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ORIGINAL ARTICLE

Snus use during the life-course and risk of the metabolic syndrome and its components

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Abstract

Objective: We aimed to investigate the association between life-course exposure to snus and prevalence of the metabolic syndrome and its components in adulthood. *Design and method:* Tobacco habits at baseline (age 16) and three follow-ups (ages 21, 30 and 43) were assessed among 880 participants in a population-based cohort in Northern Sweden. Presence of the metabolic syndrome at age 43 was ascertained using the International Diabetes Federation criteria. Odds ratios and CIs for risk of the metabolic syndrome and its components by snus use at 16, 21, 30 and 43 years were calculated using logistic regression. Cumulative snus use was defined as number of life periods (1–4) with current snus use. *Results:* At age 43, 164 participants (18.6%) were current snus users. We found no association between exclusive snus use at the ages of 16, 21, 30 and 43 years and the metabolic syndrome at age 43 years. Snus use (among non-smokers) was associated with raised triglycerides and high blood pressure in crude analysis, but not in multivariable models. There was no association between cumulative snus use and risk of the metabolic syndrome. Cumulative snus use was associated with central obesity, raised triglycerides and impaired fasting glucose/diabetes mellitus type 2 in crude analyses, but not after adjustments. ***Conclusions:*** **The health consequences of snus exposure from adolescence to mid-adulthood do not seem to include increased risk of the metabolic syndrome or its components. The cardio-metabolic risk of dual exposure to snus and cigarettes may warrant further attention.**

Key Words: *Swedish moist snuff, snus, smokeless tobacco, metabolic syndrome, metsy, obesity, hypertension, triglycerides, life-course*

Background

Snus is a moist smokeless tobacco product. Most common in Sweden, with 18% of the male population being daily users, snus is also becoming increasingly popular worldwide [1]. The scientific evidence hitherto produced on health effects from snus use is generally weak [2]. With increasing use, and the suggestion to promote snus as a strategy for smoking cessation [3], there is need for more knowledge in this field.

Snus has been suggested as a possible risk factor for developing the metabolic syndrome, a concept including risk factors strongly associated with increased morbidity and mortality in cardiovascular diseases, diabetes mellitus type two (T2DM) and cancer [4]. It also increases overall mortality [4]. The metabolic syndrome includes central obesity, hypertension, T2DM or raised fasting glucose, and abnormal serum lipids [5].

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Increased risk of obesity – the driving force behind the metabolic syndrome – has been shown in four studies on snus use [6-9]. A recent large observational study also showed an association between snus use and T2DM [10]. Further, nicotine from snus stimulates the sympathetic nervous system, resulting in immediately increased blood pressure and heart rate [11]. These effects will persist during active snus use, which averages 13–15 hours per day [2]. An association between snus use and the metabolic syndrome, if present, could partly explain the higher cardiovascular and overall mortality for snus users that has been observed in the last few years [12-15]. However, the possible association between snus use and the metabolic syndrome has only been evaluated in two studies, with inconclusive results [7,16]. These studies have included former smokers in the analyses, which may lead to residual confounding. They are also limited by cross-sectional design [16] or a follow-up of 10 years [7], while tobacco habits often shift substantially over time [2]. Regarding associations between snus and lipid levels, previous research is divergent [17].

Health hazards caused by long-term snus use are of special interest, as cardio-metabolic risk accumulates over decades. Life-course epidemiology may provide applicable theories for studying health effects of different exposures throughout life. Two important concepts are 'sensitive period' and 'accumulation of risk'. The sensitive period theory states that humans may be subject to biological programming early in life, so that exposure during this period may have an independent impact on later life health. [18] Accordingly, it could be hypothesized that adolescents exposed to snus are more prone to long-term hormonal and metabolic effects, and therefore suffer more damage from nicotine than adults. In contrast, the 'accumulation of risk' model assumes that health risks instead accumulate with long-term exposure [18], such as snus use across the life-course. We have previously shown that the metabolic syndrome indeed may be partially rooted in behavioural conditions during adolescence [19] and accumulated throughout life [20], but to our knowledge, the life-course effects of snus use on the metabolic syndrome have not been investigated previously.

This study follows a population for 27 years, from adolescence to mid-adulthood, with repeated measurements of tobacco habits. We aim to investigate the association between life-course exposure to snus and prevalence of the metabolic syndrome and its components in adulthood. Specifically, we aim (a) to describe tobacco use over life-course; (b) to evaluate whether snus use during certain life periods is associated with the development of the metabolic syndrome at age 43 (sensitive period model); and (c) to investigate whether accumulated exposure to snus during adolescence and mid-adulthood is associated with increased risk of the metabolic syndrome and its components at age 43 years (cumulative risk model).

Method

Participants

Data were derived from the 27-year prospective Northern Swedish cohort [21]. The sample consists of all students in the municipality of Luleå who in 1981 attained the 9th grade (age 16) of Swedish compulsory school (n=1083). Follow-ups have been performed in 1983, 1986, 1995 and 2008 (at ages 18, 21, 30 and 43). In 2008, 94% of the baseline sample still alive participated in the study (n=1001). The sample has been found to be representative of the corresponding age cohort of Sweden in demographic comparisons [21]. The Regional Ethical Review Board in Umeå, Sweden, approved the study.

The present study is based on data collected in 1981, 1986, 1995 and 2008. From the original study population, participants with missing information on metabolic syndrome at age 43 (n=107) were excluded. Another 14 were excluded due to missing information on tobacco habits, in total excluding 121 participants. Hence, analyses were based on 880 individuals, representing 88% of those still participating in 2008.

Procedures

Participants completed self-administered questionnaires at baseline and follow-ups [21]. Weight and height at age 16 were measured by school nurses. At age 43, participants underwent a health examination by trained medical personnel at local health care centres [19]. This included blood pressure measured according to the WHO MONICA manual [22], and venous blood sampling after overnight fast. These were analysed for glucose, high-density lipoprotein cholesterol (HDL-C) and triglycerides. The coefficient of variance at high/low concentration was 1.5/1.2% for glucose, 2.8/2.8% for HDL-C and 1.7/1.5% for triglycerides.

Measures

The metabolic syndrome was defined according to the International Diabetes Federation [5]: (a) central obesity, defined as waist circumference $\geqslant$80 cm for women and $\geqslant$94 cm for men, and (b) at least two of

the following: (i) low serum HDL-C (<1.29 mmol/l for women and <1.03 mmol/l for men), or specific therapy for that lipid abnormality; (ii) high serum triglycerides (⩾1.7 mmol/l), or specific treatment for that lipid abnormality; (iii) high blood pressure (⩾130 mm Hg systolic and/or ⩾85 mm Hg diastolic) or antihypertensive medication; and (iv) raised fasting glucose levels (⩾5.6 mmol/l) (impaired fasting glucose, IFG) or diagnosed T2DM.

Results from the age 43 health examination were used to define presence of the metabolic syndrome in each participant. Information on medication and pre-existing conditions was self-reported. Individuals reporting diabetes mellitus at age 43 (n=21) were considered as having T2DM, excluding those reporting diabetes at age 30 (n=4, who also reported having diabetes at age 21), who were considered as having type 1 diabetes. Because of lack of specific therapy for individual serum lipid abnormalities, those treated with lipid-lowering medicines and having normal triglycerides and HDL-C in blood samples were regarded as having normal serum lipids (n=8).

Information on current and former tobacco use was self-reported at baseline and at each follow-up and divided into nine categories (Supplementary Table 1): (1) never tobacco users, (2) current snus users who had never smoked, (3) current snus users who had previously smoked, (4) current smokers who had never used snus, (5) current smokers who had previously used snus, (6) current snus users who also currently smoke, (7) former snus users who had never smoked, (8) former smokers who had never used snus, and (9) former users of both snus and cigarettes, in accordance with previous assessments [23]. Former tobacco use reported at age 16 was considered non-significant and therefore regarded as never-use.

When reviewing the self-reports, it was evident that previous tobacco use was sometimes ignored or forgotten (assuming that current exposure is more accurately reported than previous exposure). Therefore, the dataset was adjusted according to previously stated tobacco use. For example, if a person stated 'current snus use, no smoking' in 1986, and then reported never-use of tobacco in 1995 and 2007, the last two follow-ups were categorized as 'former snus use, never smoking'. We adjusted 154 individuals' responses regarding former tobacco use.

For the sensitive period model, we performed analyses on the nine categories of tobacco use for baseline and each follow-up.

The cumulative model analyses were operationalized as the number of life periods (1 to 4) an individual reported current snus use. All snus users, irrespective of smoking habits, were included in the analyses due to low numbers of pure snus users (n from 9 to 38). Similarly, cumulative smoking was defined as number of life periods smoking.

Body mass index (BMI) at age 16 was calculated from the school nurses' measurements. Family history of diabetes mellitus was self-reported at age 16. Socioeconomic status in adolescence was based on parental occupation as reported at age 16. Using the classification of Statistics Sweden, they were divided into three groups. The two upper groups were combined into a socially favourable category, while the group 'manual workers' was defined as a disadvantaged category, following previous classification [19,24]. Annual alcohol consumption at age 43 was estimated from self-reports on typical frequency and quantity. It was coded as high or low using the sex-specific 80th percentile as cut-off. Physical activity during the last 12 months at age 43 was reported with six response options: daily, several times per week, once a week, several times per month, once a month, and seldom. The last three categories were collapsed based on low numbers [24].

Statistical analyses

Statistical analyses were performed using SPSS Statistics, version 19 (SPSS, Chicago, Illinois, USA). Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the metabolic syndrome and its individual components (central obesity, low HDL-C, high triglycerides, high blood pressure, IFG/T2DM). Health exams at age 16 were insufficient to determine exact presence of the metabolic syndrome. Therefore, we could not exclude prevalent cases at baseline. However, only five of the 880 participants had a BMI ⩾30 at age 16, making them eligible for diagnosis of the metabolic syndrome [5]. This number was considered too low to alter the results significantly.

Covariates with significant (p>0.05) association with the metabolic syndrome: sex, BMI and socioeconomic status at 16 years, family history of diabetes mellitus, alcohol consumption and physical activity at 43 years, were adjusted for in all multivariable models. In the cumulative model, we also adjusted for cumulative smoking. BMI after 16 years was considered part of a possible causal chain and hence not adjusted for.

The 121 participants who were excluded from the original population did not differ significantly from those included regarding gender distribution, current snus use, smoking rates at 16 and 43 years, SES and BMI at age 16, family history of diabetes mellitus, or physical activity level at age 43. They had significantly higher alcohol consumption at age 43 (p<0.001) and

Table I Descriptive statistics for participants of the Northern Swedish cohort.

	n	Never tobacco users at age 16	Current users of snus who have never smoked at age 16	Current smokers who have never used snus at age 16	Current dual users of snus and cigarettes at age 16	*p* for overall difference
		(Group 1, *n*=572)	(Group 2, *n*=81)	(Group 4, *n*=174)	(Group 6, *n*=53)	
Assessed at age 16						
Male sex	457	303 (53.0%)	68 (84.0%)	51 (29.3%)	35 (66.0%)	**0.000**
Body Mass Index (kg/m^2)	877	19.85 (2.72)	19.67 (2.43)	20.06 (2.60)	20.20 (2.98)	0.708
Socioeconomic disadvantage	333	203 (35.5%)	35 (43.2%)	76 (43.7%)	19 (35.8%)	0.195
Family history of diabetes mellitus	34	18 (3.1%)	1 (1.2%)	12 (6.9%)	3 (5.7%)	0.068
	n	Never tobacco users at age 43	Current users of snus who have never smoked at age 43	Current smokers who have never used snus at age 43	Current dual users of snus and cigarettes at age 43	*p* for overall difference
		(Group 1, *n*=308)	(Group 2, *n*=37)	(Group 4, *n*=88)	(Group 6, *n*=60)	
Assessed at age 43						
Metabolic syndrome	237	71 (23.1%)	12 (32.4%)	25 (28.4%)	20 (33.3%)	0.247
Physical inactivity (<once a week)	364	110 (35.7%)	17 (45.9%)	48 (54.5%)	38 (63.3%)	**0.000**
Alcohol consumption (cl/year)	880	272.95 (1155.91)	444.75 (452.89)	291.87 (413.71)	1034.61 (2737.09)	**0.000**

Reported values are number of participants (% of tobacco use group) for categorical variables, and mean (standard deviation) for continuous variables.
p-values calculated using chi square test or Kruskal–Wallis test.

smoked to a greater extent at age 21 (p=0.006) and 30 (p=0.007).

Among the 880 included participants, individuals with missing data on covariates (n=15) did not differ significantly from those with complete data regarding gender distribution, prevalence of the metabolic syndrome or ever-use of snus or cigarettes.

We found no significant interaction between snus use and sex on prevalence of the metabolic syndrome. Therefore, our results were not stratified by sex. Also, the number of never-smoking women using snus was too small (n from 4 to 13) to allow analyses for women separately, and separate analyses for men did not alter the conclusions.

Results

Table I shows characteristics of the cohort at baseline and the 2008 follow-up. The number of snus users that had never smoked was 81 at age 16 (9.2% of cohort), 53 at age 21 (6.0%), 57 at age 30 (6.5%) and 37 at age 43 (4.2%).

There were significantly more male snus users than female at baseline and all follow-ups. At age 43 the numbers were 7% and 1.2%, respectively (p<0.001).

At age 43, alcohol consumption was significantly higher among all categories of tobacco users than among never-users of tobacco, and 81 women (19.1%) and 156 men (34.1%) met the metabolic syndrome criteria.

Figure 1 shows tobacco use among the 880 participating subjects at baseline and follow-ups. The number of snus users increased with age. For smoking, numbers peaked at 21 years and then dropped steadily. Dual use showed a stable prevalence over the life-course.

Figure 2 shows the proportion of exclusive snus users among all snus users and exclusive smokers among all smokers. At all follow-ups, the proportion of exclusive snus users was significantly lower compared with the proportion of exclusive smokers (p<0.001), but not at baseline (p=0.094).

We found no significant risk increase compared with never-users of tobacco for metabolic syndrome, central obesity or low HDL-C for exclusive snus users at any age in the sensitive period analyses (Table II). In crude analyses, there was increased risk of high triglycerides (ages 16, 21, 30), high blood pressure (ages 21, 30, 43) and IFG/T2DM (age 21) for current exclusive snus users; however, none of these results remained significant after adjusting for confounders.

For cumulative snus use, there was a significantly increased risk of the metabolic syndrome at age 43 for those who had used snus during two life periods in crude analysis compared with never tobacco users,

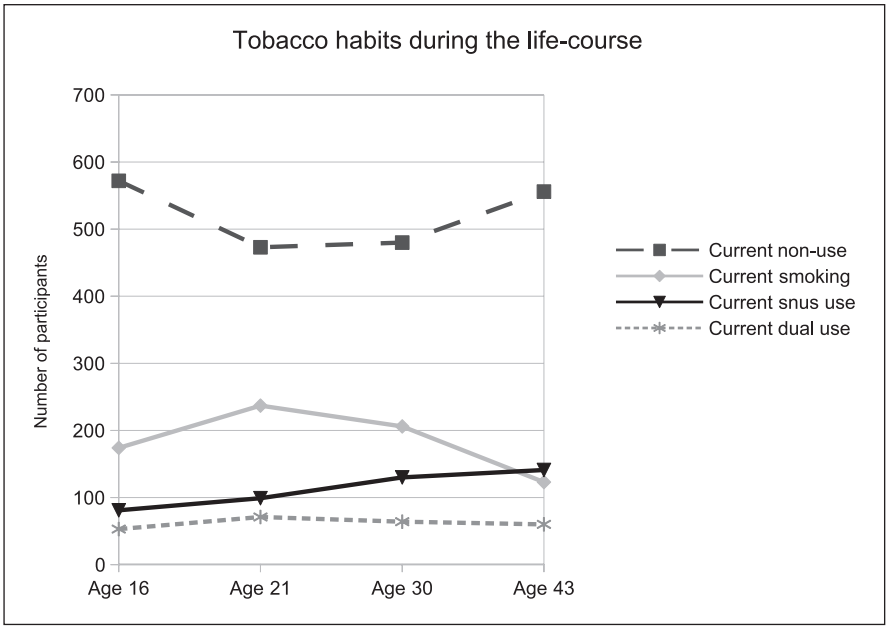

Figure 1. Self-reported current tobacco use at baseline and three follow-ups.

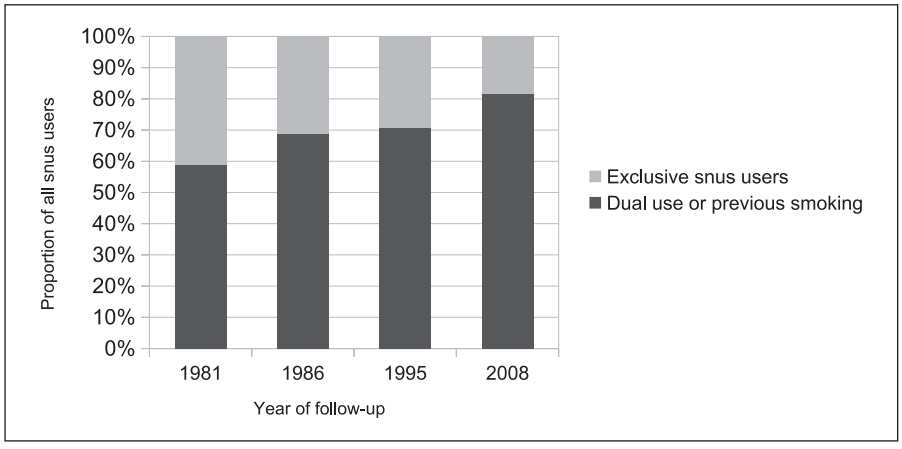

Figure 2(a). Proportion of exclusive snus users among all snus users.

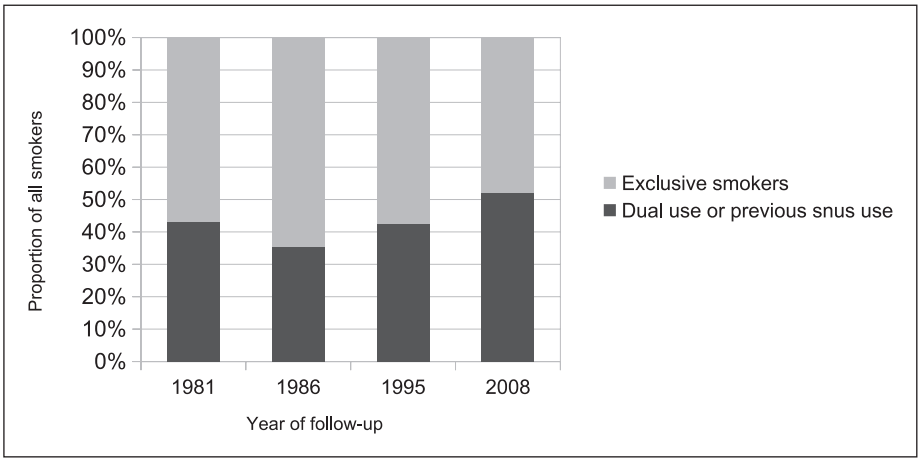

Figure 2(b). Proportion of exclusive smokers among all smokers. Reports from baseline and follow-ups.

Table II Metabolic risk for current snus users who have never smoked, evaluated at different ages (sensitive period model).

	Metabolic syndrome		Central obesity		Raised triglycerides		Low HDL-C		High blood pressure		Impaired fasting glucose or T2DM	
	Crude	Multivariable*	Crude	Multivariable*	Crude	Multivariable*	Crude	Multivariable*	Crude	Multivariable*	Crude	Multivariable*
Age 16 (1981) *n*=81	1.17 0.70–1.96	0.95 0.54–1.65	1.28 0.79–2.07	1.40 0.83–2.35	**1.83** **1.11–3.01**	1.38 0.81–2.37	1.15 0.69–1.92	1.23 0.72–2.12	1.45 0.91–2.32	1.08 0.66–1.77	1.55 0.87–2.74	1.08 0.59–1.97
Age 21 (1986) *n*=53	1.68 0.91–3.08	1.15 0.60–2.21	1.18 0.66–2.13	1.24 0.65–2.34	**2.05** **1.11–3.79**	1.27 0.66–2.45	0.83 0.43–1.61	0.84 0.41–1.70	**2.08** **1.16–3.72**	1.31 0.71–2.42	**2.20** **1.12–4.32**	1.28 0.63–2.62
Age 30 (1995) *n*=57	1.51 0.82–2.80	1.01 0.52–1.99	1.20 0.68–2.13	1.15 0.61–2.15	**2.21** **1.20–4.06**	1.37 0.71–2.63	0.61 0.30–1.23	0.53 0.25–1.12	**2.37** **1.33–4.19**	1.61 0.88–2.96	1.81 0.90–3.62	1.01 0.48–2.11
Age 43 (2008) *n*=37	1.60 0.78–3.35	1.15 0.52–2.51	1.76 0.85–3.62	1.65 0.76–3.58	1.78 0.83–3.80	1.10 0.49–2.45	0.72 0.32–1.64	0.69 0.29–1.66	**2.06** **1.04–4.09**	1.41 0.69–2.89	0.71 0.24–2.09	0.38 0.12–1.16

Reported values are odds ratios and 95% confidence intervals.
Logistic regression was used to estimate odds ratios and 95% confidence intervals.
*The multivariable model is adjusted for sex, cumulative smoking, BMI at 16 years, socioeconomic status at 16 years, family history of diabetes mellitus, alcohol consumption at 43 years and physical activity level at 43 years.

and *p* for trend was significant. The results did not remain significant after adjustments. Table III shows the results of these analyses using different multivariable models.

Supplementary Table 2 shows cumulative snus use and risk of the components of the metabolic syndrome compared with never-use of tobacco. An association with central obesity was observed in crude analyses for 1 and 4 life periods of snus use. High triglycerides were associated with snus use for 2, 3 and 4 life periods. High blood pressure was associated with snus use for 4 periods. IFG/T2DM was associated with 2 and 3 life periods of snus use. These associations did not remain significant in the fully adjusted models. No association between snus use and low HDL-C was found.

Discussion

Our main finding was that exposure to snus in different life periods and accumulated exposure to snus from adolescence until adulthood was not associated with the development of the metabolic syndrome, or its components, at age 43. Individuals who had used snus were found to have an increased OR for high triglycerides, raised blood pressure and IFG/T2DM at age 43 compared with non-tobacco users, but the associations did not remain significant after adjustment for confounders. This indicates that differences between non-tobacco users and snus users regarding the potential confounders, rather than snus use itself, may explain the associations.

Another main finding of this study was that the use of snus slowly increased from adolescence to adulthood, and that the majority of snus users at some point also had smoked. The increasing prevalence of snus use may be attributable to (a) increased snus use in the Swedish population during the study period [1], (b) smokers in the cohort shifting to snus use and (c) snus use being a more stable habit than, for example, smoking. The latter is supported by previous studies [25,26]. Smoking drastically declines from age 21 onwards, which could be an expression of the well-known negative health effects of cigarette smoking. Furthermore, the proportion of exclusive snus users among all snus users was low, a finding that has been observed in previous studies [8,9,27, 28]. Our results confirm that snus users often smoke at some point during life.

Two previous studies have investigated the relationship between snus use and the metabolic syndrome. A 10-year prospective Swedish study by Norberg et al., including over 16,000 individuals, reported an increased risk of the metabolic syndrome in heavy

Table III Cumulative snus use and risk of the metabolic syndrome.

	Model A⋆	Model B•	Model C→	Model D#
Never tobacco use	1.00	1.00	1.00	1.00
n=308				
Snus use 1 period	1.40	1.37	1.13	1.08
n=122	0.87–2.24	0.85–2.20	0.64–2.00	0.59–1.96
Snus use 2 periods	**1.64**	1.45	1.12	1.11
n=97	**1.00–2.71**	0.87–2.41	0.59–2.13	0.57–2.17
Snus use 3 periods	1.63	1.29	1.09	1.01
n=64	0.91–2.93	0.71–2.35	0.56–2.13	0.50–2.06
Snus use 4 periods	1.72	1.31	1.04	0.91
n=47	0.89–3.33	0.67–2.58	0.49–2.24	0.40–2.05
***p* for trend**	**0.018**	0.216	0.826	0.660

Reported values are odds ratios and 95% confidence intervals.
Logistic regression was used to estimate odds ratios and 95% confidence intervals.
⋆Model A: Crude
•Model B: Adjusted for sex.
→Model C: Adjusted for sex and smoking.
#Model E: Adjusted for sex, smoking, BMI at 16 years, socioeconomic status at 16 years, family history of diabetes mellitus, alcohol consumption at 43 years and physical activity level at 43 years.

snus users (>4 cans/week) [7]. In a cross-sectional study, Wändell et al. found no association between snus use and the metabolic syndrome among the 1850 middle-aged male participants [16]. Our study adds to this previous research by showing that exposure to snus from adolescence to adulthood does not seem to increase the risk of the metabolic syndrome, even with long-term use. Altogether, these three studies indicate that snus use is not a major contributor to the development of the metabolic syndrome, although an association in heavy snus users cannot be excluded.

The results from previous research on the association between snus use and risk of the metabolic syndrome components hypertension, T2DM and raised triglyceride levels are also divergent [17]. In the study by Norberg et al. [7], raised triglycerides were associated with heavy snus use. Also, an increased risk of T2DM for snus users was recently shown in a large sample study by Carlsson et al. [10]. Our study does not support these associations independently of confounders, although a type II statistical error cannot be excluded.

However, the question of increased risk of obesity or central obesity deserves special attention, as an increased risk for snus users has been shown in four previous studies [6-9]. A methodological problem in all of these studies is that ex-smokers among snus users have not been excluded. Hence, the observed association with obesity may be an effect of smoking cessation, which is a known reason for weight gain [29], and perhaps not attributable to snus use. This is supported by a cross-sectional study performed on over 800 men, which concluded that abdominal obesity in snus users is in fact limited to former smokers [27].

Methodological considerations

The main strength of this study is that it uses a cohort with long follow-up time and repeated measurements of tobacco use, and a very high retention rate. This gives us opportunity to follow individuals and assess their tobacco habits and other lifestyle factors in relationship to the outcomes, and minimizes possible recall bias. It also largely allows us to separate exclusive snus users from previous smokers, so that all remaining effects can be attributed to snus use. One of the main limitations is the size of the cohort; it is too small to allow analyses stratified by sex or by amount of snus used. It may also be that the age of 43 is too young to have attained the full effect of snus use on metabolic risk factors. Further, we cannot rule out some residual confounding, for example from changes in socioeconomic status over the life-course.

We have distinguished between two models of life-course epidemiology, which are conceptually distinct. Still, there are well-known methodological difficulties in disentangling the models from each other [30]. As snus use is highly addictive, it is possible that the two models operate in concert. Those who start using snus at an early age will also have increased risk for accumulation of snus use during life. However, we found that only a minority (*n*=47) actually reported snus use at all four follow-ups. This means that although all of those in the group with highest accumulation started early with snus, the reverse is not true; not all who used snus in adolescence kept up the habit throughout the life-course. The distinction between the two models was necessary to empirically differentiate whether there actually is a graded accumulation of risk with increased life-course periods of snus use, or if snus use at a specific life-course period matters for later health.

Further research

It can be argued that exclusive snus users are not representative of snus users in general, as a majority of these have also smoked. Therefore, we suggest studies on metabolic risk and dual use of snus and cigarettes. Moreover, the trends of dynamic tobacco patterns among snus users give rise to questions that demand further studies on shifts in tobacco use during life-course.

Conclusions

Snus use in this cohort shows an increasing prevalence from 16 to 43 years of age, and dual use or former smoking is common among current snus users. However, snus use over the life-course does not seem to be an independent risk factor for developing the metabolic syndrome or any of its components in middle age.

Conflicts of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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