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ORIGINAL ARTICLE

High consumption of smokeless tobacco ("snus") predicts increased risk of type 2 diabetes in a 10-year prospective study of middle-aged Swedish men

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Abstract

Aims: Cigarette smoking increases the risk of type 2 diabetes (T2D). In Sweden and the US, people shift from smoking cigarettes to smokeless tobacco, i.e. oral moist snuff, "snus", to attain harm-reduction. There are limited and conflicting data as to whether snus increases the risk of T2D. The present study investigated if snus use predicts the risk of T2D incidence. *Methods*: This is a prospective population-based study where middle-aged Swedish men (n=2,383), without previously diagnosed T2D, were investigated with oral glucose tolerance test (OGTT) at baseline in 1992–94 and at follow-up 10 years later. Odds ratios (Or s) for newly diagnosed T2D at follow-up were assessed among those using snus, or cigarettes, at both baseline and follow-up, adjusted for major confounders. *Results*: The Or for T2D was not significantly increased in the whole group of snus users. However, the risk of diabetes increased with increasing weekly snus consumption; Or s (CIs) for >four boxes of snus/week were 2.1 (CI 0.9–4.9), and for >five boxes/week 3.3 (CI 1.4–8.1). f or comparison, men smoking at baseline and still smoking at follow-up had an increased risk of diabetes compared with never smokers, Or 1.5 (CI 0.8–3.0), most evident for those smoking >15 cigarettes per day, Or 2.4 (CI 1.0–5.8). Tobacco use was associated with estimations of low insulin response (OGTT), but not low insulin sensitivity (HOm A). ***Conclusions*: High consumption of snus, like smoking, predicts risk of developing T2D. This should be considered when seeking harm-reduction by changing from use of cigarettes to snus. T2D risk from tobacco use may be mediated by effects on beta-cell function.**

Key Words: *Harm reduction, oral moist snuff, prediction, tobacco, type 2 diabetes*

Background

Type 2 diabetes (T2D) is a major health problem with rapidly increasing prevalence in many countries [1]. In addition to the influence of genes, lifestyle factors that decrease insulin sensitivity and/or insulin secretion are of aetiologic importance in the development of the disease [2,3]. One such factor is cigarette smoking, which has been convincingly shown to increase the risk of T2D [4–8].

In Sweden, the prevalence of male smokers has decreased markedly during recent years. At the same time, the number of users of smokeless tobacco, e.g. oral moist snuff, "snus", has increased [9]. Here, as well as in the US and Great Britain, the debate has focused on whether a change from cigarette to snus use would be a measure of harm reduction [10–15]. In addition to reduced risk of pulmonary diseases, including chronic bronchitis and pulmonary cancer, it is possible that the risk of cardiovascular diseases is lower in users of snus compared with smokers [16], although there are

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data supporting the opposite view [17]. Whether snus, like cigarette smoking, confers an increased risk of T2D has been analysed in two Swedish studies, with different outcomes [8,18]. f urthermore, a recent review has concluded that an association of snus with diabetes is not clearly established [19]. The aim of the present investigation was to assess this issue prospectively, during a 10-year period, in a cohort of middle-aged Swedish men.

Methods

Participants

The study was approved by the r esearch e thics Committee of the Karolinska Hospital. Verbal informed consent was obtained from each participant and documented in the study forms, as required by the e thics Committee and the institutional review board. The baseline investigation of the Stockholm Diabetes Prevention Programme was performed in men during 1992–1994 in four municipalities within Stockholm County. The procedures have been described in detail previously [20] and the study design is outlined in f igure 1. After addressing all men, aged 35–56 years, with a questionnaire concerning detailed family history of diabetes (f HD), we eventually selected and invited one group of 2,106 men with f HD, and 2,424 men without f HD. f HD was defined as at least one first degree relative, or at least two second degree relatives with T2D, and non-f HD was defined as the absence of T2D in first and second degree relatives. Previously diagnosed diabetes was an exclusion criterion.

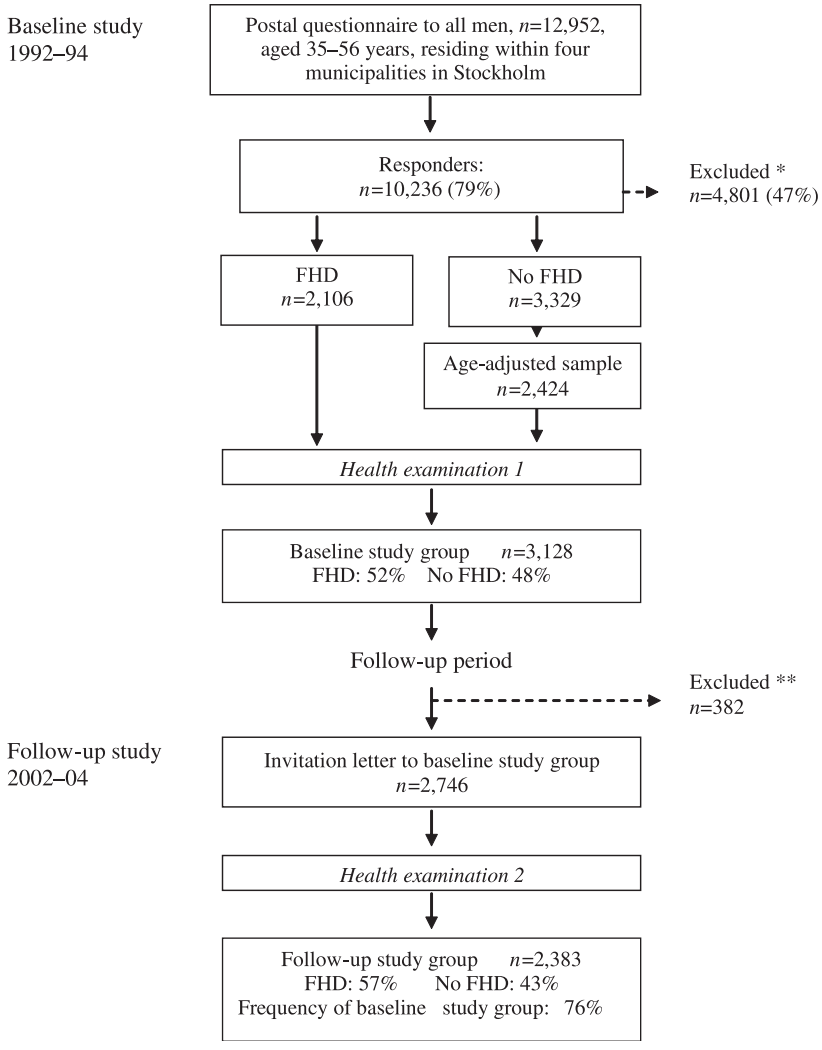

Figure 1. Design of the baseline and follow-up study of men in the Stockholm Diabetes Prevention Programme. FHD = family history of diabetes.

*e xcluded owing to already known diabetes, foreign origin, unclear or insufficient f HD.

**e xcluded owing to diagnosis of diabetes at baseline examination, moved outside Stockholm county or deceased.

Baseline study

Of the invited men (*n*=4,530) 3,128 participated in a baseline study and underwent an oral glucose tolerance test (OGTT). The participants took part in anthropometric measurements, and answered a questionnaire about lifestyle issues.

Follow-up study

f ollow-up assessments were performed 10 years after the baseline investigation. Of those who were non-diabetic at baseline and still living in the Stockholm area (*n*=2,746), 87% were reinvestigated with anthropometric measurements, OGTT, and a questionnaire. Of subjects participating at follow-up (*n*=2,383), the OGTT identified 99 men with newly diagnosed T2D, serving as cases in the present study. Controls were subjects without T2D at follow-up (*n*=2,200). Subjects diagnosed with T2D during the time period between baseline and follow-up (*n*=84) are not included in the present study.

Classification of glucose tolerance. T2D was defined according to the World Health Organization's 1998 criteria. Insulin sensitivity was assessed by the homeostasis model assessment (HOm A-Ir) estimate, which was calculated according to algorithm [(fasting glucose × fasting insulin)/22.5]. Among subjects developing T2D at follow-up, those who belonged to the highest third of HOm A-Ir at baseline were defined as insulin resistant. Insulin response was estimated in two ways: as HOm A-beta, calculated as [(20 x fasting insulin/(fasting glucose – 3.5)], or from the increment in insulin levels between 0h and 2h during OGTT. l ow insulin response among subjects developing T2D at follow-up was defined as having HOm A-beta or insulin incremental values within the lowest third at baseline.

Classification of exposure: Information on use of tobacco was obtained from the baseline and follow-up questionnaires. Subjects were asked if they had ever been daily users of snus, and if so, if they were current daily users. Based on the answers, subjects were classified into never, former or current snus users. Subjects were also asked about daily cigarette smoking and accordingly categorized into never, former or current smokers. e xposure information from both baseline and follow-up were combined, giving option to 3 x 3 combinations concerning snus use and smoking, respectively. To avoid inconsistencies, the following categories only were chosen for analyses: 1) never snus use/never smoking at both baseline and follow-up (= consistent never snus use/consistent never smoking), 2) current snus use/current smoking at both baseline and follow-up (= consistent snus use/consistent smoking) and 3) former snus use /former smoking, defined as those who answered former use at follow-up in combinations with former or current use at baseline (= former snus use/former smoking). Due to this selection, in total 246 control subjects and nine subjects with newly diagnosed T2D were excluded from analyses on snus use. Corresponding figures in analyses on smoking are 321 and 21, respectively. f urthermore, because of missing data on confounders (see below) additional subjects were excluded; in analyses on snus use 95 controls and four newly diagnosed T2D and in analyses on smoking 91 controls and four newly diagnosed T2D. Thus, the final study sample comprised 1,859 control subjects and 86 subjects with newly diagnosed T2D for analyses on snus use, whereas corresponding figures for analyses on smoking were 1,788 and 74, respectively.

Consumption of tobacco was measured as number of boxes of snus (each containing 25–50 g) used weekly or number of cigarettes smoked daily, respectively. The use of different types of snus boxes was similarly distributed among low and high consumers of snus.

Statistical analysis

Data are given as means or proportions accompanied by 95% confidence intervals (95% CI). Comparisons of continuous variables were performed by one-way ANOVA, followed by Tukey-Kramer post-hoc test if significant, and of categorical variables by Chi^2-test. f or tobacco use in association with newly diagnosed T2D at follow-up, odds ratios (Or) and 95% CI were calculated by multiple regression analysis. Adjustment was made for age (four categories, five-year interval). Additionally, we performed analysis with adjustment for other potentially confounding variables: Bm I (<25.0, 25.0–29.9, >=30.0), glucose tolerance at baseline (pre-diabetes/normal glucose tolerance (NGT)), f HD (negative/positive), physical activity (sedentary, moderately active, regular exercise), alcohol consumption (obtained from the questionnaire, asking about frequency and amount of consumption per occasion of beer, wine, dessert wine and spirit. e ach beverage was converted into ml 100% alcohol/week, using estimated content of pure alcohol per ml; 0.035 ml for medium beer, 0.055 ml for strong beer, 0.12 ml for wine, 0.19 ml for dessert wine and 0.40 ml for spirit, and a total weekly consumption was calculated from the sum of the specific beverages. According to the distribution of total alcohol consumption, the variable was categorized into tertiles: low, middle and high), and socioeconomic

position (self-reported occupational titles were classified according to the standard system defined by the governmental agency Statistics Sweden and divided into four groups; low (unskilled and skilled manual workers), middle (low-level non-manual employees), high (high-and medium-level non-manual employees), and self-employed including farmers). We fitted models in which the Or s associated with snus use were adjusted for smoking and in which Or s linked to smoking were adjusted for snus use. Analyses were based on the combined baseline and follow-up use of tobacco, and confounding variables, as well as consumption of boxes of snus or number of cigarettes were updated with follow-up data. Analyses are performed only on subjects having data on all confounders at follow-up. To better control for the effect of smoking in analysis of snus and for snus use in analysis of smoking, we also fitted models which took into account snus use among never-smokers only and smoking among never-snus users only. Statistical analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC, USA).

Results

Among men participating at both baseline and follow-up, 17.0% were current daily snus users at baseline. A slight increase in frequency was observed 10 years later when 19.7% of the men reported current daily use of snus, of whom 70.0% (n=301) were current users also at baseline. r eciprocally, the frequency of daily smoking decreased during the 10 year period. Thus, at baseline 23.7% were current daily smokers as compared to 15.6% at follow-up. Among current smokers at follow-up, 84.2% (n=287) were current smokers also at baseline. Of those quitting daily smoking during the follow-up period (n=188), 19.7% were new current daily snus users at follow-up.

Characteristics of the subjects at baseline are given in Table I. Consistent snus users were younger and had a somewhat higher Bm I as compared to consistent never snus users, p<0.001 and p=0.003, respectively. However, the change in Bm I during the time period between baseline and follow-up did not differ between the groups (data not shown). Consistent smokers were less physically active as compared to consistent never smokers, p<0.001. Among both snus users and smokers, whether consistent or former users, the alcohol consumption was higher, p<0.001. Also, the frequency of individuals in the lowest socioeconomic position was higher in relation to their respective reference group, p<0.001. f requency of high blood pressure did not differ, either between snus use groups or between smoking groups.

Associations between tobacco use and newly diagnosed T2D at follow up are presented in Table II. The Or for developing T2D did not differ in the group of all consistent snus users compared with persons who had never used snus. m ean consumption was 4.2 (3.1–5.3) and 5.3 (4.1–6.4) boxes/week at baseline and follow-up, respectively, in consistent snus users with T2D as compared to 3.3 (3.0–3.5) and 3.9 (3.7–4.2) boxes/week, respectively, in control subjects. When stratified according to boxes of snus consumed weekly, consistent snus use at a consumption of > four boxes/week was associated with T2D, Or (CI) = 2.1 (0.9–4.9) after controlling for confounders. f urther increased risks were found in persons consuming > five boxes/week, Or = 3.3 (1.4–8.1) for T2D (Table II). Adjustment for high blood pressure revealed similar results (data not shown). History of smoking was taken into account as smoking status was adjusted for in these analyses. However, in analyses on consumption of snus there were no significant differences between cases and controls in total frequencies of current or former smoking (20.0% vs 16.1%, p=0.443 and 47.5% vs 38.5%, p=0.126), whereas never smoking was less prevalent among cases (32.5% vs 45.6%, p=0.029). Specifically among high consumers of snus (>five boxes/week) no current smokers were found among cases, but one among controls, while former smoking was more prevalent among cases than among controls with high consumption of snus. To eliminate the effect of smoking, analyses were performed only in never-smokers and the Or for T2D in association with consistent use of snus was 2.3 (0.5–9.8). The number of men with T2D was, however, only three, meaning interpretation should be cautious.

Consistent smoking per se increased the risk of developing T2D, although not significantly after adjustment (Table II). f ormer smoking was not associated with newly diagnosed T2D. A dose-dependency according to number of cigarettes smoked daily was observed among consistent smokers with T2D, with a two- to three-fold increased risk when consuming more than 15 cigarettes per day (CPD). A consumption of > 20 CPD was observed in only one person with T2D. Analysis restricted to consistent smoking in never-snus users showed similar results (data not shown).

Analysis performed only in the group of subjects that were NGT when starting the follow-up period, thus excluding residual confounding effect from glucose tolerance at baseline, did not substantially change the results given above (data not shown).

Subjects who did not participate in the follow-up examination, compared with participants at follow-up, had similar snus consumption, age, alcohol

Table I. Characteristics in subjects at baseline, and number of subjects with newly diagnosed type 2 diabetes at follow-up, according to tobacco use at baseline and follow-up.

	Snus use			Smoking		
	Consistent never snus use[a]	Consistent snus use[b]	f ormer snus use[c]	Consistent never-smoking[d]	Consistent smoking[e]	f ormer smoking[f]
n	1,431	301	213	835	287	740
Age: mean (95% CI)	47.2 (46.9–47.4)	44.8 (44.2–45.3)	45.8 (45.2–46.4)	46.2 (45.9–46.6)	46.7 (46.1–47.3)	46.8 (46.4–47.1)
BmI: mean (95% CI)	25.7 (25.5–25.8)	26.4 (26.0–26.8)	25.8 (25.4–26.2)	25.6 (25.4–25.8)	25.2 (24.8–25.6)	26.1 (25.8–26.3)
Physical activity during leisure time: % sedentary (95% CI)	10.6 (9.1–12.3)	9.3 (6.5–13.1)	8.0 (5.0–12.4)	9.1 (7.3–11.2)	18.5 (14.5–23.4)	8.1 (6.4–10.3)
Alcohol consumption: % highest tertile (95% CI)	28.1 (25.7–30.5)	47.5 (41.9–53.2)	39.2 (32.9–46.0)	21.7 (19.0–24.7)	42.0 (36.3–47.9)	40.9 (37.3–44.5)
Socioeconomic position: % low (95% CI)	27.0 (24.7–29.4)	41.3 (35.8–46.9)	41.8 (35.3–48.6)	22.7 (20.0–25.7)	41.3 (35.8–47.2)	36.5 (33.1–40.1)
Blood pressure % high blood pressure[g]	13.4 (11.7–15.3)	10.0 (7.1–14.0)	13.3 (9.3–18.5)	12.4 (10.3–14.8)	10.6 (7.5–14.7)	13.4 (11.1–16.0)
f amily history of diabetes: % positive (95% CI)	50.3 (47.7–52.9)	52.5 (46.9–58.1)	57.3 (50.6–63.7)	52.0 (48.6–55.3)	54.0 (48.2–59.7)	53.8 (50.2–57.3)
Current smokers[h] among snus users/ current snus[h] users among smokers: n (%)	246 (17.2)	36 (12.0)	16 (7.6)	74 (8.9)	48 (16.8)	232 (31.4)
Type 2 diabetes, newly diagnosed at follow-up: *n* (%)	64 (4.5)	16 (5.3)	6 (2.8)	27 (3.2)	17 (5.9)	30 (4.1)

[a]Never snus users, at both baseline and follow-up, irrespective of smoking status. [b]Snus users at both baseline and follow-up, irrespective of smoking status. [c]Snus users who quit before baseline or between baseline and follow-up, irrespective of smoking status. [d]Never smokers, at both baseline and follow-up, irrespective of snus status. [e]Smokers at both baseline and follow-up, irrespective of snus status. [f]Smokers who quit before baseline or between baseline and follow-up, irrespective of snus status. [g]High blood pressure (BP) defined as having systolic BP≥140 mm Hg and diastolic BP≥90 mm Hg and/or hypertension treatment. [h]At baseline and follow-up.

Table II. Odds ratios (OR) of type 2 diabetes, newly diagnosed at follow-up, associated with tobacco use at baseline and follow-up.

	Controls	Cases: type 2 diabetes; newly diagnosed				
	n	*n*	I		II	
			Or	95% CI	Or	95% CI
Consistent never snus use[a]	1367	64	1.0		1.0	
Consistent snus use[b]	285	16	1.3	0.7–2.3	1.1	0.6–2.0
f ormer snus use[c]	207	6	0.7	0.3–1.6	0.5	0.2–1.2
Consistent never snus use[a]	1367	64	1.0		1.0	
1-5 boxes/week[d]	226	7	0.7	0.3–1.6	0.6	0.2–1.4
>5 boxes/week[d]	59	9	3.7	1.7–8.0	3.3	1.4–8.1
Consistent never smoking[e]	808	27	1.0		1.0	
Consistent smoking[f]	270	17	1.9	1.0–3.5	1.5	0.8–3.0
f ormer smoking[g]	710	30	1.3	0.7–2.2	0.9	0.5–1.7
Consistent never smoking[e]	808	27	1.0		1.0	
1–15 cigarettes/day[h]	156	7	1.3	0.6–3.1	0.8	0.3–2.1
>15 cigarettes/day[h]	105	10	2.8	1.3–6.0	2.4	1.0–5.8

[a]Never snus users, at both baseline and follow-up, irrespective of smoking status. [b]Current snus users, at both baseline and follow-up, irrespective of smoking status. [c]Snus users who quit before baseline or between baseline and follow-up, irrespective of smoking status. [d]Snus consumption among consistent snus users. [e]Never smokers, at both baseline and follow-up, irrespective of snus status. [f]Current smokers, at both baseline and follow-up, irrespective of snus status. [g]Smokers who quit before baseline or between baseline and follow-up, irrespective of snus status. [h]Cigarette consumption among consistent smokers. Nine consistent smokers among controls have missing data on cigarette consumption. I: adjusted for age. II: adjusted for age, Bm I, glucose tolerance at baseline, physical activity, alcohol consumption, socioeconomic position, family history of diabetes and smoking in analysis regarding snus use and snus use in analysis regarding smoking.

consumption, f HD and physical activity but higher Bm I, blood pressure, lower socioeconomic position, higher frequency of pre-diabetes and of smoking (data not shown).

To assess the possible mechanism behind the tobacco-induced T2D risk, we looked for associations with insulin resistance being defined as highest tertile of HOm A-Ir . No significant associations between either snus use or smoking were found (data not shown). As for the effects on insulin secretion, the HOm A-beta parameter indicated low insulin response in smokers whereas results in snus users were inconclusive (data not shown). Associations were found with low insulin secretion in both smokers and snus users, when beta cell function was evaluated by calculating insulin response as the increment in insulin between 2h and 0h in the OGTT and calculating Or of T2D patients having the lowest insulin response (lowest tertile). In smokers with a consumption of 1–15 CPD, the Or was 5.6 (1.2–26.6) and with a consumption of > 15 CPD, the Or was 12.9 (3.0–54.9). In snus users, there was an indication of association with use of > five boxes of snus/week, Or 3.3 (0.9-12.1); these results were adjusted for age, smoking for snus use, and snus use for smoking.

Discussion

Here, we show for the first time in a prospective study that men without T2D at baseline and who consume five or more boxes of snus per week, run an increased risk of developing T2D 10 years later. A similar risk was confirmed in those who smoked more than 15 CPD. These findings may be accounted for by an effect of nicotine, or another tobacco-related substance, on mechanisms regulating glucose homeostasis. Indeed, functional nicotinic receptors have been demonstrated on pancreatic beta cells [21]. Whether direct or indirect effects of nicotine are at play cannot be decided. However, a possible indirect effect could be exerted by catecholamines. Tobacco use has been shown to elicit catecholamine release,[22] that in turn may impair insulin sensitivity or insulin secretion. The mechanism behind development of T2D due to tobacco use seems more likely to involve impairment of insulin release than induction of insulin resistance, as evidenced by the association with the lowest tertile of insulin response and HOm A-beta, but not to the highest tertile of HOm A-Ir . Such an effect is in concert with the finding of an association between smoking and low C-peptide serum levels in non-diabetic subjects [23]. It is also possible that tobacco use promotes development of overweight, which in turn may enhance diabetes risk [24,25]. However, this association is debatable and may be dependent on the "dose" of tobacco use. In the present study, we have adjusted our data (in Table II) for Bm I. In addition, the change in Bm I during the time period between baseline and follow-up did not differ between the groups.

A normal sized snus portion (1 g) has a nicotine content of about 8 mg, but due to much lower

bioavailability the average nicotine intake is 1.5 mg/g, which is similar to the estimated amount of nicotine inhaled from one cigarette, 1.4 mg [26]. As an example, a snus user with a weekly consumption of five boxes (each 25 g) will be exposed to 188 mg absorbed nicotine per week and smoking 15 CPD will correspond to 147 mg absorbed nicotine per week. These data would suggest that the exposure to nicotine was, at the least, not lower in the at-risk-group of snus users compared with smokers.

The results of this prospective study strengthen the results obtained in the baseline study, in which we found a significant association between use of snus and T2D [8]. In current users of snus, consuming three or more boxes per week, the Or was 2.7 relative to men who had never used snus. A similar Or , 2.6, was shown for the association with T2D in men smoking at least 25 CPD as compared to men who never had smoked. The present results are restricted to men. f ew women reported use of snus in the baseline study, and none of them was diagnosed with T2D at follow-up. Hence, we have not been able to assess the risk of diabetes in women who use snus.

Our present findings, as well as our previous findings, that the use of snus predicts increased risk of T2D is at variance with a previous study of men in the northern part of Sweden, which concluded that diabetes risk was increased by smoking but not by snus [18]. The reasons for this discrepancy have been discussed [27,28]; one reason is likely to be our present and previous finding that a significant risk with snus is only seen in high consumers. Such separate analysis was not given in the report from the northern part of Sweden. In this context, it is of interest that another and more recent prospective study in northern Sweden found that high consumption of snus, even controlling for smoking, was independently associated with the metabolic syndrome [29].

Our study has the strength of being performed in well-characterized subjects, followed during eight to ten years in a setting where many of the subjects, at least men, were using snus. Bias due to increased diabetes risk in non-snus users among non-participants seems unlikely because the frequency of snus consumption as well as some main risk factors for T2D were the same among participants and non-participants in the follow-up study. Tobacco use was self-reported, which could be a weakness if assuming that users underestimate or deny their consumption. However, the accuracy of self-reported smoking compared with biochemical measures appears high, as confirmed in a recent study on consumption of different nicotine containing products [30]. A limitation is the small number of cases developing diabetes, especially when attempting to evaluate the effects of snus in subjects who did not have a record of previous smoking. However, being a former smoker did not increase the risk of diabetes, and there was no difference between cases and controls with regard to current smoking together with snus use. Thus, our risk estimates related to snus consumption do not appear to be influenced by current smoking. In any event, it seems unlikely that in the foreseeable future, better opportunities will be available to study the impact of snus on the risk of diabetes. Hence, we believe that our results add relevant information on the issue of harmful effects of snus.

Conclusion

In conclusion, we have demonstrated that high consumption of snus, similar to cigarette smoking, predicts the risk of developing T2D. This should be taken into account when seeking harm-reduction by changing from use of cigarettes to snus.

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