

# Use of snus and risk for cardiovascular disease: results from the Swedish Twin Registry

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**Abstract.** Hansson J, Pedersen NL, Galanti MR, Andersson T, Ahlbom A, Hallqvist J, Magnusson C (Karolinska Institutet, Stockholm; Stockholm County Council, Stockholm; Uppsala University, Uppsala; Karolinska Institutet, Stockholm; and Uppsala University, Uppsala; Sweden). Use of snus and risk for cardiovascular disease: results from the Swedish Twin Registry. *J Intern Med* 2009; **265**: 717–724.

**Objective.** To study the association between snus use and the risk for cardiovascular disease, i.e. ischemic heart disease and stroke.

**Design.** Cohort study.

**Setting.** Sweden.

**Subjects.** Sixteen thousand six hundred and forty-two male Swedish twins participating in the Screening Across the Lifespan Twin Study, conducted in 1998–2002, were followed for incident cardiovascular disease. Participants were without a history of cardiovascular disease at baseline and incident cases were

identified via the Swedish Cause of Death Register and Hospital Discharge Register.

**Results.** Overall, there was no association between use of snus and risk for cardiovascular disease. Current snus users, without a smoking history, had a relative risk of 1.00 (95% confidence interval 0.69–1.46) for cardiovascular disease as compared to non users. Corresponding relative risks for ischemic heart disease and stroke were 0.85 (95% confidence interval 0.51–1.41) and 1.18 (95% confidence interval 0.67–2.08), respectively. In smoking adjusted models, risk estimates for ischemic heart disease in relation to snus use were all close to unity regardless of timing or intensity of snus use. However, current heavy snus users (consuming more than four cans week<sup>-1</sup>) had a relative risk for stroke of 1.75 (95% confidence interval 0.95–3.21).

**Conclusion.** These data do not support any strong association between snus use and risk for cardiovascular disease.

**Keywords:** cardiovascular disease, ischemic heart disease, smokeless tobacco, snus, stroke.

## Introduction

Snus, an oral moist smokeless tobacco product commonly used in Sweden, is evoking increasing public health interest and debate [1–6]. The interest is fuelled by the unique pattern of tobacco use in Sweden – with a smoking prevalence in accordance with the World Health Organisation's goal of <20% [7] and a

widespread use of snus [8]. It is estimated that 13% and 15% of Swedish men and women, respectively, are smokers, whilst 21% of men and 4% of women are snus users [8].

Despite the widespread use, there are still uncertainties regarding the cardiovascular effects of snus use [6, 9, 10]. It is plausible that snus use confers an

increased risk for cardiovascular disease (CVD), here defined as ischemic heart disease (IHD) and stroke, since a link between cigarette smoking and CVD is well established [11]. Nicotine, which is one of the known substances in cigarette smoke affecting the cardiovascular system, reaches blood levels amongst snus users that are at least as high as those amongst smokers [12, 13]. Further, snus use has been reported to have acute cardiovascular effects including increased blood pressure [12, 14] and heart rate [14].

The available data on the association between snus use and risk for CVD were recently summarized in a meta-analysis [9]. The author concluded that no clear risk from snus is seen, but that more studies are needed. Since then, results from updates of two cohort studies have been published. One demonstrated increased risks for fatal myocardial infarction [15] as well as stroke [16], whilst the other reported null associations with incident and fatal myocardial infarction [17].

Here, we report on the association between snus use and risk for CVD overall and for IHD and stroke separately, from a survey amongst Swedish male twins where tobacco use and established risk factors for CVD had been assessed in great detail.

## Methods

### *Study population*

The study population consisted of a subset of males from the Swedish Twin Registry, the participants in a telephone interview called Screening Across the Lifespan Twin Study (SALT). The Swedish Twin Registry was established in the 1950s to study health consequences of smoking and alcohol consumption and is now the largest population-based twin registry in the world. It has been described in detail previously [18, 19].

SALT was conducted in 1998–2002 and attempted the inclusion of all Swedish twins, born in 1958 or earlier, and hence aged 40 years or older at the time. We restricted our study population to twins born in

1926–1958, and amongst those 75% – including 18 331 men – completed the interview. Subjects were excluded from the analyses if they had register-identified CVD prior to study enrolment ( $n = 1499$ ) or incomplete information on tobacco exposure ( $n = 190$ ). Hence, the final analytical samples consisted of 16 642 male twins.

### *Data collection*

The telephone interview elicited information about health, lifestyle and social factors. Information on tobacco use was ascertained through the question 'Have you ever smoked or used snus?'. Subjects stated whether they were never, former or current snus users and/or smokers, including regular and occasional use, such as 'now and then' or 'at parties'. Information about age at onset, total duration and intensity of tobacco use was recorded. The participants also reported their height and weight, leisure time physical activity, alcohol consumption, level of education, whether they had been diagnosed with diabetes mellitus, if they had had their blood pressure and cholesterol levels measured by a health professional within the last five years and if so, whether these levels were abnormal.

### *Follow-up and ascertainment of outcome*

Cases were identified via record-linkage with the Hospital Discharge Register [20] and the Cause of Death Register [21] using the twins' personal identification number (PIN), a unique identifier assigned to all Swedish residents. The Hospital Discharge Register covers all public in-patient care in Sweden and includes information on date of admission and primary as well as secondary diagnoses coded according to the International Classification of Disease (ICD). Data from some Swedish regions are available since 1964 and the register has complete national coverage since 1987 with <1% of main diagnosis and PIN missing. The analyses included in this study were based on register updates up to, and including 2005. The Cause of Death Register covers all (<0.5% missing) deaths since 1961 and includes ICD-codes for main and underlying causes of death. At the time of

our analyses, the register was updated until the end of 2003.

We defined IHD as hospitalization or death caused by myocardial infarction or coronary revascularization procedures (ICD-10 codes I20-I21, I24-I25 [excluding I25.2]; and corresponding codes in ICD 9th and ICD 8th editions) and stroke as hospitalization or death caused by acute ischemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage, transient ischemic attack and unspecified cerebral haemorrhage (ICD-10 codes I60-I61, I63-I64, G45; ICD-9 codes 430-431, 433-436; and corresponding codes in ICD 8th editions). Both main and contributing discharge diagnoses were considered.

Participants contributed person-time from the date of interview until the date of CVD diagnosis, death or end of follow-up (December 31, 2005 for hospitalization and December 31, 2003 for mortality), whichever occurred first. Only the first registered event of either IHD or stroke was considered in the analyses of all CVD. When the two outcomes were assessed separately, follow-up was censored at the first registered event of the relevant outcome regardless of events of the other.

### Statistical analyses

Subjects were categorized as never, former or current regular user of snus and cigarettes, based on the interview items outlined above. Subjects were also grouped according to nine mutually exclusive patterns of tobacco use according to these dimensions.

Cox proportional hazard models were used to estimate relative risks (RR) and corresponding 95% confidence intervals (CI), with attained age as the time variable. All analyses included a frailty component to account for the dependence within twin pairs. Overall analyses of the association between snus use and risk for CVD were stratified by smoking status or adjusted for current and former smoking status. Established risk factors of CVD (including body mass index (BMI) [ $<25.0$ ,  $\geq 25.0$  kg m<sup>-2</sup>], leisure time physical activity [ $\leq$  much less exercise than average;  $\geq$  less exercise

than average], education [primary school, upper secondary school, university education] and alcohol consumption [0, 0.1–167,  $\geq 168$  g week<sup>-1</sup>) were considered as possible confounders. When analysing the subgroup for which information on these four potential confounders were available ( $n = 13\,269$ ) with and without enclosure of the covariates in the models, the relative risk for overall CVD amongst current snus users without a history of smoking changed from 0.97 to 0.95. Hence, these covariates were not included in the final models, to avoid the potentially greater ordeal of selection bias. A potentially mediating effect of diabetes mellitus, high blood pressure and high serum cholesterol in the association between snus use and risk was explored by the introduction of these variables as explanatory factors in a separate model. The statistical analyses were run using R 2.6.0 (R Development Core team, Vienna, Austria) [22] and the SAS Statistical software, version 9.1 (SAS Institute Inc., Cary, NC, USA)

### Results

The subjects were followed for an average period of 4.9 years and during the 80 775 person-years under observation 1119; 760 and 416 incident primary events of all CVD, IHD and stroke were identified respectively.

At baseline, 16.0% of the participants reported current snus use including 6.1% who had never smoked. Former snus use was reported by 8.8%. Further details of tobacco use and other characteristics of the study subjects according to snus use are given in Table 1. Current and former snus users were about 4 years younger than those who never used snus. Snus users had higher BMI than non users, although former snus users were more physically active than non users. Least active were current snus users who also consumed more alcohol and had more education than both former and never users of snus. A history of high serum cholesterol levels was more common amongst snus users than amongst non users, whilst the opposite was true for diabetes mellitus. High blood pressure was more often reported by current users than by non users and former users.

**Table 1** Baseline characteristics and details of follow-up according to snus use at recruitment

	Snus use			
	Never use	Former use	Current use	All
	( <i>n</i> = 12 525)	( <i>n</i> = 1456)	( <i>n</i> = 2661)	( <i>n</i> = 16 642)
Cardiovascular risk factors				
Mean age at recruitment (years)	56.9	53.5	52.5	55.9
Education, primary school (%)	31.0	32.7	26.3	31.0
History of high cholesterol <sup>a</sup> (%)	9.1	12.6	11.1	9.8
History of high blood pressure <sup>b</sup> (%)	9.8	9.5	10.2	9.9
History of diabetes mellitus <sup>c</sup> (%)	4.7	4.3	3.3	4.5
Mean body mass index (kg m <sup>-2</sup> )	25.5	26.0	25.8	25.6
Sedentary lifestyle <sup>d</sup> (%)	11.4	9.6	14.5	11.7
Mean alcohol consumption (standard drinks week <sup>-1</sup> )	6.2	7.3	8.7	6.7
Tobacco use				
Snus use				
Intensity				
≤4 cans week <sup>-1</sup>	—	81.7	77.0	78.5
>4 cans week <sup>-1</sup>	—	18.3	23.0	21.6
Duration				
Mean duration (years)	—	14.8	25.9	21.7
Cigarette smoking				
Current smoker (%)	19.8	10.9	10.5	17.5
Former smoker (%)	29.7	55.1	51.4	35.4
Intensity (cigarettes day <sup>-1</sup> ) <sup>e</sup>				
1–9	20.5	18.6	19.5	20.1
10–19	37.5	38.5	40.5	38.2
≥20	41.5	42.7	39.6	41.3
Duration				
Mean (years)	30.0	22.1	23.4	27.9
Follow-up				
Person-years of follow-up	62 090	6647	12 037	80 775
Incident cardiovascular disease ( <i>n</i> )	930	85	104	1119
Incident ischemic heart disease ( <i>n</i> )	630	60	70	760
Incident stroke ( <i>n</i> )	351	29	36	416

<sup>a</sup>Self-reported high cholesterol diagnosed by medical personnel within the last five years. <sup>b</sup>Self-reported high blood pressure diagnosed by medical personnel within the last five years. <sup>c</sup>Self-reported diabetes. <sup>d</sup>Self-reported leisure time activity as 'Almost never exercise' or 'Much less exercise than average'. <sup>e</sup>Amongst all smokers, current or past.

Table 2 shows the relationship between snus use and risk for CVD, IHD and stroke according to smoking status. There was no clear association between current or past snus use and risk for CVD overall, IHD or stroke amongst never smokers. After adjustment for histories of diabetes mellitus, high blood pressure and high serum cholesterol levels, the overall RR for CVD amongst exclusive current snus users was 1.00

(95% CI 0.69–1.46), as compared with subjects who never used tobacco. The corresponding RRs for IHD and stroke were 0.85 (95% CI 0.51–1.41) and 1.18 (95% CI 0.67–2.08).

In a secondary approach, we estimated the relationship between snus use and disease risk amongst all snus users regardless of smoking history, and with

**Table 2** Relative risk for cardiovascular disease in relation to smoking and snus use at recruitment

Tobacco exposure		All cardiovascular disease			Ischemic heart disease			Stroke		
Smoking	Snus use	<i>n</i>	RR <sup>a</sup> (95% CI)	RR <sup>b</sup> (95% CI)	<i>n</i>	RR <sup>a</sup> (95% CI)	RR <sup>b</sup> (95% CI)	<i>n</i>	RR <sup>a</sup> (95% CI)	RR <sup>b</sup> (95% CI)
Never	Never	382	Referent	Referent	246	Referent	Referent	155	Referent	Referent
	Former	19	1.23 (0.76–1.99)	1.21 (0.75–1.97)	11	1.10 (0.58–2.09)	1.07 (0.56–2.03)	8	1.38 (0.67–2.86)	1.35 (0.65–2.82)
	Current	32	1.01 (0.69–1.47)	1.00 (0.69–1.46)	18	0.85 (0.51–1.40)	0.85 (0.51–1.41)	14	1.20 (0.69–2.11)	1.18 (0.67–2.08)
Former	Never	318	1.21 (1.03–1.42)	1.17 (1.00–1.38)	229	1.38 (1.13–1.68)	1.34 (1.10–1.64)	115	1.05 (0.82–1.34)	1.01 (0.78–1.30)
	Former	55	1.50 (1.11–2.03)	1.44 (1.06–1.95)	41	1.71 (1.19–2.47)	1.65 (1.14–2.39)	17	1.17 (0.70–1.16)	1.12 (0.67–1.87)
	Current	58	1.06 (0.79–1.42)	1.04 (0.78–1.39)	43	1.23 (0.86–1.74)	1.22 (0.82–1.74)	17	0.80 (0.48–1.33)	0.77 (0.46–1.29)
Current	Never	230	1.83 (1.53–2.18)	1.86 (1.56–2.22)	155	1.93 (1.54–2.42)	1.99 (1.59–2.50)	81	1.56 (1.18–2.05)	1.61 (1.22–2.13)
	Former	11	1.87 (0.98–3.55)	1.82 (0.95–3.48)	8	2.11 (0.97–4.60)	2.18 (0.99–4.79)	4	1.67 (0.60–4.62)	1.65 (0.59–4.64)
	Current	14	1.55 (0.88–2.72)	1.51 (0.86–2.65)	9	1.53 (0.75–3.11)	1.50 (0.73–3.08)	5	1.47 (0.59–3.64)	1.45 (0.58–3.62)

<sup>a</sup>Adjusted for age. <sup>b</sup>Adjusted for age, diabetes mellitus, high blood pressure, high cholesterol.**Table 3** Relative risk for cardiovascular disease in relation to snus use at recruitment

	All cardiovascular disease				Ischemic heart disease				Stroke			
	RR	RR	RR		RR	RR	RR		RR	RR	RR	
Snus use	<i>n</i>	(95% CI) <sup>a</sup>	(95% CI) <sup>b</sup>	(95% CI) <sup>c</sup>	<i>n</i>	(95% CI) <sup>a</sup>	(95% CI) <sup>b</sup>	(95% CI) <sup>c</sup>	<i>n</i>	(95% CI) <sup>a</sup>	(95% CI) <sup>b</sup>	(95% CI) <sup>c</sup>
Never	930	Referent	Referent	Referent	630	Referent	Referent	Referent	351	Referent	Referent	Referent
Ever	189	1.01 (0.86–1.20)	1.02 (0.86–1.22)	1.02 (0.85–1.21)	130	1.01 (0.82–1.24)	0.99 (0.80–1.22)	0.98 (0.79–1.22)	65	0.99 (0.75–1.30)	1.03 (0.78–1.36)	1.01 (0.76–1.34)
Former	85	1.20 (0.95–1.53)	1.21 (0.95–1.54)	1.19 (0.93–1.51)	60	1.23 (0.92–1.64)	1.19 (0.88–1.60)	1.17 (0.87–1.58)	29	1.14 (0.78–1.69)	1.19 (0.80–1.76)	1.17 (0.78–1.74)
Current	104	0.89 (0.72–1.11)	0.91 (0.73–1.13)	0.91 (0.73–1.13)	70	0.87 (0.67–1.14)	0.86 (0.66–1.13)	0.86 (0.66–1.14)	36	0.89 (0.62–1.26)	0.93 (0.65–1.33)	0.91 (0.64–1.31)
Intensity												
≤4 cans week <sup>−1</sup>	79	0.84 (0.66–1.07)	0.85 (0.66–1.08)	0.85 (0.67–1.09)	55	0.84 (0.62–1.13)	0.83 (0.61–1.12)	0.84 (0.62–1.13)	24	0.72 (0.47–1.10)	0.75 (0.49–1.15)	0.75 (0.49–1.15)
>4 cans week <sup>−1</sup>	24	1.12 (0.73–1.71)	1.18 (0.77–1.81)	1.15 (0.75–1.77)	14	0.92 (0.52–1.62)	0.94 (0.53–1.66)	0.92 (0.52–1.63)	12	1.66 (0.92–3.02)	1.81 (0.99–3.29)	1.75 (0.95–3.21)
Duration												
<20 years	34	0.98 (0.69–1.40)	0.96 (0.67–1.39)	0.97 (0.67–1.40)	22	0.93 (0.59–1.46)	0.86 (0.54–1.36)	0.87 (0.55–1.38)	13	1.06 (0.60–1.87)	1.11 (0.63–1.98)	1.13 (0.63–2.01)
≥20 years	68	0.84 (0.65–1.09)	0.87 (0.67–1.13)	0.87 (0.67–1.13)	47	0.83 (0.60–1.15)	0.85 (0.62–1.17)	0.85 (0.62–1.18)	22	0.77 (0.50–1.21)	0.81 (0.52–1.27)	0.80 (0.51–1.25)

<sup>a</sup>Adjusted for age. <sup>b</sup>Adjusted for age, and smoking status (former or current). <sup>c</sup>Adjusted for age, smoking status (former or current), diabetes mellitus, high blood pressure, and high cholesterol.

adjustment for smoking status and potentially mediating factors (diabetes mellitus, high blood pressure, high serum cholesterol) (Table 3). The risks for CVD overall, IHD and stroke, in men who were current or former users of snus, did not differ materially from those in men who had never used snus. In the fully adjusted model, the RR for CVD amongst current as compared to never users of snus was 0.91 (95% CI 0.73–1.13), whilst RRs for IHD and stroke were 0.86 (95% CI 0.66–1.14) and 0.91 (95% CI 0.64–1.31) respectively.

Light as well as heavy use of snus appeared unrelated to risk for IHD (Table 3). However, current snus users who reported a consumption of more than four cans week<sup>-1</sup> (3.7% of the study population) had a seemingly increased risk for stroke (RR 1.75, 95% CI 0.95–3.21) as compared to never users in the full model, based on 12 exposed cases. There was no trend in risk for either CVD, IHD or stroke with duration of snus use and the overall RR for CVD amongst long-term current users was 0.87 (95% CI 0.67–1.13) as compared to never users.

## Discussion

We found no clear evidence of an association between snus use and risk for CVD in these data from the Swedish Twin Registry. We had access to recently attained and detailed information on tobacco use and were able to consider established risk factors for CVD as potential confounders. The results contribute to the limited available evidence regarding the impact of snus use on cardiovascular health and are in agreement with those from prior studies [9, 15, 17, 23]. In 2007, a meta-analysis [9], financially supported by the tobacco industry, of the five available studies on snus and risk for CVD, including 306 events of IHD amongst nonsmoking snus users, demonstrated a RR for IHD of 1.06 (95% CI 0.83–1.37). The corresponding result for stroke (based on the two available studies and 60 exposed cases), was 1.17 (95% CI 0.80–1.70). Recent updates from the Swedish Construction Workers Cohort presented some evidence of increased risks for fatal – but not incident – myocardial infarction [15] and stroke [16], in line with

prior findings from that cohort [24]. However, in an update of the MONICA-study, a null association with incident as well as fatal myocardial infarctions [17], was presented.

We found an indication of an increased risk for stroke, but not IHD, amongst current snus users who consumed more than four cans of snus per week (based on 12 exposed cases). Even if this excess risk appears biologically possible in the light of the effects of nicotine on the cardiovascular system [11], it should be interpreted with caution, since moderate use and increasing duration did not indicate any consistent pattern of risk. As far as we know this dose–response relationship has not been investigated earlier for stroke. However, two previous studies have presented data on the dose–response relationship between snus use and myocardial infarction [15, 25]. In one study, an increased risk for fatal myocardial infarction (RR 1.96, 95% CI 1.08–3.58) was seen not only amongst heavy users (use of  $\geq 50$  g day<sup>-1</sup>), but also amongst light users (use of  $<12.5$  g day<sup>-1</sup>) (RR 1.45, 95% CI 1.09–1.93). However, no risk increase was seen with moderate use [15]. The other study found no increased risk for overall myocardial infarction amongst light ( $\leq 1$  cans week<sup>-1</sup>) or heavy users ( $\geq 2$  cans week<sup>-1</sup>) [25].

Nicotine exposure, and therefore snus use, may be implicated in CVD pathogenesis. Nicotine has acute sympathoexcitatory effects, resulting in increased heart rate and vasomotor tone [26]. Furthermore, nicotine is thought to induce endothelial oxidative and inflammatory stress [26]. The few available studies of snus use and atherosclerosis – a central feature of CVD [11] – and atherosclerotic markers are, however, cross-sectional and have yielded conflicting results [27–29]. Studies on the effect of snus use and risk for high blood pressure and hypertension, a major risk factor for stroke in particular [11], have also yielded contradicting results. One cohort study found a moderate association between snus use and risk for hypertension as well as high blood pressure [30], whilst an other cohort study found no increased risk for hypertension amongst snus users [31]. Further, elevated blood pressure amongst snus users was found in a



cross-sectional study [32] and an association between snus use and hypertension was found in an analysis of controls in a case-control study [33]. Yet, three cross-sectional studies found no increased risk for high blood pressure [12, 13, 34].

Although this study is not truly population-based, but restricted to twins, we judge its external validity to be high as it is unlikely that the biological effects of tobacco use are different for twins than for the general population. Regrettably, analyses were restricted to men since snus use was uncommon amongst women (prevalence  $\approx 1\%$ ). We were not able to address the relationship between snus use and fatal CVD, because of the low number of cardiovascular deaths. Furthermore, the Hospital Discharge Register was not complete until 1987 and thus, the prevalent cases of CVD, which occurred in earlier years, may have been overlooked and not excluded from the analyses. Even so, this misclassification of outcome is nondifferential with regard to snus use. The resulting bias, if any, will be towards the null, i.e. causing an underestimation of the risk amongst snus users. Strengths of our study include the prospective design and the detailed as well as up-to-date information on tobacco use and potential confounding and mediating factors. Furthermore, we could reproduce established associations between smoking and risk for CVD (Table 2), vouching for the validity of our data. Smoking is a strong risk factor for CVD and a potentially important confounder of the relationship between snus use on risk for such disease. Therefore, we restricted our primary analyses to never smokers. Nevertheless, the resulting estimates did not differ materially from smoking-adjusted results obtained from the full dataset. Exploratory analyses of dose-response associations were consequently conducted amongst all subjects to maximize statistical power.

In conclusion, these data from the Swedish Twin Registry do not support any strong association between snus use and incidence of IHD, stroke or CVD overall. Further studies addressing cardiovascular effects, especially cardiovascular mortality and risk for stroke in relation to snus use are needed.

## Conflict of interest statement

No conflicts of interest to declare.

## Acknowledgements

This study was funded by grants from The Swedish Research Council (grant no:2007-3185).

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