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Use of Swedish smokeless tobacco (snus) and the risk of Type 2 diabetes and latent autoimmune diabetes of adulthood (LADA)

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Abstract

Aims It has been suggested that moist snuff (snus), a smokeless tobacco product that is high in nicotine and widespread in Scandinavia, increases the risk of Type 2 diabetes. Previous studies are however few, contradictory and, with regard to autoimmune diabetes, lacking. Our aim was to study the association between snus use and the risk of Type 2 diabetes and latent autoimmune diabetes of adulthood (LADA).

Method Analyses were based on incident cases (Type 2 diabetes, $n = 724$; LADA, $n = 200$) and population-based controls ($n = 699$) from a Swedish case–control study. Additional analyses were performed on cross-sectional data from the Norwegian HUNT study ($n = 21\,473$) with 829 prevalent cases of Type 2 diabetes. Odds ratios (OR) were estimated adjusted for age, BMI family history of diabetes and smoking. Only men were included.

Results No association between snus use and Type 2 diabetes or LADA was seen in the Swedish data. For Type 2 diabetes, the OR for > 10 box-years was 1.00 [95% confidence interval (CI), 0.47 to 2.11] and for LADA 1.01 (95% CI, 0.45 to 2.29). Similarly, in HUNT, the OR for Type 2 diabetes in ever-users was estimated at 0.91 (95% CI, 0.75 to 1.10) and in heavy users at 0.92 (95% CI, 0.46 to 1.83).

Conclusion The risk of Type 2 diabetes and LADA is unrelated to the use of snus, despite its high nicotine content. This opens the possibility of the increased risk of Type 2 diabetes seen in smokers may not be attributed to nicotine, but to other substances in tobacco smoke.

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Introduction

Cigarette smoking is a known risk factor for Type 2 diabetes [1] and is associated with impaired insulin sensitivity [2], proposedly linked to exposure to nicotine [2]. Swedish moist snuff (snus) is a smokeless tobacco product traditionally used most frequently by men; the prevalence of snus use among women is low [3]. Users place a portion or sachet of snus between the gum and upper lip [4]. The nicotine content of snus is higher than that of cigarettes [5]; it may consequently also promote Type 2 diabetes. Few studies have addressed this question and the results are inconclusive [6–8]. Smoking is common among snus users, and one reason for the conflicting results may be insufficient adjustment for smoking. One way to handle this confounding factor is to restrict the analyses to those who have never smoked. However, studies conducted to date have been too small to allow for such analyses. Also, previous studies have not had the power to analyse the impact of different degrees of snus use on Type 2 diabetes.

Nicotine is known to have anti-inflammatory [9] and immune-modulating [10,11] effects, which, theoretically, might increase or decrease the risk of autoimmune diabetes. In a previous study, smokers displayed a reduced risk of latent autoimmune diabetes of adulthood (LADA) [12]. It could be hypothesized that snus with its higher nicotine

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What's new?

- The risk of Type 2 diabetes and latent autoimmune diabetes of adulthood (LADA) is not significantly affected by the use of snus, despite its high nicotine content.
- These results raise the possibility that the excess risk of Type 2 diabetes seen in smokers is due to components of tobacco smoke other than nicotine.

content may have a stronger protective effect than smoking. In line with that notion, snus has been linked to a reduced risk of multiple sclerosis, which is also an autoimmune disease [13]. Whether snus use indeed reduces the risk of autoimmune diabetes remains to be investigated.

The aim of this study was to clarify the role of snus use in the development of Type 2 diabetes and LADA, taking into account dose and duration of use, and co-exposure to smoking. These clarifications are important because 20% of men in Sweden use snus on a daily basis [14] and its use is steadily on the rise in Norway and the USA [15].

Methods

ESTRID study

This study was based on data from the epidemiological study of risk factors for LADA and Type 2 diabetes (ESTRID) [16]. ESTRID is a sub-study of All New Diabetes in Scania (ANDIS; http://andis.ludc.med.lu.se). ANDIS is a large-scale study with the aim of registering all new cases of diabetes in the region of Scania (Southern Sweden; ~ 1 300 000 inhabitants) to improve the classification of diabetes into subgroups on the basis of genetic and phenotypic information. All people with new-onset LADA recorded in ANDIS since 2010, together with a random sample of people with Type 2 diabetes (four per LADA case), were invited to participate in the ESTRID. Controls aged ≥ 35 years were randomly selected from the population of Scania without diabetes. Six controls were selected per LADA case, corresponding to one control per case of diabetes (LADA or Type 2). ESTRID is a density-sampled case–control study [17]; it included incident cases and controls that were matched according to participation date and residential area [17]. In 2012, ESTRID expanded the recruitment to All New Diabetes in Uppsala (ANDIU; http://www.andiu.se/), a sister study to ANDIS conducted in the County of Uppsala (middle of Sweden; ~ 300 000 inhabitants) (Fig. S1).

This study is based on cases and controls collected until July 2015, with a participation rate of 81% (cases) and 66% (controls). The analysis was restricted to men because snus use is very rare in women (4.3% of female participants). Those eligible for the current investigation were thus all men with complete data on snus use and covariates of interest, including 200 LADA cases, 724 Type 2 diabetes cases and 699 controls. Of the participants, 97% came from Scania and 3% from Uppsala. Each participant provided informed consent and ethical approval was obtained from ethical review board in Stockholm.

Tobacco habits and covariates

Participants in ESTRID filled out an extensive questionnaire covering lifestyle, health and sociodemographic factors. People with diabetes received questionnaires as close as possible to the time of diagnosis. Questions regarding lifetime use of snus included number of snus boxes consumed per week (each containing 25–50 g), separate for every period, and we used this to calculate the duration of snus use. One box-year was defined as consuming one box of snus per day for one year (calculated in ever-snus users). In addition, intensity of snus use was assessed in two categories in ever-snus users (light, < 5 boxes/week; and heavy, ≥ 5 boxes/week). Information on smoking was obtained in a similar fashion. The cumulative dose of smoking (pack-year) was assessed in ever-smokers. One pack-year was regarded as smoking 20 cigarettes per day for one year. We defined an index date for each case as the year of diagnosis, and for each control as the year of participation. The exposure to different forms of tobacco was assessed for the period prior to the index year.

Classification of people with diabetes

All people diagnosed with diabetes within the healthcare system of each county provided blood samples for serological analyses upon diagnosis. Glutamic acid decarboxylase antibodies (GAD antibodies) were measured by enzyme-linked immunosorbent assay (RSR Ltd, Cardiff, UK). The cut-off for positivity was 10 IU/ml [18]. At a cut-off level of 10.7 IU/ml, the sensitivity was 84% and the specificity was 98% [18]. C-Peptide status was analysed by IMMULITE 2000 (Siemens Healthcare Diagnostics Product Ltd, Llanberis, UK) or by Cobas e 601 analyser (Roche Diagnostics, Mannheim, Germany) [19]. People with diabetes with age-at-onset ≥ 35 years were classified as having LADA if they were GAD antibody positive (≥ 10 IU/ml) with C-peptide ≥ 0.2 nmol/l (IMMULITE)/or ≥ 0.3 nmol/l (Cobas e 601), and as Type 2 diabetes cases if they were GAD antibody negative (< 10 IU/ml) with C-peptide ≥ 0.6 nmol/l (IMMULITE)/or ≥ 0.72 nmol/l (Cobas e 601). This is in line with generally used criteria for defining LADA [20], except for C-peptide levels, which were used as an indicator of preserved insulin secretion. Fasting plasma glucose and C-peptide measurements were used to calculate the parameters homeostasis model assessment of insulin resistance (HOMA-IR) to estimate insulin resistance and HOMA-%B to assess β-cell function [21].

Norwegian HUNT study

HUNT is a large population-based study which consists of three consecutive health surveys conducted between 1984 and 2008 in the Nord-Trøndelag County in Norway [22]. Information on snus use was available for the HUNT3 survey, performed between 2006 and 2008. All inhabitants aged ≥ 20 years were invited to participate in the HUNT3 survey. The attendance rate was 54% (n = 50 839). We restricted the analyses to men (n = 21 473) because of the low prevalence of snus use among women (4.4%). People with Type 2 diabetes were diagnosed at ≥ 35 years and were GAD antibody negative (< 0.08 antibody index; n = 829). GAD antibody positivity was used to identify adult-onset autoimmune diabetes (n = 41; including people with LADA and Type 1 diabetes with adult onset), but as the number of affected individuals who used snus was so small (n = 10), these persons were omitted from further analyses.

Information on snus use and other lifestyle factors was collected by questionnaire. Participants were asked whether they had ever used snus (on a daily basis/occasionally) and if so, the number of boxes consumed per month. 'Ever' consumers were classified as light (< 3 boxes/week) and heavy (≥ 3 boxes/week) users. The HUNT surveys were conducted according to regulations from the Norwegian Data Inspectorate and the Regional Committee for Medical Research Ethics, including informed consent from participants.

Statistical methods

Conditional logistic regression (matched for participation date and residential) was used to analyse ESTRID data to estimate the association between snus use and Type 2 diabetes and LADA in terms of the odds ratio (OR) and its 95% confidence interval (CI) (SAS 9.4; SAS Institute, Cary, NC, USA). OR values were interpreted as incidence rate ratios because this case–control study included incident cases and controls sampled by incidence density sampling method (i.e. controls are sampled from the risk set each time a case is diagnosed) [17]. Cross-sectional data was used to calculate ORs by logistic regression models. All analyses were adjusted for age (years, continuous), BMI (calculated as kg/m^2, continuous), family history of diabetes (yes/no) and smoking (pack-year, continuous), unless otherwise stated. Further adjustment for educational level, alcohol consumption and physical activity did not alter the results (change in OR < 10%).

Results

General characteristics of the study populations

In ESTRID, mean age was 63 years in people with Type 2 diabetes, 57 years in people with LADA and 58 years in controls (Table 1). Compared with people with LADA, those with Type 2 diabetes were older and heavier, and had higher prevalence of a family history of diabetes and lower educational level. People with LADA were less insulin resistant, had lower levels of HOMA-β and were more likely to be insulin treated (44% of LADA vs. 6% of Type 2 diabetes). The median duration of diabetes was 5.4 months in people with Type 2 diabetes and 8.0 months in the group with LADA.

Compared with ESTRID participants, those taking part in HUNT were slightly older and leaner, and had lower

Table 1 Characteristics of men with Type 2 diabetes and LADA from ANDIS/ANDIU and controls participating in ESTRID, 2010–2015

	Controls	Type 2 diabetes	LADA	*P*-value*
Characteristics				
No. individuals	699	724	200	–
Age, mean, years (SD)	58 (13)	63 (10)	57 (12)	< 0.0001
Low education level, *N* (%)	176 (25)	257 (36)	49 (24)	0.0038
BMI, mean, kg/m^2 (SD)	26.7 (3.8)	30.6 (5.0)	28.1 (4.9)	< 0.0001
Overweight (25 ≤ BMI), *N* (%)	454 (65)	674 (93)	145 (72)	< 0.0001
Physically inactive, *N* (%)	113 (16)	167 (23)	42 (21)	0.5676
Ever snus user, *N* (%)	222 (32)	209 (29)	64 (32)	0.4308
Never-smoker, *N* (%)	326 (47)	243 (34)	87 (43)	0.0156
Family history of diabetes, *N* (%)	154 (22)	340 (47)	75 (37)	0.0198
Non-drinkers, *N* (%)†	53 (8)	73 (10)	19 (9)	0.8942
Insulin treatment, *N* (%)‡	–	42 (6)	86 (44)	< 0.0001
C-peptide, mean (SD), nmol/l‡	–	1.30 (0.56)	0.83 (0.57)	< 0.0001
HOMA-IR, mean (SD)‡	–	5.9 (13)	5.4 (12)	0.6650
HOMA-β, mean (SD)‡	–	68 (37)	45 (37)	< 0.0001
GAD antibodies, median (interquartile range), IU/ml‡	–	–	128 (20–250)	

ANDIS, all new diabetes in Scania study; ESTRID, epidemiological study of risk factors for LADA and Type 2 diabetes; LADA, latent autoimmune diabetes of adulthood; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostatic model assessment of β-cell function; GAD, glutamic acid decarboxylase.
*p for difference between LADA and Type 2 diabetes.
†Non-drinkers including abstainers and former drinkers of alcohol.
‡The information is available only for people with Type 2 diabetes and LADA.

Table 2 Characteristics of men with and without diabetes in the HUNT3 survey (2006–2008)

	Individuals without diabetes	Type 2 diabetes
Characteristics		
No. individuals	2 0603	829
Age, mean, years (SD)	53 (15)	65 (10)
Low education level, *N* (%)	4 124 (27)	290 (39)
BMI, mean, kg/m^2 (SD)	27.4 (3.7)	29.6 (4.4)
Overweight (25 ≤ BMI), *N* (%)	15 187 (73)	724 (87)
Physically inactive, *N* (%)	5 529 (27)	218 (26)
Ever snus user, *N* (%)	5 777 (28)	157 (19)
Never smoker, *N* (%)	8 798 (43)	211 (25)
Family history of diabetes, *N* (%)	7 570 (37)	597 (72)
Non-drinkers, *N* (%)*	493 (3)	35 (5)
C-peptide, mean (SD), nmol/l†	–	0.86 (0.48)

*Non-drinkers including abstainers and former drinkers of alcohol.
†The information is available only for people with Type 2 diabetes.

prevalence of smoking (Table 2). The prevalence of ever-snus use in HUNT (28%) was as common as in ESTRID (30%).

Comparing the characteristics of participants by tobacco use shows that snus users were younger, less likely to have a low level of education, more physically active, and less likely to be alcohol abstainers compared with smokers and those who do not use tobacco (Table S1). The findings were similar in HUNT and ESTRID, and no other clear differences were seen between the groups.

Snus use and Type 2 diabetes

No association was observed between snus use and Type 2 diabetes in ESTRID (OR, 0.96; 95% CI, 0.67 to 1.37) (Table 3) or in HUNT (OR, 0.91; 95% CI, 0.75 to 1.10) (Table 4). In never-smokers, high snus consumption (ever-users) was not associated with Type 2 diabetes in either ESTRID (Table 3) [OR, 1.01; 95% CI, 0.42 to 2.41 (≥ 5 box/week)] or HUNT [OR, 0.89; 95% CI, 0.21 to 3.78 (≥ 3 boxes/week)] (Table 4). Additional adjustment for educational level, alcohol consumption and physical activity did not change the results [OR, 1.02; 95% CI, 0.46 to 2.26 (≥ 10 box/year) in ESTRID]. Raising the cut-off in ESTRID to ≥ 7 boxes/week indicates an OR of 1.23 (95% CI, 0.34 to 4.47) in ever-users, the results were similar in current heavy snus users (OR, 1.23; 95% CI, 0.30 to 5.12).

Snus use and LADA

In ESTRID, there was no indication of an excess risk of LADA in snus users, but the confidence limits were wide. In never-smokers, OR was estimated at 0.67 (95% CI, 0.24 to 1.86) for ≥ 5 box/week and at 1.01 (95% CI, 0.45 to 2.29) for ≥ 10 box-year (Table 5).

Co-exposure to smoking and snus use

Combining exposure from snus use and cigarettes showed that only smoking was associated with the risk of diabetes (Tables S2 and S3). In ESTRID, those who only smoke cigarettes ('ever') had increased risk (OR, 1.59; 95% CI, 1.16 to 2.18) of Type 2 diabetes (the details are reported

Table 3 Odds ratio of Type 2 diabetes in relation to snus use in men, results from ESTRID, 2010–2015

	Overall				Smoking status					
					Ever-smokers			Never-smokers		
	No. controls	No. cases	Age adjusted OR (95% CI)	Adjustment for age, smoking, BMI and FHD OR (95% CI)	No. controls	No. cases	OR (95% CI)*	No. controls	No. cases	OR (95% CI)
Snus use										
Never	477	515	Reference	Reference	223	310	Reference	223	205	Reference
Former	89	80	0.90 (0.63–1.28)	0.63 (0.41–0.95)	58	58	0.63 (0.39–1.37)	104	11	0.53 (0.20–1.39)
Current	133	129	1.13 (0.84–1.53)	0.96 (0.67–1.37)	92	92	0.91 (0.39–1.01)	36	27	1.17 (0.58–2.37)
Boxes per week (ever snus users)										
Never	477	515	Reference	Reference	223	310	Reference	254	205	Reference
Light snus users (< 5)	161	143	0.90 (0.69–1.20)	0.78 (0.56–1.09)	115	121	0.78 (0.53–1.14)	46	22	0.83 (0.41–1.71)
Heavy snus users (≥ 5)	55	62	1.54 (1.00–2.36)	0.95 (0.57–1.58)	29	46	0.92 (0.49–1.72)	26	16	1.01 (0.42–2.41)
Box-years in ever snus users										
Never	388	390	Reference	Reference	223	310	Reference	254	205	Reference
< 10	123	92	0.89 (0.66–1.20)	0.74 (0.52–1.06)	104	105	0.77 (0.52–1.15)	39	13	0.74 (0.31–1.77)
≥ 10	55	68	1.44 (0.99–2.10)	1.05 (0.67–1.63)	36	60	1.00 (0.57–1.74)	32	22	1.00 (0.47–2.11)

ESTRID, epidemiological study of risk factors for LADA and Type 2 diabetes; OR, odds ratio; FHD, family history of diabetes.
*OR adjusted for age, BMI and family history of diabetes.

Table 4 Odds ratio of Type 2 diabetes in relation to snus use in men, results from HUNT3 survey, 2006–2008

	Overall				Smoking status					
					Ever-smokers			Never-smokers		
	No. individuals without diabetes	No. cases	Age adjusted OR (95% CI)	Adjustment for age, smoking, BMI and FHD OR (95% CI)	No. individuals without diabetes	No. cases	OR (95% CI)*	No. individuals without diabetes	No. cases	OR (95% CI)*
Snus use										
Never	14 826	672	Reference	Reference	7 807	488	Reference	7 019	184	Reference
Ever	5 777	157	1.00 (0.83–1.20)	0.0.91 (0.75–1.10)	3 998	130	0.86 (0.70–1.07)	1 779	27	1.12 (0.72–1.72)
Boxes per week (ever snus users)										
Never	14 804	669	Reference	Reference	7 791	488	Reference	7 013	181	Reference
Light snus users (< 3)	5 073	130	0.96 (0.79–1.18)	0.88 (0.72–1.08)	3 521	107	0.82 (0.65–1.03)	1 552	23	1.15 (0.72–1.82)
Heavy snus users (≥ 3)	438	9	1.15 (0.58–2.26)	0.92 (0.46–1.83)	262	7	0.90 (0.41–2.00)	176	2	0.89 (0.21–3.78)

OR, odds ratio; FHD, family history of diabetes.
*OR adjusted for age, BMI and family history of diabetes.

elsewhere [23]), a risk that was even more pronounced in heavy smokers (OR, 2.20; 95% CI, 1.40 to 3.45); whereas no increased risk was seen in those who use only snus, or in those who combine snus use and smoking (Table S2). Similar findings were seen in HUNT; in those who only smoke, the OR for Type 2 diabetes was 1.63 (95% CI, 1.36 to 1.96) (Table S3). As for Type 2 diabetes, any combination of tobacco use was unrelated to the risk of LADA, the OR of LADA for individuals combining snus and cigarettes consumption was estimated at 0.97 (95% CI, 0.62 to 1.52) (Table S2).

Discussion

The main finding of this study is the lack of an association between snus use and Type 2 diabetes and LADA, this being in contrast to the effects of smoking documented here and previously [1]. For Type 2 diabetes, our negative findings regarding snus use agree with observations from the MONICA study from Northern Sweden [8], but are in contrast to one cross-sectional [6] and one prospective study [7] based on the Stockholm Diabetes Prevention Program. Confounding from smoking may have contributed to conflicting results. Notably, we did see indications of an increased risk of diabetes in snus users, which disappeared when the analysis was restricted to those who had never smoked. In previous studies, small numbers hampered the analyses of snus users who had never smoked; none of those studies included more than six cases [6–8]. In this context, it is worthy of note that there are no data on the risk of diabetes in relation to the use of other forms of smokeless tobacco such as chewing tobacco. However, US data indicate that use of smokeless tobacco (chewing tobacco) is unrelated to mortality in people with diabetes [24].

We confirm epidemiological and experimental studies linking smoking to an increased risk of Type 2 diabetes [1], proposedly mediated by mechanisms including insulin resistance [2]. Why smoking, but not snus use associates with risk of diabetes is not clear, but this fits with previous findings in cardiovascular diseases such as stroke and myocardial infarction [25–27], indicating that the risk induced by smoking by far exceeds that related to snus use. A lesser degree of toxicity may be due to lower levels of many toxins, e.g. nitrosamine in snus than in cigarettes [28]. In this context, it should be noted that pipe smoking, which provides an exposure to nicotine that is fairly similar to cigarette smoking, is associated with a lower risk of heart disease than cigarette smoking [29], suggesting that substances in cigarette smoke other than nicotine might be important for the risk of Type 2 diabetes.

We previously found a reduced risk of LADA in smokers [12] and based on this we hypothesized that snus may be associated with an even more pronounced risk reduction, due to its high nicotine content. By contrast, data from ESTRID indicate that snus use is unrelated to the risk of LADA and

Table 5 Odds ratio of LADA in relation to snus use in men, results from ESTRID, 2010–2015

	Overall			Smoking status					
			Age and sex adjusted	Adjustment for age, smoking, BMI and FHD	Ever-smokers			Never-smokers		
	No. controls	No. cases	OR (95% CI)	OR (95% CI)	No. controls	No. cases	OR (95% CI)*	No. controls	No. cases	OR (95% CI)*
Snus use										
Never	477	136	Reference	Reference	223	66	Reference	254	70	Reference
Former	89	19	0.69 (0.40–1.18)	0.60 (0.34-1.04)	58	15	0.70 (0.36–1.35)	31	4	0.46 (0.15–1.43)
Current	133	45	1.11 (0.74–1.66)	1.01 (0.67-1.54)	92	32	1.08 (0.64–1.80)	41	13	0.98 (0.45–2.11)
Boxes per week (ever snus users)										
Never	477	136	Reference	Reference	223	66	Reference	254	70	Reference
Light snus users (< 5)	161	39	0.79 (0.52–1.18)	0.71 (0.46–1.09)	115	29	0.76 (0.46–1.27)	46	10	0.75 (0.34–1.67)
Heavy snus users (≥ 5)	55	22	1.36 (0.78–2.36)	1.18 (0.67–2.10)	29	16	1.64 (0.80–3.35)	26	6	0.67 (0.24–1.86)
Box-year in ever snus users										
Never	477	136	Reference	Reference	223	66	Reference	254	70	Reference
< 10	143	28	0.64 (0.41–1.01)	0.56 (0.35–0.91)	104	23	0.67 (0.39–1.16)	39	5	0.46 (0.16–1.31)
≥ 10	68	33	1.61 (1.00–2.59)	1.45 (0.89–2.37)	36	22	1.82 (0.96–3.46)	32	11	1.01 (0.45–2.29)

LADA, latent autoimmune diabetes of adulthood; ESTRID, epidemiological study of risk factors for LADA and Type 2 diabetes; FHD, family history of diabetes; OR, odds ratio.
*OR adjusted for age, BMI and family history of diabetes.

furthermore, that heavy smoking may increase the risk [23]. These findings are compatible with both negative and beneficial effects of nicotine on the pathogenesis of LADA and the lack of association with overall risk may reflect that a potential beneficial effect on autoimmunity is counterbalanced by increased insulin resistance. However, with regard to other autoimmune diseases such as rheumatoid arthritis [30] and Crohn's disease [31], for which insulin resistance is not part of the pathogenesis, similar null results have been reported in relation to snus use.

One of the strengths of this study is that it was population-based using incident cases that were identified in large well-characterized diabetes registries (ANDIS/ANDIU) with randomly selected population controls. The number of cases was relatively large and we had detailed information on the history of tobacco use and a large number of potential confounders. Recall bias is a potential problem because both studies were based on retrospective data of tobacco use. ESTRID is based on incident cases, which minimizes this problem; furthermore, only information from the years prior to diagnosis was included in our analysis. The HUNT data were based on prevalent cases and hence, recall bias may be more pronounced, e.g. people with diabetes may have quit using tobacco several years ago following diagnosis, thereby underestimating previous use. Importantly, the association between smoking and Type 2 diabetes in both HUNT and ESTRID was similar to reports from prospective studies with tobacco habits assessed several years prior to onset [1,12]. Furthermore, by restricting a major part of our analyses to never-smokers, we avoid bias that may arise from people shifting from smoking to snus use or vice versa following diagnosis. This is the most extensive analysis conducted to date on the risk of Type 2 diabetes in relation to snus use. As a consequence, we could perform separate analysis in never-smokers, thereby minimizing confounding from smoking. However, we cannot exclude the possibility that snus use has a small effect on the risk of diabetes, which we did not have enough power to detect. With our current sample size and snus use prevalence (30%), we have 85% power to detect an OR of 1.5 (or 0.65) for Type 2 diabetes. Further, the number of heavy snus users was limited and thus we cannot exclude an effect in the highest consumption group.

It has been suggested that tobacco use is related to unfavourable social and lifestyle behaviours in general [32,33]. By contrast, the snus users investigated here were younger, more physically active, and had higher educational levels than both smokers and those who had never used tobacco, which may reduce their risk of diabetes. We did find that the results persisted after adjustment for a number of factors, including physical activity and education; however, it is possible that the lack of association between snus and Type 2 diabetes is due to residual confounding.

In conclusion, our findings extend to diabetes previous notions that snus is generally less harmful than other tobacco products [25–27,34]. However, even though this is the largest study on snus use and diabetes to date, further studies with an even larger sample size would be necessary in order to rule out modest effects of snus use on the risk of diabetes and effects pertaining to very high consumption.

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Competing interests

None declared.

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Author contributions

All authors contributed in writing the manuscript, interpretation of the data and critically reviewed the paper, and read and approved the final manuscript. BR was responsible for analysing the data and writing the paper. BR had access to all data in this study and takes responsibility for the integrity of the data and accuracy the data analysis.

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Supporting Information

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

Figure S1. ESTRID study design.
Table S1. Characteristics of individuals according to tobacco consumption in ESTRID (2010–2015) and HUNT3 (2006–2008).
Table S2. OR of LADA and Type 2 diabetes for different combination of smoking and snus use, results from ESTRID, 2010–2015.
Table S3. OR Type 2 diabetes for different combination of smoking and snus use, results from HUNT3 survey, 2006–2008.