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DIABETES MELLITUS

Association between metabolic effects and tobacco use in 60-year-old Swedish men

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Abstract There is a controversy whether use of smokeless tobacco is associated with an increased risk of diabetes. A population-based cross-sectional study was undertaken of 1,859 men, aged 60 years, in Stockholm County. No significant association was found between risk of diabetes and any use of tobacco, even if an association between snuff and risk of diabetes could not be excluded.

Keywords Diabetes · Metabolic syndrome · Smokeless tobacco · Smoking · Sweden

Introduction

Tobacco use is still one of the most important causes of myocardial infarction in men globally, as concluded in the INTERHEART Study, but this refers mostly to smoking [1]. The association between cardiovascular disease and smokeless tobacco seems to be modest [2]. As regards risk of myocardial infarction, no significant excess overall risk has been found in several studies [3–7], although the opposite was found in two other studies, [6, 7]. Besides, no excess risk of stroke with smokeless tobacco has been found in Swedish studies [5, 8].

As regards metabolic factors, an increased risk of type 2 diabetes is shown among active smokers and ex-smokers [9]. Smoking cessation results in increase in weight and central fat [10], but one study found the risk of diabetes to be highest during the first five smoke-free years, and reverted to that of never-smokers after 20 years [11]. In a review oral smokeless tobacco was not associated with higher overall incidence diabetes [2]. Swedish studies have found diverging results, i.e. no increased risk in one study [12], an increased risk of metabolic syndrome only in another [13], and an increased risk of diabetes among high consumers of snuff in a third [14].

The aim of this study was to study the possible association between use of tobacco, including smokeless tobacco, and metabolic syndrome and diabetes.

This study was based on a population-based random sample of every third 60-year-old man and woman living in Stockholm County from August 1997 to March 1999. The participants underwent a physical examination including laboratory tests, and a comprehensive questionnaire, including medical data, and questions on demographic, socio-economic and life style factors, was completed. Due to the low prevalence of smokeless tobacco use among women in the study base, only men were included. Response rate among men was 73% ($n = 2036$), and a complete record of tobacco habits was available for 1972. When excluding subjects with known diabetes 1859 men remained and were included in the study.

Use of tobacco was coded as never users of tobacco ($n = 594$), former smokers ($n = 737$), former smokers but

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current daily users of snuff ($n = 113$), current daily smokers ($n = 360$), former snuffers ($n = 12$), current snuffers ($n = 16$) and current daily smokers and snuffers ($n = 27$). Current smokeless tobacco use was dichotomized into high (≥3 cans/week) or low (<3 cans/week) consumption. Total time of smoking was dichotomized into long (≥20 years) or short.

Metabolic syndrome was defined by the criteria from the National Cholesterol Education Program Adult Treatment Panel III (ATP III), revised in 2005 [15], from the European Group for the Study of Insulin Resistance (EGIR) [16], and from the International Diabetes Federation (IDF) [17].

Newly diagnosed diabetes was defined as fasting morning serum (fS) glucose levels ≥7.0 mmol/l in subjects with no known diagnosis of diabetes.

Employment was defined according to working status (yes, full or part-time/no). *Education level* was defined as (1) low level or no education/compulsory school, (2) secondary/12-year school, or (3) university or college. *Living conditions* were defined as living in an apartment (yes/no). *Physical activity* during leisure time the past year was asked for, and categorized as: (1) inactive, (2) light activity at least 2 h/week, (3) moderate activity 1–2 times/week, and (4) intensive activity ≥3 times/week. Categories 1 and 2 were classified as "inactive" and categories 3 and 4 as "active". *Alcohol intake* was calculated as average daily intake of alcohol, but was in the further analyses dichotomized into high intake (>30 g/day) or not [18].

Analyses were performed by STATA 9.0, using ANOVA, chi-square analysis and multiple logistic regression analysis. Metabolic syndrome and newly diagnosed diabetes were dependent variables in the logistic regression analysis, and use of tobacco, and important socio-economic and lifestyle factors as independent variables. Waist circumference is included in the definitions of the metabolic syndrome and was entered only in the analysis as regards diabetes. Significant factors in univariate analyses were entered in multivariate analyses, but only significant covariates were included in final model. Duration of smoking and dosage of snuff were included in a second regression analysis as regards diabetes, owing to co-linearity between these factors and tobacco habits. All analyses were two-tailed, with suggested significance levels of $P < 0.005$ in multiple comparisons (10 different and independent comparisons), and $P < 0.05$ in the multiple logistic regression.

Table 1 shows the proportion of participants in the different tobacco categories. Altogether 78 subjects were diagnosed with diabetes, and 529, 392 and 663, respectively, with ATP III, EGIR and IDF definitions of the metabolic syndrome. Regarding the use of smokeless

Table 1 Medical, socio-economic and lifestyle data for men aged 60 years by use of tobacco ($n = 1859$)

	Never used tobacco	Ex-smokers	Ex-smokers and current snuffers	Current smokers	Ex-snuffers	Current snuffers	Current smokers and snuffers	Difference *P*-value
Men (*n*)	594	737	113	360	12	16	27	
BMI (kg/m^2)	26.6 (3.7)	27.4 (3.6)	27.2 (3.4)	26.1 (3.8)	27.2 (3.2)	25.8 (3.4)	25.9 (3.5)	<0.001
Waist (cm)	96.1 (10.4)	98.9 (10.0)	99.1 (9.5)	96.2 (10.8)	96.5 (6.9)	95.8 (7.5)	95.9 (8.6)	<0.001
Diabetes, newly diagnosed	16 (2.7%)	34 (4.6%)	8 (7.0%)	16 (4.4%)	1 (8.3%)	1 (6.3%)	2 (7.4%)	0.38
Hypertension, all	344 (58.0%)	464 (63.0%)	68 (60.2%)	215 (59.7%)	8 (66.7%)	11 (68.8%)	14 (51.9%)	0.53
MetSyn (ATP III)	140 (23.6%)	233 (31.6%)	32 (28.3%)	108 (30.0%)	2 (16.7%)	5 (31.3%)	9 (33.3%)	0.058
MetSyn (EGIR)	104 (17.5%)	183 (24.8%)	26 (23.0%)	72 (20.0%)	2 (16.7%)	2 (12.5%)	3 (11.1%)	0.033
MetSyn (IDF)	185 (31.3%)	295 (40.0%)	42 (37.2%)	124 (34.4%)	2 (16.7%)	7 (43.8%)	8 (29.6%)	0.027
Employment	453 (76.5%)	532 (72.3%)	78 (69.0%)	238 (66.3%)	7 (58.3%)	13 (81.3%)	17 (63.0%)	0.019
Educational level								0.001
Compulsory school	301 (50.9%)	399 (54.2%)	74 (66.1%)	228 (63.9%)	8 (66.7%)	9 (56.3%)	23 (85.2%)	
Secondary school	101 (17.1%)	115 (15.6%)	17 (15.2%)	48 (13.5%)	0 (0%)	2 (12.5%)	0 (0%)	
University	189 (32.0%)	222 (30.2%)	21 (18.8%)	81 (22.7%)	4 (33.3%)	5 (31.3%)	4 (14.8%)	
Living in apartment	229 (39.4%)	312 (43.2%)	45 (40.5%)	194 (57.1%)	3 (27.3%)	7 (43.8%)	8 (29.6%)	<0.001
Regular physical activity	229 (38.8%)	276 (37.9%)	37 (32.2%)	79 (22.6%)	5 (41.7%)	8 (50.0%)	5 (19.2%)	<0.001
Total intake of alcohol (g/day)	13.4 (13.7)	19.9 (16.7)	23.3 (19.1)	22.9 (18.3)	13.0 (11.7)	19.5 (10.5)	23.4 (20.9)	<0.001

Mean values (standard deviation), or numbers (percentage). Metabolic syndrome (MetSyn) is shown by different definitions

P-values obtained by ANOVAs or chi-square-analyses between all groups. Recommended significance level is $P < 0.005$ owing to multiple comparisons

tobacco, 38% of the subjects were classified as high consumers, i.e. ≥3 cans/week.

Table 2 shows the results from the logistic regression analysis. Regardless of definition, metabolic syndrome was significantly more prevalent among ex-smokers. For newly diagnosed diabetes neither group of tobacco users nor smoking duration and snuff dosage showed a significantly increased risk.

The examined cohort of 60-year-old males had tobacco habits (22% were smokers and 7% were smokeless tobacco users) comparable to those of the general Swedish population of the same age, i.e. 23% smokers and 10% smokeless tobacco users (Statistics Sweden).

The study does have some limitations. It was performed as a cross-sectional study, thus precluding conclusions on causality, and the power to detect associations between tobacco use and diabetes was low. Glucose values were measured as fasting values, why we could not detect subjects with IGT.

We found no significant association between the metabolic syndrome and use of snuff, in contrast to an earlier study using the IDF definition [13]. Besides, we found no association between use of snuff and risk of diabetes. However, any use of tobacco, whether current of former, was associated with high ORs for newly diagnosed diabetes, with the highest ORs among current or former snuff users. Furthermore, a tendency to a dose-response association between use of snuff and risk of diabetes could be indicated. Thus, our results cannot exclude the possibility that snuff use, especially with high dosage, could involve an increased risk of type 2 diabetes, which is in line with the findings by Persson et al. [14].

As regards possible metabolic influence of smokeless tobacco use, there are clear patho-physiological reasons this, as it involves equal or higher systemic nicotine exposure than smoking [19]. Nicotine causes an increased sympathetic activity with release of both cathecolamines and other neurotransmittors such as acetylcholine, vasopressin, dopamine and growth hormone [20, 21]. The constant exposure to nicotine might modulate the stress response within the hypothalamic-pituitary-adrenal axis and which could predispose for type 2-diabetes in continuous smokeless tobacco users.

The appearance of high intake of alcohol as an independent risk factor for diabetes in the examined cohort has been reported earlier [18]. As shown in most population surveys, there is a covariance of several healthy lifestyle habits, i.e. no tobacco use, low alcohol consumption, low BMI and waist circumference, as well as high physical activity.

As conclusion, we found a significant association among ex-smokers with the metabolic syndrome regardless of definition of this, probably due to increase in weight and central fat after smoking cessation [10]. As regards use of

Table 2 Logistic regression (odds ratio (OR) with 95% confidence interval (CI)) for risk of having prevalent metabolic syndrome or newly diagnosed diabetes in men ($n = 1859$), by different groups of tobacco users

Variates	Metabolic syndrome			Newly diagnosed diabetes	
	ATP III	EGIR	IDF	Model 1	Model 2
Ex-smokers	1.49 (1.15–1.92)	1.55 (1.17–2.06)	1.44 (1.14–1.83)	1.41 (0.76–2.60)	–
Ex-smokers, current snuffers	1.14 (0.71–1.82)	1.29 (0.78–2.14)	1.18 (0.76–1.83)	1.71 (0.67–4.35)	–
Current smokers	1.18 (0.86–1.62)	0.95 (0.66–1.37)	1.00 (0.74–1.35)	1.40 (0.68–2.89)	–
Ex-snuffers	0.69 (0.14–3.28)	0.97 (0.20–4.67)	0.48 (0.10–2.26)	3.10 (0.36–26.84)	–
Current snuffers	1.55 (0.52–4.62)	0.71 (0.16–3.24)	1.81 (0.65–5.02)	2.12 (0.25–17.71)	–
Current smokers and snuffers	1.46 (0.63–3.41)	0.47 (0.14–1.63)	0.85 (0.36–2.02)	2.48 (0.52–11.82)	–
Smoking duration, short (<20 years)	–	–	–	–	1.30 (0.64–2.66)
Smoking duration, long (≥20 years)	–	–	–	–	1.46 (0.79–2.68)
Snuff, low consumers (<3 cans/w)	–	–	–	–	1.30 (0.49–3.40)
Snuff, high consumers (≥3 cans/w)	–	–	–	–	1.80 (0.67–4.85)
Waist 94–101	–	–	–	2.16 (1.03–4.54)	2.04 (0.97–4.32)
Waist > 101	–	–	–	4.92 (2.50–9.67)	4.75 (2.42–9.31)
Employment	0.68 (0.54–0.86)	0.64 (0.50–0.83)	0.72 (0.58–0.91)	–	–
Secondary school	0.77 (0.57–1.05)	0.69 (0.49–0.99)	0.86 (0.64–1.14)	–	–
University	0.82 (0.64–1.05)	0.63 (0.48–0.84)	0.90 (0.71–1.13)	–	–
Living in apartment	1.44 (1.16–1.78)	1.19 (0.94–1.51)	1.42 (1.16–1.74)	–	–
Regular physical activity	0.70 (0.56–0.88)	0.52 (0.40–0.68)	0.73 (0.59–0.91)	–	–
High alcohol intake (>30 g/day) versus not	1.48 (1.15–1.91)	1.22 (0.91–1.63)	1.65 (1.29–2.11)	2.25 (1.39–3.65)	2.15 (1.32–3.52)

Multivariate models for different definitions of the metabolic syndrome, and 2 models for newly diagnosed diabetes

snuff no significant association with metabolic syndrome and diabetes was found, even if such an association cannot be excluded. Certainly, further studies are needed to elucidate this topic.

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