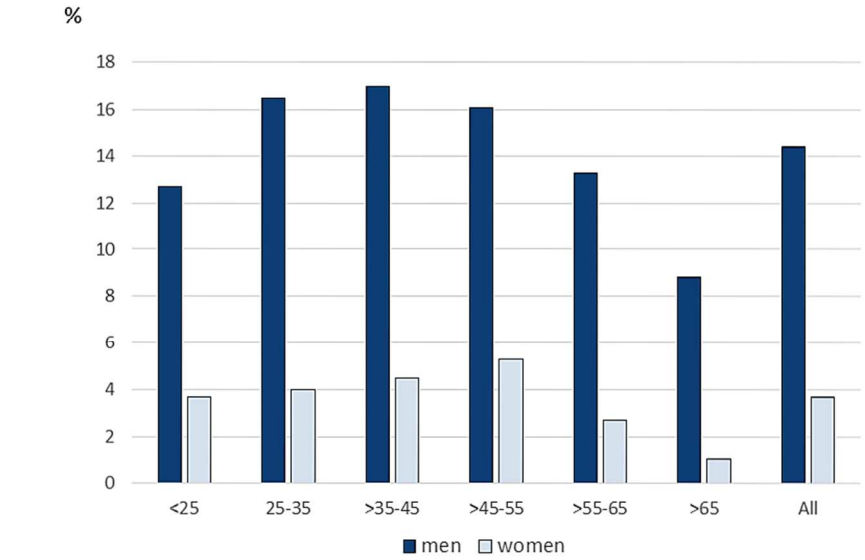
Figure 1: **Proportion of men and women using snus among age groups.**

Figure 1



253x190mm (96 x 96 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

Snus has an adverse impact on asthma, respiratory symptoms and snoring: A cross sectional population study.

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 3**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 3**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 4-6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 4**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **Page 4**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 4-6**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 4-6**
Bias	9	Describe any efforts to address potential sources of bias **Page 6**
Study size	10	Explain how the study size was arrived at **Page 4**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe

		which groupings were chosen and why **Page 4-6**	
Statistical methods	12	*(a)*	Describe all statistical methods, including those used to control for confounding **Page 6**
		(b)	Describe any methods used to examine subgroups and interactions **Page 6**
		(*c*) Explain how missing data were addressed **No imputations used as very little missing data**	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy not applicable	
		(*e*) Describe any sensitivity analyses not performed	

Continued on next page

Results		
Participants	13*	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyse **Page 4**
		(b) Give reasons for non-participation at each stage **Page 4**
		(c) Consider use of a flow diagram **Not done since there is only one stage**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Table 1**
		(b) Indicate number of participants with missing data for each variable of interest **Not done as very few**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **Not applicable**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures **Table 3**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Table3**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Page 11-13**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page 15**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 16-17**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 17**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Page 17**
Other information		
Funding Yes	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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An investigation on the use of snus and its association to respiratory and sleep related symptoms: A cross sectional population study.

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An investigation on the use of snus and its association to respiratory and sleep related symptoms: A cross sectional population study.

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Abstract

Introduction: Studies of the health effects of moist oral tobacco - snus have produced inconsistent results. The main objective of this study is to examine the health effects of snus use on asthma, respiratory symptoms and sleep-related problems, a field that has not been investigated before.

Methods and material: This cross-sectional study was based on a postal questionnaire completed by 26,697 (59.3%) participants aged 16-75 and living in Sweden. The questionnaire included questions on tobacco use, asthma, respiratory symptoms and sleeping problems. The association of snus use with asthma, respiratory symptoms and sleep-related symptoms was mainly tested in never-smokers (n=16,082).

Results: The current use of snus in never-smokers was associated with an increased risk of asthma (OR [95% CI] = 1.51 [1.28-1.77]), asthmatic symptoms, chronic bronchitis and chronic rhinosinusitis. This association was not present among ex-snus users. Snoring was independently related to both the former and current use of snus ((OR [95% CI] = 1.37 [1.12-1.68]) and (OR [95% CI] = 1.59 [1.34-1.89] respectively)). A higher risk of difficulty inducing sleep was seen among snus users.

Conclusion: Snus use was associated with a higher prevalence of asthma, respiratory symptoms and snoring. Health-care professionals should be aware of these possible adverse effects of snus use.

Keywords: snus, tobacco, asthma, chronic bronchitis, snoring, sleep disturbances

Strengths and limitations of the study

- This is one of the first studies to investigate the association between the use of snus and respiratory and sleep related symptoms
- The population is large which enables us to investigate subgroups such as never-smokers
- The data is self-reported and some subjects may therefore be misclassified
- The study is cross-sectional which makes it difficult to distinguish between causes and outcomes

Introduction

Snus is a smokeless, moist tobacco product consisting mainly of tobacco, salt, water, humectants and flavouring [1]. The tobacco in snus contains a number of harmful substances, including nicotine and tobacco-specific nitrosamines (TSNAs)[2]. In Sweden, where it is a very popular tobacco alternative, with 18% males and 4% females being current users, snus is regulated under food legislation [3 4]. The highest proportion of snus users is found among men aged 40 [5]. In the mid-1990s, the prevalence of snus use among Swedish men surpassed the prevalence of smoking. The proportion of female snus users is rising, but it has still not reached the prevalence for women smokers [5]. Compared with smoking, it has been suggested that the addiction to snus use is stronger, due to a lower cessation rate [6] and reports of greater experience of nicotine dependence [7] , however, other data suggest that snus cessation may be less difficult than cigarette cessation [8]. Some authors have suggested that snus is as a good alternative for smoking cessation, due to the beneficial health effects compared with cigarettes [9].

Studies aiming to identify the risk of health effects as a result of snus use have not reported consistent results. A significant increase in pancreatic cancer has been observed [10 11], but reports regarding the association between snus use and oral and pharyngeal cancer are inconclusive. [10-12]. Snus use appears to increase the risk of short-term case fatality after suffering from acute myocardial infarction [13] and stroke [14]. An increased risk of heart failure among snus users has been reported, with a particularly high risk of non-ischaemic heart failure among elderly men [15].

There is only sparse evidence regarding the potential effect of snus on respiratory health and sleep. An association between snus and asthma has been reported in one study [16] and an elevated risk of insufficient sleep was found among smokeless tobacco users in another [17]. The main objective of this paper was to investigate the health effects of snus use on asthma, respiratory symptoms and sleep-related problems in a large general population sample.

Methods

Study design and participants

This cross-sectional study is based on observations from a postal questionnaire sent to 45,000 randomly selected subjects as part of the the Global Allergy and Asthma European Network (GA^{2}LEN) survey in 2008 [18]. In Sweden 26,697 (59.3%) participants responded. The subjects were aged 16-75 and lived in four Swedish cities (Uppsala, Stockholm, Umeå and Gothenburg) [16].

Ethical approval was granted by the Regional Ethical Review Board in Uppsala, Sweden.

GA^{2}LEN questionnaire

The questionnaire included questions on respiratory symptoms, asthma and smoking. The questions also covered gender, age, weight and height. Body mass index (BMI) was calculated using the values of weight and height. In Sweden, the questionnaire also included questions on the use of snus and sleep-related symptoms. Listed below are definitions relevant to this paper.

Snus *users* were defined as those giving a positive answer to both the questions ''Have you ever used snus every day for at least six months?'' and ''Do you currently use snus?''.

Smokers were defined as those giving a positive answer to the questions ''Have you ever smoked at least one cigarette a day for at least one year?'' and ''Have you smoked at all during the last month?''. Based on the answers to questions on snus use and smoking, the participants were divided into four groups: tobacco free, snus users, smokers and dual users.

Based on answers to the questions on snus use and smoking, the subjects were further divided into never-, ex- and current snus users, as well as into never-, ex- and current smokers.

Asthma was defined as a positive answer to either of the questions ''Have you had an asthma attack during the last 12 months?'' or ''Are you currently taking any asthma medication including inhalers, sprays or tablets?''. Childhood asthma was defined as reporting having had an attack of asthma before the age of thirteen years.

Questions regarding a*sthmatic symptoms* during the last 12 months included: (i) wheezing in the chest; (ii) wheezing together with breathlessness; (iii) wheezing without having a cold; (iv) waking up with tightness in the chest; (v) waking up with shortness of breath and (vi) waking up with a coughing attack.

Chronic bronchitis was defined as a positive answer to the question: ''Are you used to having a cough almost every day with sputum production that lasts for at least three months every year during the winter?''.

Allergic rhinitis was defined as a positive answer to the question ''Have you had hay fever or a runny nose because of other allergies during the last twelve months?''.

Chronic rhinosinusitis was defined as suggested by the EP^{3}OS criteria 2007 [19]. It was considered to be present if participants stated that the following symptoms had been present for more than 12 weeks during the last 12 months: (i) nasal blockage, as well as one of the subsequent symptoms: (ii) facial pain or pressure, (iii) discoloured nasal discharge or (iv) reduction or loss of smell. The disease was also considered to be present if both symptoms (ii) and (iii) were reported.

Sleep-related problems examined in this study were (i) snoring that is loud and interrupting, (ii) difficulty inducing sleep (DIS), as in having a hard time falling asleep at night, (iii) difficulty maintaining sleep (DMS), as in repeatedly waking up during the night, (iv) being sleepy

during the day (EDS) and (v) early morning awakening (EMA), as in waking up too early and having a hard time falling asleep again [20]. Each group included subjects who claimed they had the problem at least three to five times a week. The use of hypnotics was defined as a positive answer to the question ''Do you take medication for sleeping problems?''.

Educational level was divided into three categories. (i) College was defined as having attended college/university for more than two and a half years. (ii) High school was defined as having attended high school or vocational school for more than two years. (iii) Elementary school was defined as any education below the level of high school.

Activity level was divided into three categories depending on hours spent on intensive exercising per week. (i) Physically inactive was defined as zero hours a week. (ii) Moderately physically active was defined as half an hour up to three hours a week. (iii) Vigorously physically active was defined as four up to seven hours a week.

Data analysis

For statistical analyses, Stata version 12 was used. When comparing the characteristics of the study population, univariate analyses using the chi square test were used. Multivariate logistic regression models were used to study independent associations between various symptoms and different groups of tobacco use after adjusting for potential confounders; gender, age, BMI, centre, educational level and physical activity. Sub-analyses were performed in never-smokers and in never-smokers with reported asthma. Analyses of possible heterogeneity between the centre were performed using random effects meta-analysis. A p-value of < 0.05 was regarded as statistically significant.

Results

The frequency of snus use among men was highest in the 25-35 age group. The number of snus-using women was highest in the 45-55 age group, with a steep decrease thereafter. In overall terms, 18.0% of men and 4.7% of women in the study population used snus (Figure 1).

In the whole population, snus use and dual use were highest in the 25-35 age group, while smoking was most prevalent at the ages of 55-65. The group of snus users had a higher BMI than the other groups. They were also more likely to be ex-smokers than persons in the tobacco-free group. Educational level and physical activity level were higher among snus users compared with smokers and dual users but lower compared with those who were tobacco free (Table 1).

Table 1: Characteristics of the study population (%).

		Tobacco users			
	Tobacco free (n=20,699)	Snus (n=2,265)	Smokers (n=3,136)	Smokers and snus (n=597)	*p*-value
Women	57.7	23.5	62.9	25.0	<0.001
Age (years)					<0.001
16-25	15.4	12.8	12.4	15.2	
25-35	21.4	23.2	17.4	26.7	
35-45	17.6	21.5	16.7	16.8	
45-55	15.4	19.7	20.0	21.5	
55-65	17.7	16.5	23.2	14.9	
>65	12.4	7.2	10.1	6.7	
Body mass index					<0.001
<20	8.6	4.7	9.9	5.8	
20-25	51.9	46.6	48.9	48.1	
25-30	30.1	36.2	30.9	35.3	
>30	9.5	12.4	10.3	10.9	
Ex-smokers	26.8	48.1	-	-	<0.001
Educational level					<0.001
Elementary school	15.0	12.5	23.6	18.6	
High school	31.6	42.9	40.7	45.8	
College	53.5	44.7	35.7	35.6	
Activity level					<0.001
Physically inactive	18.1	19.3	32.8	27.8	
Moderately physically active	62.8	62.0	55.1	58.7	
Vigorously physically active	19.0	18.7	12.1	13.5	

Tobacco use and symptoms

In Table 2, we examined the association between tobacco use and symptoms after adjusting for likely confounders. Having asthma was independently related to using snus but not to smoking or the dual use of snus and cigarettes. Although the strongest associations with

respiratory symptoms were found among smokers and dual users, snus users were more likely to suffer from wheezing and night-time chest tightness, as well as chronic bronchitis, allergic rhinitis and chronic rhinosinusitis, compared with the tobacco-free group. Snoring, DIS, EDS and the use of hypnotics were associated with all three groups of tobacco use. Snus users had a decreased risk of DMS (Table 2). The corresponding unadjusted associations were fairly similar to the adjusted estimates (online supplementary Table S1).

Table 2: The independent association between tobacco use and respiratory health and sleep-related symptoms (adjusted* odds ratio (95% CI)).

	Tobacco users		
	Snus users (*n* =2,265)	Smokers (*n*= 3,136)	Smokers and snus users (*n*=597)
Asthma	**1.51 (1.28-1.77)**	0.96 (0.82-1.13)	0.93 (0.65-1.33)
Asthmatic symptoms			
Wheezing	**1.50 (1.33-1.69)**	**2.89 (2.64-3.17)**	**2.09 (1.71-2.55)**
Wheezing and breathlessness	**1.42 (1.23-1.65)**	**2.11 (1.89-2.37)**	**1.46 (1.12-1.90)**
Wheezing without having a cold	**1.50 (1.30-1.73)**	**2.67 (2.40-2.98)**	**2.17 (1.73-2.73)**
Night-time chest tightness	**1.21 (1.05-1.40)**	**1.57 (1.40-1.75)**	**1.43 (1.12-1.82)**
Night-time attacks of breathlessness	1.02 (0.83-1.24)	**1.44 (1.24-1.67)**	**1.58 (1.16-2.13)**
Night-time coughing	1.10 (0.99-1.23)	**1.79 (1.64-1.94)**	**1.79 (1.49-2.15)**
Chronic bronchitis	**1.19 (1.03-1.37)**	**2.39 (2.16-2.65)**	**1.85 (1.48-2.31)**
Allergic rhinitis	**1.17 (1.05-1.30)**	1.01 (0.91-1.11)	0.92 (0.75-1.13)
Chronic rhinosinusitis	**1.28 (1.09-1.50)**	**1.78 (1.57-2.02)**	**1.78 (1.38-2.29)**
Sleeping problems			
Snoring	**1.41 (1.25-1.58)**	**1.78 (1.60-1.97)**	**2.16 (1.77-2.63)**
DIS[a]	**1.76 (1.56-1.99)**	**1.98 (1.79-2.19)**	**2.95 (2.43-3.58)**
DMS[b]	**0.74 (0.66-0.83)**	0.97 (0.88-1.06)	0.91 (0.75-1.12)
EDS[c]	**1.18 (1.07-1.31)**	**1.29 (1.19-1.41)**	**1.38 (1.16-1.65)**
EMA[d]	0.87 (0.76-1.00)	**1.14 (1.03-1.27)**	0.91 (0.70-1.17)
Use of hypnotics	**1.33 (1.07-1.65)**	**2.08 (1.81-2.39)**	**2.77 (2.05-3.74)**

. [a]DIS, difficulty initiating sleep; [b]DMS, difficulty maintaining sleep; [c]EDS, excessive day sleepiness; [d]EMA, early morning awakening at least three to five nights/week

Associations with a *p*-value of < 0.05 are marked as bold

*Adjusted for gender, age, BMI, centre, educational level and physical activity

Snus use in never-smokers

In never-smokers, there was an association between snus use and asthma, all the asthmatic symptoms, chronic bronchitis and chronic rhinosinusitis. Sleeping problems with an increased risk among snus users were snoring and DIS. Also among never-smokers, snus users had a decreased risk of DMS (Table 3). The associations to asthma and nocturnal breathlessness became statistically non-significant when excluding subjects who have had attacks of asthma before the age of thirteen (n=1466) (adjusted OR (95% CI) 1.24 (0.89-1.71) and 1.32 (0.97-1.77), respectively. All the other association above remained statistically significant,

No significant heterogeneity between the centres was found between snus use and the health outcomes except for bronchitis where the association was particularly strong in Stockholm (adjusted OR (95% CI) 2.35 (1.52-3.62)) whereas no significant association was found in Uppsala (OR 0.97 (0.60-1.57), $p_{heterogneity}$=0.04. The pooled estimates of the meta analyses were very similar to those found in table 3 (data not shown).

Table 3: Association between snus and respiratory health and sleep-related symptoms in never-smokers (%) and adjusted odds ratio (OR).

	Never smoked			
	Tobacco free (*n* =14,914)	Snus users (*n* =1,168)	*p*-Value	OR (95% CI)
Asthma	6.9	10.1	<0.001	**1.49 (1.20-1.85)**
Asthmatic symptoms				
Wheezing	12.9	18.8	<0.001	**1.56 (1.32-1.84)**
Wheezing and breathlessness	8.2	10.9	0.002	**1.38 (1.12-1.69)**
Wheezing without having a cold	8.0	11.8	<0.001	**1.48 (1.21-1.80)**
Night-time chest tightness	9.4	12.0	0.004	**1.41 (1.16-1.71)**
Night-time attacks of breathlessness	4.8	6.1	0.045	**1.39 (1.07-1.82)**
Night-time coughing	23.1	23.1	0.987	**1.27 (1.09-1.47)**
Chronic bronchitis	9.0	12.5	<0.001	**1.47 (1.21-1.78)**
Allergic rhinitis	24.7	28.0	0.012	1.14 (0.99-1.31)
Chronic rhinosinusitis	7.1	9.3	0.005	**1.37 (1.11-1.70)**
Sleeping problems				
Snoring	11.7	19.0	<0.001	**1.53 (1.29-1.82)**
DIS[a]	11.1	16.5	<0.001	**1.71 (1.44-2.03)**
DMS[b]	25.3	15.8	<0.001	**0.71 (0.59-0.84)**
EDS[c]	28.7	29.8	0.433	1.08 (0.94-1.24)
EMA[d]	12.7	9.0	<0.001	0.83 (0.67-1.04)
Use of hypnotics	4.0	3.1	0.143	1.24 (0.85-1.80)

DIS[a], difficulty inducing sleep; DMS[b], difficulty maintaining sleep; EDS[c], excessive daytime sleepiness; EMA[d], early morning awakening at least three to five nights/week

[e]Associations with a *p*-value of < 0.05 are marked as bold

[f]Adjusted for gender, age, BMI, centre, educational level and physical activity

When snus users among asthma patients who had never smoked were examined, the only symptom with a significantly elevated risk was snoring (OR [95% CI] = 2.68 [1.58-4.55]).

History of snus use in never-smokers

Current snus use was an independent risk factor for having asthma, asthmatic symptoms, chronic bronchitis and chronic rhinosinusitis, while being an ex-snus user was not (Table 4). Snoring was independently related to both the former and the current use of snus. A higher risk of DIS was seen among current snus users. Current snus users had a decreased risk of DMS, whereas ex-snus use was an independent risk factor for the problem. Being an ex-snus user was also an independent risk factor for EMA (Table 4).

Table 4: Association between a history of snus use and respiratory health and sleep-related symptoms among never-smokers (adjusted odds ratio (95% CI).

	Ex-snus users (*n*=832)	Snus users (*n*=1,169)
Asthma	1.06 (0.79-1.40)	1.50 (1.21-1.86)
Asthmatic symptoms		
Wheezing	1.10 (0.89-1.36)	1.56 (1.32-1.84)
Wheezing and breathlessness	1.00 (0.76-1.31)	1.37 (1.12-1.69)
Wheezing without having a cold	1.24 (0.97-1.59)	1.51 (1.23-1.84)
Night-time chest tightness	1.01 (0.78-1.30)	1.41 (1.16-1.71)
Night-time attacks of breathlessness	1.27 (0.92-1.76)	1.42 (1.09-1.86)
Night-time coughing	1.14 (0.96-1.37)	1.29 (1.11-1.50)
Chronic bronchitis	0.91 (0.70-1.19)	1.45 (1.20-1.76)
Allergic rhinitis	0.95 (0.80-1.12)	1.13 (0.98-1.30)
Chronic rhinosinusitis	0.95 (0.71-1.28)	1.36 (1.10-1.70)
Sleeping problems		
Snoring	1.37 (1.12-1.68)	1.59 (1.34-1.89)
DIS[a]	0.81 (0.62-1.05)	1.68 (1.41-2.00)
DMS[b]	1.20 (1.01-1.42)	0.72 (0.60-0.85)
EDS[c]	1.00 (0.85 -1.18)	1.08 (0.94-1.24)
EMA[d]	1.28 (1.03-1.59)	0.85 (0.69-1.06)
Use of hypnotics	1.32 (0.87-2.01)	1.26 (0.87-1.84)

. [a]DIS, difficulty initiating sleep; [b]DMS, difficulty maintaining sleep; [c]EDS, excessive day sleepiness; [d]EMA, early morning awakening at least three to five nights/week

[e]Associations with a *p*-value of < 0.05 are marked as bold

[f]Adjusted for gender, age, BMI, centre, educational level and physical activity

Discussion

Our results reveal a previously unknown association between snus use and negative health effects on the respiratory tract. An increased risk of asthma, asthmatic and other respiratory symptoms was observed among snus users. An association between snus use and sleep-related problems was mixed with an increased risk of snoring and DIS but a decreased risk of DMS.

In the present study, 18% of men and 4.7% of women use snus either exclusively or in combination with smoking. This is similar to the prevalence of snus use reported in a Swedish official statistics [4]. According to our findings, snus use is proportionally higher in younger age groups and among men than women, indicating an earlier initiation.

When compared with the tobacco-free group, a significant risk of asthma was observed among snus users but not among smokers and dual users. There is a possibility of reverse causation. Smoking is known to cause negative effects on asthma [21], the switch from smoking to snus use among asthmatic patients could possibly explain some of the association between snus use and asthma. However, the fact that snus users who had never smoked also had an elevated risk of asthma and asthmatic symptoms excludes this possibility. This difference between snus users and smokers also raised concerns about whether asthmatic patients could be more prone to initiating snus use than cigarette smoking. Because the association with asthma and asthmatic symptoms was only present among current snus users but not ex-users of snus, this seems an unlikely explanation. We also found an association between snus use and respiratory symptoms when excluding participants that had childhood asthma. These findings suggest that snus causes an alteration in the lower respiratory tract, resulting in an increased likelihood of suffering from asthma and asthmatic symptoms. As asthmatic patients are a growing challenge among health professionals today [22], these results deserve attention and further investigation. Similarly, to asthma and asthmatic symptoms, the risk of chronic bronchitis and chronic rhinosinusitis was only elevated among current snus users but not ex-snus users.

Current snus use was associated with snoring and, as the association remained present among ex-snus users, this suggests a partly irreversible effect from snus use on factors leading to snoring. Snoring is caused by high frequency oscillation of the soft palate, pharyngeal wall, epiglottis and tongue during sleep, due to the limited flow of air through the upper airways [23]. The causes of limited airflow among patients who snore are diverse [24] [25]. There are data indicating that, once snoring occurs, it causes progressive irreversible local neurogenic lesions, caused by the trauma of snoring [26]. In former studies, hypnotics [27] and alcohol consumption [28] have been associated with snoring. Adjustment for the use of hypnotics did not have any impact on the risk (results not shown), excluding it as an interfering factor in this study. However, we were not able to adjust for alcohol consumption, as the GA^{2}LEN questionnaire did not include any questions about alcohol. It could thus serve as a confounder in our results. Obesity, gender, age and cigarette smoking are also possible confounders [27], all of which were adjusted for in our analyses.

In the group of snus users who had never smoked, being an asthma patient elevated the risk of snoring from 1.53 to 2.68. This implies that being an asthmatic patient increases the sensitivity to possible effects of snus use contributing to snoring. A deterioration in health-related quality of life in asthmatic patients suffering from snoring has been reported [29]. The possible prevention of snoring by reducing snus initiation among those suffering from asthma should therefore be prioritised.

The risk of DMS was decreased among current snus users but increased among ex-snus users. Ex-snus users also ran an increased risk of EMA. These results suggest that snus use improves sleep and that a cessation leads to exacerbation. In spite of this, current snus users had an increased risk of DIS, but ex-snus users did not, which indicates mixed effects on the quality of sleep.

The biological explanation for the association between snus use and health outcomes in the present study are unknown. Gastroesophageal reflux is associated with both smoking [30], respiratory symptoms and snoring [31] , but the association between reflux and snus use is less

clear [32]. Snus use was in one study found to be associated with an increased transfer factor for nitric oxide and a decrease in alveolar nitric oxide concentration indicating that snus may have an effect also on the lower airways [33].

The main strength of this study is the use of a large database from a random general population sample. The response rate was lowest in Gothenburg, or 54.9%, and highest in Uppsala, or 59.1% [20]. This response rate is somewhat lower than that previous epidemiological studies of the Swedish population have achieved [34 35], which is a limitation. In addition, the fact that this is a cross-sectional study makes it difficult to distinguish between causes and outcomes. A longitudinal study would be beneficial in order to indicate whether causation is present between snus use and these symptoms or only a connection. The fact that participants reported their history of snus use was, however, a great advantage, which helped us to draw conclusions about associations. It would have been beneficial to include questions on the amount of snus used. We also lack data on alcohol consumption, which is a limitation as there are studies showing an association between use of snus and a higher use of alcohol [36]. It is also possible that some of the association between snus use and snoring is related to higher alcohol use in participants using snus [37]. Another limitation is the fact that the answers to the questionnaire are self-reported which might lead to under- or overestimation in some categories, especially those demanding more than a yes or no answer [16]. It is, however, unlikely that the degree of under- or overestimation would differ between groups of tobacco use. We did not adjust for passive smoking, but we know from previous studies that the prevalence of passive smoking is very low in Sweden (<10%) [38] so we do not think that this has influenced our results.

To the best of the authors' knowledge, this field of effects has not been examined before. Further investigations will be needed to draw conclusions on possible reasons for limited airflow in the upper airways, an inflamed/mucus-secreting respiratory tract and a mixed impact on the quality of sleep among snus users. Moreover, these results should be supported by further studies. Our results are important when considering tobacco control policies and can provide input to the discussion of whether snus is a good alternative for smoking cessation.

Acknowledgements and Funding

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Conflicts of interest

None of the authors have declared any conflicts of interest

Authors' contributions

AG and CJ analysed the data and wrote the first draft of the manuscript. ISO, RM, LE, BF, EL, KF and CJ supervised the study and contributed to the design of present data analyses. All co-authors revised critically the manuscript.

Data sharing

Data sharing: The dataset is still subject to further analyses, but will continue to be held and managed by the Department of Medical Sciences, Uppsala University, Uppsala, Sweden. Relevant anonymised data are available on reasonable request from the authors.

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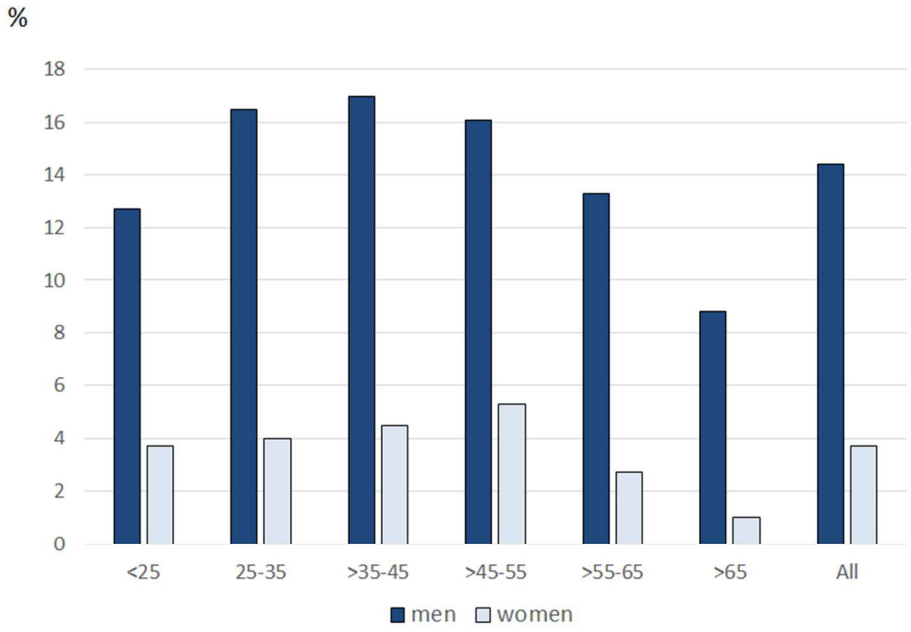
Figure 1: **Proportion of men and women using snus among age groups.**

Figure 1



299x213mm (72 x 72 DPI)

Supplementary data

Table S1: The crude association between tobacco use and respiratory health and sleep-related symptoms (unadjusted odds ratio (95% CI)).

	Tobacco users		
	Snus users (*n* =2,265)	Smokers (*n*= 3,136)	Smokers and snus users (*n*=597)
Asthma	**1.39 (1.19-1.61)**	0.93 (0.79-1.08)	0.83 (0.57-1.18)
Asthmatic symptoms			
Wheezing	**1.47 (1.31-1.64)**	**2.78 (2.55-3.03)**	**1.93 (1.59-2.34)**
Wheezing and breathlessness	**1.36 (1.18-1.56)**	**2.09 (1.88-2.33)**	**1.35 (1.04-1.74)**
Wheezing without having a cold	**1.50 (1.31-1.72)**	**2.64 (2.38-2.92)**	**2.09 (1.68-2.61)**
Night-time chest tightness	**1.16 (1.01-1.32)**	**1.68 (1.51-1.87)**	**1.44 (1.14-1.82)**
Night-time attacks of breathlessness	1.06 (0.88-1.28)	**1.56 (1.35-1.80)**	**1.67 (1.24-2.23)**
Night-time coughing	0.91 (0.82-1.01)	**1.74 (1.61-1.89)**	**1.47 (1.23-1.75)**
Chronic bronchitis	**1.22 (1.07-1.40)**	**2.56 (2.32-2.65)**	**1.95 (1.57-2.41)**
Allergic rhinitis	**1.16 (1.05-1.28)**	0.93 (0.85-1.02)	0.88 (0.72-1.07)
Chronic rhinosinusitis	**1.27 (1.09-1.48)**	**1.89 (1.68-2.13)**	**1.92 (1.50-2.44)**
Sleeping problems			
Snoring	**1.74 (1.56-1.94)**	**1.74 (1.58-1.91)**	**2.44 (2.04-2.93)**
DIS[a]	**1.60 (1.43-1.80)**	**2.21 (2.01-2.43)**	**2.90 (2.41-3.49)**
DMS[b]	**0.65 (0.58-0.72)**	1.07 (0.98-1.16)	**0.77 (0.63-0.93)**
EDS[c]	**1.13 (1.03-1.24)**	**1.35 (1.25-1.47)**	**1.41 (1.19-1.67)**
EMA[d]	**0.80 (0.70-0.91)**	**1.31 (1.18-1.44)**	0.83 (0.65-1.07)
Use of hypnotics	1.02 (0.83-1.24)	**2.39 (2.10-2.72)**	**1.99 (1.49-2.64)**

[a]DIS, difficulty initiating sleep; [b]DMS, difficulty maintaining sleep; [c]EDS, excessive day sleepiness; [d]EMA, early morning awakening at least three to five nights/week

Associations with a *p*-value of < 0.05 are marked as bold

STROBE Statement—checklist of items that should be included in reports of observational studies

Snus has an adverse impact on asthma, respiratory symptoms and snoring: A cross sectional population study.

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 3**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 3**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 4-6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 4**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **Page 4**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 4-6**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 4-6**
Bias	9	Describe any efforts to address potential sources of bias **Page 6**
Study size	10	Explain how the study size was arrived at **Page 4**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe

		which groupings were chosen and why **Page 4-6**	
Statistical methods	12	*(a)*	Describe all statistical methods, including those used to control for confounding **Page 6**
		(b)	Describe any methods used to examine subgroups and interactions **Page 6**
		(*c*) Explain how missing data were addressed **No imputations used as very little missing data**	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy not applicable	
		(*e*) Describe any sensitivity analyses not performed	

Continued on next page

Results		
Participants	13*	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyse **Page 4**
		(b) Give reasons for non-participation at each stage **Page 4**
		(c) Consider use of a flow diagram **Not done since there is only one stage**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Table 1**
		(b) Indicate number of participants with missing data for each variable of interest **Not done as very few**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **Not applicable**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures **Table 3**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Table3**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Page 11-13**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page 15**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 16-17**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 17**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Page 17**
Other information		
Funding Yes	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.