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Smokeless tobacco (snus) is associated with an increased risk of type 2 diabetes: results from five pooled cohorts

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Abstract. Carlsson S, Andersson T, Araghi M, Galanti R, Lager A, Lundberg M, Nilsson P, Norberg M, Pedersen NL, Trolle-Lagerros Y, Magnusson C (Karolinska Institutet; Stockholm County Council; Stockholm; Skåne University Hospital, Malmö; Umeå University, Umeå; Sweden). Smokeless tobacco (snus) is associated with an increased risk of type 2 diabetes: results from five pooled cohorts. *J Intern Med* 2017; **281**: 398–406.

Background. Smoking and nicotine exposure increase insulin resistance and the risk of type 2 diabetes. Swedish smokeless tobacco (snus) is high in nicotine, and its use is prevalent in Scandinavian countries, but few studies have investigated snus use in relation to diabetes risk.

Objective. To explore the association between snus use and risk of type 2 diabetes using pooled data from five cohorts.

Methods. Analyses were based on prospective studies conducted between 1990 and 2013 including 54 531 never-smoking men and 2441 incident cases of type 2 diabetes identified through screening, self-reporting and hospital and prescription registries. Hazard ratios (HRs) and 95% confidence intervals (CIs) were assessed and adjusted for age, body mass index, educational level, alcohol consumption and physical activity.

Results. Compared to never users, the HR of type 2 diabetes was 1.15 (95% CI: 1.00–1.32) in current users of snus. In individuals consuming 5–6 boxes per week, the HR was 1.42 (95% CI: 1.07–1.87); in those consuming ≥7 boxes per week, the HR was 1.68 (95% CI: 1.17–2.41). Each additional box of snus consumed per week yielded an HR of 1.08 (95% CI: 1.01–1.16).

Conclusion. Our findings indicate that high consumption of snus is a risk factor for type 2 diabetes. The risk was similar to that in smokers, implying that smokers will not reduce their risk of type 2 diabetes by changing to snus use. The results also support the notion that nicotine increases the risk of type 2 diabetes.

Keywords: meta-analysis, public health, tobacco, type 2 diabetes.

Introduction

Snus is a Swedish smokeless tobacco product that is commonly used in Scandinavia, and 11% of the Swedish population are daily users [1]. It is high in nicotine, but the content of other potentially toxic compounds including nitrosamines is low compared to cigarettes and to other smokeless tobacco products [2, 3]. The sale of snus is banned in the European Union, but Swedish snus is sold in the USA and consumption is also high in Norway. Snus is arguably a less harmful tobacco product than cigarettes [4] as its association with cardiovascular disease and cancer is much weaker [5–9]. However, few studies have investigated its influence on diabetes risk.

Smoking is a well-known risk factor for type 2 diabetes [10]. The association has been attributed to smoking/nicotine-induced insulin resistance [11, 12], but increased systemic inflammation [13] and adverse effects on pancreatic tissue and β-cell function may also contribute to the excess risk [14]. Snus provides similar or even higher nicotine exposure than cigarettes and hence may be a potent promoter of insulin resistance [15].

Results of studies to date are inconclusive; findings from two small studies based on the Stockholm Diabetes Prevention Programme indicated an increased risk of type 2 diabetes in snus users [16, 17]. By contrast, no association was found in the Swedish MONICA study or in a recent analysis based on two Scandinavian studies in which only never smokers were included, thereby minimizing confounding due to smoking [18, 19]. Despite the latter being the largest study to date including >700 cases, numbers of high consumers were small and therefore risk estimates unstable. There is thus a clear need for additional studies.

To clarify the association between snus use and diabetes risk, we took advantage of a large Swedish pooling project with data from five prospective studies with more than three times more cases than in previous studies. We investigated the risk of type 2 diabetes in relation to the amount and duration of snus use among never-smoking men. This is important given that use of smokeless tobacco is prevalent and increasing in Scandinavia as well as in the USA [20–23]. In addition, such clarification will further our understanding of the health effects of nicotine *per se*, with implications also for users of e-cigarettes [24].

Materials and methods

Study population

We used individual participant data from five Swedish cohort studies conducted between 1991 and 2013: three population-based studies, the Västerbotten Intervention Programme [25], the Stockholm Public Health Cohort [26] and the Malmö Diet and Cancer Study [27]; a study including participants in a national fundraising event, the National March Cohort [28]; and a national twin study, the Screening Across the Lifespan Twin study (SALT) [29]. We restricted the study population to male never smokers, because snus use is rare in women and to minimize confounding from smoking. After exclusion of prevalent cases of diabetes at baseline ($n = 2388$), our sample for analysis included 54 531 never-smoking men. An overview of the included studies is shown in Table 1. The current project was approved by the Stockholm Regional Ethics Review Board (registration number 2009/971-31/3).

Assessment of tobacco use and potential confounders

Information on tobacco use was collected by questionnaire in all studies, except in SALT in which telephone interviews were used. Individuals were classified as never, former and current users, and current users were categorized according to number of boxes consumed per week and duration of snus use. Information on the amount of snus used was available in all studies (although only for the participants in the 2010 subcohort of the Stockholm Public Health Cohort) except the National March Cohort, and information on duration of use was recorded in all studies except the Malmö Diet and Cancer Study. In addition, the Malmö Diet and Cancer Study did not obtain information on previous use; hence, any former users were included in the reference category of never users. Two of the studies, the Västerbotten Intervention Programme and Stockholm Public Health Cohort, included repeated assessment of tobacco habits and body mass index (BMI) during follow-up. Baseline information on education, alcohol consumption, physical activity and BMI used to control for confounding was primarily obtained by self-report, but the Stockholm Public Health Cohort included registry data on education and anthropometric measurements that were available for calculation of BMI in the Västerbotten Intervention Programme and the Malmö Diet and Cancer Study. Categorization of variables is shown in Table S1.

Identification of diabetes cases

We used all available information collected within each study to identify prevalent diabetes at baseline and incident diabetes during follow-up. Diagnoses of type 2 diabetes were thus identified using several sources and dated according to the first available record. First, registered diagnoses from hospital admissions since 1987 and outpatient specialist care since 2001 were obtained in all studies by record linkage to the National Patient Register, using the unique personal identification number assigned to all Swedish residents. This registry contains information on primary and additional diagnoses coded according to the Swedish version of the International Classification of Disease ninth revision (ICD-9) from 1986 to 1996 (code 250 for diabetes) and ICD-10 thereafter (code E11 for type 2 diabetes and E14 for unspecified diabetes) [30]. Secondly, prescriptions for glucose-lowering drugs were retrieved for all studies from

Table 1 *Information about the included Swedish cohorts*

	Västerbotten Intervention Programme	Stockholm Public Health Cohort	SALT	Malmö Diet and Cancer Study	National March Cohort	Pooled
Study population	Population-based, Västerbotten County	Population-based, Stockholm County	Twins born in Sweden 1926–1958	Population-based, City of Malmö	Participants in national fundraising event	
No. of participants	22 681	14 519	7498	2944	6889	54 531
Mean age at baseline (years)	45	49	56	59	49	49
Baseline	1992–2013	2002–2010	1998–2002	1991–1996	1997	
End of follow-up	2013	2012	2010	2012	2010	
Mean follow-up (years)	11.6	5.6	9.8	16.3	12.7	10.3
No. of person-years	264 924	86 310	77 348	49 848	72 173	550 603
Current snus users (%)	17	13	13	2	6	13
Additional snus information						
Duration	X	X (for subset)	X		X	
Amount	X	X (for subset)	X	X		
Former users	X	X	X		X	
Identification of diabetes cases	Screening, self-report, national prescription and patient registry	Self-report, national prescription and patient registry	Self-report (baseline), national prescription and patient registry	Self-report and local, national diabetes, prescription and patient registries	Self-report (baseline only), national prescription and patient registries	
No. of incident cases	1033	237	405	461	305	2441
Weight in pooled analysis	0.66	0.11	0.17	0.04	0.03	

SALT, Screening Across the Lifespan Twin study; X, information was available.

the Prescribed Drug Register [31]. This is a national registry that records all prescriptions since July 2005, according to the Anatomical Therapeutic Chemical (ATC) classification system. ATC group A10 (insulin and oral antidiabetic drugs) was used to identify diabetes. Thirdly, all studies included information on self-reported diabetes at baseline, as well as during follow-up in three studies (Västerbotten Intervention Programme, Stockholm Public Health Cohort and Malmö Diet and Cancer Study). Fourthly, participants from two studies (Västerbotten Intervention Programme and Malmö Diet and Cancer Study) underwent screening with oral glucose tolerance tests at baseline and during follow-up, and individuals with 2-h glucose levels ≥12.2 mmol L^{-1} (capillary blood) were classified as having diabetes as stipulated by the World Health Organization. Finally, the Malmö Diet and Cancer Study obtained information from a local diabetes registry and the National Diabetes Register, both of which were used to identify cases [32]. To distinguish between type 2 diabetes and type 1 diabetes, we excluded all cases occurring before 35 years of age and those with a recorded diagnosis of type 1 diabetes according the patient registries.

Statistical analysis

Study-specific hazard ratios (HRs) and their corresponding confidence intervals (CIs) for the association between snus use and type 2 diabetes were assessed by discrete proportional hazard regression and adjusted for age, calendar time, BMI, physical activity, education and alcohol consumption [33, 34]. Age and calendar time in years were combined into a categorical variable to account for both age and the fact that assessment of diabetes changed during follow-up (primarily because of the introduction of the Prescribed Drug Register in 2005).

Person-time was assessed from the date of baseline to the date of censoring or diagnosis based on (i) first recording in the National Prescribed Drug Register, inpatient or outpatient registries, (ii) self-reported diabetes by questionnaire or (iii) screening-detected diabetes, or the end of follow-up, whichever came first. Interaction terms for snus and the timescale variables age and calendar time were nonsignificant ($P > 0.2$), indicating that the assumption of proportional hazards was not violated. Study-specific HRs were calculated and pooled using the inverse variance method [35]. We estimated the fraction of cases attributable to snus use by scoring the fully adjusted model using the original data, but with the exposed set as unexposed.

Results

Characteristics

A total of 54 531 men were included in this study of whom 2441 developed diabetes over 556 777 person-years; this corresponds to an incidence of 4.4 per 1000. Of the incident cases, the first registration was by self-report, through screening and from the prescription, inpatient and outpatient registries for 8%, 3%, 59%, 19% and 10%, respectively. Mean age at baseline was 49 years, and the average follow-up period was 10 years. The prevalence of snus use was 13% in the pooled cohort; the rate was highest in the Västerbotten Intervention Programme (17%) and lowest in the Malmö Diet and Cancer Study (2%) (Table 1). Mean consumption among current users was four boxes of snus per week, and 31% of users consumed >4 boxes per week. Snus use tended to be more prevalent in individuals with high alcohol consumption, high BMI, young age and secondary school education (Table S1). No clear association was seen between snus use and physical activity level. The HRs of diabetes in relation to age, BMI, physical activity, education and alcohol consumption are shown in Table S2.

Snus use and the risk of type 2 diabetes

Overall, current snus users tended to have an increased risk of diabetes (pooled HR 1.15, 95% CI: 1.00–1.32), in contrast to former users (pooled HR 0.86, 95% CI: 0.71–1.05) (Fig. 1). A clear indication of an excess risk was only seen in the Västerbotten Intervention Programme, but CIs in the other studies were wide. Heterogeneity expressed as I^2 was 37%, indicating low–moderate heterogeneity across studies. Analyses of the dose–response relationship indicated that the risk was increased from consumption levels above four boxes per week and at consumption levels of ≥7 boxes per week, estimated HR was 1.68 (95% CI: 1.17–2.41) (Fig. 2). Tendencies towards increased risks in the highest consumption group (≥7 boxes per week) were seen in all studies (Table 2). In snus users, each additional box of snus consumed per week yielded an HR of 1.08 (95% CI: 1.01–1.16). There was no clear association between duration of snus use and the risk of type 2 diabetes (Table 2), possibly reflecting a lower absolute risk of diabetes

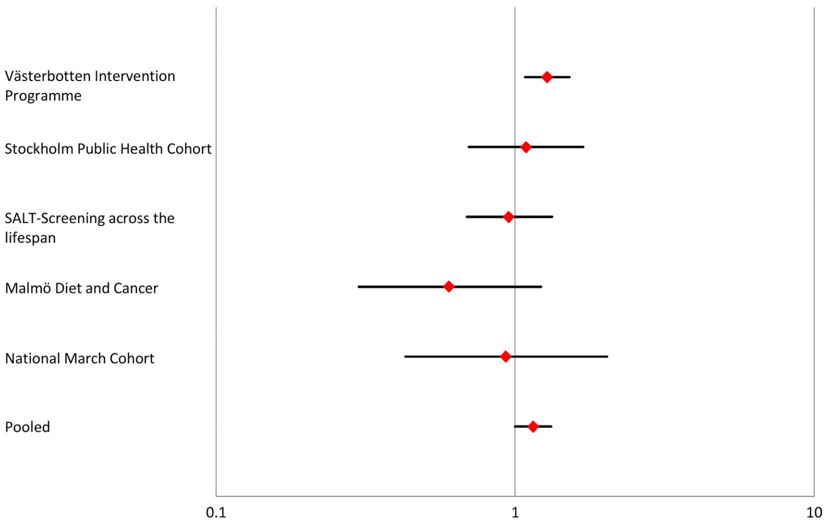

Fig. 1 *Current snus use and risk of type 2 diabetes. Study-specific and pooled hazard ratios and 95% confidence intervals.*

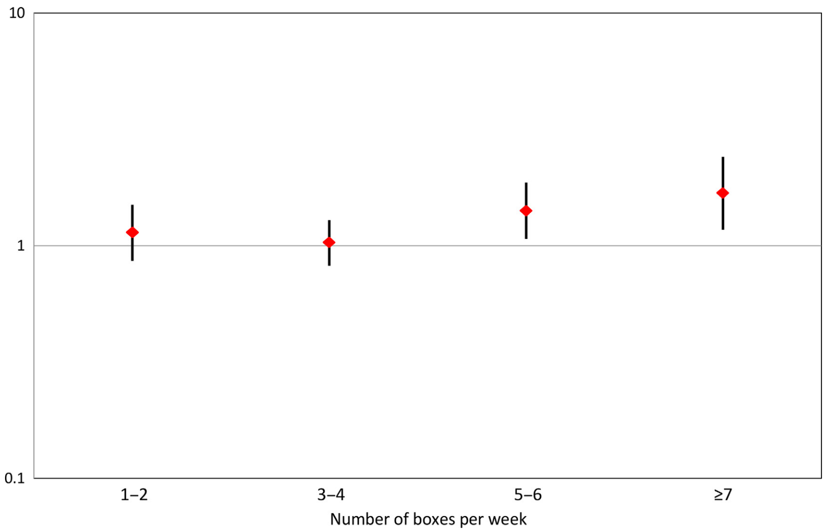

Fig. 2 *Number of boxes of snus consumed per week and risk of type 2 diabetes. Pooled hazard ratios and 95% confidence intervals.*

in younger individuals (who also have shorter duration of disease), leading to higher HRs in the short-duration group. From the calculation of attributable fractions, it appeared that, under the assumption of a causal effect and no measurement error, 13% of all cases of type 2 diabetes among the snus users could be attributed to snus use.

Sensitivity analyses were performed based on data from the Västerbotten Intervention Programme. First, we adjusted the HRs for family history of diabetes, but this had minor influence: HR 1.80, 95% CI: 1.15–2.83 in high (≥7 boxes per week) consumers. We then excluded all individuals in this study who were prescribed insulin during the first year following diabetes diagnosis in an attempt to exclude any remaining individuals with type 1 diabetes. This was performed for the period in which we had access to data from the prescription registry, that is 2006–2013, and again, the HRs were virtually unchanged: HR 1.75, 95% CI: 1.03–2.99 in high consumers.

Discussion

Findings from this large pooling project indicate that a high consumption of snus increases the risk of type 2 diabetes. In fact, our calculation of the

Table 2 *Snus use and risk of type 2 diabetes: study-specific and pooled results*

	Västerbotten Intervention Programme		Stockholm Public Health Cohort[a]		SALT		Malmö Diet and Cancer Study[b]		National March Cohort[c]		Pooled	
	Cases/ person-years	HR (95% CI)	Cases/ person-years	HR (95% CI)	Cases/ person-years	HR (95% CI)	Cases/ person-years	HR (95% CI)	Cases/ person-years	HR (95% CI)	Cases/ person-years	HR (95% CI)
Snus use												
Never	794/200 493	Reference	193/68 502	Reference	349/63 166	Reference	453/48 743	Reference	286/64 751	Reference	2075/445 655	Reference
Current	165/41 029	1.28 (1.08–1.52)	25/11 060	1.09 (0.70–1.69)	43/9469	0.95 (0.69–1.33)	8/1105	0.60 (0.30–1.22)	7/3104	0.93 (0.43–2.03)	248/65 767	1.15 (1.00–1.32)
Former	74/23 402	0.84 (0.66–1.07)	19/6748	1.10 (0.67–1.78)	13/4713	0.66 (0.38–1.16)			12/4318	0.94 (0.51–1.71)	118/39 181	0.86 (0.71–1.05)
Number of boxes per week (current users only)												
1–2	40/10 916	1.12 (0.81–1.54)	0/277	–	11/1792	1.17 (0.64–2.15)	3/265	1.19 (0.37–3.78)			54/12 973	1.14 (0.86–1.50)
3–4	60/16 859	1.17 (0.89–1.52)	3/1153	1.50 (0.45–5.00)	18/5363	0.74 (0.45–1.20)	2/432	0.32 (0.08–1.28)			83/23 807	1.03 (0.82–1.29)
5–6	45/10 007	1.48 (1.09–2.02)	2/520	2.62 (0.62–11.02)	5/1142	1.02 (0.42–2.50)	2/268	0.71 (0.17–2.89)			54/11 937	1.42 (1.07–1.87)
≥7	20/3247	1.79 (1.14–2.80)	1/417	1.50 (0.20–11.28)	9/1129	1.51 (0.76–2.98)	1/58	1.30 (0.18–9.39)			31/4851	1.68 (1.17–2.41)
1–4	100/27 775	1.15 (0.93–1.42)	3/1430	1.15 (0.35–3.81)	29/7155	0.86 (0.58–1.27)	5/697	0.56 (0.23–1.37)			137/37 057	1.08 (0.90–1.29)
≥4	65/13 254	1.56 (1.20–2.03)	3/937	2.09 (0.63–6.93)	14/2271	1.29 (0.74–2.24)	3/326	0.84 (0.27–2.65)			85/16 788	1.43 (1.15–1.79)
Duration of snus use (current users only)												
<30 years	58/23 671	1.40 (1.06–1.84)	2/1547	1.96 (0.45–8.58)	6/2068	0.82 (0.36–1.87)			0/1854	–	66/27 286	1.34 (1.03–1.73)
≥30 years	107/17 358	1.22 (1.00–1.51)	4/1020	1.17 (0.41–3.36)	35/7254	0.97 (0.68–1.40)			6/1137	1.50 (0.65–3.46)	152/26 769	1.17 (0.98–1.39)

[a]Information on number of boxes and years of snus use was only available for a subset of participants who responded to the 2010 questionnaire. The reference group of never smokers consisted of 58 cases per 26 860 person-years. [b]Information on year of snus use was not available. [c]Information on number of boxes consumed was not available. HRs were adjusted for age, calendar year, body mass index, physical activity, education and alcohol consumption.
HR, hazard ratio; CI, confidence interval; SALT, Screening Across the Lifespan Twin study.

attributable fractions suggests that 13% of cases among snus users were attributed to their snus habit. Our results were consistent with the findings of two small previous studies [16, 17]. By contrast, no association was found in two other studies, including a recent study by us [18, 19]. However, lack of power precluded the possibility of drawing any firm conclusions regarding the risk in high consumers in these previous studies.

We observed elevated risks at consumption levels above four boxes per week and in those consuming ≥7 boxes per week, HR was estimated at 1.68. By comparison, Pan *et al.* [10] reported an HR of 1.57 in heavy smokers (corresponding to one pack of cigarettes per day) in the latest meta-analysis based on 88 observational studies. Hence, smoking and snus use appear to be equally strong risk factors for type 2 diabetes. This is plausible because mechanistic studies also point to nicotine as the possible mediator of such a risk increase. Nicotine can inhibit insulin sensitivity and may stimulate release of cortisol, thus promoting abdominal obesity and subsequently insulin resistance [11, 12, 36]. The nicotine content of one portion of snus is higher than that of one cigarette, but only 10–20% of the nicotine in snus reaches the blood stream [37]. Experimental studies indicate that nicotine is absorbed more rapidly from cigarettes, and after consumption of one cigarette, compared with one portion of snus, the smoker will have a higher peak concentration; however, nicotine levels will be higher in the snus users after 2 h [15]. It has also been shown that regular users of snus and cigarettes tend to have similar blood nicotine levels [38].

A particular strength of this study is the size which enabled restriction of the sample to never smokers, and hence careful control for confounding by smoking, as well as analyses of dose–response relationships. We also adjusted for several other diabetes risk factors including BMI, physical activity, alcohol consumption and education. Information on family history of diabetes was only available in the Västerbotten Intervention Programme, but a sensitivity analysis did not indicate that history of diabetes was a confounder. One concern is that there was no uniform way to identify diabetes patients across all studies. Hence, to optimize case ascertainment, we relied on different sources for each study, including national and local health registries, self-reporting and screening. The incidence of diabetes in the pooled cohort was in line with previous Swedish reports, implying that the assessment method was robust [39]. Furthermore, data from the National Prescribed Drug Register, which has complete information on pharmacologically treated diabetes in Sweden, were available from 2005 in all studies. With regard to the validity of self-reporting, it is noteworthy that when we compared prescription data to self-reports in a subset, we found that 92% of individuals with self-reported diabetes had been prescribed antidiabetic drugs. Undiagnosed diabetes is of concern but, fortunately, the largest and most influential study (Västerbotten Intervention Programme) was also the most detailed as incidence of diabetes could be assessed through screening as well as through self-reporting and registry data. Furthermore, repeated information on both BMI and tobacco use was available during follow-up, allowing us to take into account lifestyle changes after baseline. We used age at onset above 35 years as an indicator of type 2 diabetes and excluded all patients with records of type 1 diabetes in the patient registries. A sensitivity analysis in which we also excluded all cases with insulin prescribed during the first year following diagnosis yielded similar results. Yet, some cases of type 1 diabetes or LADA (latent autoimmune diabetes in adults) may have been misclassified as type 2 diabetes in our main analysis (but this is unlikely to be dependent on snus use), and hence dilute the associations.

The prevalence of snus use varied greatly between studies, which is to be expected as its use has a known north–south gradient in Sweden. Nevertheless, for high consumers (≥7 boxes per week**),** we consistently found HR values >1 across all studies underlining the robustness of the findings. Self-reported information on tobacco use is a limitation. However, the questionnaire used to elicit information about tobacco use in the Västerbotten Intervention Programme has been validated, and the correlation between self-reported number of boxes of snus used per week was highly correlated with plasma cotinine concentrations ($r = 0.60$, $P = 0.003$) [40]. It is possible that some snus users started smoking during follow-up. Yet, in analyses using updated tobacco exposure employed as a time-varying covariate during follow-up (in the two cohorts in which such data were available), excess risks were still noted in high consumers. Indeed, 91% of participants in the Västerbotten Intervention Programme were stable never smokers at baseline and follow-up, and only 1% of never smokers reported onset of daily smoking. We could not differentiate between loose and portion-packed snus which have different nicotine yields and hence may affect type 2 diabetes risk differently [38].

Conclusion

Our findings indicate that high consumption of snus increases the risk of type 2 diabetes. This is in contrast to findings for cardiovascular disease as well as cancer [5–9, 41]. The diabetes-promoting effect of cigarettes and snus is hence likely to be mediated by nicotine, whereas the tobacco-related risks of cardiovascular disease and cancer may be due to other components of cigarette smoke. In conclusion, these findings suggest that any health benefit of changing from smoking to snus use does not include reduction in diabetes risk. In addition, this novel finding warrants attention from public health authorities, in the light of the diabetes epidemic and increasing popularity of snus as well as other smoke-free modes of nicotine use such as e-cigarettes [24, 42]. We could not explore the association between snus use and diabetes risk in women, and this is an important topic for future studies.

Author contributions

All authors have made substantial contributions to (i) the conception or design of the study, or the acquisition, analysis or interpretation of the data and (ii) drafting of the manuscript or revising it critically for important intellectual content; all authors have also approved the final version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest statement

No conflicts of interest to declare.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Numbers (and percentages) of snus users at baseline across categories of age, BMI, alcohol consumption, education and physical activity.

Table S2. The risk of type 2 diabetes in relation to age, BMI, alcohol consumption, education and physical activity.

