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Smokeless tobacco (snus) and risk of heart failure: results from two Swedish cohorts

Gabriel Arefalk[1,*], Maria-Pia Hergens[2,*], Erik Ingelsson[1,2], Johan Ärnlöv[1,3], Karl Michaëlsson[1], Lars Lind[1], Weimin Ye[2], Olof Nyrén[2], Mats Lambe[2] and Johan Sundström[1]

Abstract

Background: Oral moist snuff (snus) is discussed as a safer alternative to smoking, and its use is increasing. Based on its documented effect on blood pressure, we hypothesized that use of snus increases the risk of heart failure.

Design: Two independent Swedish prospective cohorts; the Uppsala Longitudinal Study of Adult Men (ULSAM), a community-based sample of 1076 elderly men, and the Construction Workers Cohort (CWC), a sample of 118,425 never-smoking male construction workers.

Methods: Cox proportional hazards models were used to investigate possible associations of snus use with risk of a first hospitalization for heart failure.

Results: In ULSAM, 95 men were hospitalized for heart failure, during a median follow up of 8.9 years. In a model adjusted for established risk factors including past and present smoking exposure, current snus use was associated with a higher risk of heart failure [hazard ratio (HR) 2.08, 95% confidence interval (CI) 1.03–4.22] relative to non-use. Snus use was particularly associated with risk of non-ischaemic heart failure (HR 2.55, 95% CI 1.12–5.82). In CWC, 545 men were hospitalized for heart failure, during a median follow up of 18 years. In multivariable-adjusted models, current snus use was moderately associated with a higher risk of heart failure (HR 1.28, 95% CI 1.00–1.64) and non-ischaemic heart failure (HR 1.28, 95% CI 0.97–1.68) relative to never tobacco use.

Conclusion: Data from two independent cohorts suggest that use of snus may be associated with a higher risk of heart failure.

Keywords

Epidemiology, heart failure, risk factors, smokeless tobacco, snus

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Introduction

The use of oral moist snuff (snus), a form of smokeless tobacco, is increasing in Scandinavia and the USA. Today, about 20% of the Swedish male adult population are daily users of snus.[1] At present, the USA constitutes the world's largest snuff market, with an annual growth rate of more than 6% and with sales exceeding 1.2 billion cans in 2009.[2] The volume is projected to double in the next decade, but it may increase even faster in response to trends towards smoking bans in public places.[3] Long-term health effects of snus use have not been as thoroughly studied as for smoking.

Previous investigations regarding cardiovascular effects of smokeless tobacco have generally focused on risk for atherosclerotic events. Findings have been inconsistent regarding risk of myocardial infarction and stroke,[4,5] although an increased risk for fatal such events has been reported in a meta-analysis.[4] Smokeless administration of tobacco may indeed circumvent the atherogenic effects of smoked tobacco, but it is possible that the potent autonomic and haemodynamic effects of nicotine per se are detrimental for cardiovascular tissues. Smokeless tobacco increases

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epinephrine levels,[6] impairs endothelial function[7,8] and increases blood pressure and heart rate.[6,8–10] High blood pressure is the most important risk factor for heart failure,[11] a condition associated with considerable morbidity and mortality accounting for 1–2% of the total healthcare costs in industrialized countries.[12]

We hypothesized that use of smokeless tobacco (in the form of snus) increases the risk for subsequent heart failure, mainly of non-ischaemic origin and chiefly by increasing blood pressure and heart rate. Using two independent study samples, we examined possible associations between snus use and the risk of hospitalization for heart failure.

Methods

Study samples

Uppsala Longitudinal Study of Adult Men (ULSAM). In 1970–73, all 50-year-old men residing in Uppsala County in Central Sweden were invited to a health survey. Participation rate was 82% ($n = 2322$). At a re-investigation in 1991–95 at approximately age 71, the baseline of the present study, 73% of surviving men participated ($n = 1221$).[13] We excluded participants hospitalized for heart failure before baseline ($n = 14$) and those lacking information on smokeless tobacco use ($n = 131$), rendering a sample of 1076 individuals for the present study. In a secondary analysis, we excluded individuals who had suffered a myocardial infarction before baseline ($n = 81$), leaving 995 persons in this subsample.

Construction Workers Cohort (CWC). Preventive health check-ups were offered to all employees in the Swedish construction industry between 1969 and 1993 and about 75% of the employees participated. This cohort has been described previously.[14] The design of questions about tobacco habits used until 1975 was suboptimal and no information regarding tobacco use was collected between 1975 and 1977.[15] The study population of the present study was therefore restricted to subjects with visits from 1 January 1978 or later, and the first visit from this date defined the baseline. To avoid confounding from smoking, all former or current tobacco smokers were excluded. In total, 118,425 participants remained for the present study. The mean age at baseline was 31.5 years. In a secondary analysis, we excluded workers with a myocardial infarction prior to entry ($n = 310$), leaving 118,115 persons in this subsample.

Baseline examinations

ULSAM. Information on smokeless tobacco use was collected using a self-administered questionnaire including the questions: 'Do you use snus?' and 'How many tins of snus do you consume per week?' The baseline examination has been described in detail previously[13] and on the ULSAM study's website (www.pubcare.uu.se/ULSAM). Covariates are described in Supplementary Table 1.

CWC. Snus variables taken into account included amount (g/week), duration, and time since cessation. Ever snus use was defined as consumption of at least 1 g/day for at least 1 year. Tobacco information, blood pressure measurement, and body mass index were obtained at baseline.

In both cohorts, previous myocardial infarctions were defined using the Swedish Hospital Discharge Register (ICD-7 codes 420.10, 420.17; ICD-8 and 9 codes 410; ICD-10 codes I21 and I22).

Follow up and outcome measures

ULSAM. Follow up commenced at the examination at age 71 (in 1991–95) and continued until first hospitalization for heart failure, emigration, death, or 31 December 2002, whichever occurred first. Median follow-up time was 8.9 years, rendering in total 8370 person-years at risk (PYAR). The primary endpoint, first hospitalization for heart failure, was validated through chart review[16] using the definition proposed by the European Society of Cardiology.[17] The secondary endpoint was a first hospitalization for non-ischaemic heart failure. For the analyses of this endpoint, participants who had sustained a myocardial infarction before baseline were excluded and those who suffered a myocardial infarction during follow up were censored at time of this event.

CWC. Follow up was from baseline until the date of a first hospitalization for heart failure, death, relocation to a county with incomplete coverage by the Swedish Hospital Discharge Register, emigration, or 31 December 2003, whichever occurred first. Median follow-up time was 18 years, yielding more than 2 million PYAR. The primary outcome, first hospitalization for heart failure, was defined using the Swedish Hospital Discharge Register, with the following codes: ICD-7 434.1, 434.2, 440.99, 441.99; ICD-8 427.00, 427.10, 428.99; ICD-9 428; ICD-10 I50, I11.0. The secondary outcome was defined as in ULSAM. Only cases with heart failure as the main reason for hospitalization were considered, based on the experience of the chart review.[16]

Statistical analyses

Distributional properties were assessed. Associations between snus use and risk of heart failure were estimated

Table 1. Characteristics of participants in the Uppsala Longitudinal Study of Adult Men

Variable	Total sample ($n = 1076$)	Snus users ($n = 78$)	Snus non-users ($n = 998$)
Age (years)	71.0±0.6	71.0 ± 0.6	71.0 ± 0.6
Current smoking dose			
Non-smokers	839 (78.0)	16 (20.5)	823 (82.5)
Moderate smokers (≤10 cigarettes/day)	167 (15.5)	56 (71.8)	111 (11.1)
Heavy smokers (>10 cigarettes/day).	70 (6.5)	6 (7.7)	64 (6.4)
Pack-years of smoking			
Never smokers	335 (31.3)	5 (6.4)	330 (33.1)
Low exposure (<33 pack-years)	371 (34.5)	30 (38.5)	341 (34.2)
High exposure (≥33 pack-years)	370 (34.4)	43 (55.1)	327 (32.8)
Diabetes prevalence	188 (17.5)	17 (21.8)	171 (17.1)
ECG-left ventricular hypertrophy	79 (7.9)	7 (9.6)	72 (7.8)
Body mass index (kg/m^2)	26.2 (3.3)	26.9 (3.6)	26.2 (3.3)
Office systolic blood pressure (mmHg)	146.8 (18.6)	146.4 (19.2)	146.8 (18.6)
Antihypertensive medication use	372 (34.6)	23 (29.5)	349 (35.0)
Diurnal blood pressure			
24-h systolic blood pressure (mmHg)	132.8 ± 15.5	135.2 ± 14.7	132.7 ± 15.6
24-h diastolic blood pressure (mmHg)	75.1 ± 7.7	75.0 ± 7.0	75.1 ± 7.7
Daytime systolic blood pressure (mmHg)	140.1 ± 16.2	140.9 ± 15.2	140.0 ± 16.2
Daytime diastolic blood pressure (mmHg)	79.6 ± 8.6	78.8 ± 8.0	79.7 ± 8.6
Diurnal heart rates			
24-h heart rate (beats/min)	69.3 ± 10.1	71.1 ± 9.1	69.2 ± 10.2
Daytime heart rate (beats/min)	71.5 ± 10.7	73.1 ± 9.7	71.3 ± 10.7
Occupational classification			
High	190 (17.7)	3 (3.9)	187 (18.8)
Middle	412 (38.4)	21 (26.9)	391 (39.3)
Low	472 (44.0)	54 (69.2)	418 (42.0)
Alcohol use			
Teetotallers	196 (19.9)	16 (22.9)	180 (19.7)
Moderate users (<15 units/week)	750 (76.1)	48 (68.6)	702 (76.6)
Heavy users (≥15 units/week)	40 (4.1)	6 (8.8)	32 (3.8)
Myocardial infarction before baseline	81 (7.5)	2 (2.6)	79 (7.9)
Myocardial infarction during follow up	74 (6.9)	8 (10.3)	66 (6.6)

Values are mean ± standard deviations or *n* (%). ECG, electrocardiogram.

using Cox proportional hazards models. In order to minimize potential bias, the directed acyclic graph approach was used to identify suitable models. Models investigated are described in Supplementary Table 2. In addition; for ULSAM, the heart failure risks of snus use vs. smoking and the relative excess risk due to interaction (RERI) between snus use and smoking was investigated; and for CWC, a sensitivity analysis was performed (statistical descriptions and results are presented in Supplementary Table 3). Proportional hazard assumptions were confirmed graphically and by Schoenfeld's tests. Two-tailed significance values were given with $p < 0.05$ regarded as significant. All analyses were specified a priori and conducted using STATA 10.1 (College Station, USA) for ULSAM and SAS 9.1 (Cary, USA) for CWC.

Ethical approval

Participants gave informed consent and the studies, in accordance to the Declaration of Helsinki, were approved by the Regional Ethics Committees of Uppsala (ULSAM) and Umeå (CWC) Universities.

Results

ULSAM

Characteristics of the cohort are presented in Table 1. The median snus consumption among the users was 1 tin/week (range 0.5–7 tins/week).

Table 2. Risk of heart failure in snus users relative to snus non-users in the Uppsala Longitudinal Study of Adult Men ($n = 1076$)

Variable	Cases	Age-adjusted model (A)	Main model (B)	Mechanistic model (C)
Snus non-use	81	Ref	Ref	Ref
Snus use	14	2.42 (1.37–4.27)	2.08 (1.03–4.22)	2.09 (1.00–4.39)

Values are hazard ratio (95% confidence interval). Model A: age-adjusted. Model B: as model A and further adjusted for current smoking dose, pack-years of smoking, diabetes, body mass index, occupational classification, alcohol use, and myocardial infarction before baseline. Model C: as model B and further adjusted for office systolic blood pressure, antihypertensive medication use, electrocardiogram-left ventricular hypertrophy and replacing myocardial infarction before baseline with myocardial infarction during follow up (as a time-dependent covariate).

Table 3. Characteristics in the cohort of never-smoking male construction workers ($n = 118,425$)

Variable	Never tobacco users ($n = 83,705$)	Former snus users ($n = 2439$)	Current snus users ($n = 32,281$)
Age (years)	33.4±13.4	31.1 ± 10.1	26.7 ± 9.6
Body mass index (kg/m^2)	24.2 ± 3.1	24.2 ± 3.1	23.7 ± 3.1
Region of residence			
North	22,433 (26.8)	780 (32.0)	9620 (29.8)
Middle	43,610 (52.1)	1271 (52.1)	16,721 (51.8)
South	17,662 (21.1)	388 (15.9)	5940 (18.4)
Systolic blood pressure (mmHg)	131.1 ± 12.5	130.6 ± 12.5	129.3 ± 12.3
Diastolic blood pressure (mmHg)	78.3 ± 10.5	77.4 ± 9.8	75.9 ± 9.9
Myocardial infarction before baseline	156 (0.2)	2 (0.1)	24 (0.1)
Myocardial infarction during follow up	2133 (2.5)	18 (0.7)	252 (0.8)

Values are mean ± standard deviations or *n* (%).

During follow up, 95 of the 1076 men experienced a first hospitalization for heart failure. Age-adjusted incidence rate for heart failure among snus users was 229/10,000 person-years-at-risk (PYAR), and among non-users 97/10,000 PYAR. Cumulative incidence by snus use status is presented in Figure 1. Age-adjusted incidence rate for non-ischaemic heart failure among snus users was 209/10,000 PYAR, and among snus non-users 65/10,000 PYAR.

In the multivariable-adjusted main model B (Table 2), snus use was associated with a more than doubled risk for subsequent heart failure, relative to non-use. In secondary mechanistic analyses, adding office systolic blood pressure, antihypertensive medication, electrocardiogra (ECG)-left ventricular hypertrophy and myocardial infarction during follow up (as a time-dependent covariate) as covariates (Table 2, model C), snus use was still a significant predictor of heart failure. Replacing the office systolic blood pressure covariate with 24-h or daytime heart rates and systolic and diastolic blood pressures, estimates for snus use were attenuated [hazard ratio (HR) 1.98, 95% confidence interval (CI) 0.86–4.55] and 1.83, 0.80–4.23, respectively). When adjusting model C additionally for urinary albumin excretion rate, the HR for snus use was 2.43 (95% CI 1.14–5.17). When adjusting model C additionally for CRP, the risk associated with snus use was of borderline statistical significance (HR 1.99, 95% CI 0.94–4.22).

In the subsample without myocardial infarction before baseline, snus use was also associated with a significantly increased risk of non-ischaemic heart failure relative to non-use (HR 2.55, 95% CI 1.12–5.82; main model B, Supplementary Table 4a).

CWC

Baseline characteristics of the cohort are presented in Table 3. The mean snus consumption among current users was 22.5 g/day. During follow up, 545 workers were hospitalized with heart failure. Age-adjusted incidence rate for heart failure among current snus users was 3.5/10,000 PYAR and among never users of any tobacco 2.5/10,000 PYAR. Cumulative incidence by snus use status is presented in Figure 2. Age-adjusted incidence rate for non-ischaemic heart failure among current snus users was 4.0/10,000 PYAR and among never users of any tobacco 1.9/10,000 PYAR.

Current snus use was associated with a higher risk of heart failure relative to never users of any tobacco

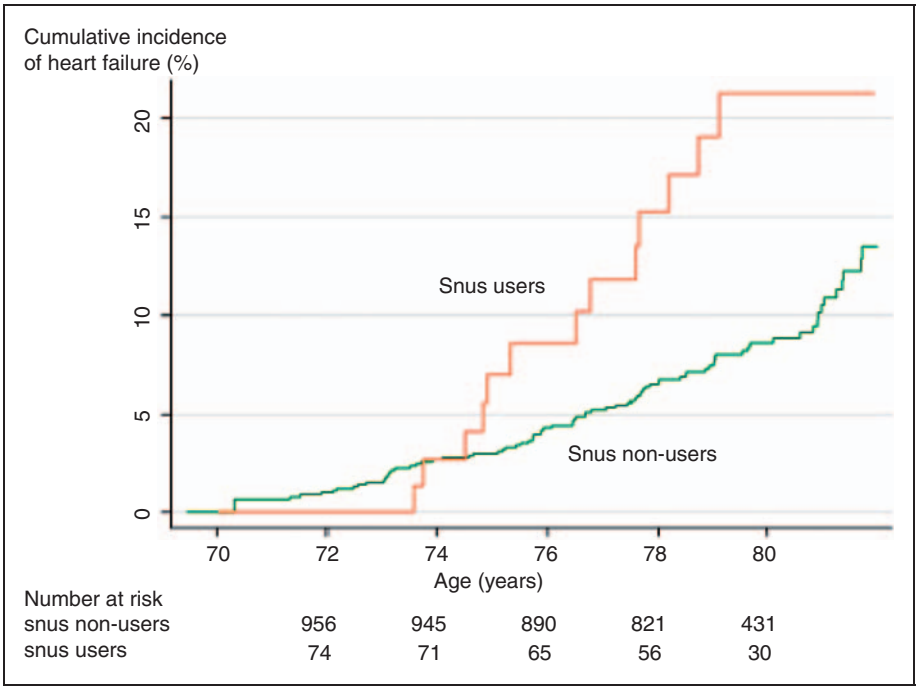

Figure 1. Cumulative incidence of heart failure among snus users and snus non-users in the Uppsala Longitudinal Study of Adult Men ($n = 1076$).

Table 4. Risk of heart failure by snus exposure categories among never-smoking male construction workers ($n = 118{,}425$)

Variable	Cases	Age-adjusted models (A)	Main model (B)	Mechanistic model (C)
Never tobacco use	464	Ref	Ref	Ref
Current snus use	75	1.35 (1.05–1.72)	1.28 (1.00–1.64)	1.24 (0.97–1.59)
<12.5 g/day	28	1.19 (0.81–1.74)	1.18 (0.80–1.73)	1.15 (0.78–1.68)
12.5–24.9 g/day	35	1.57 (1.11–2.21)	1.46 (1.03–2.06)	1.40 (0.99–1.98)
25–49.9 g/day	8	1.13 (0.56–2.27)	1.03 (0.51–2.08)	1.02 (0.50–2.06)
≥50 g/day	4	1.48 (0.55–3.98)	1.25 (0.47–3.84)	1.24 (0.46–3.34)
p trend		0.9	0.9	0.9
Former snus use	6	1.02 (0.46–2.29)	1.00 (0.45–2.23)	0.99 (0.44–2.22)

Values are hazard ratio (95% confidence interval). Models A: age-adjusted. Model B: as model A and further adjusted for body mass index, region of residence and myocardial infarction before baseline. Model C: as model B and further adjusted for systolic and diastolic blood pressures and replacing myocardial infarction before baseline with myocardial infarction during follow up (as a time-dependent covariate).

(Table 4, model A). Adjustment for body mass index, region of residence, and myocardial infarction before baseline rendered similar results (Table 4, model B). No clear dose–response relationship was observed among these current users (Table 4). Further adjustment for blood pressure and myocardial infarction during follow up attenuated hazard ratios marginally (Table 4, model C).

Current snus use was associated with a higher risk of non-ischaemic heart failure relative to never use in the age-adjusted model, (hazard ratio 1.38 [1.05–1.81]), but estimates were attenuated in the multivariable-adjusted main model B (hazard ratio 1.28 [0.97–1.68]) and the mechanistic model C (Supplementary Table 4b).

Discussion

Primary observations

In the population-based cohort of elderly men (ULSAM), use of oral moist snuff (snus) was associated with a more than doubled risk for subsequent heart failure of any kind as well as for non-ischaemic heart

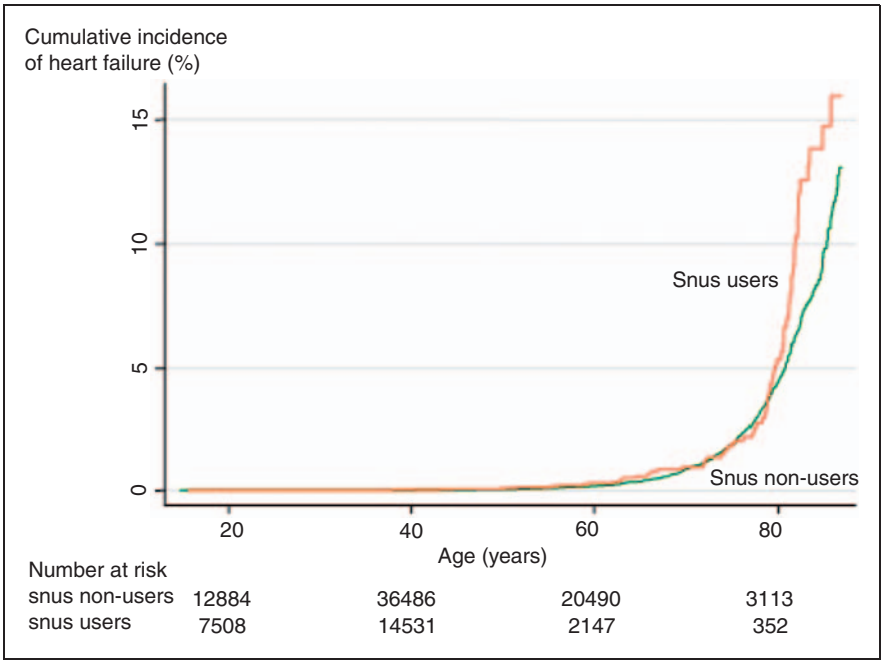

Figure 2. Cumulative incidence of heart failure among current snus users and never tobacco users in the cohort of never-smoking construction workers ($n = 118{,}425$).

failure. The data suggest that this risk may partly be mediated through haemodynamic effects.

In the much larger and younger cohort of never-smoking male construction workers, snus use was associated with an approximately 25–30% elevated risk of heart failure and non-ischaemic heart failure. This risk elevation was of borderline statistical significance and without any evident dose–risk trend.

The heart failure risk associated with snus use was higher in the ULSAM cohort than in the CWC cohort. The association in the general population may be lower than the point estimate obtained in ULSAM because of residual confounding of smoking and considering imprecision due to limited sample size. On the other hand, the association may be stronger than that observed in CWC because of non-differential misclassification of exposure due to potential change of snus using habits during the long follow up without updated exposure information.

Comparisons with previous studies

To our knowledge, no previous studies have examined possible associations between smokeless tobacco use and subsequent risk of heart failure. With only one exception,[18] no increase in risk of myocardial infarction incidence has been observed.[5,14,19–25] The risk of myocardial infarction mortality has been elevated in some studies, suggesting an increased case fatality, with a 13% increased risk in a recent meta-analysis.[4] Admittedly based on subsamples, the similar strength of associations observed in the present cohorts between snus use and both overall heart failure and non-ischaemic heart failure suggest that the snus-related risk to the myocardium goes beyond the potential link to coronary events. An increased risk of heart failure in combination with an increased case fatality rate after myocardial infarction in smokeless tobacco users may indicate direct detrimental effects of smokeless tobacco on the myocardium.

Potential mechanisms

The acute haemodynamic effects of smokeless tobacco include raised heart rate and elevated blood pressure.[6,8,9] The evidence regarding smokeless tobacco as a cause of sustained hypertension is limited, although some longitudinal data indicates that such an association may exist.[10] In ULSAM, hazard ratios for snus use were attenuated in models adjusting for ambulatory, particularly daytime, blood pressure, and heart rate. This may indicate that part of the effect of snus use on heart failure risk is mediated by diurnal changes in haemodynamic workload.

In addition to its haemodynamic effects, snuff has potent neurohormonal effects. Smokeless tobacco has been shown to increase epinephrine levels by 50%.[6] Experimentally, subhypertensive catecholamine (norepinephrine) doses may induce cardiac hypertrophy.[26] Because left ventricular hypertrophy is a predictor of

heart failure,[27] this suggests a possible link between snuff use and heart failure. In the ULSAM study, the association of snus use with heart failure risk was independent of ECG-left ventricular hypertrophy, but the sensitivity of ECG for detection of anatomical left ventricular hypertrophy is generally low.

Furthermore, acute snuff effects include impaired endothelial function, measured as flow-mediated vasodilatation.[7,8] The addition of urinary albumin excretion rate to ULSAM models (as a measure of vascular dysfunction, partly related to endothelial function) did not attenuate the risk estimate for snus use.

Smokeless tobacco also contains a certain amount of sodium chloride, which theoretically could lead to fluid retention, thus aggravating a latent heart failure. However, this risk has been considered small.[28]

Strengths and limitations

ULSAM. This prospective study is based on a well-characterized cohort. All the heart failure diagnoses have been validated, minimizing the risk of including false-positive cases.

The major limitation in ULSAM was that the non-smoking snus users were too few to study separately; we had to include men who smoked concomitantly. Smoking was adjusted for by using a current smoking dose variable as well as a pack-year variable. To exclude residual confounding by effects of recent smoking cessation, we performed a secondary analysis of models B, further subdividing former smokers into those who quit smoking less than vs. more than 10 years before baseline. Results were unaffected by this (data not shown). Nevertheless, as the majority of the exposed group in the present study was current or former smokers, residual confounding by smoking cannot be excluded despite thorough adjustment.

The limited sample size did not permit the study of dose–response relations. The cohort consists of elderly men of white Northern European descent and the interpretation should cautiously be extrapolated to women or other ethnic groups.

CWC. The size of the cohort and the high prevalence of exposure among the construction workers made it possible for us to restrict this sample to never-smoking men.

We only had information on daily smoking; relations of snus use to occasional or environmental smoking and subsequent smoking habits are somewhat unknown. In previous studies from this cohort, never-smoking snus users were more likely than never users of any tobacco to exhibit later indications of smoking,[15] but no excess risk of myocardial infarction or lung cancer has been observed.[14,29]

The lack of a dose–response effect is difficult to interpret; a few possible explanations merit consideration. Firstly, one explanation may be lack of power in the highest snus user groups. In the multivariable-adjusted model B, there is a strong association in moderate snus users (12.5–24.9 g/day), but not in minimal users (<12.5 g/day). The numbers of heavy snus users (25–49.9 g/day) and very heavy snus users (>50 g/day) were small and the mean ages were low. Heart failure is a diagnosis primarily of the elderly, and the present study population rendered only eight cases among heavy users and four cases among very heavy users. Secondly, it is also difficult to know whether the doses we chose for categorization really reflect the clinically important differences.

Although the restriction to construction workers should have limited the scope for confounding by socioeconomic status, we lacked information on other potential confounders such as alcohol consumption and diabetes.

Conclusions

In this study based on two independent Swedish cohorts, we observed an increased risk for subsequent heart failure among elderly male users of Swedish snus and a similar, but less pronounced association in a younger and larger cohort of never-smoking men. The ULSAM cohort provides solid control for a variety of confounding factors, but may hold a risk of overestimation of the risk in the general population (due to potential residual confounding of smoking). The CWC cohort adds statistical precision, but instead a risk of underestimation may be present (due to potential non-differential misclassification of exposure). Our findings need confirmation in future studies and underlying mechanisms remain to be elucidated.

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Conflict of interest

None declared.

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