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FULL RESEARCH PAPER
Cardiovascular disease

Smoking timing, genetic susceptibility, and the risk of incident atrial fibrillation: a large prospective cohort study

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See the editorial comment for this article 'High nicotine dependence: does knowing your genetic susceptibility for atrial fibrillation help to quit smoking?', by M.-L. Løchen and V. Aboyans, https://doi.org/10.1093/eurjpc/zwae328.

Aims Although smoking is a well-known risk factor for atrial fibrillation (AF), the association of smoking timing with AF risk remains unclear. This study aimed to prospectively investigate the association of smoking timing with the risk of incident AF and test the modification effect of genetic susceptibility.

Methods and results A total of 305 627 participants with detailed information for time from waking to the first cigarette were enrolled from UK Biobank database. The Cox proportional hazard model was employed to assess the relationship between smoking timing and AF risk. The weighted genetic risk score for AF was calculated. Over a median 12.2-year follow-up, 13 410 AF cases were documented. Compared with non-smokers, time from waking to the first cigarette showed gradient inverse associations with the risk of incident AF (*P*-trend <0.001). The adjusted hazard ratio related to smoking timing was 1.13 [95% confidence interval (CI): 0.96–1.34] for >120 min, 1.20 (95% CI: 1.01–1.42) for 61–120 min, 1.34 (95% CI: 1.19–1.51) for 30–60 min, 1.43 (95% CI: 1.26–1.63) for 5–15 min, and 1.49 (95% CI: 1.24–1.63) for <5 min, respectively. Additionally, we found that the increased risk of AF related to shorter time from waking to the first cigarette was strengthened by the genetic susceptibility to AF.

Conclusion Our findings suggest gradient inverse association between time from waking to the first cigarette and risk of incident AF, and the association is strengthened by the genetic susceptibility to AF.

Lay summary

- Our study aimed to analyse the relationship between the time from waking to the first cigarette and incidence of atrial fibrillation (AF), and the modification role of genetic susceptibility.
- Shorter time from waking to the first cigarette was related to the elevated risk of incident AF.
- Genetic susceptibility to AF strengthened the gradient inverse association of time from waking to the first cigarette with the incidence of AF.

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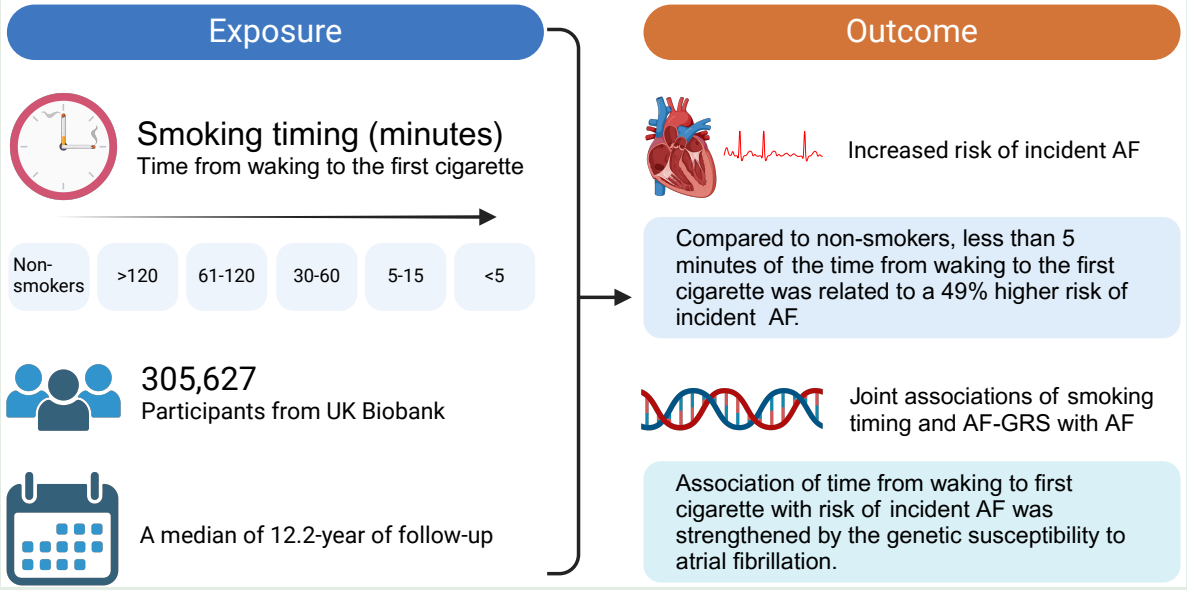
Graphical Abstract



Keywords Smoking timing • Genetic susceptibility • Atrial fibrillation • UK Biobank

Introduction

Atrial fibrillation (AF), the predominant form of cardiac arrhythmia, is associated with a range of cardiovascular diseases and increased mortality risks.[1,2] Over the past few decades, the incidence and prevalence of AF have increased following a reverse U-shape in men, imposing a huge burden on public health globally.[3] Despite the well-documented relationship between smoking quantity and AF risk, there is a notable gap in understanding how the timing of smoking impacts this risk. Specifically, the potential influence of when smokers consume their first cigarette of the day on the development of AF has not been adequately explored. Emerging evidence indicates that the timing patterns of human behaviours such as physical activity and sleep are associated with health status and risk of incident AF regardless of the quantities of these factors.[4]

Smokers tend to reduce their daily cigarette consumption but show a tendency to smoke their first cigarette earlier in the day.[5] Recent research on the smoking timing has consistently shown that smoking the first cigarette earlier in the day is linked with deeper nicotine reliance and challenges in quitting.[6–8] Nicotine can be related to hyperthyroidism,[9] which can also trigger AF.[10] Additionally, shorter time from waking to the first cigarette has been related to a higher prevalence of hypertension[11] and lower HDL[12] after adjusting for the daily cigarettes smoked.[13,14] Both of hypertension and lower HDL have been associated with the risk of incident AF.[15,16] Additionally, increasing evidence suggests that smoking behaviour affects the circadian rhythm,[17] which has been associated with human health and the onset of cardiovascular disease.[18] We assumed smoking timing might be more relevant to metabolic circadian regulation. Therefore, we hypothesized that the timing of smoking was associated with the risk of incident AF.

In the present study, we prospectively investigated the association between smoking timing and the risk of incident AF in UK Biobank cohort. We particularly investigated the modification effect of genetic risk on this relationship.

Methods

Study population

The UK Biobank is a large database containing genetic and health information from roughly half a million UK residents. Individuals aged between 40 and 69 years were recruited between 2006 and 2010 with ongoing follow-up. By collecting and storing the genetic and health data of 500 000 volunteer participants, the UK Biobank offers a rich resource for researchers worldwide to advance our understanding of the genetic and environmental determinants of disease.[19] The UK Biobank study was approved by the National Health and Social Care Information Management Board and the North West Multicentre Research Ethics Committee (11/NW/0382) and the Institutional Review Board of Tulane University (2018-1872).

Participant recruitment

We included 502 505 participants from the UK Biobank in our study. Out of these, 193 127 participants without information for exposure were excluded. Additionally, 1961 participants reported AF and 1790 participants diagnosed with AF before or at baseline were excluded. Finally, a total of 305 627 participants were included in this study (*Figure 1*).

Exposure

We gathered the information of smoking status and timing of the first cigarette after waking via baseline touch-screen questionnaires. Participants who selected 'Never' to smoking status were set as the reference group (non-smokers). All current smokers were asked, 'How soon after waking do you smoke your first cigarette of the day?'. They could choose from five options: <5, 5–15, 30–60, 61–120, or >120 min. All participants were grouped into six categories: non-smokers, >120, 61–120, 30–60, 5–15 min, and under 5 min.

Outcome

Information on the incident AF was defined by analysing hospital inpatient records, which included data on admissions and diagnoses from the

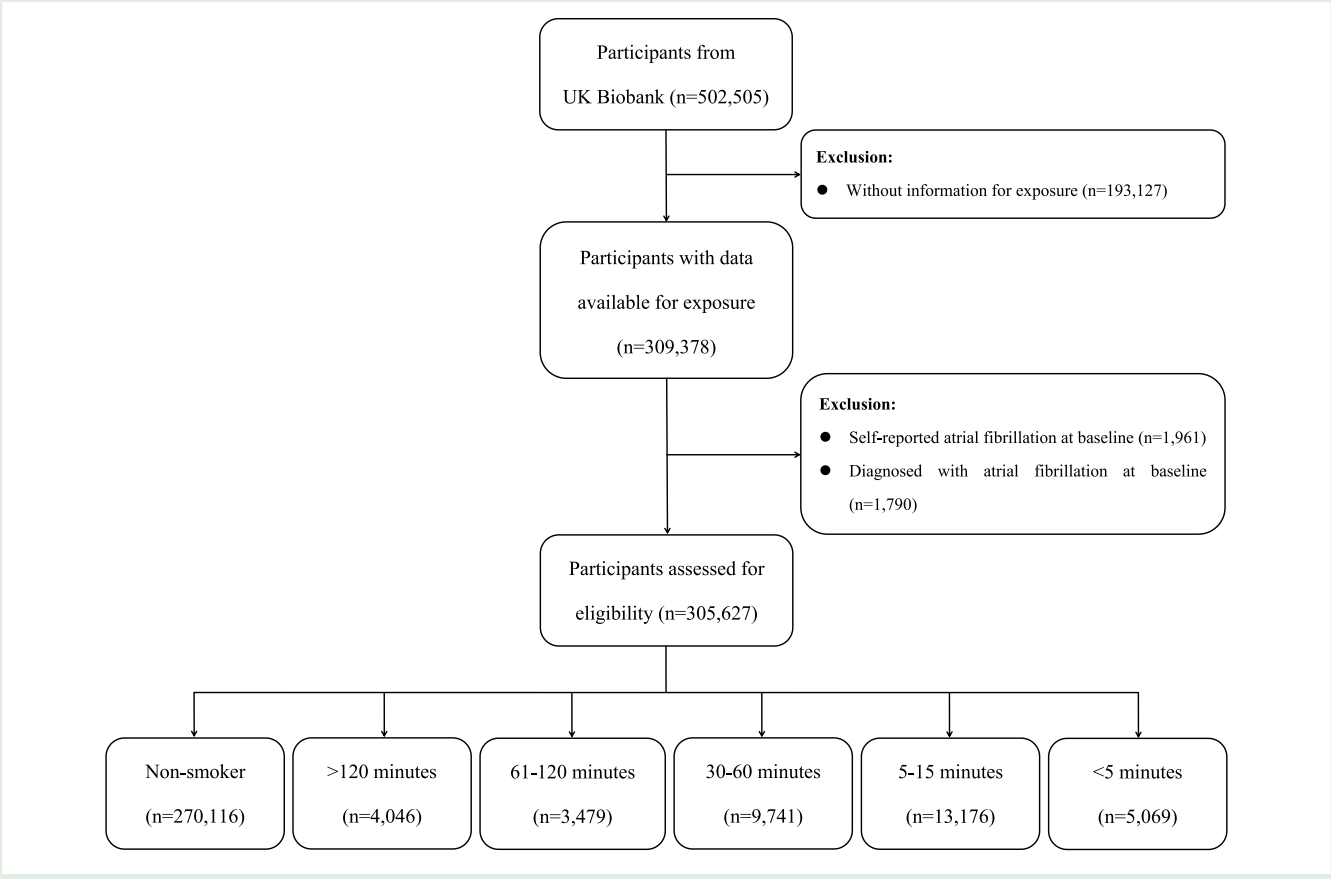


Figure 1 Flow chart.

Hospital Episode Statistics for England, Scottish Morbidity Record data for Scotland, and the Patient Episode Database for Wales. The participants with AF were defined based on International Classification of Diseases, 10th Revision (ICD 10) codes I48 and procedure codes K621–K624.[20] The detailed disease definition is shown in Supplementary material online, *Table S1*. The timing of incident AF was collected from cumulative medical records of hospital diagnoses, collected until 31 May 2021. The follow-up duration was determined starting from the recruitment date to either the first AF diagnosis, loss of follow-up, death, or the conclusion of the current monitoring period, whichever happened first.

Genotype data

The UK Biobank team performed the genotyping, imputation, and quality control of the genetic data. The detailed information can be found elsewhere.[21] From the most up-to-date genome-wide association study (GWAS) meta-analysis, a total of 134 independent single-nucleotide variations (SNVs) (formerly SNPs) related to AF were identified (GWAS).[22] The detailed information for the 134 independent SNVs is indicated in Supplementary material online, *Table S2*. We calculated the genetic risk score (GRS) of AF through the weighted method: GRS = (β1 × SNP1 + β2 × SNP2 + … + β134 × SNP134) × (134/sum of the β coefficients). According to the number of risk alleles, each SNV was coded as 0, 1, and 2. The β coefficient could be obtained from the reported GWAS meta-analysis.[22] For this study, the GRS of AF varied between 84.6 and 147, with a higher score signifying a greater genetic inclination towards AF. Based on the three-tier distribution of AF-GRS, participants were categorized into low, intermediate, or high genetic risk groups for AF.

Covariates

Age, sex, ethnic background, Townsend deprivation index, education years, alcohol intake frequency, pack years of smoking, and daily cigarette smoked were self-reported. We calculated the body mass index (BMI) through dividing weight in kilograms by the square of height in metres (kg/m^2). We created the healthy diet score ranging from 0 to 5 based on intake of vegetables, fruits, fish, processed meats, and unprocessed red meats (see Supplementary material online, *Table S3*). Each one point was added for each favourable diet factor: vegetable intake ≥ four tablespoons/day, fruit intake ≥ three pieces/day; fish intake ≥ twice/week, unprocessed red meat intake ≤ twice/week, and processed meat intake ≤ twice/week, which has been showed in our previous research.[23,24] We classified participants into two groups based on their total moderate physical activity minutes per week, following global recommendations for physical activity and health.[25] One minute of vigorous physical activity was considered equivalent to 2 min of moderate physical activity. The two groups were defined as follows: <150 or ≥150 min/week. Hypertension was defined as either having a systolic blood pressure of 140 mmHg or more, a diastolic blood pressure of 90 mmHg or more, or if the individual was taking antihypertensive medication. High cholesterol/diabetes were identified either by a self-reported history of high cholesterol/diabetes or using cholesterol-lowering drugs/insulin. The detailed information can be obtained on the UK Biobank website (www.ukbiobank.ac.uk).

Statistical analysis

The continuous variables were shown as mean ± standard deviation (SD) and categorical variables were indicated as counts and percentages. The association of smoking timing was assessed using the Cox proportional hazard regression models and the proportionality of hazards was authenticated via

Schoenfeld residuals and Kaplan–Meier methods, with all analyses adhering to predefined conditions. Model 1 was adjusted for age (years) and sex (women and men). Model 2 was further adjusted for ethnic background (white or others), Townsend deprivation index (continuous), education years (continuous), BMI (18.5–<25, 25–<30, or ≥30 kg/m^2), alcohol intake (<3 or ≥3 times/week), healthy diet score (<3 or ≥3), physical activity (≥150 or <150 min/week), hypertension (yes or no), diabetes (yes or no), and high cholesterol (yes or no). Model 3 was further adjusted for pack years of smoking and daily cigarette smoked. Missing values for categorical predictors and continuous variables were imputed with an indicator category for missing data and mean values, respectively. Supplementary material online, *Table S4* provides a thorough account of the count and percentage of participants with missing covariates.

Additionally, we performed a series of subgroup analyses stratified by age (<60 or ≥60 years), sex (women or men), ethnic background (others or white), Townsend deprivation index (<median or ≥ median), education years (<10 or ≥10 years), BMI (<25, 25–<30, or ≥30 kg/m^2), alcohol intake frequency (<3 or ≥3 times/week), healthy diet score (<3 or ≥3), physical activity (<150 or ≥150 min/week), hypertension (no or yes), diabetes (no or yes), and high cholesterol (no or yes). We used the same Cox model by adding interaction terms.

Moreover, we performed joint analysis of smoking timing with pack years of smoking and daily cigarette smoked on the risk of incident AF. We also performed a joint analysis of smoking timing and AF-GRS on the risk of incident AF.

Sensitivity analyses

In order to assess the stability of the results, we performed three sensitivity analyses. Firstly, we removed those participants within 2 years of AF onset. Secondly, we excluded the participants with missing data for covariates. Thirdly, the missing data of all covariates were imputed using multiple imputation. Fourthly, we removed those participants who achieved cigarette cessation within the first 2 years of follow-up. Our statistical examinations were accomplished using SAS version 9.4 (SAS Institute, Cary, NC, USA) and a two-sided $P < 0.05$ was defined as statistically significant.

Results

Baseline characteristics

The baseline characteristics of included participants are indicated in *Table 1*. Individuals with shorter time from waking to the first cigarette were predominantly male and obese, had lower socioeconomic backgrounds, shorter education years, less frequent alcohol intake, unhealthy diets, poorer health conditions, and tended to smoke more cigarettes daily with greater pack years of smoking.

Association between smoking timing and risk of incident atrial fibrillation

During a median follow-up time of 12.2 years, we found a total of 13 410 incident AF among the 305 627 participants. In Model 1, adjusted for age and sex, we observed a graded inverse association between the time from waking to the first cigarette and the risk of incident AF, compared with non-smokers. The hazard ratio (HR) for smoking timing was 1.14 (95% CI: 0.97–1.33) for >120 min, 1.28 (1.10–1.49) for 61–120 min, 1.51 (1.39–1.65) for 30–60 min, 1.68 (1.56–1.80) for

Table 1 Baseline characteristics

Characteristics	Non-smoker (*n* = 270 116)	Time from waking to first cigarette (min)				
		>120 (*n* = 4046)	61–120 (*n* = 3479)	30–60 (*n* = 9741)	5–15 (*n* = 13 176)	<5 (*n* = 5069)
Age, years, mean (SD)	55.8 (8.1)	53.2 (8.1)	54.4 (8.3)	55.2 (8.1)	54.7 (7.9)	53.4 (7.7)
Female, *n* (%)	160 837 (59.5)	2334 (57.7)	1744 (50.1)	5056 (51.9)	6760 (51.3)	2257 (44.5)
White ethnic, *n* (%)	245 022 (90.7)	3492 (86.3)	3059 (87.9)	8725 (89.6)	11 792 (89.5)	4457 (87.9)
Townsend deprivation index, mean (SD)	−1.6 (2.9)	−0.2 (3.4)	−0.3 (3.4)	0.1 (3.4)	0.7 (3.5)	1.7 (3.6)
Education years, mean (SD)	15.3 (5.0)	15.0 (5.0)	14.1 (5.2)	13.6 (5.2)	12.9 (5.3)	12.3 (5.3)
BMI, kg/m^2, *n* (%)						
<25	96 240 (35.6)	1660 (41)	1286 (37)	3587 (36.8)	5148 (39.1)	1977 (39)
25–<30	111 552 (41.3)	1674 (41.4)	1400 (40.2)	3892 (40)	5053 (38.4)	1865 (36.8)
≥30	60 936 (22.6)	693 (17.1)	757 (21.8)	2178 (22.4)	2850 (21.6)	1167 (23)
Alcohol intake frequency, times/week, *n* (%)						
<3	168 397 (62.3)	1656 (40.9)	1933 (55.6)	6001 (61.6)	8147 (61.8)	3133 (61.8)
≥3	101 517 (37.6)	2387 (59)	1540 (44.3)	3721 (38.2)	4997 (37.9)	1910 (37.7)
Healthy diet score, *n* (%)						
<3	81 479 (30.2)	1456 (36)	1445 (41.5)	4298 (44.1)	6759 (51.3)	2968 (58.6)
≥3	177 833 (65.8)	2399 (59.3)	1821 (52.3)	4846 (49.8)	5447 (41.3)	1650 (32.6)
Physical activity, min/week, *n* (%)						
<150	68 222 (25.3)	1073 (26.5)	842 (24.2)	2305 (23.7)	3031 (23)	1138 (22.5)
≥150	145 623 (53.9)	2086 (51.6)	1720 (49.4)	4629 (47.5)	5815 (44.1)	1988 (39.2)
Hypertension, *n* (%)	135 872 (50.3)	1569 (38.8)	1591 (45.7)	4728 (48.5)	6475 (49.1)	2523 (49.8)
Diabetes, *n* (%)	11 827 (4.4)	134 (3.3)	165 (4.7)	534 (5.5)	736 (5.6)	357 (7)
High cholesterol, *n* (%)	40 697 (15.1)	508 (12.6)	576 (16.6)	1955 (20.1)	2801 (21.3)	1202 (23.7)
Pack years of smoking, mean (SD)	0.0 (0.0)	11.2 (8.5)	19.3 (11.6)	25.6 (14.2)	33.5 (16.6)	42.5 (23.4)
Daily cigarette smoked, mean (SD)	0.0 (0.0)	6.5 (4.1)	10.8 (5.3)	13.9 (6.1)	18.0 (7.1)	22.9 (10.2)

5–15 min, and 1.90 (1.69–2.12) for <5 min, respectively (*P*-trend < 0.001). After further adjusted for ethnic background, Townsend deprivation index, education years, body mass index, alcohol intake, healthy diet score, physical activity, hypertension, diabetes, high cholesterol, pack years of smoking, and daily cigarette smoked, the results did not change significantly (*Table 2*).

Stratified analysis

Stratified analysis was conducted according to traditional risk factors to assess the potential modifying effects of potential risk factors on the relationship between smoking timing and risk of incident AF (*Table 3*). The association between smoking timing and incident AF risk was found to be stronger in participants aged under 60 years (*P*-interaction < 0.001). For smoking timing of <15 min, the adjusted HR was 1.55 (95% CI 1.27–1.91) in participants under 60 years, compared with 1.45 (95% CI 1.23–1.72) in those aged 60 years or older (*Table 3*). No significant interaction was found between smoking timing and other traditional risk factors in relation to the risk of incident AF.

Joint association of smoking timing and smoking amount with risk of incident atrial fibrillation

Joint analysis indicated that participants with a greater number of pack years of smoking and shortest time from waking to the first cigarette (<15 min) had the highest risk of incident AF, with an HR of 1.58 (95% CI: 1.33–1.88). A similar pattern emerged in the joint analysis of smoking timing and daily cigarette consumption in relation to the risk of incident AF. Heavy smokers with the shortest time from waking to the first cigarette (<15 min) had the highest risk of incident AF (HR 1.51, 95% CI: 1.26–1.81) (*Figure 2*).

Joint associations of smoking timing and atrial fibrillation-genetic risk score with risk of incident atrial fibrillation

We analysed how the smoking timing and AF-GRS jointly affected the risk of incident AF. The results showed that individuals with both high AF-GRS and short time from waking to the first cigarette had the most elevated AF risk, although the interaction between smoking timing and AF-GRS was not statistically significant. Participants with high AF-GRS and the shortest time from waking to the first cigarette faced a 220% higher risk of incident AF (95% CI: 154–302%) compared with those with low AF-GRS and the longest time from waking to the first cigarette (*Figure 3*).

Sensitivity analyses

Several sensitivity analyses were conducted to assess the stability of our results. We observed that the findings remained consistent after removing participants who developed AF within the first 2 years of follow-up (see Supplementary material online, *Table S5*). When we excluded participants with missing covariates, the results remained unchanged (see Supplementary material online, *Table S6*). Moreover, all the missing values for all covariates were imputed using multiple imputation, and the findings did not change significantly (see Supplementary material online, *Table S7*). Additionally, we observed that the findings remained consistent after excluding persons who achieved cigarette cessation within the first 2 years of follow-up (see Supplementary material online, *Table S8*).

Table 2 Hazard ratios and 95% confidence intervals for association of time from waking to the first cigarette with the outcome of atrial fibrillation

	Non-smoker	Time from waking to the first cigarette (min)				
		>120	61–120	30–60	5–15	<5	*P*-trend
Case, *n*	11 424	149	167	572	793	305	
Person-years	3 216 823	47 856	40 197	111 792	150 449	56 817	
Model 1	1.00 (reference)	1.14 (0.97–1.33)	1.28 (1.10–1.49)	1.51 (1.39–1.65)	1.68 (1.56–1.80)	1.90 (1.69–2.12)	<0.001
Model 2	1.00 (reference)	1.17 (0.99–1.37)	1.26 (1.08–1.47)	1.43 (1.31–1.56)	1.56 (1.44–1.68)	1.65 (1.47–1.86)	<0.001
Model 3	1.00 (reference)	1.13 (0.96–1.34)	1.20 (1.01–1.42)	1.34 (1.19–1.51)	1.43 (1.26–1.63)	1.49 (1.24–1.79)	<0.001

Estimates are from Cox proportional hazard regression models. Number of observations = 305 627.
Model 1: adjusted for age and sex.
Model 2: Model 1 + ethnic background, Townsend deprivation index, education years, body mass index, alcohol intake frequency, healthy diet score, physical activity, hypertension, diabetes, and high cholesterol.
Model 3: Model 2 + pack years of smoking and daily cigarette smoked.

Table 3 Association of time from waking to first cigarette with the risk of incident atrial fibrillation stratified by potential risk factors via Model 3

Subgroup	Non-smoker	Time from waking to the first cigarette (min)			*P*-trend	*P*-interaction
		>60	30–60	<15		
Age (years)						<0.001
<60	1.00 (reference)	1.25 (1.03–1.52)	1.59 (1.32–1.93)	1.55 (1.27–1.91)	<0.001	
≥60	1.00 (reference)	1.14 (0.98–1.34)	1.34 (1.15–1.56)	1.45 (1.23–1.72)	<0.001	
Sex						0.48
Women	1.00 (reference)	1.25 (1.03–1.52)	1.27 (1.04–1.56)	1.40 (1.12–1.75)	0.002	
Men	1.00 (reference)	1.11 (0.94–1.30)	1.35 (1.17–1.57)	1.44 (1.22–1.70)	<0.001	
Ethnic background						0.73
Others	1.00 (reference)	0.99 (0.63–1.55)	1.24 (0.81–1.89)	1.46 (0.94–2.27)	0.12	
White	1.00 (reference)	1.19 (1.04–1.35)	1.35 (1.19–1.52)	1.44 (1.26–1.65)	<0.001	
Townsend deprivation index						0.09
<Median	1.00 (reference)	1.30 (1.05–1.60)	1.42 (1.13–1.78)	1.37 (1.05–1.81)	0.004	
≥Median	1.00 (reference)	1.12 (0.96–1.31)	1.33 (1.15–1.52)	1.49 (1.28–1.73)	<0.001	
Education (years)						0.57
<10	1.00 (reference)	1.16 (0.92–1.46)	1.29 (1.07–1.57)	1.50 (1.22–1.83)	<0.001	
≥10	1.00 (reference)	1.15 (0.99–1.33)	1.36 (1.17–1.58)	1.39 (1.16–1.65)	<0.001	
Body mass index (kg/m^2)						0.07
18.5–<25	1.00 (reference)	1.00 (0.79–1.27)	1.36 (1.10–1.68)	1.45 (1.14–1.83)	<0.001	
25–<30	1.00 (reference)	1.07 (0.88–1.31)	1.31 (1.08–1.59)	1.34 (1.08–1.67)	0.005	
≥30	1.00 (reference)	1.39 (1.12–1.74)	1.25 (1.00–1.56)	1.40 (1.10–1.79)	0.004	
Alcohol intake (times/week)						0.12
<3	1.00 (reference)	1.27 (1.07–1.50)	1.25 (1.07–1.46)	1.38 (1.16–1.63)	<0.001	
≥3	1.00 (reference)	1.06 (0.88–1.27)	1.47 (1.22–1.77)	1.53 (1.25–1.89)	<0.001	
Healthy diet score						0.60
<3	1.00 (reference)	1.08 (0.89–1.32)	1.34 (1.13–1.59)	1.35 (1.12–1.62)	<0.001	
≥3	1.00 (reference)	1.19 (1.00–1.41)	1.29 (1.08–1.55)	1.49 (1.22–1.84)	<0.001	
Physical activity (min/week)						0.69
<150	1.00 (reference)	1.17 (0.91–1.51)	1.22 (0.95–1.58)	1.36 (1.03–1.78)	0.03	
≥150	1.00 (reference)	1.05 (0.87–1.26)	1.39 (1.16–1.66)	1.44 (1.17–1.77)	<0.001	
Hypertension						0.12
No	1.00 (reference)	0.96 (0.77–1.20)	1.31 (1.06–1.62)	1.36 (1.08–1.73)	0.01	
Yes	1.00 (reference)	1.28 (1.10–1.49)	1.35 (1.17–1.56)	1.48 (1.26–1.73)	<0.001	
Diabetes						0.94
No	1.00 (reference)	1.13 (0.99–1.29)	1.31 (1.16–1.49)	1.40 (1.21–1.61)	<0.001	
Yes	1.00 (reference)	1.38 (0.93–2.05)	1.41 (1.00–1.99)	1.65 (1.15–2.38)	0.006	
High cholesterol						0.27
No	1.00 (reference)	1.17 (1.00–1.36)	1.36 (1.17–1.59)	1.39 (1.17–1.65)	<0.001	
Yes	1.00 (reference)	1.16 (0.93–1.44)	1.25 (1.03–1.52)	1.47 (1.20–1.80)	<0.001	

Estimates are from Cox proportional hazard regression models. Number of observations = 305 627.
Model 3: Adjusted for age, sex, ethnic background, Townsend deprivation index, education years, body mass index, alcohol intake frequency, healthy diet score, physical activity, hypertension, diabetes high cholesterol, pack years of smoking, and daily cigarette smoked.

Discussion

In this prospective cohort study of UK Biobank participants, we observed that time from waking to the first cigarette showed gradient inverse associations with the risk of incident AF, regardless of additional adjustment for pack years of smoking and daily cigarette smoked. Additionally, we observed that the association between smoking timing and AF risk was strengthened by the pack years of smoking, daily cigarette smoked, and genetic susceptibility to AF.

To the best of our knowledge, this is the first prospective study to explore the associations between smoking timing and the risk of incident AF. Our findings were partly supported by prior studies. For instance, a study using the National Health and Nutrition Survey (NHANES), which included 3903 adult smokers, found a significant association between an earlier first cigarette and reduced HDL levels and a decreased LDL/HDL ratio.[12] Previous research has identified low HDL[26] and low LDL/HDL ratio[27] as factors associated with an increased risk of incident AF. Similarly, a study involving 941 current daily smokers aged 17–79

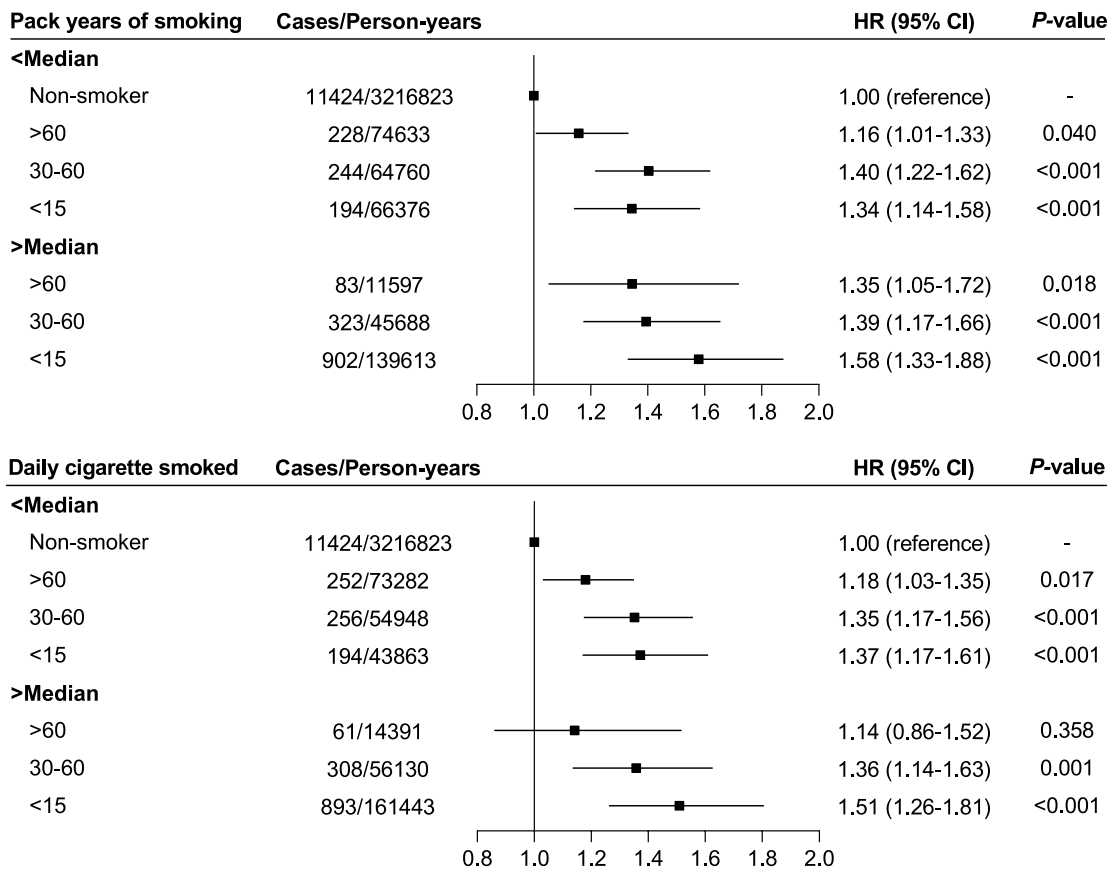


Figure 2 Joint association of smoking timing with (*A*) pack years of smoking and (*B*) daily cigarette smoked in relation to the risk of atrial fibrillation via Model 3. Estimates are from Cox proportional hazard regression models. Number of observations = 305 627. Model 3: adjusted for age, sex, ethnic background, Townsend deprivation index, education years, body mass index, alcohol intake frequency, healthy diet score, physical activity, hypertension, diabetes, high cholesterol, pack years of smoking, and daily cigarette smoked.

from the Korea National Health and Nutrition Examination Survey revealed a higher risk of hypertension among those who smoked their first cigarette within 5 min of waking.[11] Moreover, a systematic review and meta-analysis of cohort studies has demonstrated a significant association of hypertension with increased risk of incident AF.[28]

Several studies indicated that smoking was a risk factor for AF[29–31] and previous studies have shown a proportional relationship between smoking quantity and AF risk, with the risk increasing in proportion to the pack years of smoking and the number of cigarettes smoked daily.[28,32] However, the relation between the smoking timing and risk of incident AF remains unclear. Our research aligns with emerging evidence that links the timing of lifestyle habits such as exercise and eating, to cardiovascular disease risks,[4] highlighting the importance of the timing of behavioural and lifestyle patterns in relation to health. Our study provides new insight into relationship between smoking timing and AF, suggesting this trend in smoking timing is associated with an elevated risk of incident AF, a relationship that persists regardless of the pack years of smoking or the number of daily cigarettes smoked.

The abnormal timing patterns of lifestyle factors such as physical activity and eating have been associated with disruption of circadian rhythm.[33] Circadian rhythm, which refers to physiological and behavioural cycles[34] and circadian rhythm, has been related to AF in epidemiological data.[35] Existing evidence suggests that nearly all cardiovascular variables in humans, including blood pressure,[36] heart rate,[36] circulating catecholamines,[37] and vascular endothelial function,[38] exhibit circadian fluctuations. Epidemiological studies highlight noticeable circadian fluctuation in AF episodes.[39] Circadian rhythm can modulate the functions of the autonomic nervous system as well as various cardiac ion channels, playing an important role in the underlying mechanisms of AF.[40–42] Moreover, a recent study suggests that smoking may disrupt circadian balance.[17] We hypothesize that smoking timing might influence circadian rhythm, thereby increasing the risk of incident AF. Further studies are necessary to explore the mechanisms by which smoking timing disrupts circadian rhythms and its relation to the risk of incident AF.

Previous studies on the smoking timing have consistently shown that smoking the first cigarette earlier in the day is linked with deeper nicotine reliance and challenges in quitting.[6–8] Higher nicotine blood levels observed in patients with greater nicotine dependence can lead to several adverse cardiovascular effects.[43] Nicotine is known to increase heart rate,[44] elevate blood pressure,[45] and induce endothelial dysfunction,[46] all of which are contributory factors to the development of AF. Additionally, deep inhalation practices associated with high nicotine dependence can increase the deposition of other harmful substances

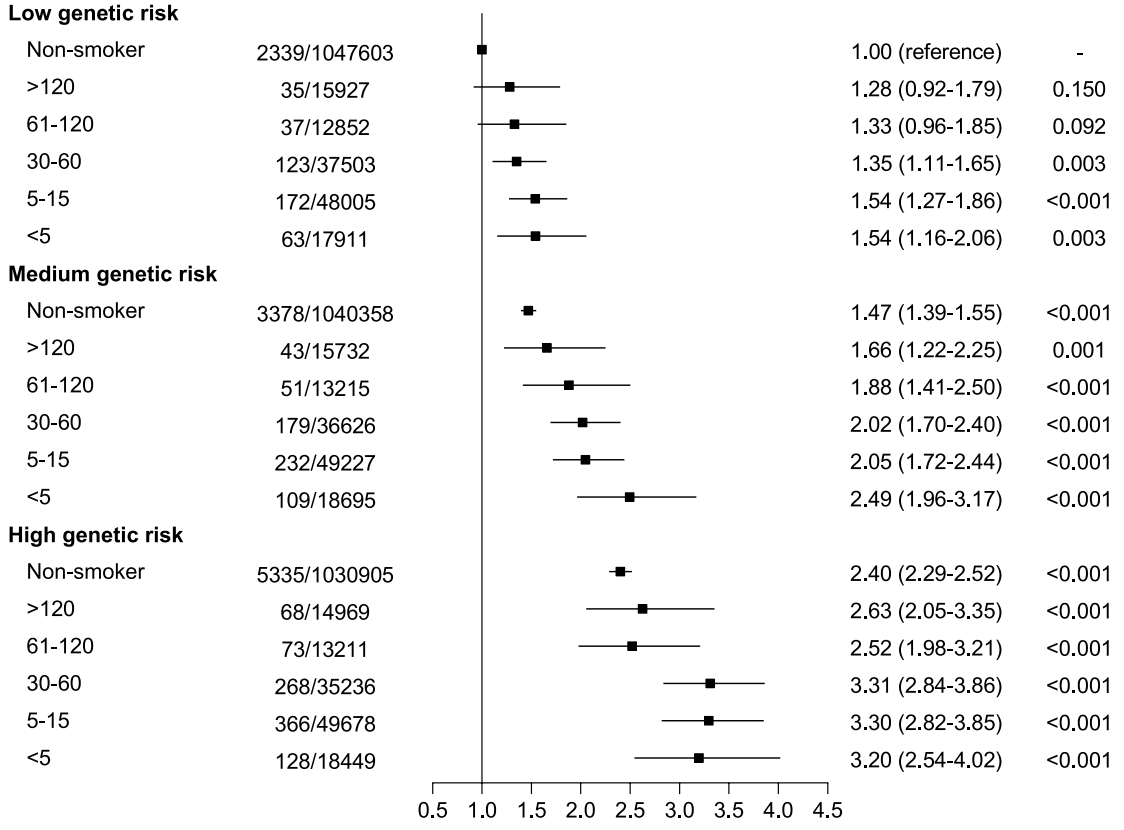


Figure 3 Joint association of smoking timing with atrial fibrillation-genetic risk score in relation to the risk of atrial fibrillation via Model 3. Estimates are from Cox proportional hazard regression models. Number of observations = 305 627. Model 3: adjusted for age, sex, ethnic background, Townsend deprivation index, education years, body mass index, alcohol intake frequency, healthy diet score, physical activity, hypertension, diabetes, high cholesterol, pack years of smoking, daily cigarette smoked, genotyping batch, and the first 10 genetic principal components.

found in cigarette smoke, such as carbon monoxide and tar, which further strain cardiovascular health. The physiological stress induced by these factors may trigger or exacerbate the electrophysiological disturbances in the atria, leading to AF. Additionally, the difficulty in cessation faced by highly nicotine-dependent individuals significantly impacts their risk profile. The sustained exposure to smoking over an extended period not only continues to subject these individuals to the direct harmful effects of nicotine and other chemicals but also hampers the body's ability to recover from the damage caused by smoking. This prolonged exposure can lead to chronic inflammation[47] and oxidative stress,[48] both of which are critical in the pathogenesis of AF.[49,50]

While previous research has highlighted the role of genetic susceptibility in the risk of incident AF,[22] our study is the first to investigate the combined effects of genetic factors and smoking timing on this risk. Our study indicated that AF risk increased monotonically with increasing genetic risk and decreasing time from waking to the first cigarette, suggesting that extending the time from waking to the first cigarette could be beneficial, especially for individuals with high genetic susceptibility. Additionally, we found that the association of smoking timing with the risk of incident AF was stronger in participants with age < 60 years old. In participants aged over 60, the risk of incident AF is usually the result of the accumulation of multiple factors, including long-term living habits, and smoking timing may be only one risk factor among many. The association of smoking timing with the risk of incident AF may therefore be relatively unobvious. Additionally, we observed that individuals with shorter time from waking to the first cigarette were predominantly male. In the stratified analysis, we found that the association of smoking timing with the risk of incident AF was stronger in males except for >60 min group, while no significant interaction was found. Further research is needed to confirm the sex differences in the relationship between smoking timing and risk of incident AF.

Cigarette smoking accounts for 50% of all preventable deaths among smokers and a lifelong smoker faces a 50% risk of dying from smoking-related causes and is likely to lose an average of 10 years from their life expectancy.[51] Smoking-attributed CVD morbidity and mortality are declining globally, but significant variation persists, indicating a need for targeted interventions to reduce smoking-related CVD burden.[52] Atrial fibrillation remains a significant health concern due to its consequences, including stroke and heart failure. Previous study explores the interplay between AF, lifestyle choices, and dietary habits, focusing on non-pharmacological methods of managing AF and the role of lifestyle changes in treatment strategies.[53] Alterations of RyR2 and mitochondrial ROS generation form a vicious cycle in the development of AF, suggesting that targeting this mechanism could be effective in preventing and treating AF.[54] Cigarette smoking is a major cause of cardiovascular diseases and an independent risk factor for AF, with a

detailed mechanistic understanding implicating the IKACh current in AF perpetuation through an Arf6/PIP5K-dependent pathway.[55] There is a substantial global burden of CVDs in youths and young adults, highlighting the need for effective primary prevention strategies and responsive healthcare systems for young people.[56] In the Tromsø Study, AF incidence trends were influenced by blood pressure changes in women and BMI changes in men.[3] Lifestyle modifications could have prevented a significant proportion of AF cases in Tromsø, Norway,[57] and reducing alcohol consumption is likely to impact AF prevalence in Ireland.[58] Finally, risk factor burden and genetic predisposition are associated with the 10-year risk of AF, aiding in the identification of high-risk individuals for primary prevention.[59]

In the current study, we found that time from waking to the first cigarette indicated gradient inverse association with the risk of incident AF, and this risk is strengthened by the genetic susceptibility to AF. It is important to emphasize that the gradient inverse association between the time from waking to the first cigarette and the risk of incident AF highlights a critical window for intervention. The results suggest that individuals who smoke immediately upon waking are at a significantly higher risk for developing AF, which is further exacerbated by genetic susceptibility. Clinicians should consider advising patients, especially those with a known genetic predisposition to AF, to delay their first cigarette of the day as a potential strategy to mitigate AF risk. This insight offers a tangible behavioural modification that could be incorporated into smoking cessation programmes and personalized risk management plans, thereby potentially reducing the incidence of AF in high-risk populations. Furthermore, these findings underscore the need for integrating genetic risk assessments in routine clinical practice to better identify and manage patients at heightened risk for AF due to both genetic and lifestyle factors. To further validate our findings, we suggest conducting similar studies in diverse populations and using longer follow-up periods to evaluate the effects of modifying smoking timing on AF incidence. Moreover, Mendelian randomization analysis may provide evidence for the potential causality. Additionally, more detailed genetic analyses and mechanistic studies could provide deeper insights into the biological interactions between smoking timing and genetic susceptibility in relation to AF risk.

Our study has several strengths. Firstly, it explores the role of genetic susceptibility in modifying the relationship between smoking timing and AF risk, paving the way for precise prevention strategies tailored for high-risk populations. Secondly, the study provides comprehensive and detailed information on covariates. Thirdly, the study's large sample size, prospective cohort design, and consistent findings across multiple sensitivity analyses enhance the robustness and reliability of the results. However, there were some limitations existing in our study. Firstly, although the pack years of smoking and daily cigarette smoke were adjusted in our study, we could not rule out the influence of residual confounding effects due to correlation between smoking timing and smoking amount. Secondly, the study's observational nature means we cannot conclusively determine a cause–effect relationship between physical frailty and premature mortality. Thirdly, the voluntary participation in the UK Biobank may not be representative of the wider population, underscoring the need for additional research to validate our findings. Fourthly, the time from waking to the first cigarette was only recorded at the baseline. Consequently, we could not account for any behavioural changes that may have occurred over time before the onset of the disease. Fifthly, the assessment of the time from waking to the first cigarette relied on self-reported answers, introducing the possibility of misclassification and recall bias. Misclassification might affect our results by incorrectly categorization, potentially leading to an underestimation or overestimation of the observed associations between smoking timing and the risk of incident AF. Finally, only two variables including time from waking to the first cigarette and the amount of cigarettes smoked daily from the Fagerstrom questionnaire could be obtained from UK Biobank cohort, potentially restricting a comprehensive assessment of nicotine dependence.

Conclusions

In the present study, time from waking to the first cigarette showed gradient inverse associations with the risk of incident AF, and the associations appeared to be strengthened by the genetic susceptibility to AF.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Author contribution

L.Q. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. J.Z. and L.Q.: concept and design; acquisition, analysis, or interpretation of data; drafting of the manuscript. All authors: critical revision of the manuscript for important intellectual content. J.Z.: statistical analysis.

Transparency statement

L.Q. affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Ethical approval

The UK Biobank study was approved by the National Health and Social Care Information Management Board and the North West Multicentre Research Ethics Committee (11/NW/0382) and the Institutional Review Board of Tulane University (2018-1872).

Conflict of interest: The authors declare no conflicts of interest.

Data availability

This study has been conducted using the UK Biobank Resource, approved project number 29256. The UK Biobank will make the source data available to all bona fide researchers for all types of health-related research that is in the public interest, without preferential or exclusive access for any persons. All researchers will be subject to the same application process and approval criteria as specified by UK Biobank. For more details on the access procedure, see the UK Biobank website: http://www.ukbiobank.ac.uk/register-apply.

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