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RESEARCH ARTICLE

Swedish Snuff (Snus), Cigarette Smoking, and Risk of Type 2 Diabetes

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Introduction: Cigarette smoking is a known risk factor for Type 2 diabetes, but evidence regarding former smoking and moist snuff (snus) use and Type 2 diabetes risk is inconclusive. This study investigated the relationships of cigarette smoking and Swedish snus use with the risk of Type 2 diabetes in a cohort of middle-aged and elderly participants.

Methods: Participants (N=36,742; age range=56−95 years) were followed for incident Type 2 diabetes and death between 2009 and 2017 through linkage to the Swedish National Patient, Prescribed Drug and Death Registers. Cox proportional hazards regression was used to obtain hazard ratios and 95% CIs adjusted for potential confounders, including physical activity, education, BMI, and alcohol intake. Analyses were conducted in 2021–2022.

Results: Former and current smoking was associated with an increased risk of Type 2 diabetes (hazard ratios [95% CI]=1.17 [1.07, 1.29] and 1.57 [1.36, 1.81], respectively). In those who stopped smoking, Type 2 diabetes risk remained elevated up to approximately 15 years after cessation. In participants who have never smoked, snus use was linked to a higher risk of Type 2 diabetes in the model adjusted for age and sex (hazard ratio [95% CI]=1.49 [1.04, 2.15]), but this was attenuated after multivariable adjustment (hazard ratio [95% Cl]=1.29 [0.89, 1.86]).

Conclusions: This study indicates that current and former smoking are associated with an increased risk of Type 2 diabetes in middle-aged and older individuals. There was less evidence of an association of snus use with the risk of Type 2 diabetes, suggesting that compounds other than nicotine may underlie the detrimental association of smoking with the risk of Type 2 diabetes.
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INTRODUCTION

The prevalence of Type 2 diabetes (T2D) is increasing worldwide, and it is important to study the modifiable risk factors for the prevention of T2D and its complications. Several cohort studies and meta-analyses have reported a link between active and passive cigarette smoking and an increased risk of T2D.[1] Moreover, a recent Mendelian randomization study provided genetic evidence of a causal association between smoking initiation and T2D.[2]

Smokeless tobacco (e.g., snuff, snus, and chewing tobacco) is sometimes considered a relatively safe alternative to cigarettes, especially among younger adults[3] and those who switch from cigarettes to smokeless tobacco.[4] The composition of smokeless tobacco products varies considerably, but the nicotine content of a single portion is usually comparable with that in a single cigarette.[5] However, the total amount of absorbed

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nicotine from smokeless tobacco use is greater than that from smoking cigarettes.[6,7] This may contribute to the development of T2D in both people who use combustible and smokeless tobacco because nicotine-induced insulin resistance has been previously described.[8] Oral moist snuff (snus) is the most common form of smokeless tobacco in Sweden. It has recently been estimated that 22% of Swedish men and 5% of women regularly use snus, although smoking rates are among the lowest among European countries and comprise 11% of women and men aged 16−84 years.[9]

Most cohort studies on the relationship between smoking and T2D have reported an increased risk of T2D in those who currently smoke.[10−12] Findings regarding former smoking are less consistent,[1] potentially because of an impact of time since quitting. A few studies, mainly conducted in Sweden, have explored the association between snus use and the risk of T2D, but the results are inconclusive.[11,13−15] The risk of developing T2D increases with age; however, little is known about the link between snus use and the risk of diabetes in older individuals, especially after taking smoking history into account.

The objective of this study was to explore the associations of cigarette smoking (particularly time since smoking cessation) and Swedish snus use with the risk of T2D in a population-based cohort of middle-aged and older women and men. The relationship between snus use and T2D was explored in the entire sample as well as in a subgroup of people who have never smoked.

METHODS

Study Population

Data from the Swedish Infrastructure for Medical Population-based Life-course Environmental Research were used. Details of the study cohorts are shown in Appendix Text 1 (available online). In total, 47,812 participants completed structured questionnaires regarding lifestyle and other risk factors for T2D and other diseases in 2008/2009. In this analysis, participants who died before the start of follow-up as well as those who had missing information on snus use or cigarette smoking were excluded. Furthermore, 4,420 participants were excluded owing to a previous primary/secondary diagnosis of any type of diabetes mellitus on the basis of in- and outpatient data; the International Classification of Diseases (ICD), Eight Revision (Codes 249−250); ICD, Ninth Revision (Code 250); and ICD-10 (Codes E10, E11, and E14) or the National Diabetes Register or who had received a prescription of glucose-lowering drugs (based on the Anatomical Therapeutic Chemical Classification [ATC] Code A10) before the start of baseline or self-reported diabetes at baseline (Appendix Figure 1, available online). Of them, 1,033 were diagnosed with Type 1 diabetes on the basis of information from the Swedish patient and diabetes registers. This left 36,742 eligible participants (16,356 women and 20,386 men). The study was conducted following the Helsinki declaration, and all participants provided written informed consent. The Swedish Ethical Review Authority approved the study.

Measures

Information on education, weight, height, cohabitation, smoking, snus use, physical activity, alcohol, and coffee consumption over the preceding year was obtained from the structured questionnaires. Participants reported whether they used snus regularly (i.e., >5 portions of snus per week) with the following alternatives: *no, I have never used snus regularly* (defined as never snus users); *Yes, I use snus* (defined as current snus users); and *Yes, but I quit using snus* (defined as former snus users). Moreover, former snus users (n=2,588, 7% of total) informed how many years previously they stopped using snus. Most ever-using participants stopped using snus long before the start of the follow-up (mean [SD] =19.1 [14.4] years, available n=2,562); therefore, former snus users and never users were combined into one group for analysis. Thus, snus use was categorized as non-use (i.e., including participants who never used snus regularly or former snus users) and current snus use (at baseline). In addition, participants reported whether they smoked cigarettes regularly (i.e., >5 cigarettes per week) with the following answer alternatives: *no, I have never smoked cigarettes regularly* (defined as never smokers); *Yes, I smoke* (defined as current smokers); and *Yes, but I stopped smoking* (defined as former smokers). Former smokers reported how many years previously they had quit smoking (mean [SD]=24.7 [13.3] years, available n=14,004).

Information on T2D or no diabetes was ascertained by linkage to the Swedish National Patient Register using the unique personal identification number, which is assigned to all Swedish residents. The Patient Register contains information on all inpatient diagnoses since 1987 and outpatient specialist care since 2001.[16] In addition, available records of the prescriptions of glucose-lowering drugs (ATC Code A10) retrieved from the Swedish Prescribed Drug Register,[17] which contains records of all dispensed prescribed drugs in Sweden since July 2005, were used. Incident cases were dated on the basis of the first available record containing the ICD-10 codes (E11 and E14, a main or secondary diagnosis) or ATC Code A10. Information on death was received from the Cause of Death Register. Participants were followed up from July 1, 2009 to the first date of diagnosis of T2D/prescription of glucose-lowering drug; death from any cause; or December 31, 2017, whichever occurred first.

Statistical Analysis

Descriptive data are shown as the number of participants (%) for categorical variables and as the mean (SD) for continuous variables. Cox proportional hazards regression models were used to obtain hazard ratios (HR) with 95% CI, with age as the time scale and sex as a stratification variable. The basic model included both cigarette smoking and snus use. In a multivariable model, the following covariates were added: education (less than high school, high school, or university), cohabitation (yes/no), walking/bicycling (never/seldom, <20 minutes/day, 20−40 minutes/day, >40 minutes/day), exercise (almost never, <1 hour/week, 1 hour/week, 2−3 hours/week, 4−5 hours/week, ≥5 hours/week), BMI (categorical variable <22.5 kg/m^2, 22.5−24.9 kg/m^2, 25.0−29.9 kg/m^2, or ≥30 kg/m^2), alcohol consumption (never drinkers, past or current drinkers of <1 drink/week, 1 to <7 drinks/week, 7 to <15 drinks/week, 15−21 drinks/week, >21 drinks/week), and coffee consumption (filtered or unfiltered coffee, cups/day). To further reduce confounding from smoking in the analysis of snus use

and T2D, additional analysis was conducted, including only participants who reported never smoking.

Most participants who stopped smoking reported how many years previously they had stopped smoking (available n=14,004). To investigate the risk of T2D by years since smoking cessation among former smokers, Cox regression analysis using restricted cubic splines for the time since smoking cessation with 3 knots and a reference age of 45 years was performed.[18] On the basis of the splines, numerical estimates for the time since smoking cessation in former smokers were presented.

Insulin prescription is becoming more common in patients with T2D,[19] but to avoid including participants with Type 1 diabetes, a sensitivity analysis was conducted in which insulin prescriptions (ATC Code A10A) as a sole indication of T2D were omitted, that is, ICD-10 codes E11 and E14, and noninsulin antidiabetic drugs were taken into account (ATC Code A10B). Another sensitivity analysis that was based on a subgroup of people who have never smoked was conducted, using never snus users as the reference group.

The Schoenfeld residuals test was applied to assess proportional hazards assumptions. The link of snus use or smoking status with T2D did not differ by sex (p for multiplicative interaction >0.05, sex was added as a covariate not as a stratification variable), and all analyses were performed for men and women combined. The proportion of missing data on potential confounders used in the analysis was ≤3%. A separate category was created for variables with missing data. The statistical analyses were conducted using Stata, Version 15.1 (StataCorp, College Station, TX).

RESULTS

Of the 36,742 participants, 5.5% reported current snus use, 38% reported former cigarette smoking, and 9% reported current smoking (Table 1). People who reported former and current cigarette smoking were more likely to be men, were somewhat younger, had lower educational attainment, had higher alcohol intake, and reported more snus use and higher coffee consumption than those who never smoked. Those who smoked at baseline had a lower level of physical activity and were more likely to report living alone but were less likely to have overweight or obesity than participants who never smoked. In contrast, those who stopped smoking were more likely to have overweight or obesity at baseline and more often reported not living alone than people who never smoked (Table 1). Participants who used snus were younger, had lower educational attainment, were more likely to be men, had higher alcohol intake and coffee consumption, were less physically active, reported more often not living alone and former and current smoking, and had higher BMI than people who have not used snus (Table 1).

Among the 36,742 women and men free of diabetes at baseline, 2,264 had an inpatient or outpatient diagnosis and/or antidiabetic treatment during 282,097 person-years of follow-up and were considered as having T2D. This corresponds to an incidence rate of 8.0 per 1,000 person-years. Among participants with unspecified diabetes on the first available record, 56 (53%) were later diagnosed with T2D. The mean age (SD) at diagnosis was 74.5 (7.3) years. The incidence of diabetes was higher among men than among women (7.2% vs 4.9%, respectively). An increased risk of T2D was found among people who reported former and current

Table 1. Baseline Characteristics of the Study Population According to Reports of Smoking and Snus Use at Baseline, N=36,742

Characteristics	Total	Smoking status			Snus use	
		Never smokers	Former smokers	Current smokers	Non-snus users	Current snus users
Number of participants	36,742	19,369	14,091	3,282	34,706	2,036
Age at baseline, years, mean (SD)	69.8 (7.9)	70.9 (8.3)	68.9 (7.5)	67.4 (6.7)	70.1 (7.9)	65.8 (6.7)
Men, %	55.5	49.6	64.1	53.4	53.3	93.3
Education >12 years, %	23.4	24.7	23.1	17.2	23.7	18.0
Cohabiting, %	70.3	68.9	74.4	61.0	69.9	77.2
Walking/bicycling >40 minutes/day, %	34.2	34.9	34.6	28.6	34.4	31.6
Exercise ≥ 2 hours/week, %	15.9	16.5	16.5	9.6	16.1	12.0
BMI, kg/m^2, %						
25.0–29.9	41.4	39.6	45.1	36.4	41.0	49.0
≥30.0	11.4	10.3	13.3	9.8	11.3	13.8
Cigarette smoking, %						
Former smokers	38.4				36.6	68.8
Current smokers	8.9				8.7	12.9
Current snus use, %		1.9	9.9	8.0		
Alcohol intake ≥15 drinks/week, %	3.6	2.3	5.2	4.2	3.4	7.3
Coffee consumption, cups/day, mean (SD)	2.7 (1.8)	2.5 (1.6)	2.8 (1.7)	3.6 (2.2)	2.7 (1.7)	3.2 (2.0)

Table 2. Hazard Ratios (95% CIs) of Type 2 Diabetes According to Cigarette Smoking and Snus Use in 36,742 Swedish Middle-Aged and Older Adults, 2009–2017

Tobacco use	Number of noncases	Number of cases	Basic model[a]	Multivariable model[b]
Total cohort (N=36,742)				
Cigarette smoking				
Nonsmokers	18,326	1,043	1.00 (ref)	1.00 (ref)
Former smokers	13,119	972	**1.24 (1.14. 1.36)**	**1.17 (1.07, 1.29)**
Current smokers	3,033	249	**1.51 (1.31, 1.74)**	**1.57 (1.36, 1.81)**
Current snus use				
Nonusers	32,609	2097	1.00 (ref)	1.00 (ref)
Current users	1869	167	1.11 (0.94, 1.30)	1.05 (0.89, 1.23)
Never smokers (*n*=19,369)				
Current snus use				
Nonusers	17,983	1,012	1.00 (ref)	1.00 (ref)
Current users	343	31	**1.49 (1.04, 2.15)**	1.29 (0.89, 1.86)

Note: Boldface indicates statistical significance ($p < 0.05$).
[a]The Cox proportional hazards regression model was adjusted for age (underlying time scale), sex (as a stratification variable), and snus use (in the analysis of smoking) or cigarette smoking (in the analysis of snus use).
[b]The Cox proportional hazards regression model was adjusted for the same factors as in the basic model and additionally for education, cohabiting status, walking/bicycling, exercise, BMI, alcohol intake, and coffee consumption.

cigarette smoking compared with those who reported never smoking (HRs [95% CIs]=1.17 [1.07, 1.29] and 1.57 [1.36, 1.81], respectively, $p \leq 0.001$) in models adjusted for snus use, age, sex, education, alcohol intake, coffee consumption, cohabitation status, walking/bicycling, exercise, and BMI (Table 2).

A multivariable analysis in those who stopped smoking using restricted cubic splines revealed that the risk of incident T2D decreased over time since quitting at baseline, but the increased risk appeared to remain for at least about 15 years after smoking cessation (Figure 1). The HRs (95% CIs) for T2D in the participants who stopped smoking 5, 10, 15, and 20 years before baseline compared with those who stopped at a reference of 45 years before were 1.53 [1.25, 1.87], 1.38 [1.14, 1.68], 1.26 [1.03, 1.54], and 1.16 [0.95, 1.43], respectively.

In contrast, current snus use was not linked to the risk of T2D (multivariable HR adjusted for smoking and other covariates=1.05 [95% CI=0.89, 1.23], p=0.58) (Table 2). When restricting the analysis to people who never smoked (n=19,369), current snus use was associated with an increased risk of T2D in the model adjusted for age and sex (HR [95% CI]=1.49 [1.04, 2.15], p=0.032), but the association was attenuated after adjustment for other potential confounders (HR=1.29 [95% CI=0.89, 1.86], p=0.17).

In the first sensitivity analysis, incident cases were dated on the basis of the first available record containing the ICD-10 codes (E11 and E14, as a main or secondary diagnosis) or ATC Code A10b, that is, noninsulin diabetes drugs only. This analysis revealed results similar to those presented in Table 2 (Appendix Table 1, available online). In another sensitivity analysis that was based on a subgroup of people who never smoked, the results for current snus use were very similar when using never snus users as a reference group. Former snus use

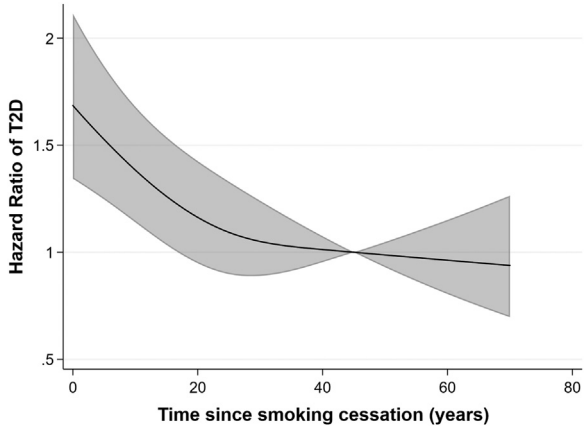

Figure 1. Multivariable hazard ratios (black solid line) and 95% CIs (gray area) of T2D according to years since smoking cessation in 14,004 former smokers.
Note: The Cox proportional hazards regression model was adjusted for age (underlying time scale), sex (as a stratification variable), education, alcohol intake, coffee consumption, cohabiting status, walking/bicycling, exercise, snus use, and BMI. The time since smoking cessation was modeled using a restricted cubic spline function with 3 knots and a reference of 45 years.
T2D, Type 2 diabetes.

was not associated with the risk of developing T2D (Appendix Table 2, available online).

DISCUSSION

In this large cohort study of 36,742 middle-aged and older individuals, we found that former and current smoking was associated with 17% and 57% increased risks of T2D, respectively. In those who stopped smoking, the risk of incident T2D decreases over time after quitting but remained elevated up to 15 years after cessation. The association of snus use with the risk of T2D was not statistically significant in the analyses adjusted for smoking that were based on the entire cohort. In participants who never smoked, snus use was linked to a higher risk of T2D in a basic model, but this relationship attenuated in a fully adjusted analysis.

Given that nicotine exposure may increase insulin resistance[8] and that the total amount of absorbed nicotine in snus is higher than that in cigarettes,[7] investigating the link between cigarette smoking, snus use, and incidence of T2D may shed light on the effect of nicotine on the risk of T2D. A strong association of former and current smoking with T2D observed in this study is consistent with the findings of previous cohort studies and meta-analyses.[1,10–12,20] Most but not all cohort studies have shown an increased risk of diabetes in current cigarette smokers.[10–12] However, the findings of the link between former smoking and T2D are inconsistent because several cohort studies did not observe an association,[21,22] and because the strength of the association differs by the time since quitting smoking.[1] Prospective studies of the influence of smoking cessation on the risk of T2D indicated that quitting smoking was linked to a higher risk of T2D during the first years of smoking cessation than continuing smoking, although the risk decreased over time to become lower than that of continuing smokers.[21,23] Weight gain during the first years of smoking cessation and systemic inflammation could partially explain the excess diabetes risk in new quitters.[23] The findings of this study indicate that although the risk of T2D in former smokers decreased over time since quitting, it may take >15 years of smoking cessation to decrease the risk of T2D to that of never smokers. Although the exact mechanism remains unclear, this may be in part related to the overall harm of smoking (e.g., systemic inflammation, smoking-induced pancreatic damage, insulin resistance, and metabolic dysregulation) and less healthy lifestyle during the years of smoking and increase in weight after smoking cessation.

The association of snuff use and subsequent risk of T2D is less well studied. In this study, no association between snus use and risk of T2D in the entire study population, in the analysis adjusted for age, sex, and smoking or in a model adjusted for other confounders, was observed, which is in line with the results from several cross-sectional and case-control studies.[13,15] In the analysis confined to participants who never smoked, a modestly higher risk of T2D could not be ruled out. Thus, in those who never smoked, snus use was linked to a higher risk of T2D in the age- and sex-adjusted model, but the relationship was attenuated in a fully adjusted model. A recent Swedish Twin Registry study showed an increased risk of T2D in those who used snus (n=40,247; HR=1.19, 95% CI=1.01, 1.41) in analyses adjusted for smoking and other confounders.[11] Likewise, a pooled analysis of 5 cohorts of 54,531 middle-aged never-smoking men (mean age at baseline 49 years), including 2,441 T2D cases, showed a 15% increased risk of T2D in individuals who used snus (HR=1.15, 95% CI=1.00, 1.32).[14] Given the inconsistency in the results, further large-scale studies of snuff use and T2D are needed.

Experimental studies have shown that nicotine absorption occurs more rapidly from smoking cigarettes than from using snuff, but the total amount of absorbed nicotine is higher for snuff products than for cigarettes.[6,7] Experimental and clinical evidence suggests that nicotine may induce insulin resistance[24,25] and increase concentrations of glucose counter-regulatory hormones (e.g., cortisol),[26] thereby increasing the risk of T2D. However, human experimental studies of the acute effect of nicotine (e.g., administered as a transdermal nicotine patch[27] or snus use[28]) on insulin sensitivity in apparently healthy participants who smoked have shown less pronounced evidence of impaired insulin sensitivity than studies of cigarette smoking exposure.[28] Likewise, another study has shown that participants who smoked cigarettes but not those who used snuff had increased urinary cortisol levels compared with those who have not used tobacco.[29] The findings of this study regarding the positive association of former and current smoking with the risk of T2D and lack of strong evidence of the link between snus use and T2D also suggest that combustion products or other constituents of cigarettes rather than nicotine may contribute to the development of T2D.

The important strengths of this cohort study are the large sample size that enables the stratification of participants according to cigarette smoking and snus use, the ability to adjust for potential confounders, and the large number of T2D cases. In addition, the objective assessment of incident cases was accomplished by linkage to nationwide population-based registers and the Prescribed Drug Register using the unique personal identity number. To ensure that the participants of this study were free from diabetes at baseline, exclusions of prevalent diabetes based on self-reports, nationwide

population-based registers, Prescribed Drug Register, and National Diabetes Register were performed. In addition, regression analysis with a restricted cubic spline function was used, which allowed us to evaluate a nonlinear risk of T2D in former smokers and visualize the risk at different time points after smoking cessation.

LIMITATIONS

This study has several limitations. Tobacco use was self-reported, and the information on the duration of snus use and smoking before baseline was not available. The proportion of participants who used snus in the study was relatively small compared with recent estimates of snus use in Sweden,[9] which could potentially be explained by the older age of participants in this study as well as the different time periods when the baseline information was collected. The number of T2D cases in those who used snus but never smoked was relatively low. Information on the potential confounders was collected at baseline, and some lifestyle characteristics (including smoking status and snus use) could change over time. Finally, the findings of this study are mainly applicable to Swedish moist snuff (snus), which has different characteristics from, for example, those of American snuff[30] or other smokeless tobacco products.

CONCLUSIONS

This study suggests that current and former smoking are associated with an increased risk of developing T2D in middle-aged and older participants. There was less evidence of an association of Swedish snus use with the risk of T2D, suggesting that compounds other than nicotine may have a larger adverse effect on the development of T2D.

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CREDIT AUTHOR STATEMENT

Olga E. Titova: Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing - original draft. John A. Baron: Writing - review & editing. Tove Fall: Writing - review & editing. Karl Michaëlsson: Funding acquisition, Writing - review & editing. Susanna C. Larsson: Conceptualization, Funding acquisition, Supervision, Writing - review & editing.

SUPPLEMENTAL MATERIAL

Supplemental materials associated with this article can be found in the online version at https://doi.org/10.1016/j.amepre.2023.01.016.

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