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Influence of smoking and snus on the prevalence and incidence of type 2 diabetes amongst men: the northern Sweden MONICA study

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Abstract. Eliasson M, Asplund K, Nasic S, Rodu B (Sunderby Hospital, Luleå and Umeå University, Umeå, Sweden; and University of Alabama at Birmingham, AL, USA). Influence of smoking and snus on the prevalence and incidence of type 2 diabetes amongst men: the northern Sweden MONICA study. *J Intern Med* 2004; **256**: 101–110.

Objective. To explore the effect of smoking and smokeless tobacco, 'snus', on the risk of type 2 diabetes.

Design. Population-based cross-sectional and prospective follow-up study in northern Sweden.

Subjects. A total of 3384 men, aged 25–74 years, who participated in the MONICA study in 1986, 1990, 1994 or 1999, 1170 of whom had an oral glucose tolerance test. In 1999, 1757 men from previous cohorts returned for re-examination.

Main outcome measures. We compared the prevalence of type 2 diabetes or pathological glucose tolerance (PGT) amongst tobacco users to that of nonusers at entry into the study and at follow-up, using odds ratios.

Results. Compared with never users, the age-adjusted risk of prevalent clinically diagnosed diabetes for ever smokers was 1.88 (CI 1.17–3.0) and for smokers 1.74 (0.94–3.2). Corresponding odds ratios for snus users were 1.34 (0.65–2.7) and 1.18 (0.48–2.9). We found no increased risk of prevalent PGT in snus users or smokers. Former smokers and snus users had an insignificantly increased risk for PGT. Compared with nonusers, the age-adjusted risk of developing clinically diagnosed diabetes during follow-up was 4.63 (1.37–16) in consistent exclusive smokers, 3.20 (1.16–8.8) in ex-smokers and no cases in consistent snus users. The risk of PGT during follow-up was not increased in consistent tobacco users but evident, although not statistically significant, in those who quit snus during the follow-up period, 1.85 (0.60–5.7). Adjustment for physical activity and alcohol consumption did not change the major findings.

Conclusions. The risk of diabetes for snus users was not significantly increased. Smoking was associated with prevalent and incident cases of diabetes. Ex-tobacco users tended towards more PGT.

Keywords: cohort studies, diabetes mellitus, epidemiology, incidence, prevalence, smokeless tobacco.

Introduction

Cigarette smoking was first pointed out as a risk factor for type 2 diabetes in men in the late 1980s [1] and later confirmed in large cohort studies, in both men and women and most prominently amongst heavy smokers [2–4]. A recent paper summarizes the 15 published prospective epidemiologic studies on this subject [4].

In Sweden, the low prevalence of smoking amongst men appears to be associated with the use of smokeless tobacco in the form of moist oral snuff, or snus [5, 6]. In northern Sweden, the use of snus in men increased from 22 to 30% between 1986 and 1999 whilst smoking decreased from 23 to 14% [5]. Snus delivers the same amount of nicotine as cigarettes but the use of snus seems to carry less risk of cardiovascular disease [7] and little is known regarding the impact on glucose metabolism and the development of type 2 diabetes.

Recently, a large Swedish cross-sectional study showed that the prevalence of type 2 diabetes,

diagnosed by an oral glucose tolerance test (OGTT), was equally increased for smokers and snus users with high tobacco consumption compared with nontobacco users [8]. Interestingly, there were no increases in the risk for impaired glucose tolerance (IGT). In spite of the widespread use of smokeless tobacco in Scandinavia and North America, no other prevalence or incidence studies have been published on this topic.

Our aim was to explore the effect of smoking and snus use on type 2 diabetes in a population-based, cross-sectional and prospective follow-up study.

Methods

This study used data from the northern Sweden component of the World Health Organisation Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA) study. Briefly, information was collected during four population-based surveys in 1986, 1990, 1994 and 1999 (Fig. 1). In addition, follow-up information on about 70% of participants from the first three surveys was collected in 1999, with duration of follow-up of 5, 9 and 13 years (1994, 1990 and 1986 cohorts, respectively) [9].

Baseline surveys

Subjects were randomly selected from population registers, stratified for age (25–64 years in the first two surveys, 25–74 in the latter) and gender, in the two most northern counties of Sweden (Norrbotten and Västerbotten; target population 320 000 in 1999). Details of sampling and selection appear elsewhere [5, 9]. Participants completed a questionnaire that was focused on cardiovascular disease risk factors. As the primary focus of the present report is on the influence of smoking and snus use on type 2 diabetes, we limited the present analyses to men aged 25–74 years at study entry. In the 1990 cohort, plasma nicotine and cotinine were measured in a randomly selected subgroup of 321 subjects to validate self-reported tobacco habits [10].

Responses to tobacco-related questions were used to designate three mutually exclusive categories of smokers: ex, current, or never and three identical categories of snus users. We classified as current smokers persons who smoked at least one cigarette daily. Subjects smoking cigars or pipe were excluded. Ex-smokers were persons who reported quitting more than one month prior to completing their survey. We categorized persons who used any amount of snus each day as users but also explored the data using a categorization into less than two boxes per week, two to three boxes per week or greater than three boxes per week.

The prevalence of self-reported clinically diagnosed, known diabetes (kDM) at entry for all years combined was determined for groups of former or current tobacco users and for never users of tobacco (reference group).

A 75-g OGTT was performed after an overnight fast in a randomly selected subset of subjects

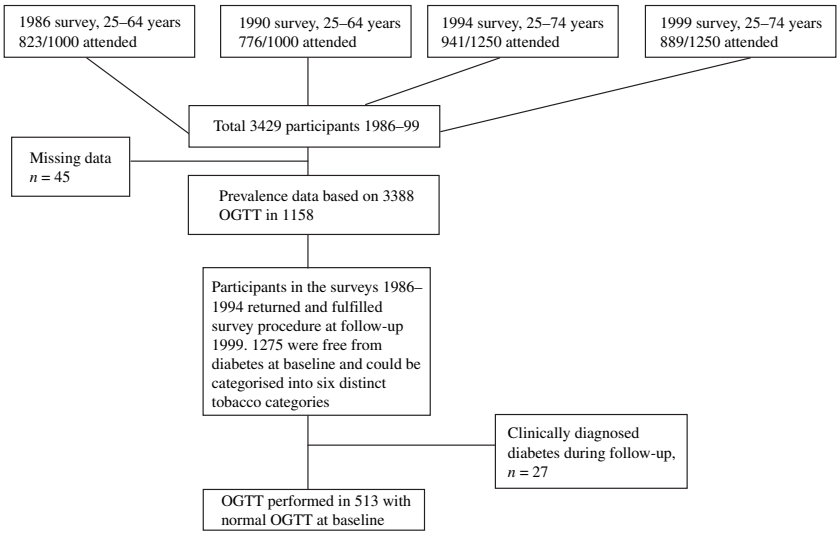

Fig. 1 Design of the population based surveys and number of participants in the northern Sweden MONICA Study on the influence of snus on the prevalence and incidence of diabetes.

without kDM [11]. Venous plasma glucose samples were analysed by the hexokinase method (Boehringer Mannheim Automated Analysis for BM/Hitachi System 717: Boehringer Mannheim, GmbH, Mannheim, Germany). Glucose tolerance was classified according to WHO criteria from 1999 [12].

- Normal glucose tolerance – fasting glucose <7 mmol L^{-1} and postload glucose <7.8 mmol L^{-1}
- Impaired glucose tolerance – fasting glucose <7 mmol L^{-1} and postload glucose 7.8–11.0 mmol L^{-1} and
- Diabetes – fasting glucose ≥ 7.0 mmol L^{-1} and/or postload glucose ≥ 11.1 mmol L^{-1}.

Subjects with IGT or diabetes at OGTT were pooled as pathological glucose tolerance (PGT).

Weight was measured with a balance scale to the nearest 0.2 kg, and height was measured to the nearest centimetre. BMI was calculated as total body weight (kg)/height (m^2). Waist circumference was measured midway between the lower rib margin and the iliac crest, which in most occasions was identical with the level of the umbilicus. All measurements were carried out in a standing position whilst breathing normally, and participants were asked to wear light underwear and remove shoes. For the measurement of waist circumference, the recording was carried out after a gentle breath-out. Using a questionnaire, self-reported leisure time physical activity was initially coded according to a six-point scale but dichotomized into one group with sedentary behaviour (no or slight physical activity <2 h $week^{-1}$) and one group with more intensive activity. Alcohol consumption was calculated as the percentage of total energy derived from alcohol.

Follow-up examination

In 1999, all participants, alive and still living in the area, were recalled for a follow-up examination. The same questionnaire and anthropometrical measurements as in the baseline survey were used. Altogether 69.2% (1757/2540) of previous participants turned up for re-examination and had valid data on tobacco use. Subjects who had a normal glucose tolerance or IGT at baseline and at follow-up answered 'no' to the question 'Do you have diabetes mellitus?' were once more offered an OGTT.

Participants who denied having diabetes in the baseline survey and answered affirmative to the question, 'Do you have diabetes mellitus?' at follow-up were defined as incident cases of known diabetes mellitus (kDM). In November 2002, a questionnaire exploring details related to the diagnosis of diabetes, and to the type and duration of current hypoglycaemic treatment was sent to them. Case records were scrutinized to confirm diabetes diagnosis and initial date of insulin therapy. An algorithm from AusDiab was used to classify cases in subtypes [13]. Subjects who started their insulin treatment within 2 years of diagnosis were classified as type 1. However, for subjects fulfilling these criteria but with an age of 40 or above at onset, current BMI had to be <27 to be classified as type 1. All other cases were classified as type 2.

Tobacco use was categorized according to use at baseline and during follow-up as:

1 Referent group (no tobacco at entry – no tobacco at follow-up).
2 Consistent snus users (exclusive snus at entry – exclusive snus at follow-up).
3 Consistent smokers (exclusive smoker at entry – exclusive smoker at follow-up).
4 Snus users who quit before entry or between entry and the follow-up (exclusive snus or ex-snus user at entry – no tobacco at follow-up).
5 Smokers who quit before entry or between entry and diabetes onset for kDM (and follow-up for PGT) (exclusive smoker or ex-smoker – no tobacco at follow-up).
6 Smokers who 'switched' to snus (exclusive smokers at entry – exclusive snus at follow-up) or (declared at entry as 'snus user with history of smoke' with unchanged status at follow-up).

Institutional review boards at Umeå University and the University of Alabama at Birmingham approved this study. The Research Ethics Committee of Umeå University and the National Computer Data Inspection Board approved the northern Sweden MONICA Study.

Statistics

In order to compare the prevalence of kDM and PGT amongst subjects in different tobacco use categories, an analysis by means of logistic regression was performed. We started with a model including only a variable for tobacco use, and then we stepwise included variables for age, waist circumference, for physical activity and alcohol consumption to adjust for possible confounding effects. We also tested a

model that included a variable for BMI instead of waist circumference. For incidence data, the model also included length of follow-up and annual percentage weight gain. The results of comparisons are presented as odds ratios (OR) with 95% confidence intervals (CI).

Results

Prevalence of kDM and PGT according to tobacco use

In the four cross-sectional surveys there were 3429 men in 1986 and 1990 aged 25–64, and in 1994 and 1990 aged 25–74 years (Fig. 1). Of these, 35 men (1.0%) were missing information on tobacco use and another 10 were missing data on prevalent diabetes and were excluded from the analysis. The final study population consisted of 3384 men, of whom 127 had kDM (Table 1).

Compared with never users, diabetes was more prevalent amongst current exclusive smokers, who were somewhat older but did not differ significantly in BMI or waist circumference. Exclusive snus users were much younger but with similar BMI and waist measurement. Although diabetes was less common than in the two previous categories, the differences were not statistically significant. Ex-smokers, whether ex-users of snus or not, were older, heavier and more abdominal obese and also had the highest prevalence of diabetes. Ex-snus users were similar to never users in these aspects. Sedentary physical activity was present amongst 60% of never users of tobacco and amongst 59% of current snus users (95% CI for the difference −4.8 to 7.5%). Current smokers were sedentary in 78% (95% CI for the difference against nonusers 13–22%).

An OGTT was performed in 1170 men without kDM. In 33 subjects, diabetes was diagnosed and IGT in 66 subjects. These two categories were pooled and designated as PGT. As information on tobacco use is missing in 12 men, the analysis was based on 1158 men with 98 cases of PGT (Table 1). The prevalence of PGT was 8.2% in never users and did not differ significantly in most groups of tobacco users with the exception of ex-smokers, who never used snuff, who had a prevalence of 14.5% (CI for difference 0.9–13.0%) and exclusive snus users who had a somewhat lower prevalence of 5.0% (CI for difference

Table 1 Prevalence of known diabetes (kDM) in 3384 men and of pathological glucose tolerance (PGT) in 1158 men with selected clinical characteristics according to tobacco use groups

	Age (years) [mean (CI)]	Waist circumference (cm) [mean (CI)]	BMI [mean (CI)]	Prevalence kDM [% (CI)] (cases/total)	Prevalence PGT [% (CI)] (cases/total)
Never use (n = 1203)	47.9 (47.1–48.6)	92.4 (91.9–92.9)	25.9 (25.7–26.1)	2.4 (1.7–3.4) (29/1201)	8.2 (5.9–11.1) (35/429)
Current tobacco user categories (n = 1311)					
Exclusive smokers (n = 414)	49.5 (48.3–50.6)	93.1 (92.1–94.0)	25.7 (25.4–26.1)	4.1 (2.6–6.5) (17/412)	7.9 (4.5–13.6) (11/139)
Exclusive snus users (n = 314)	41.0 (39.5–42.4)	91.6 (90.5–92.7)	25.9 (25.5–26.3)	1.9 (0.9–4.1) (6/314)	5.0 (2.2–11.2) (5/100)
Combined users (n = 129)	45.7 (43.6–47.8)	94.2 (92.5–96.0)	26.3 (25.6–27.0)	0.8 (0.1–4.3) (1/127)	1.9 (0.3–10.1) (1/52)
Smokers with history of snus use (n = 106)	43.8 (41.5–46.2)	93.3 (91.2–95.4)	26.0 (25.2–26.7)	4.8 (2.1–10.7) (5/105)	3.4 (0.6–17.2) (1/29)
Snus users with history of smoking (n = 348)	47.3 (46.1–48.6)	94.7 (93.6–95.8)	26.6 (26.2–27.0)	5.2 (3.3–8.0) (18/347)	9.8 (5.4–17.1) (10/102)
Ex-users with no current tobacco use (n = 880)					
Ex-smokers, ex-snus users (n = 244)	50.7 (49.2–52.2)	95.6 (94.4–96.8)	26.8 (26.3–27.2)	6.6 (4.1–10.4) (16/243)	6.0 (2.6–13.3) (5/83)
Ex-smoker, never used snus (n = 475)	55.0 (54.0–56.0)	95.3 (94.5–96.1)	26.5 (26.2–26.8)	6.3 (4.5–8.9) (30/474)	14.5 (10.0–20.7) (24/165)
Ex-snus user, never smoked (n = 161)	45.2 (43.3–47.2)	93.1 (91.5–94.6)	26.1 (25.5–26.6)	3.1 (1.3–7.1) (5/161)	10.2 (4.7–20.5) (6/59)
Total				n = 3384	n = 1158

−3.4–7.3%). Further analysis focused on adjusting for differences in age and obesity.

Age-adjusted OR for diabetes for ever smokers was increased to 1.88 (1.17–3.03) and still significant after adjustment for waist (Table 2). After adjustment also for alcohol consumption the odds ratio decreased somewhat, 1.65 (0.92–2,95). Ever-users (lifetime) of snus (exclusively) had an insignificantly increased odds ratio (OR) 1.34 (0.65–2.73) that declined further when taking also waist circumference into account. If alcohol consumption was also adjusted for, the OR decreased further to 1.10 (0.45–2,65). Using BMI instead of waist circumference decreased the multiple-adjusted OR for snus users (1.17, 0.57–2,41) and increased it for smokers (1.93, 1.20–3.13).

Focusing on current tobacco use, the risk of current smokers was still increased, although not statistically significant (Table 2) whilst the risk, adjusted for age, of ex-smokers was almost doubled and only slightly attenuated by adjusting for waist circumference. Current snus users had no increased risk of diabetes whilst ex-snus users had a multiple-adjusted OR of 1.45 but with wide confidence intervals, overlapping one. Adjustment for BMI gave similar ORs. We also analysed the prevalence of diabetes in exclusive snus users according to the amount of snus used per week but found no sign of any dose–response relationship (data not shown).

When undergoing an OGTT, neither ever users (lifetime) of snus nor smokers had any increased risk of PGT after adjustment for age (Table 3). Based on a small number of cases, the age and waist adjusted OR for diabetes at OGTT (compared with normal glucose tolerance, and excluding subjects with IGT) amongst exclusive ever snus users was 1.32 (0.4–4.34) and for ever smokers 1.51 (0.64–3.58).

Current snus users and smokers had similar risk of PGT, which did not differ from that of never users (Table 3). Ex-smokers and ex-snus users had identical odds ratios (1.45 and 1.48) although the confidence intervals included one. In exclusive ever snus users we found no cases of PGT at all in the group with highest consumption (>4 boxes/week) and the rough prevalence in those using less than five boxes was 6.3% compared with the prevalence in nonusers (8.1%). Further adjustment for leisure time physical activity did not change the direction of the estimates or significance of the odds ratios, neither for prevalent clinically diagnosed diabetes, nor for PGT.

Incidence of kDM and PGT according to tobacco use

In 1999, 1757 men returned for a re-examination. Subjects who at baseline had kDM or diabetes at OGTT were excluded. During an average follow-up of 8.7 years, or 15 726 person-years, 38 subjects had a validated kDM. Information on baseline and follow-up tobacco use allowed us to classify 1275 of the men into six distinct exclusive categories

Table 2 Odds ratios for prevalent known diabetes for pooled categories of lifetime and current exclusive tobacco use, adjusted stepwise for age and waist circumference (95% confidence intervals)

Tobacco use ($n = 2567$)	Adjusted for age	Adjusted for age and waist
Never use ($n = 1203$)[a]	1.00	1.00
Ever smoking (exclusively) ($n = 889$)[b]	1.88 (1.17–3.03)	1.77 (1.10–2.87)
Ever snus users (exclusively) ($n = 475$)[c]	1.34 (0.65–2.73)	1.21 (0.59–2.49)
Current smoker ($n = 414$)	1.74 (0.94–3.22)	1.62 (0.86–3.05)
Current snus user ($n = 314$)	1.18 (0.48–2.90)	1.06 (0.43–2.64)
Ex-smoker ($n = 475$)	1.98 (1.16–3.36)	1.87 (1.10–3.20)
Ex-snus user ($n = 161$)	1.58 (0.59–4.21)	1.45 (0.54–3.87)

[a]Reference group. [b]Current or ex-smokers without any history of snus using. [c]Current or ex-snus users without any history of smoking.

Table 3 Odds ratios for pathological glucose tolerance according to lifetime and current tobacco, adjusted stepwise for age and waist circumference (95% confidence intervals)

Tobacco use ($n = 892$)	Adjusted for age	Adjusted for age and waist
Never use[a]	1.00	1.00
Ever smoking (exclusively)[b]	1.23 (0.74–2.03)	1.23 (0.74–2.04)
Ever snus users (exclusively)[c]	1.08 (0.52–2.23)	1.05 (0.51–2.17)
Current smoker[d]	0.91 (0.44–1.85)	0.94 (0.46–1.92)
Current snus user[e]	0.78 (0.29–2.09)	0.78 (0.29–2.09)
Ex-smoker[d]	1.48 (0.84–2.61)	1.45 (0.82–2.56)
Ex-snus user[e]	1.57 (0.61–4.00)	1.48 (0.57–3.80)

[a]Reference group. [b]Current or ex-smokers without any history of snus using. [c]Current or ex-snus users without any history of smoking. [d]Only smokers without any history of snus using included. [e]Only snus users without any history of smoking included.

(Table 4). Snus users, whether current user or ex users, were younger and ex-smokers older and heavier. In this group, 27 new cases of kDM developed, a rough incidence of 2.5 cases per 1000 person-years. Snus users did not differ from never users but consistent smokers or smokers who quit had a fourfold higher rough incidence of diabetes. Smokers who switched to snus during the follow-up period had an intermediate risk of developing clinically diagnosed diabetes. Due to the lack of incident cases in current snus users, no estimation of a dose effect was possible.

In a logistic regression, odds ratios were calculated stepwise adjusted for age, follow-up, waist circumference and annual percentage weight gain (Table 5). Compared with consistent nontobacco users, exclusive snus users did not show any increased risk of kDM, as there were no cases of diabetes in this category. In contrast, consistent smokers had fourfold increased risk with no attenuation after adjustment for possible confounders. In ex-smokers, the risk was substantially increased.

An OGTT was performed in 744 men who at baseline did not have kDM or diabetes at OGTT (Table 6). Of these, 513 men with normal glucose tolerance at baseline, belonging to one of the six the tobacco categories, form the population at risk for IGT or diabetes. The only category where an increased multivariate OR was discerned was in ex-snus users. Based on three cases of diabetes, OR was 3.97 (0.86–18.3) and for PGT 1.85 (0.6–5.7). The only two snus users who developed diabetes belonged to the group with lowest consumption (<2 boxes per week).

Further adjustment for leisure time physical activity and alcohol consumption did not change the direction of the estimates or significance of the odds ratios, neither for the incidence of clinically diagnosed diabetes, nor for PGT.

Discussion

Whereas the present results confirm previous observations that smoking and ex-smoking are

Table 4 Incidence of known diabetes over an average of 8.5 years of follow-up according to tobacco use at baseline and changes during follow-up (95% confidence interval)

Tobacco use	Age at baseline (years) [mean (CI)]	Waist circumference (cm) [mean (CI)]	BMI (kg/m^b) [mean (CI)]	Incidence kDM [% (CI)] (cases/total)
Consistent no use	46.8 (45.8–47.8)	91.8 (91.0–92.5)	25.7 (25.4–26.0)	1.0 (0.5–2.2) (6/585)
Consistent exclusive smokers	48.7 (46.6–50.8)	92.2 (90.5–93.9)	25.6 (25.0–26.2)	4.5 (1.9–10.0) (5/112)
Consistent exclusive snus users	39.8 (37.4–42.2)	89.3 (87.5–91.0)	25.2 (24.6–25.7)	0 (0–3.6) (0/103)
Ex-snus users[a]	42.0 (39.5–44.6)	91.5 (89.1–93.9)	25.7 (24.9–26.5)	1.4 (0.2–7.4) (1/73)
Ex-smokers[b]	53.1 (51.8–54.3)	93.9 (92.9–94.9)	26.0 (25.6–26.3)	4.3 (2.5–7.4) (12/279)
Smokers who switched to snus[c]	44.1 (42.2–46.0)	93.4 (91.5–95.3)	26.3 (25.6–27.0)	2.4 (0.8–6.9) (3/123)
Total	47.2 (46.6–47.9)	92.2 (91.7–92.7)	25.8 (25.6–26.0)	2.1 (1.5–3.1) (27/1275)

[a]Snus users, without any history of smoking, who quit before baseline or during the follow-up. [b]Smokers, without any history of snus using, who quit before baseline or smokers who quit after baseline but before diabetes onset. [c]Snus users (by examination 1999) with history of smoking either before or after baseline.

Table 5 Odds ratios for incident known diabetes for categories of tobacco use, at baseline and during follow-up

Tobacco status between baseline and follow-up	a	b	c	d
Consistent no tobacco (ref. group)	1.00	1.00	1.00	1.00
Consistent exclusive snus users	0 cases	0 cases	0 cases	0 cases
Consistent exclusive smokers	4.51 (1.35–15.0)	4.63 (1.37–15.6)	5.37 (1.52–19.0)	4.61 (1.37–15.5)
Ex-smokers	4.34 (1.61–11.7)	3.20 (1.16–8.81)	3.70 (1.30–10.6)	3.13 (1.13–8.67)
Ex-snus users[e]	1.34 (0.16–11.3)	1.75 (0.20–15.1)	1.66 (0.19–14.7)	1.72 (0.20–14.8)
Smokers who switched to snus	2.41 (0.59–9.8)	3.24 (0.78–13.5)	3.08 (0.71–13.0)	3.25 (0.78–13.6)

OR could not be calculated for exclusive snus users due to no cases. Adjusted for: (a) age, (b) age and follow-up, (c) age, follow-up and waist, (d) age, follow-up and annual percentage weight gain between baseline and follow-up. [e]Notice a small number of observations and cases in this category, which makes estimates of ORs uncertain particularly after adjustments.

Table 6 Odds ratios of IGT, diabetes and PGT by OGTT associated with tobacco use. Population at risk for IGT and PGT were subjects with normal glucose tolerance at baseline. For the calculation of ORs for diabetes subjects with IGT at baseline were also included in population at risk

	Normal GT	IGT		Diabetes		PGT	
Tobacco use	*n*	*n*	OR (CI)[a]	*n*	OR (CI)[a]	*n*	OR (CI)[a]
Consistent no use	217	32	1.00	6	1.00	38	1.00
Consistent exclusive smokers	25	3	0.68 (0.19–2.44)	1	0.66 (0.08–5.58)	4	0.77 (0.25–2.41)
Consistent exclusive snus users	38	1	0.23 (0.03–1.80)	1	0.91 (0.10–8.01)	2	0.45 (0.10–2.04)
Ex-smokers[b]	92	9	0.48 (0.21–1.08)	7	1.27 (0.48–3.34)	16	0.73 (0.38–1.43)
Ex-snus users[c]	20	2	0.75 (0.16–3.57)	3	3.97 (0.86–18.33)	5	1.85 (0.60–5.70)
Smokers who switched to snus[d]	47	9	1.18 (0.51–2.74)	0	0 cases	9	1.05 (0.46–2.44)
Total	439	56		18		74	

[a]Adjusted for age, waist and length of the follow-up period. [b]Ex-smokers, without any history of snus using, who quit before baseline or during the follow-up. [c]Ex-snus users, without any history of smoking, who quit before baseline or during the follow-up. [d]Snus users with history of smoking either before or after baseline.

distinctively risk factors for type 2 diabetes, a new observation is that the use of snus does not seem to carry the same increased risk. The estimates for snus users are slightly, but insignificantly, elevated with wide confidence intervals and compatible, at the most, with an excess risk that is much smaller than that of smokers. In former smokers and snus users, the risk of prevalent PGT was somewhat increased, but not significantly so.

Ever being a smoker increased the risk of having a known diagnosis of diabetes, more so being an ex-smoker than current smoker. In a cross-sectional design this may be due to the fact that once a person is being diagnosed with diabetes he will strongly be urged to stop smoking. Thus, causality between smoking cessation and diabetes cannot be claimed from these findings. In contrast, ever being a snus user did not significantly increase kDM in excess of that of nontobacco users.

By using an OGTT, cases of undiagnosed diabetes and IGT can be identified, a procedure which could not be biased as the subjects are not aware of their PGT. Lifetime or current tobacco use was not associated with PGT in the cross-sectional part but this was slightly more common in ex-tobacco users.

Our incidence data based on more than 15 000 person-years form a stronger basis for analysis than the cross-sectional analysis. New cases of type 2 diabetes were diagnosed three to four times more often in smokers, whether current or former, than in nontobacco users or snus users. In contrast, no new cases of diabetes were found amongst exclusive snus users. It is possible that diabetes could be sought more actively by general practitioners in subjects who smoke, as a part of cardiovascular risk reduction, thereby leading to active case finding and inflation of our estimates. As many Swedish doctors look upon snus use a risk factor, the same argument should apply to the snus data.

To repeat an OGTT after many years, in subjects who previously had a normal glucose tolerance at baseline, avoids this caveat. In this smaller group, no significant risk increase was found in any tobacco group but five of 20 ex-snus users had a PGT giving an odds ratio of 1.85 (0.60–5.70) which may be a chance finding, but deserves further exploration.

This report is the first population-based, cross-sectional and longitudinal study of the influence of smokeless tobacco use, in the form of snus, on the occurrence of diabetes. Although over 3000 subjects were included, the number of diabetes cases is small, which is the major limitation of our results, leaving us with wide confidence intervals and risk of type II errors. However, the risk of misclassification of tobacco exposure is low because of the biochemical validation of tobacco use [10]. Case ascertainment of incident cases of diabetes was by OGTT in half of the subjects and careful scrutinizing of case records for all clinically diagnosed incident cases minimized the risk of misclassification bias. Confounding due to different levels of physical activity or alcohol consumption amongst users and nonusers of snus seem not to explain the results. Admittedly, we were not able to adjust for diabetes heredity but in the 1999 cohort information on diabetes in the family was provided. A family history of diabetes was just as common amongst current snus users as in nonusers.

In a review of 15 studies on smoking and diabetes [4], only one-third showed a positive relationship but most early studies were lacking in exposure data and the three largest and most recent studies, all found strong and consistent risk increases in heavy smokers [2–4]. In these studies, a strong dose–response gradient was reported. In the US Physicians' Health Study, 21 000 men were followed for 12 years and reported a multivariate-adjusted risk of diabetes associated with current smoking (more than 19 cigarettes per day) of 1.7 [3]. Increased risk of diabetes in smokers has also been reported in women during long-term follow-up in the Nurses Health Study [2]. Quitting smoking reduces the risk to the rate of nonsmokers after 5 years in women, and after 10 years in men [4]. Studies using diabetes confirmed by measurement of blood glucose are scarce, but in a Japanese report current male smokers had a multivariate-adjusted relative risk of diabetes of 1.5 [14].

A cross-sectional study found an increased prevalence of type 2 diabetes, based on an OGTT, both in heavy smokers and snus users [8]. The results are based on 3218 Swedish men, aged 35–56 years, half of whom had a strong family history of diabetes and half of whom composed a randomly selected subset without any family history. Thus, the study includes 25% of those initially invited to participate and mixes two clearly different groups. Tobacco habits were classified as never, current or former use of snus or cigarettes. There were 13 cases of diabetes amongst 492 current snus users, giving a multivariate-adjusted odds ratio of 1.5 (CI 0.8–30). All cases, except one, consumed more than three boxes snus per week, thus the odds ratio for this group versus never users was 2.7 (1.3–5.5) and similar to that of heavy smokers. Based on only four cases of diabetes amongst 121 snus users who never smoked, the odds ratio for diabetes increased to 3.9 (CI 1.1–14). Calculations were adjusted for age and BMI categories, family history of diabetes, physical activity and alcohol consumption but not for waist circumference. An interaction with family history was evident for smokers but not for snus users. There was no impact on the prevalence of IGT, neither for smokers, nor for snus users, and no consistent pattern in insulin resistance (by HOMA) or insulin response.

We could not reproduce these results, which may be due to the fact that the previous study included such large group with strong heredity for type 2 diabetes, thus being more vulnerable for putative risk factors. However, we included data on the incidence of both diagnosed and unknown diabetes, thereby extending the investigations much further without any evidence that current snus use predicted diabetes in the general population.

Snus and glucose metabolism

In a small study of university students, blood glucose did not differ between nonusers, snus users or smokers, although the two latter groups had higher serum insulin levels, and urinary cortisol excretion was higher in smokers [15, 16]. Similar glucose levels in nonusers and snus users had also been reported in other studies [17]. In a previous report from the northern Sweden MONICA study, the 1990 cohort was explored regarding tobacco habits and metabolic variables, whilst tobacco use was validated with plasma nicotine and cotinine measurements in a subset of 321 subjects [10]. Smoking men had higher waist-hip ratio than nonsmokers and snus users but fasting and postload glucose and insulin levels did not differ between groups.

Smokers and long-term users of nicotine gum are insulin-resistant in euglycaemic clamp studies, and acute smoking, but not snus exposure, impairs insulin sensitivity [18–21]. The mechanism behind the relationship between smoking and insulin resistance is unclear but muscle biopsies in habitual smokers show that basal glucose transport is increased and insulin-stimulated glucose transport is impaired [22].

Explanations of the association between smoking and diabetes

The importance of abdominal obesity for the development of type 2 diabetes, as measured by waist-hip ratio or waist circumference, was pointed out almost 20 years ago [23, 24]. Smoking, current as well as past, has repeatedly been associated with increased abdominal obesity [10, 25–27] and in a cross-sectional study, adjustment for waist-hip ratio slightly attenuated the relation between smoking and prevalent self-reported diabetes [26]. It is therefore tempting to explain smokers increased risk of diabetes by their abdominal obesity, *i.e.* greater intraabdominal fat mass leading to insulin resistance. As none of the large prospective studies on

diabetes and smoking have made any adjustment for waist circumference, only for BMI, this question has remained unanswered. We chose to adjust for waist circumference but found very little change in the risk estimates. An alternative analysis, using BMI instead, gave similar results supporting the notion that abdominal obesity may not be the link between smoking and diabetes. It should be noted that the subjects included in the MONICA study were rather young and at baseline many of them were below the diabetes-prone age groups.

We confirm previous reports that smoking, current or former, is a risk factor for type 2 diabetes in men, especially clinically diagnosed, but cannot find any substantial increase of risk in users of Swedish snus.

Conflict of interest statement

None of the authors had any financial or other personal conflict of interest with regard to any of the sponsors.

The sponsors had no scientific input or other influence in regard to this project, including design, analysis, interpretation or preparation of the manuscript.

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