

Smoking, plasma cotinine and risk of atrial fibrillation: the Hordaland Health Study

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Abstract. Zuo H, Nygård O, Vollset SE, Ueland PM, Ulvik A, Midttun Ø, Meyer K, Igland J, Sulo G, Tell GS, (University of Bergen, Haukeland University Hospital, The Norwegian Institute of Public Health, Bevital A/S, Bergen, Norway.). Smoking, plasma cotinine and risk of atrial fibrillation: the Hordaland Health Study. *J Intern Med* 2018; **283**: 73–82.

Background. Cigarette smoking has been identified as a major modifiable risk factor for coronary heart disease and mortality. However, findings on the relationship between smoking and atrial fibrillation (AF) have been inconsistent. Furthermore, findings from previous studies were based on self-reported smoking.

Objective. To examine the associations of smoking status and plasma cotinine levels, a marker of nicotine exposure, with risk of incident AF in the Hordaland Health Study.

Methods. We conducted a prospective analysis of 6682 adults aged 46–74 years without known AF at baseline. Participants were followed via linkage to the Cardiovascular Disease in Norway (CVDNOR)

project and the Cause of Death Registry. Smoking status was assessed by both questionnaire and plasma cotinine levels.

Results. A total of 538 participants developed AF over a median follow-up period of 11 years. Using questionnaire data, current smoking (HR: 1.41, 95% CI: 1.09–1.83), but not former smoking (HR: 1.03, 95% CI: 0.83–1.28), was associated with an increased risk of AF after adjustment for gender, age, body mass index, hypertension, physical activity and education. Using plasma cotinine only, the adjusted HR (95% CI) was 1.40 (1.12–1.75) for participants with cotinine ≥ 85 nmol L⁻¹ compared to those with cotinine < 85 nmol L⁻¹. However, the risk increased with elevated plasma cotinine levels until 1199 nmol L⁻¹ (HR: 1.55, 95% CI: 1.16–2.05 at the third group vs. the reference group) and plateaued at higher levels.

Conclusions. Current, but not former smokers, had a higher risk of developing AF. Use of plasma cotinine measurement corroborated this finding.

Keywords: atrial fibrillation, cohort, cotinine, risk, smoking.

Introduction

Cigarette smoking has been identified as a major modifiable risk factor for coronary heart disease and mortality [1, 2]. Smoking affects all phases of atherosclerosis from endothelial dysfunction [3] to acute clinical events[4]. However, the observations on the relation between smoking and atrial fibrillation (AF) have been inconsistent[5].

Prospective epidemiological studies on the association between smoking and AF [6–14] have been reported during the past two decades. Two population-based studies[6, 7] and one hospital-based

study[8] that specifically investigated the association between smoking and AF risk demonstrated a significantly higher risk of developing AF amongst current smokers, followed by former smokers, compared with never smokers. This is also reported in a recent meta-analysis[5]. However, most studies [9–14] found no significant association. Accordingly, smoking was not included as a predictor in a multivariate risk prediction model for AF in the Framingham Heart Study [15], but was included in the Atherosclerosis Risk in Communities (ARIC) Study[16]. The lack of an association has been attributed to varying study design and data analyses, including combining current and

former smokers [6], small number of cases, and adjustment for mediating factors [17].

Results from experimental and human studies suggest several mechanisms linking smoking with AF, including oxidative stress [18, 19], inflammation (as indicated by inflammatory markers such as C-reactive protein (CRP)) [18], atrial electrical alterations [20] and atrial fibrosis [21, 22]. These adverse effects are probably mediated by nicotine and other chemicals, including carbon monoxide and polycyclic aromatic hydrocarbons [6]. In addition, smoking-related impairment of lung function, myocardial infarction and heart failure also predispose to AF [23].

Of note, findings from previous studies were based on self-reported smoking, which may be prone to inaccuracy and misclassification, resulting in a biased estimation. The objectively measured smoking biomarker, cotinine, can provide a measure of recent nicotine exposure including both active and passive smoking [24]. Cotinine is a metabolite of nicotine which is chemically stable and has a half-life of about 20 h [25]. To the best of our knowledge, no study has investigated the association of smoking with AF risk using cotinine measurement.

The aim of the present study was to examine the associations of smoking status and plasma cotinine levels with risk of incident AF in a community-based prospective cohort in Norway, the Hordaland Health Study (HUSK).

Methods

Study population

Hordaland Health Study is a community-based study with baseline surveys conducted during 1997-1999 as collaboration between the University of Bergen, the National Institute of Public Health and the Municipal Health Service in Hordaland, Western Norway (<http://husk.b.uib.no>). Details of the study design and methodology have been described elsewhere [26, 27]. The source population in the current study was 17 361 participants born during 1925-1927 and 1950-1951 and residing in the city of Bergen or the neighbouring suburban municipalities who participated in an earlier study in 1992-1993 [27]. Of these, 9187 participants were invited to the HUSK study, and a total of 7074 participants met for physical examinations and completed self-administered questionnaires [27], yielding a participation rate of 77%. The current

study cohort comprised 7050 men and women who donated blood samples. Of the 7050 participants, we excluded 65 who had been hospitalized with AF before enrolment. Participants with missing data on plasma cotinine ($n = 94$) and no self-reported smoking information ($n = 209$) were also excluded. The final study cohort thus included 6682 participants (2950 men and 3732 women). The Regional Committee for Medical and Health Research Ethics in Western Norway (REK-Vest) approved the study protocol. Written informed consent was obtained from all participants.

Cotinine and CRP assay

Nonfasting plasma specimens were collected at baseline and stored at -80°C until analysis. Plasma cotinine and high-sensitivity CRP were measured at Bevital A/S (www.bevital.no) using liquid chromatography/tandem mass spectrometry [28] and the immuno-MALDI-MS method [29], respectively. The coefficients of variation for cotinine were 2.3%–2.9% (within-day) and 5.5%–6.2% (between-day), and the limit of detection was 1 nmol L^{-1} [28]. For participants with plasma cotinine levels below the limit of detection ($n = 2831$), their cotinine levels were imputed by assigning a random number between 0 and 1 when displaying the distribution.

Classification of smoking status

All subjects were categorized as never, former or current smokers based on their self-reported smoking status at baseline. Never smokers had no history of cigarette, cigar or pipe smoking. Former smokers reported smoking daily but quit before the baseline survey. Current smokers were those who reported smoking daily at the time of blood sample collection.

To minimize potential misclassification of self-reported smoking status, we used plasma cotinine to construct a secondary index of smoking status. For the cotinine-corrected smoking status, never smokers were defined as self-reported never smokers who had plasma cotinine levels $<85\text{ nmol L}^{-1}$ (15 ng mL^{-1}) [30, 31]. Former smokers were defined as self-reported ex-smokers who had plasma cotinine levels $<85\text{ nmol L}^{-1}$. Current smokers were defined as individuals who had plasma cotinine levels $\geq 85\text{ nmol L}^{-1}$, regardless of self-reported status. Consequently, 25 were excluded because they reported themselves as current smokers but had a cotinine concentration

<85 nmol L⁻¹, and 194 reclassified as current smokers because they reported themselves as never ($n = 37$) or former ($n = 157$) smokers but had a cotinine concentration ≥ 85 nmol L⁻¹.

Follow-up and outcome ascertainment

The cohort participants were followed up from baseline to the date of AF diagnosis, death, emigration or 31 December 2009 (the end of follow-up), whichever came first. AF cases were ascertained via record linkage to national hospital discharge diagnoses data obtained through the Cardiovascular Disease in Norway (CVDNOR) project, 1994–2009 [32–34]. The primary outcome was hospitalization or death attributed to AF (ICD-9 code: 427.3; ICD-10 code: I48). Information on death was collected from the Cause of Death Registry at Statistics Norway and coded according to ICD-10. If more than one AF event occurred in a participant during the follow-up period, only the first event was considered. An 11-digit personal identifier, unique to each Norwegian resident, was used to link baseline variables with study end-points.

Other baseline factors

Information on gender, age, education (highest level of completed education), physical activity and a history of CVD (myocardial infarction, angina or stroke) at baseline was collected via self-administered questionnaires. Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared. Participants were considered to have hypertension at baseline if they reported use of antihypertensive medication or had a blood pressure $\geq 140/90$ mm Hg [35]. Diabetes at baseline was defined based on self-reported use of hypoglycemic medication and blood glucose level, as previously described [36].

Statistical analysis

Baseline characteristics of self-reported never, former and current smokers were summarized using percentages and medians (interquartile ranges). Participants with different smoking status were compared using Chi-square tests for categorical and Kruskal–Wallis tests for continuous variables. Natural log-transformation was applied to plasma cotinine and CRP to achieve less skewed distributions. Spearman's partial correlation coefficient was calculated to examine relation between number of cigarettes per day and plasma cotinine

levels amongst self-reported current smokers. Their nonlinear relationship was examined by a generalized additive model (GAM) [37].

Cox proportional hazards regression was used to calculate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). We compared former and current smokers with never smokers with adjustment for *a priori* selected potential confounding variables: gender and age (46–49 years vs. 70–74 years), BMI (normal, overweight or obese), hypertension (yes/no), physical activity (none/light or moderate/vigorous) and education (≤ 10 , 11–13 or ≥ 14 years). Risk estimates were also calculated according to smoking intensity or history, i.e. number of cigarettes per day amongst current smokers and years since quit amongst former smokers using never smokers as the reference group. The analysis was carried out based on both self-reported and cotinine-corrected smoking status.

Further, we repeated the Cox analysis using the exposure variable plasma cotinine as a categorical (dichotomous and four categories) measure. The four categories were obtained as follows: participants with a plasma cotinine level below the detection limit were used as the reference group, those with plasma cotinine level between 1 and 85 nmol L⁻¹ as the second group, and the remaining participants (current smokers) were further divided into two groups by the median of plasma cotinine levels. To take into account the possible competing risk from mortality, we analysed the association between plasma cotinine and risk of AF using competing risk regression [38]. We also examined the association after additional adjustment for CRP. Tests for interactions with potential confounders were performed based on first-degree multiplicative models. Sensitivity analyses were performed to determine the robustness of findings in the primary analysis. We restricted the analyses to participants who had no history of CVD or diabetes at baseline.

Statistical analyses were conducted with the SAS statistical program (version 9.4; SAS Institute, Inc., Cary, NC) and R (version 3.3.1, www.r-project.org). All tests were two-sided, and a P value < 0.05 was considered statistically significant.

Results

Baseline characteristics of the study participants are shown in Table 1. Compared with self-reported

Table 1 Baseline characteristics of the study participants by self-reported smoking status, the Hordaland Health Study (n = 6682)

	Never smokers (n = 2724)	Former smokers (n = 2244)	Current smokers (n = 1714)	P-value ^a
Age (%)				
46–49 years	48.4	44.5	71.7	<0.001
70–74 years	51.6	55.5	28.3	
Men (%)	31.2	59.5	44.8	<0.001
Years of follow-up	10.9 (10.7–11.3)	10.9 (10.6–11.2)	10.9 (10.6–11.3)	<0.001
BMI (kg m ⁻²)	25.6 (23.2–28.2)	25.9 (23.7–28.2)	24.4 (22.2–26.8)	<0.001
Physical activity (%)				
None/light	43.0	42.4	45.1	0.218
Moderate/vigorous	57.0	57.6	54.9	
Hypertension (%)	46.0	46.4	30.5	<0.001
CVD (%)	8.6	14.7	6.0	<0.001
Diabetes (%)	2.5	3.9	1.3	<0.001
Education (years)				
≤10	30.3	28.4	35.9	<0.001
11–13	36.1	43.3	44.9	
≥14	33.6	28.3	19.2	
Plasma CRP (mg L ⁻¹)	1.37 (0.60, 3.20)	1.61 (0.71, 3.63)	1.88 (0.83, 4.05)	<0.001
Plasma cotinine (nmol L ⁻¹)	<LOD (<LOD–1.75)	<LOD (<LOD–3.11)	1223 (838–1617)	<0.001

BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; LOD, limit of detection.

Values are given as medians (interquartile ranges) or percentages.

^aChi-square tests for categorical and Kruskal–Wallis tests for continuous variables.

never and former smokers, current smokers were in general younger, had a lower BMI, lower education level and lower prevalence of hypertension, CVD and diabetes at baseline ($P < 0.001$). The highest proportion of women (68.8%) was found amongst never smokers. Plasma CRP was the highest amongst current smokers, followed by former and never smokers. Plasma cotinine was considerably higher amongst current smokers than nonsmokers, and slightly higher amongst former smokers than amongst never smokers. A bimodal distribution of plasma cotinine levels was therefore observed (Fig. 1). Baseline characteristics according to smoking status were essentially the same for cotinine-corrected smoking (data not shown).

Number of cigarettes per day was positively correlated with plasma cotinine levels amongst self-reported current smokers (Spearman's rho = 0.45, $P < 0.001$). However, the relation was nonlinear, showing the strongest increase at below ~10 cigarettes per day, and levelling off at ~15 cigarettes per day (Fig. 2).

During a median follow-up period of 11 years, 538 new AF cases (313 men and 225 women) were identified. Self-reported current smoking was significantly associated with an increased risk of AF after adjustment for gender, age, BMI, hypertension, physical activity and education (HR: 1.41, 95% CI: 1.09–1.83). Former smoking did not show an increased risk (HR: 1.03, 95% CI: 0.83–1.28), independent of number of years since smoking cessation (Table 2). There was no dose–response relationship between smoking intensity and risk of AF amongst current smokers. Similar risk estimates were obtained for cotinine-corrected smoking status (Table 2).

Plasma cotinine level was significantly associated with AF risk, after adjustment for gender, age and other confounders (Table 3). The HR (95% CI) was 1.17 (95% CI: 1.06–1.29 per SD increment). Additional adjustment for CRP did not materially change the risk estimates. There was no significant interaction between plasma cotinine and confounders including gender, age, BMI,

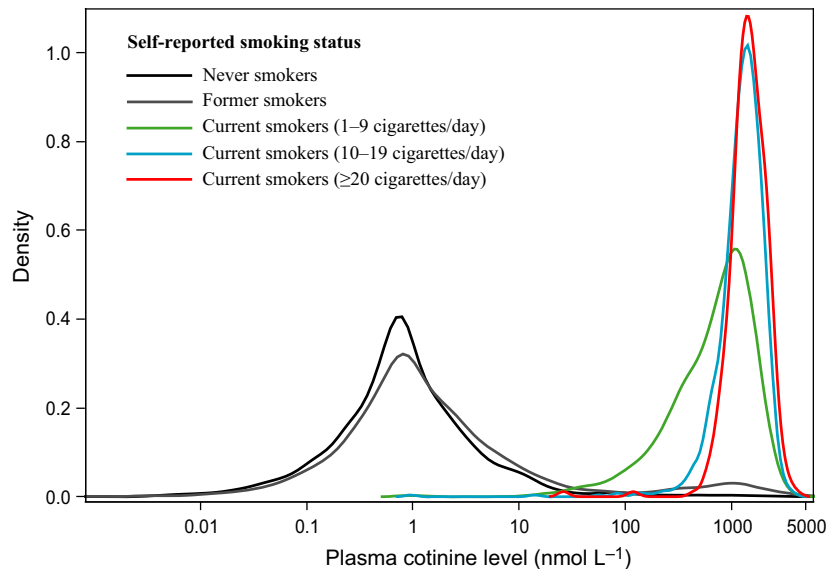


Fig. 1 Density plot of plasma cotinine by self-reported smoking status, the Hordaland Health Study. Plasma cotinine was log-transformed. Participants were classified into five categories: never smokers, former smokers and current smokers, with the latter category further classified as light smokers (1–9 cigarettes/day), moderate smokers (10–19 cigarettes/day) and heavy smokers (≥ 20 cigarettes/day). Note that 38.1% of self-reported never smokers and 49.0% of former smokers had detectable plasma cotinine levels (≥ 1 nmol L⁻¹), presumably due to second-hand smoking or nicotine exposure from other sources. Of them, 37 never and 157 former smokers with cotinine levels ≥ 85 nmol L⁻¹ were reclassified to current smokers in the following analyses using cotinine-corrected smoking status. Also, note that plasma cotinine levels were imputed by assigning a random number between 0 and 1 for participants with plasma cotinine levels below the limit of detection ($n = 2831$), just for visualizing the distribution of plasma cotinine levels.

hypertension, physical activity and education for the association with the risk (data not shown). The adjusted HR (95% CI) was 1.40 (1.12–1.75) for participants with cotinine level ≥ 85 nmol L⁻¹ compared to those with cotinine level < 85 nmol L⁻¹. The corresponding adjusted HR (95% CI) was 1.30 (0.98–1.72) in men and 1.65 (1.14–2.40) in women, when stratified by gender. Analysis of plasma cotinine in four categories showed that the risk increased until the third group (HR: 1.55, 95% CI: 1.16–2.05 for those with cotinine of 87–1199 nmol L⁻¹ vs. the reference group). However, the risk declined and was nonsignificant in the top category of plasma cotinine (Table 3, Fig. 3). The nonlinear association between plasma cotinine level and AF risk remained essentially unchanged using competing risk regression. And also, we did not observe a stronger effect by competing risk of mortality amongst the older participants (data not shown).

In sensitivity analyses, restricting the study population to 6016 participants without a history of CVD yielded a similar association for plasma

cotinine (HR/SD: 1.17, 95% CI: 1.05–1.31). The risk estimates remained unchanged when we further excluded 127 participants with diabetes at baseline.

Discussion

Principal findings

To the best of our knowledge, this is the first study to evaluate the association between smoking status ascertained by cotinine measurement and risk of AF. Our study found that baseline current, but not former smokers, had a higher risk of developing AF. The association was largely independent of hypertension, CVD, diabetes and CRP at baseline. Plasma cotinine levels as a measure of recent nicotine exposure gave similar risk amongst current smokers as was found using questionnaire data. However, the association between intensity of smoking exposure and the AF risk was nonlinear. In addition, the misclassification of smoking status based on self-report was of minor importance in our study.

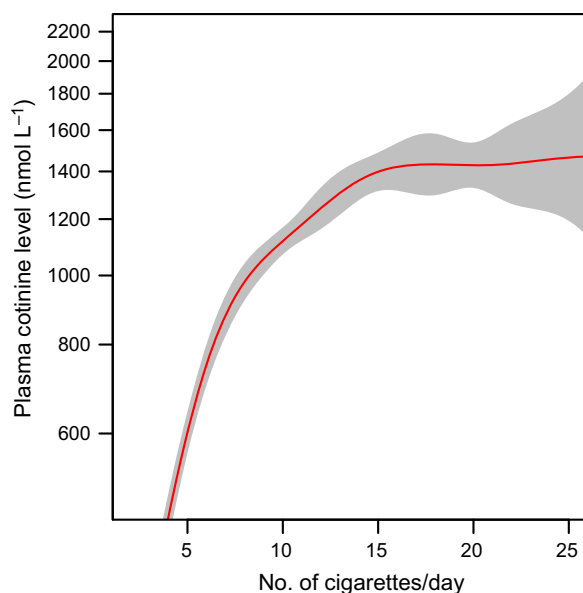


Fig. 2 Relationship between number of cigarettes per day and plasma cotinine level amongst self-reported current smokers, by generalized additive model (GAM). The model was adjusted for gender and age.

Smoking and AF risk

Current smoking was associated with an excess risk of AF of about 40%, whilst former smoking showed essentially no association. The latter observation is in line with a Japanese study [8], but not with the Rotterdam [6] and the ARIC studies [7]. The risk estimate for current smoking in our study is similar to the finding of the meta-analysis (risk ratio of 1.39) [5]. Higher risk estimates were observed in the Rotterdam [6] and the ARIC studies [7], with participant enrolment about 10 years before that of the HUSK cohort. The declining smoking prevalence in society [39, 40] is expected to reduce population exposure to second-hand smoke, which may explain the lower risk estimate in HUSK.

Smoking cessation appeared to eliminate the excess risk of AF, which is of public health importance. Lower AF risk adds to the established benefit from smoking cessation including reducing cardiovascular disease and deaths [2]. However, our observation may not apply to areas where exposure to second-hand smoke is still high.

Use of cotinine measurement in our study corroborated the findings for self-reported smoking behaviour. We noted a strong agreement in risk estimates

according to self-reported smoking and plasma cotinine measurement. Only minor changes in the estimates for smoking were observed after correction for plasma cotinine, and the estimates were almost the same using self-report or cotinine only to classify smokers and nonsmokers. The association of smoking and cotinine with AF risk was largely independent of baseline hypertension, CVD, diabetes and inflammation measured by CRP, which indicates mechanisms not closely linked to those conditions. In addition, stratified analyses by gender suggest that women may be more susceptible to AF induced by smoking than men.

Nonlinear association

The excess AF risk in current smokers increased with self-reported cigarette consumption in a nonlinear dose-response manner. This is in agreement with the results from the Rotterdam Study [6] and the Japanese study [8], but not the ARIC study [7]. Likewise, we observed a nonlinear relation between plasma cotinine levels and the risk of developing AF. The risk increased significantly with elevated plasma cotinine but plateaued and diminished gradually at higher levels, perhaps explaining why most earlier studies [9–14] did not show a strong risk amongst smokers.

It is unlikely that the observed nonlinear relationship is fully explained by competing risk of death after enrolment amongst smokers [6], because the association remained when we took the competing risk of death into account and there was no a stronger effect by competing risk of mortality amongst the older participants. In animal experiments, a biphasic effect of nicotine on inducible atrial tachycardia and AF has been reported [20], pointing to a threshold mechanism, similar to the reported nonlinear dose-response relationships between smoking and coronary heart disease [4, 41]. The detrimental effect on AF can be elicited by small doses of toxic substances from smoking. When reaching a certain level (threshold point) by increased smoking intensity, the underlying biochemical and cellular processes become saturated or even antagonistic, exhibiting a less increased risk of AF. However, the observed nonlinear relationship and underlying mechanisms require further investigation.

Misclassification bias of smoking status

Differential misclassification could lead to biased estimates of the true association. In our study, we

Table 2 HRs and 95% CIs for AF risk by smoking status, the Hordaland health study

Smoking status	Self-reported only			Cotinine-corrected ^a		
	Cases/No.	Model 1	Model 2	Cases/No.	Model 1	Model 2
Never smoking	200/2724	1	1	197/2687	1	1
Former smoking	226/2244	1.07 (0.87–1.31)	1.03 (0.83–1.28)	207/2087	1.03 (0.84–1.27)	1.00 (0.80–1.25)
Years since quitted smoking						
1–9	44/579	1.05 (0.75–1.47)	0.89 (0.61–1.29)	34/484	0.95 (0.65–1.37)	0.80 (0.53–1.21)
10–19	53/586	1.17 (0.86–1.60)	1.21 (0.87–1.68)	50/556	1.17 (0.85–1.62)	1.20 (0.86–1.68)
≥20	129/1079	1.03 (0.81–1.31)	1.02 (0.79–1.32)	123/1047	1.01 (0.79–1.29)	1.01 (0.78–1.31)
Current smoking	112/1714	1.48 (1.17–1.88)	1.41 (1.09–1.83)	130/1883	1.50 (1.19–1.88)	1.41 (1.10–1.82)
No. of cigarettes/day						
1–9	44/506	1.55 (1.12–2.16)	1.56 (1.08–2.25)	46/542	1.41 (1.02–1.95)	1.37 (0.95–1.98)
10–19	51/877	1.51 (1.10–2.07)	1.50 (1.05–2.12)	59/938	1.63 (1.21–2.21)	1.60 (1.14–2.23)
≥20	13/293	1.68 (0.94–3.01)	1.64 (0.89–3.02)	15/326	1.56 (0.91–2.69)	1.44 (0.80–2.58)
Missing	4/38	0.87 (0.32–2.35)	0.88 (0.32–2.39)	10/77	1.39 (0.73–2.65)	1.51 (0.79–2.89)

AF, atrial fibrillation.

^aCotinine-corrected smoking status: never smokers were defined as self-reported never smokers who had plasma cotinine levels <85 nmol L⁻¹; former smokers were defined as self-reported ex-smokers who had plasma cotinine levels <85 nmol L⁻¹; current smokers were defined as individuals who had plasma cotinine levels ≥85 nmol L⁻¹.

Model 1: adjusted for gender and age (46–49 years vs. 70–74 years).

Model 2: adjusted for gender, age (46–49 years vs. 70–74 years), BMI (normal, overweight or obese), hypertension (yes/no), physical activity (none/light or moderate/vigorous) and education (≤10, 11–13 or ≥14 years).

estimated misclassifications of never, former and current smokers at 1.4%, 7.0% and 1.5%, respectively, based on plasma cotinine levels (85 nmol L⁻¹ as the cut-off point). Thus, in the present study cohort, self-report was essentially reliable for never and current smokers, but less so for former smokers. Interestingly, self-reported smoking status tended to

underreport current smokers identified by cotinine measurement as former smokers rather than never smokers. As expected from Fig. 1, the cotinine concentrations across the whole distribution for each smoking category increased in the order the never, former, light smokers (1–9 cigarettes/day), moderate smokers (10–19 cigarettes/day) and heavy smokers

Table 3 HRs and 95% CIs for AF risk by plasma cotinine levels, the Hordaland Health Study (n = 6682)

Plasma cotinine (nmol L ⁻¹)	Cases/No.	Model 1	Model 2
Dichotomous			
<85	408/4799	1	1
≥85	130/1883	1.46 (1.20–1.79)	1.40 (1.12–1.75)
Four categories			
<1	261/2831	1	1
1–83	147/1968	1.08 (0.88–1.32)	1.10 (0.89–1.37)
87–1199	71/941	1.53 (1.17–1.99)	1.55 (1.16–2.05)
≥1199	59/942	1.47 (1.10–1.96)	1.34 (0.96–1.85)
P for trend		<0.001	0.006

AF, atrial fibrillation.

Model 1: adjusted for gender and age (46–49 years vs. 70–74 years).

Model 2: adjusted for gender, age (46–49 years vs. 70–74 years), BMI (normal, overweight or obese), hypertension (yes/no), physical activity (none/light or moderate/vigorous) and education (≤10, 11–13 or ≥14 years).

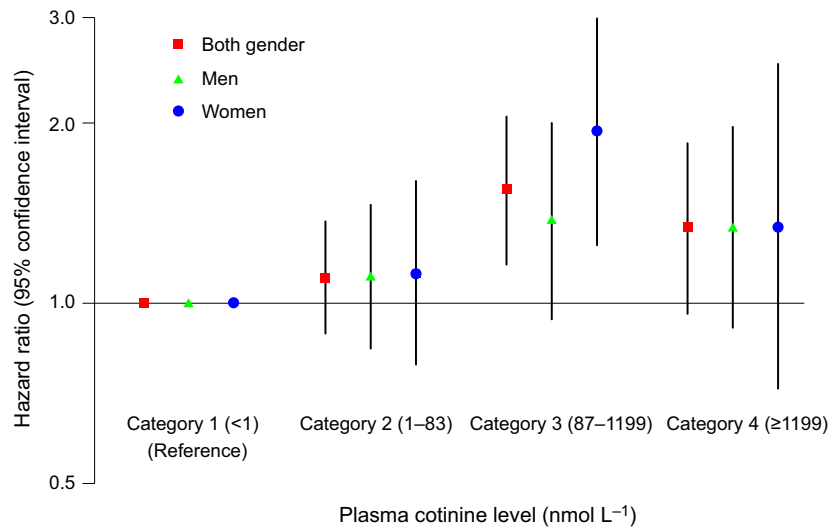


Fig. 3 Multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) by four categories of plasma cotinine levels for AF risk in all participants and stratified by gender (the first category as reference). Data were adjusted for gender, age (46-49 years vs. 70-74 years), BMI (normal, overweight or obese), hypertension (yes/no), physical activity (none/light or moderate/vigorous) and education (≤ 10 , 11-13 or ≥ 14 years).

(≥ 20 cigarettes/day). Thus, it is likely that misclassifications primarily affected adjacent categories.

Self-report and cotinine measurement may provide complementary information on smoking status: self-reported smoking gives information on smoking habit and history, whereas plasma cotinine reflects recent nicotine exposure including second-hand smoke. When comparing findings across studies, we should be aware that self-reported smoking may be imprecise to some extent. Nicotine exposures within the same smoking category may differ according to tobacco product, nicotine content and inhalation technique [42], which could explain discrepancy across studies.

Strengths and limitations

The strengths of our study include measurement of plasma cotinine, large sample size, complete and long-term follow-up and multivariate adjustment for confounders. Plasma cotinine provided an accurate measure of recent smoking exposure and allowed us to correct the self-reported smoking status and to precisely estimate smoking-related AF risk. The cotinine-based correction may not have been correct in all cases, however, as use of smokeless tobacco and other sources of nicotine may have misclassified a minority of the participants. Furthermore, the chosen cut-off of 85 nmol

L⁻¹, whilst reasonable, may not have been optimal [43]. Another weakness is that smoking habits and exposure to smoke after the baseline examination were not available. The proportion of daily smokers amongst 16-74 years in Norway decreased from about 30% in 1997-1999 to 21% in 2009 [44]. If smoking behaviours of our participants changed accordingly during the period, we would have underestimated the role of smoking on the AF risk. Moreover, the ascertainment of AF was based on hospitalization data only, not including persons who received the diagnosis during an outpatient visit or from a private specialist in cardiology, which means that cases with asymptomatic or paroxysmal AF cases without hospitalization might not have been included.

Conclusions

Our prospective study with baseline cotinine measurement expands evidence from previous studies based on questionnaires showing that current smokers, but not former smokers, had a higher risk of developing AF. This association suggests that the incidence of AF in the population may be lowered by smoking cessation.

Conflict of interest statement

No conflicts of interest to declare.

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