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Title

Snus and risk of gastroesophageal reflux. A population-based case-control study: The HUNT study

Short title

Snus and gastroesophageal reflux

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Abstract

Objective

Tobacco smoking is a risk factor for gastroesophageal reflux, but whether other tobacco products increase the risk is unclear. The aim of this study was to investigate if snus increases the risk of gastroesophageal reflux symptoms (GERS).

Material and Methods

The study was based on the third Nord-Trøndelag health study (HUNT3), a population-based study of all adult residents in Nord-Trøndelag County, Norway, performed in 2006−2009. The association between self-reported severe heartburn/regurgitation and snus use was assessed by logistic regression.

Results

Compared to never snus users, daily snus users had a reduced risk of GERS (OR 0.77, 95% CI 0.64−0.93), while previous snus users and those using <2 boxes of snus/month had an increased risk (OR 1.20, 95% CI 1.00−1.46 and 1.41, 95% CI 1.02−1.96, respectively). There was no association between age when starting using snus and GERS. Snus users who started using snus to quit or cut down on cigarette smoking, who started using both snus and cigarettes or cigarettes alone had an increased risk of GERS. Snus users <30 years of age had an increased risk of GERS (OR 1.49, 95% CI 1.02−2.16), while those aged between 50−60 and 60−70 years had a reduced risk (OR 0.67, 95% CI 0.49−0.93 and 0.51, 95% CI 0.28−0.94, respectively).

Conclusions

Daily snus users had a reduced risk of GERS. However, previous snus users and subgroups of snus users had an increased risk of GERS indicating reverse causality, such that snus use could increase the risk of GERS.

Key words

Health surveys, oral tobacco, smokeless tobacco, snuff

Text

Introduction

Snus is a form of smokeless tobacco that has been used for decades in the Scandinavian countries. It is consumed by placing a portion under the upper lip in front of the gingiva and is increasingly popular amongst young people (1). The snus market is rapidly spreading worldwide and snus was recently launched in the US (2, 3). Previous studies have estimated that around 22% of men and 4% of women are using snus, and the prevalence of women using snus is increasing (2, 4, 5).

The exposure time of snus is higher than for smoking; with an average duration time of 60−70 minutes per portion, giving twice as large the amount of nicotine (6, 7). It consists of tobacco, water, sodium chloride, sodium carbonate, humectants, and flavoring agents, and large amounts of these contents are swallowed into the digestive tract (1, 8, 9).

Gastroesophageal reflux disease (GERD) is caused by abnormal backflow of gastric contents into the esophagus, producing symptoms and mucosal damage (10, 11). The main symptoms of GERD are heartburn and regurgitation, and the prevalence of GERD in Western adult populations is up to 30% (12, 13). GERD is associated with reduced health related quality of life (14) and work productivity (15), and an increased risk of esophageal adenocarcinoma (16). Genetic predispositions and lifestyle factors, including obesity and tobacco smoking, increase the risk of GERD (17). Due to the existing evidence of tobacco smoking as a causal factor for GERD, snus has been proposed as a similar risk factor for the development of GERD (17-20). A study by Aro et al. found an association between snus use and histological

changes in the esophagus associated with GERD (basal cell hyperplasia and elongation of papillae) (21).

In general, the documentation of the health effects of snus is sparse, and the continuous product development of snus and changes in its ingredients makes interpretation of old research troublesome (9).

The aim of this study was to investigate if snus is a risk factor for gastroesophageal reflux symptoms (GERS), using a large population-based study from Norway.

Methods

Material

The Nord-Trøndelag health study (HUNT) is an on-going population based cohort study. Nord-Trøndelag is a county in the central part of Norway with about 135,000 inhabitants (in 2014). All residents above 20 years of age were asked to participate in three health surveys; HUNT1 (1984—1986), HUNT2 (1995—1997), and HUNT3 (2006—2008) (22). In HUNT1, 77,212 individuals (89% of the total population) participated and the corresponding numbers were 65,237 (70%) and 50,807 (54%) in HUNT2 and HUNT3, respectively. This makes HUNT the largest population based study in Norway, and also one of the largest internationally. Data on health-related items were gathered through self-reported questionnaires, clinical examinations, and blood samples of the participants.

As snus use was assessed in HUNT3 only, the present study is based on HUNT3. In addition, a short questionnaire for non-participants (the QNP) sent out in 2009 to those who did not participate in HUNT3 was also included (n=7,591).

Assessment of snus use

In HUNT3 and the QNP, the participants were asked, "Do you use, or have you previously used snus?" with the possible answers "no, never", "yes, but I quit", "yes, occasionally", and "yes, daily".

For those "ever" using snus, HUNT3 included four additional questions regarding snus. The participants were asked about their consumption of snus per month, at what age they started using snus, their motivation to start using snus, and what type of tobacco they started with. These additional questions were not included in the QNP.

Assessment of gastroesophageal reflux symptoms

GERS was assessed with the question "To what degree have you had acid regurgitation or heartburn during the last 12 months" with the alternatives "never", "a little", or "much" complaint. Previous validations of this question found that 95−98% of those reporting much complaint had symptoms at least weekly, thereby fulfilling the Montreal criteria for GERD (11, 23, 24).

Those reporting much complaint were defined as the case group (“Severe GERS”), while those reporting never complaint were defined as controls (“No GERS”). Those reporting a little complaint were excluded from our analysis.

Assessment of co-variables

In the present study age, sex, tobacco smoking, body mass index (BMI), and physical exercise were taken into consideration as potential confounders.

The participants were asked, "Do you smoke?" with the alternatives: "no, I have never smoked", "no, I quit smoking", "yes, occasionally", or "yes, daily".

Trained personnel measured the weight and height of the participants in HUNT3, while weight and height were self-reported in the QNP. BMI was calculated as weight (kg)/height (m)^2 and categorized into normal weight (<25.0), overweight (25.0−29.9), and obese (≥30.0) according to the World Health Organization's classification.

Physical exercise was assessed by the question "How often do you exercise?" with the options "less than once a week", "once a week", "2−3 times a week", or "nearly every day", and further categorized into ≥ or < weekly, based on the self-reported frequency.

Statistical analysis

The risk of GERS among snus users compared to not snus users in HUNT3/QNP was estimated using multivariable logistic regression, reporting odds ratios (ORs) with 95% confidence intervals (CIs). We present crude ORs, age and sex adjusted ORs, and fully adjusted ORs, including adjustments for age, sex, smoking status, BMI, and physical exercise. The additional questions regarding snus were used in separate sub-analyses. As these additional questions only were included in HUNT3, the participants in QNP were excluded in these sub-analyses.

We tested the main model for interactions, and based on these results we performed analyses stratified by age and smoking status.

Statistical software: STATA 14.0 (StataCorp LP, College Station, TX)

Informed consent and ethical approval

All participants in HUNT gave written informed consent on participation that their data could be used in future medical research. Ethical approval was obtained from the Regional

Committee for Medical and Health Research Ethics (reference: 2012/1290/REK midt) before the study was initiated.

Results

In total, 58,634 individuals participated in HUNT3 and the QNP and 2,993 (5.1%) had severe GERS (cases) and 26,610 (45.4%) had no GERS (controls; Table I).

Characteristics

The cases were older than the controls (mean age 54.3 and 50.1 years, respectively). The participation rate was higher among women than men, but the proportion of cases was higher among men than women (11.8% and 10.8%, respectively).

Daily snus use was less common among cases than controls (5.4% and 7.3%, respectively). On the other hand, previous snus use and occasional snus use were more common among cases. The cases using snus were older than the controls using snus (mean age 43.3 and 41.8 years, respectively). The mean age at the start of their snus use was similar for both groups. Snus consumption (boxes per month) was higher for cases than for controls. More cases than controls started using snus to quit or cut down on smoking, and more cases than controls started with cigarettes first. Compared to the controls, more cases were current or previous tobacco smokers, had a higher BMI, and exercised less frequently.

Associations

Compared to never snus users, daily snus users had a reduced risk of severe GERS; fully adjusted OR 0.77 (95% CI 0.64−0.93; Table II). However, previous snus users had increased

risk of severe GERS; fully adjusted OR 1.20 (1.00−1.46). Moreover, those using <2 boxes per month had increased risk of severe GERS; fully adjusted OR 1.41 (1.02−1.96), while there was no statistically significant association between snus use and use of ≥2 boxes of snus per month.

There was no association between age when starting using snus and severe GERS (Table III). Compared to those reporting no specific motivation to start using snus, those snus users who started using snus to quit or cut down on smoking had an increased risk of severe GERS; adjusted OR 1.50 (1.13−1.99) and 1.88 (1.35−2.61), respectively. Snus users, who started with both snus and cigarettes, or cigarettes alone, also had an increased risk of severe GERS; fully adjusted OR 2.26 (1.17−4.35) and 1.76 (1.30−2.39), respectively.

Snus use interacted with age and tobacco smoking status. Stratified analyses showed that snus users <30 years of age had increased risk of severe GERS; fully adjusted OR 1.49 (1.02−2.16) (Table IV and Figure), while those between 50−60 and 60−70 years of age had reduced risk; fully adjusted OR 0.67 (0.49−0.93) and 0.51 (0.28−0.94), respectively. Snus users who never or previously had smoked had a reduced risk of severe GERS; fully adjusted OR 0.75 (0.54−1.03) and 0.62 (0.48−0.79), respectively. Moreover, snus users who were occasionally or daily smokers seemed to have an increased risk of severe GERS, however, this association did not reach statistical significance; fully adjusted OR 1.39 (0.94−2.04) and 1.12 (0.78−1.61), respectively (Table IV).

Discussion

This large population-based observational study showed that daily snus users had a reduced risk of severe GERS compared with not snus users. However, previous snus users and

subgroups of snus users had an increased risk of severe GERS: those consuming <2 boxes of snus per month, snus users who started with both snus and cigarettes or cigarettes alone, snus users who started using snus to quit or cut down cigarette smoking, and snus users <30 years of age. In snus users the risk of severe GERS was reduced with increasing age.

The large population-based study design facilitates subgroup analyses and reduces the risk of selection bias. However, it is known that those participating in population-based studies have higher socioeconomic status compared to those not participating. As diseases and health related risk factors are often related to socioeconomic status, this makes selection bias possible (25, 26) and might weaken the external validity of the results. Except for lower average income and education, and the lack of a large city, the population in Nord-Trøndelag is representative of the Norwegian population at large (27). The extensive questionnaires used in HUNT also allowed adjustments for possible confounders of the association between snus use and GERS. Alcohol use is associated with snus use and some studies have also found an association between alcohol use and reflux, while other studies have not found any association (28). In our previous studies on GERS using the HUNT material, alcohol use was not associated with reflux (17, 20) and, thus, we have not included alcohol use as a possible confounder in this study. All questionnaires used in this study were self-reported. Even if self-reported questionnaires are validated (29), we cannot exclude possible information bias in our study (30).

In HUNT, more men than women were using snus, current snus users were younger than not snus users, snus use was associated with lower education, higher alcohol consumption, and less physical exercise, and smoking rates were lower among daily snus users (2).

According to the Montreal definition, GERD is "a condition that develops when reflux of stomach contents causes troublesome symptoms and/or complications. (…) In population-

based studies, mild symptoms occurring two or more days a week, or moderate/severe symptoms occurring more than one day a week, are often considered troublesome by patients" (11). The HUNT study was initiated before the Montreal consensus and did not use this definition. However, the question used in HUNT has been validated and these validations have shown that participants reporting severe complaints in HUNT have at least weekly symptoms (23, 24).

We have no information available on whether the participants were taking anti-reflux medications. This could have reduced the proportion of participants reporting GERS. In addition, participants with GERS may also have developed Barrett's esophagus which has the potential to reduce symptoms. However, only a small percentage of the participants are expected to develop Barrett's so this should not have influenced the overall results.

In this study we hypothesized that snus use would increase the risk of GERS. However, the overall result was that snus use seems to protect against GERS. We believe this could be explained by reverse causality, meaning that those with severe GERS because of snus stop their exposure to snus (20). The results of the subgroup analyses support this assumption. Previous snus users developing GERS may have quit using snus as a result of snus inducing GERS. This is also supported by the declining trend from high risk of GERS among young snus users to low risk with increasing age. This is the opposite of the trend in prevalence of GERS seen in the total population (24). If reverse causality is the explanation, our results will wrongfully suggest that snus has a protective effect against GERS and persons with a lower predisposition of developing GERS will continue using snus.

If snus increases the risk of GERS, one would presume an increasing prevalence with increasing doses; a dose-response relationship. However, in this study we found that those using <2 boxes per month were more likely to have GERS than those with a higher

consumption. Again, if our theory of reverse causality is true, this may be explained by GERS inducing a reduced exposure to snus. One could argue that GERS induced by snus should disappear when quitting snus. However, individuals with GERS probably have several risk factors, including a genetic predisposition, but snus is maybe one factor which is recognizable as a trigger of GERS and probably easier to deal with than other risk factors. So, even if snus is stopped and this has an effect on GERS, it is unlikely that this would make all the complaints disappear. A previous study on this topic, the Kalixanda study, found histological changes associated with GERD in the mucosa of snus users, supporting an increased risk of GERS with snus use (21). However, the study did not find any link between snus consumption and GERS. If our findings are not caused by reverse causality, snus may indeed have a protective effect against GERS and this makes our results highly controversial. In this case, the protective effect of snus could be explained by increased saliva section in snus users (31), the relatively high pH (approximately 8.5) (8, 32) or other unknown effects of the snus contents on the esophageal or gastric mucosa, e.g. creating a barrier effect or reducing acid secretion, respectively. However, these protective effects would likely affect all age groups and cannot explain the reduced risk of GERS exclusively seen in the older snus users.

In conclusion, this study found that daily snus users overall had a reduced risk of GERS. However, subgroups of snus users had an increased risk of GERS and we propose that the overall result could be due to reverse causality and that snus use actually increases the risk of GERS. Further research is needed to conclude whether snus use is a risk factor for the development of GERS. A study combining a detailed questionnaire on reflux symptoms, anti-reflux medication and risk factors with objective investigations with endoscopy and pH-measurements may increase the evidence on this topic.

In 2017-2018, HUNT4 will be conducted and the same population as in HUNT3 will be re-invited to participate. This provides an excellent opportunity to follow snus users prospectively and to investigate further whether the reduced risk of GERS seen in this study is related to reverse causality or not.

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Declaration of interest

None

The present manuscript has not been published, simultaneously submitted or already accepted for publication elsewhere.

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Tables

Table I. Characteristics of individuals reporting severe GERS (cases) and no GERS (controls) in HUNT3/QNP, compared with the total population

	Cases with severe GERS HUNT3/QNP	**Controls with no GERS HUNT3/QNP**	**Total population HUNT3/QNP**
Number	2,993 (5.1%)	26,610 (45.4%)	58,634 (100%)
Age, years			
Mean (s.d.)	54.3 (15.0)	50.1 (16.3)	51.8 (16.4)
Median (range)	55 (19–98)	50 (19–102)	52 (19–102)
Sex			
Women, no. (%)	1,629 (54.4)	15,024 (56.5)	31,563 (53.8)
Men, no. (%)	1,364 (45.6)	11,586 (43.5)	27,071 (46.2)
Snus status			
Never, no. (%)	2,438 (81.5)	21,935 (82.4)	47,486 (81.0)
Previous, no. (%)	163 (5.5)	1,179 (4.4)	2,820 (4.8)
Occasionally, no. (%)	101 (3.4)	882 (3.3)	1,998 (3.4)
Daily, no. (%)	161 (5.4)	1,943 (7.3)	4,201 (7.2)
Missing, no. (%)	130 (4.3)	671 (2.5)	2,129 (3.6)

Age snus users, years			
Mean (s.d.)	43.4 (13.5)	41.8 (15.1)	42.3 (14.6)
Median (range)	43 (19–91)	41 (19–98)	42 (19–98)
Age starting with snus, years			
Mean (s.d.)	25 (12.3)	24.6 (11.5)	24.4 (11.6)
Median (range)	20 (7–70)	20 (8–80)	20 (7–80)
Missing, no. (%)	31 (8.3)	142 (4.8)	522 (7.0)
Snus consumption, boxes/month			
0, no. (%)	2,176 (72.7)	17,865 (67.1)	41,575 (70.9)
>0<2, no. (%)	47 (1.6)	342 (1.3)	838 (1.4)
≥2<8, no. (%)	215 (7.2)	1,811 (6.8)	4,479 (7.6)
≥8, no. (%)	70 (2.3)	488 (1.8)	1,333 (2.3)
Missing, no. (%)	485 (16.2)	6,104 (22.9)	10,409 (17.8)
Motivation to start using snus			
None, no. (%)	191 (51.3)	1,809 (61.6)	4,380 (58.3)
Quit smoking, no. (%)	101 (27.2)	596 (20.3)	1,664 (22.2)
Cut down on smoking, no. (%)	65 (17.5)	308 (10.5)	876 (11.7)
Missing, no. (%)	15 (4.0)	222 (7.6)	591 (7.9)
Tobacco type started with first			
Snus, no. (%)	72 (19.4)	694 (23.7)	1,748 (23.3)
Snus and cigarettes, no. (%)	13 (3.5)	73 (2.5)	209 (2.8)
Cigarettes, no. (%)	213 (57.3)	1,214 (41.4)	3,351 (44.6)

Missing, no. (%)	74 (19.9)	954 (33.0)	2,203 (29.3)
Smoking status			
Never smokers, no. (%)	977 (32.6)	12,351 (46.4)	24,521 (41.8)
Previous smokers, no. (%)	1,176 (39.3)	7,666 (28.8)	18,241 (31.1)
Current smokers, no. (%)	768 (25.7)	6,008 (22.6)	14,335 (24.5)
Missing, no. (%)	72 (2.4)	585 (2.2)	1,537 (2.6)
BMI, kg/m^2			
Mean (s.d.)	28.8 (4.5)	26.3 (4.2)	27 (4.4)
Median (range)	28 (14−51)	25.8 (12−55)	26.6 (12−56)
Missing, no. (%)	28 (0.9)	347 (1.3)	858 (1.5)
Physical exercise			
<Weekly, no. (%)	1,284 (42.9)	9,598 (36.1)	22,511 (38.4)
≥Weekly, no. (%)	1,426 (47.6)	15,372 (57.8)	31,737 (54.1)
Missing, no. (%)	283 (9.5)	1,640 (6.2)	4,386 (7.5)

Abbreviations: BMI, body mass index; GERS, gastroesophageal reflux symptoms (self-reported degree of complaints with heartburn or acid regurgitation during the previous 12 months); HUNT3/QNP, the third wave of the Nord-Trøndelag health study and the questionnaire to non-participants (2006–2009)

Table II. The odds ratio (95% confidence interval) of severe GERS compared with no GERS, by snus status (HUNT3/QNP) and snus consumption (HUNT3 only)

Snus status	**Unadjusted**	**Adjusted for age and sex**	**Fully adjusted**[a]
Never	Reference	Reference	Reference
Previous	1.24 (1.05−1.47)	1.33 (1.12−1.59)	1.20 (1.00−1.46)
Occasionally	1.03 (0.83−1.27)	1.23 (0.99−1.53)	1.21 (0.96−1.52)
Daily	0.75 (0.63−0.88)	0.84 (0.70−0.99)	0.77 (0.64−0.93)
Snus consumption, boxes/month			
0	Reference	Reference	Reference
<2	1.13 (0.83−1.54)	1.33 (0.98−1.82)	1.41 (1.02−1.96)
2−8	0.97 (0.84−1.13)	1.04 (0.89−1.21)	0.93 (0.78−1.10)
>8	1.18 (0.91−1.52)	1.34 (1.03−1.74)	1.16 (0.88−1.54)

a) Adjusted for age, sex, smoking status, BMI, and physical exercise

Abbreviations: BMI, body mass index; GERS, gastroesophageal reflux symptoms (self-reported degree of complaints with heartburn or acid regurgitation during the previous 12 months); HUNT3/QNP, the third wave of the Nord-Trøndelag health study and the questionnaire to non-participants (2006–2009)

Table III. The odds ratio (95% confidence interval) of severe GERS compared with no GERS, by age starting using snus, motivation to start with snus and type of tobacco started with first, in HUNT3

Age starting with snus	**Unadjusted**	**Adjusted for sex**	**Fully adjusted[a]**
<20	Reference	Reference	Reference
20–30	1.06 (0.80–1.39)	1.06 (0.81–1.40)	1.06 (0.78–1.44)
30–40	0.88 (0.61–1.29)	0.88 (0.60–1.28)	0.70 (0.45–1.07)
40–50	1.28 (0.87–1.89)	1.27 (0.86–1.87)	1.02 (0.66–1.56)
50–60	1.39 (0.83–2.32)	1.35 (0.81–2.26)	1.02 (0.59–1.79)
60-70	1.12 (0.44–2.90)	1.09 (0.42–2.82)	1.13 (0.42–3.00)
≥70	1.42 (0.17–1.90)	1.35 (0.16–11.30)	1.91 (0.22–17.01)
Motivation to start using snus	**Unadjusted**	**Adjusted for age and sex**	**Fully adjusted[b]**
None	Reference	Reference	Reference
Quit smoking	1.55 (1.20–1.99)	1.52 (1.17–1.98)	1.50 (1.13–1.99)
Cut down smoking	1.93 (1.42–2.61)	1.91 (1.40–2.59)	1.88 (1.35–2.61)
Type of tobacco started with first	**Unadjusted**	**Adjusted for age and sex**	**Fully adjusted[b]**
Snus	Reference	Reference	Reference
Snus and cigarettes	1.72 (0.91–3.25)	1.73 (0.92–3.28)	2.26 (1.17–4.35)
Cigarettes	1.77 (1.35–2.31)	1.72 (1.30–2.29)	1.76 (1.30–2.39)

a) Adjusted for sex, smoking status, BMI, and physical exercise

b) Adjusted for age, sex, BMI and physical exercise

Abbreviations: GERS, gastroesophageal reflux symptoms (self-reported degree of complaints with heartburn or acid regurgitation during the previous 12 months); HUNT3, the third wave of the Nord-Trøndelag health study (2006–2009)

Table IV. The odds ratio and (95% confidence interval) of severe GERS compared with no GERS among snus users, stratified by age and smoking status, in HUNT3/QNP

Age stratified	**Unadjusted**	**Adjusted for sex**	**Fully adjusted[a]**
<30	1.37 (0.99−1.90)	1.44 (1.02−2.03)	1.49 (1.02−2.16)
30<40	0.98 (0.70−1.37)	0.80 (0.56−1.13)	0.74 (0.50−1.08)
40<50	1.11 (0.87−1.42)	0.96 (0.75−1.25)	0.96 (0.72−1.26)
50<60	0.85 (0.64−1.14)	0.76 (0.56−1.02)	0.67 (0.49−0.93)
60<70	0.57 (0.34−0.95)	0.65 (0.39−1.10)	0.51 (0.28−0.94)
70<80	0.58 (0.27−1.26)	0.70 (0.32−1.55)	0.58 (0.23−1.46)
≥80	0.80 (0.24−2.66)	0.82 (0.25−2.76)	0.91 (0.21−4.03)
Stratified by smoking status	**Unadjusted**	**Adjusted for age and sex**	**Fully adjusted[b]**
Never	0.62 (0.47−0.83)	0.76 (0.57−1.03)	0.75 (0.54−1.03)
Previous	0.60 (0.48−0.75)	0.63 (0.50−0.80)	0.62 (0.48−0.79)
Occasionally	1.24 (0.90−1.71)	1.33 (0.93−1.92)	1.39 (0.94−2.04)
Daily	1.32 (0.9−1.80)	1.14 (0.82−1.59)	1.12 (0.78−1.61)

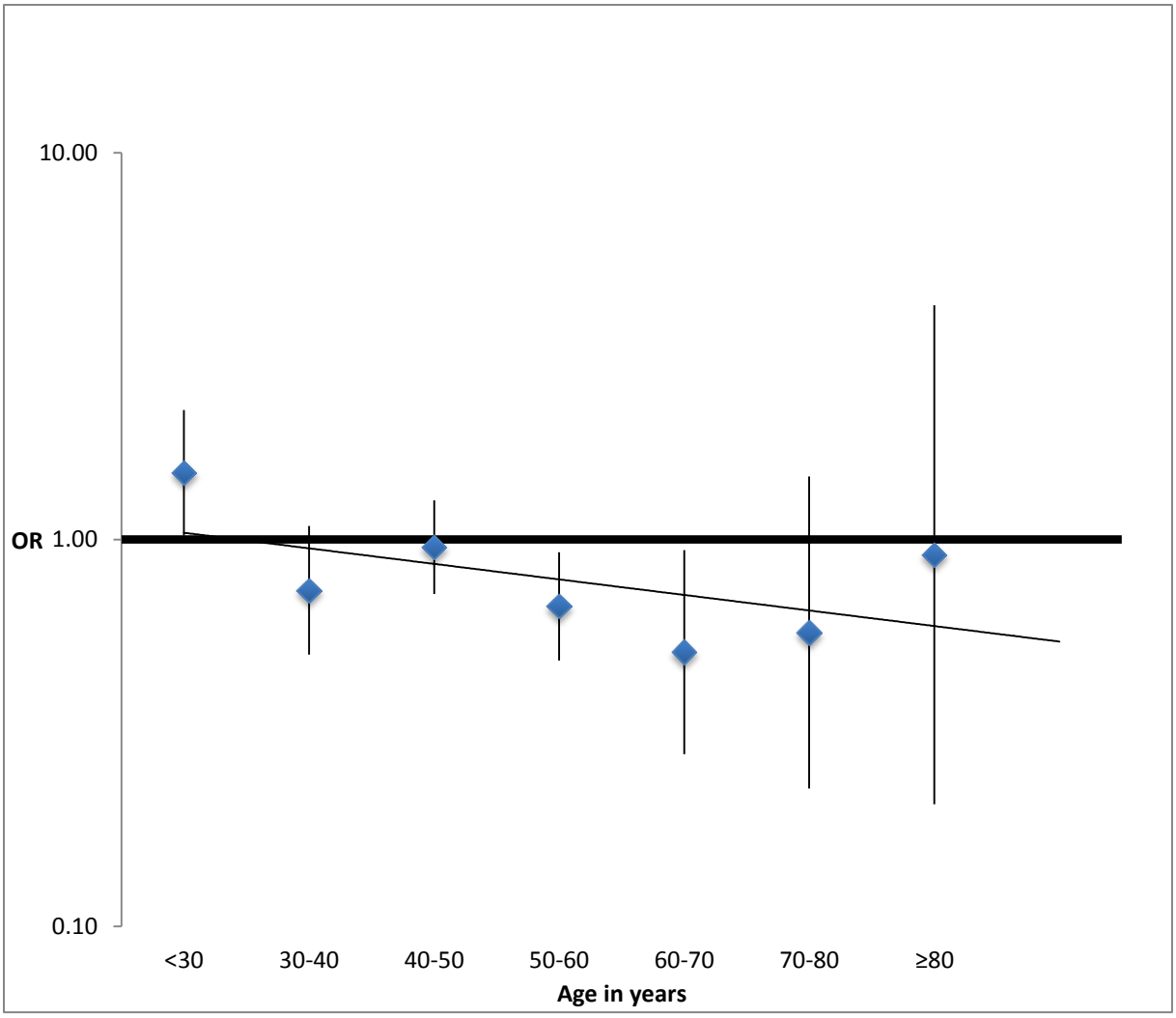
a) Adjusted for sex, smoking status, BMI, and physical exercise

b) Adjusted for age, sex, BMI, and physical exercise

Abbreviations: BMI, body mass index; GERS, gastroesophageal reflux symptoms (self-reported degree of complaints with heartburn or acid regurgitation during the previous 12 months); HUNT3/QNP, the third wave of the Nord-Trøndelag health study and the questionnaire to non-participants (2006–2009)

Figure legends

Figure. The odds ratio (OR) and 95% confidence interval (vertical lines) of severe gastroesophageal reflux symptoms (GERS; self-reported degree of complaints with heartburn or acid regurgitation during the previous 12 months) compared with no GERS among snus users in different age categories in the third wave of the Nord-Trøndelag health study (HUNT3) and the questionnaire to non-participants (QNP) performed 2006-2009. Adjusted for sex, smoking status, BMI, and physical exercise.


10.00
OR 1.00
0.10
<30
30-40
40-50
50-60
60-70
70-80
≥80
Age in years