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# Smoking cessation and the incidence of pre-diabetes and type 2 diabetes: a cohort study

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ABSTRACT

*Aims:* Smoking cessation has been suggested to increase the short-term risk of type 2 diabetes mellitus (T2DM). This study aimed at assessing the association between smoking cessation and incidence of T2DM and impaired fasting glucose (IFG).
*Methods:* Data from participants in the CoLaus study, Switzerland, aged 35–75 at baseline and followed for 5.5 years were used. Participants were classified as smokers, recent (≤5 years), long-term (>5 years) quitters, and non-smokers at baseline. Outcomes were IFG (fasting serum glucose (FSG) 5.6–6.99 mmol/l) and T2DM (FSG ≥7.0 mmol/l and/or treatment) at follow up.
*Results:* 3,166 participants (63% women) had normal baseline FSG, of whom 26.7% were smokers, 6.5% recent quitters, and 23.5% long-term quitters. During follow-up 1,311 participants (41.4%) developed IFG (33.6% women, 54.7% men) and 47 (1.5%) developed T2DM (1.1% women, 2.1% men). Former smokers did not have statistically significant increased odds of IFG compared with smokers after adjustment for age, education, physical activity, hypercholesterolemia, hypertension and alcohol intake, with OR of 1.29 [95% confidence interval 0.94–1.76] for recent quitters and 1.03 [0.84–1.27] for long-term quitters. Former smokers did not have significant increased odds of T2DM compared with smokers with multivariable-adjusted OR of 1.53 [0.58–4.00] for recent quitters and 0.64 [0.27–1.48] for long-term quitters. Adjustment for body-mass index and waist circumference attenuated the association between recent quitting and IFG (OR 1.07 [0.78–1.48]) and T2DM (OR 1.28 [0.48–3.40].
*Conclusion:* In this middle-aged population, smoking cessation was not associated with an increased risk of IFG or T2DM.



## 1. Introduction

Smoking is as an established risk factor for type 2 diabetes (T2DM) (Athyros, Katsiki, Doumas, Karagiannis, & Mikhailidis, 2013; Willi, Bodenmann, Ghali, Faris, & Cornuz, 2007) and increases the risk of micro- and macro-vascular complications (Clair, Cohen, Eichler, Selby, & Rigotti, 2015; Eliasson, 2003; Turner et al., 1998). The increased risk is due to different mechanisms: smoking is toxic on the pancreatic beta cells (Hartwig et al., 2000), acts on inflammatory pathways (Arnson, Shoenfeld, & Amital, 2010), induces oxidative stress, and favours central obesity (Chiolero, Faeh, Paccaud, & Cornuz, 2008) and insulin resistance (Eliasson, 2003; Facchini, Hollenbeck, Jeppesen, Chen, & Reaven, 1992). As a consequence, to quit smoking should reverse or at least lower this increased metabolic risk. However, the reversible character of the pro-diabetogenic effects of smoking has not yet been proven. Besides, smoking cessation is associated in most cases with weight gain (Aubin, Farley, Lycett, Lahmek, & Aveyard, 2012), which is a known risk factor for T2DM. Weight gain is also an important barrier to smoking cessation in many smokers (Luostarinen et al., 2013).

Studies on metabolic risk after smoking cessation show controversial results. A meta-analysis estimated that the risk of developing T2DM for ex-smokers was not as high as that of smokers, but was still 23% higher relatively to non smokers (Willi et al., 2007). The incidence of T2DM after smoking cessation has been investigated in six prospective studies (Hur et al., 2007; Luo et al., 2013; Oba et al., 2012; Wannamethee, Shaper, & Perry, 2001; Will, Galuska, Ford, Mokdad, & Calle, 2001; Yeh, Duncan, Schmidt, Wang, & Brancati, 2010) and all showed an increased risk compared with never smoking in the first years following smoking cessation.

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The development of metabolic risk goes through a continuum from normoglycemia to impaired fasting glucose (IFG), a pre-diabetic state, and T2DM. IFG is the key state in which life style measures are effective to prevent disease (Orozco et al., 2008). Only few studies considered the risk of developing impaired fasting glucose following a smoking quit attempt and most focused on established T2DM.

Furthermore gender/sex disparities might exist concerning metabolic risk after smoking cessation. Studies suggest that women might gain more weight at smoking cessation (Flegal, Troiano, Pamuk, Kuczmarski, & Campbell, 1995) and the effect of smoking on their health also differs from men (Chiolero et al., 2008; Tanko & Christiansen, 2004).

Our study aimed at assessing whether the incidence of T2DM as well as IFG increases after smoking cessation in a middle-aged European population and test for an interaction with gender.

## 2. Subjects, material and methods

### 2.1. CoLaus study

Data from a Swiss prospective observational cohort study (CoLaus) were used. The CoLaus study has been accepted by the Ethics Committee of the Canton de Vaud. The sampling procedure of the CoLaus study has been described previously (Firmann et al., 2008). Recruitment began in June 2003 and ended in May 2006. The following inclusion criteria were applied: (i) written informed consent; (ii) age 35–75 years; (iii) willingness to take part in the examination and to have a blood sample drawn. Participation rate was 41% and 6,733 participants (3,544 women and 3,189 men) were recruited. A follow up interview at 5.5 years was completed in 2012.

### 2.2. Participants

For the present study, 5,064 participants who completed follow-up were selected. Ninety of them (0.8%) were further excluded because of missing data for smoking status, fasting serum glucose (FSG), treatment for T2DM, body-mass index (BMI) or waist circumference at baseline or follow up. Participants with T2DM (n = 278) or IFG (n = 1530) at baseline were also excluded, leaving 3,166 participants with FSG ≤5.6 mmol/l and no treatment for T2DM.

### 2.3. Variables

#### 2.3.1. Impaired fasting glucose and T2DM

The primary outcomes were the cumulative 5.5-year incidences of IFG and of T2DM. Serum glucose was measured at baseline and 5.5-year follow-up from blood samples drawn after an 8-hour fasting. T2DM was defined as FSG ≥7 mmol/l or presence of an oral anti-diabetic or insulin treatment. IFG was defined as FSG between 5.60 and 6.99 mmol/l and no treatment for T2DM.

#### 2.3.2. Smoking status

Smoking status and years since quitting were self-reported. Participants were categorised in four groups: current smokers if they reported smoking ≥1 cigarette/day or ≥1 pipe or cigar/day at baseline; recent quitters if they reported quitting smoking ≤5 years before baseline; long-term quitters if they reported quitting >5 years before baseline, and as never smokers otherwise. We considered pipe and cigar smoking as equivalent to cigarette smoking because they represented a minority of smokers (7%) and because all types of tobacco combustion are harmful (Katsiki, Papadopoulou, Fachantidou, & Mikhailidis, 2013).

Exposure of interest was smoking cessation > 5 years or ≤ 5 years before baseline, with smokers as the control group.

#### 2.3.3. Other variables

BMI was calculated based on weight and height measured at baseline. Waist circumference was measured at a level midway between the lower rib margin and the iliac crest.

Baseline BMI ($kg/m^2$) and weight gain during follow up (weight at follow up minus weight at baseline in kilograms) was calculated in women and men.

We defined participants as physically active if they exercised at least 20 minutes of leisure time physical activity per week (Ponte et al., 2013; Stringhini et al., 2012). Alcohol consumption was defined as reported standard units consumed per week. High level of education was defined as having completed at least secondary school (>9 years of school) (Firmann et al., 2008). As participants were included from an urban area, they were mainly with middle to high socio-economic status. Hypercholesterolemia was defined as LDL cholesterol ≥4·1 mmol/l or taking a lipid lowering treatment; hypertension was defined as a systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg and/or taking an antihypertensive drug treatment.

### 2.4. Statistical analysis

#### 2.4.1. Basis analysis

Statistical analysis was conducted using Stata version 12·0 (StataCorp, College Station, Texas). Descriptive results were presented as number of participants (percentage) or as mean ± standard deviation. Between-group comparisons were performed using Student t-test for continuous variables and Fischer's exact test for proportions.

Analyses were stratified by sex. The associations between smoking status and incidences of IFG and T2DM were assessed separately. We used logistic regressions to estimate the odds ratio (ORs) and 95% confidence intervals (CI) of developing IFG or T2DM in recent quitters, long-term quitters and never smokers compared with smokers. Three levels of adjustment were performed: age only (model 1); age, education, leisure-time physical activity, alcohol consumption, hypercholesterolemia, and hypertension (model 2), and all variables in model 2 plus BMI, and waist circumference (model 3). We adjusted for waist circumference and BMI in a separate model because they might be mediators rather than confounders in the relationship between smoking cessation and development of IFG or T2DM.

Finally, we tested the interaction for sex in the association between smoking status and IFG or T2DM incidence using an interaction term in the fully adjusted non-stratified model.

A two-sided p-value $<0.05$ was considered as statistically significant.

#### 2.4.2. Sensitivity analyses

We tested whether participants with inconsistent smoking status during the 5.5 years of follow-up influenced results. These participants (n = 343, 10.8%) were excluded, and the association between smoking status and IFG or T2DM by smoking status was assessed in the remaining 2823 (89.2%) participants using the fully adjusted model (model 3). We also repeated the analyses without excluding participants with IFG at baseline (n = 1,530, 30.8%). This was done to test whether selecting participants with normal FSG introduced a bias towards T2DM resistant smokers and ex-smokers.

We also adjusted the multivariate analysis to weight change defined as weight at follow up minus weight at baseline (model 4).

Finally, in post-hoc analyses we analysed the change in glycaemia as a continuous variable between baseline and follow up in each smoking category by Wilcoxon Ranksum test and between categories by Kruskall Wallis test.

## 3. Results

### 3.1. Subjects

The baseline characteristics of the participants free from IFG and T2DM are summarized in Table 1. There were 63% of women, mean age was 50.7 years and the majority had a high educational level. There were 846 smokers (26.7%), 207 recent quitters (6.5%), 743