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CLINICAL RESEARCH
Epidemiology and Prevention

Long-term night shift work is associated with the risk of atrial fibrillation and coronary heart disease

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Aims The aim of this study was to test whether current and past night shift work was associated with incident atrial fibrillation (AF) and whether this association was modified by genetic vulnerability. Its associations with coronary heart disease (CHD), stroke, and heart failure (HF) were measured as a secondary aim.

Methods and results This cohort study included 283 657 participants in paid employment or self-employed without AF and 276 009 participants free of CHD, stroke, and HF at baseline in the UK Biobank. Current and lifetime night shift work information was obtained. Cox proportional hazard models were used. Weighted genetic risk score for AF was calculated. During a median follow-up of 10.4 years, 5777 incident AF cases were documented. From 'day workers', 'shift but never/rarely night shifts', and 'some night shifts' to 'usual/permanent night shifts', there was a significant increasing trend in the risk of incident AF (*P* for trend 0.013). Usual or permanent night shifts were associated with the highest risk [hazard ratio (HR) 1.16, 95% confidence interval (CI) 1.02–1.32]. Considering a person's lifetime work schedule and compared with shift workers never working nights, participants with a duration over 10 years and an average 3–8 nights/month frequency of night shift work exposure possessed higher AF risk (HR 1.18, 95% CI 0.99–1.40 and HR 1.22, 95% CI 1.02–1.45, respectively). These associations between current and lifetime night shifts and AF were not modified by genetic predisposition to AF. Usual/permanent current night shifts, ≥10 years and 3–8 nights/month of lifetime night shifts were significantly associated with a higher risk of incident CHD (HR 1.22, 95% CI 1.11–1.35, HR 1.37, 95% CI 1.20–1.58 and HR 1.35, 95% CI 1.18–1.55, respectively). These associations in stroke and HF were not significant.

Conclusion Both current and lifetime night shift exposures were associated with increased AF risk, regardless of genetic AF risk. Night shift exposure also increased the risk of CHD but not stroke or HF. Whether decreasing night shift work frequency and duration might represent another avenue to improve heart health during working life and beyond warrants further study.

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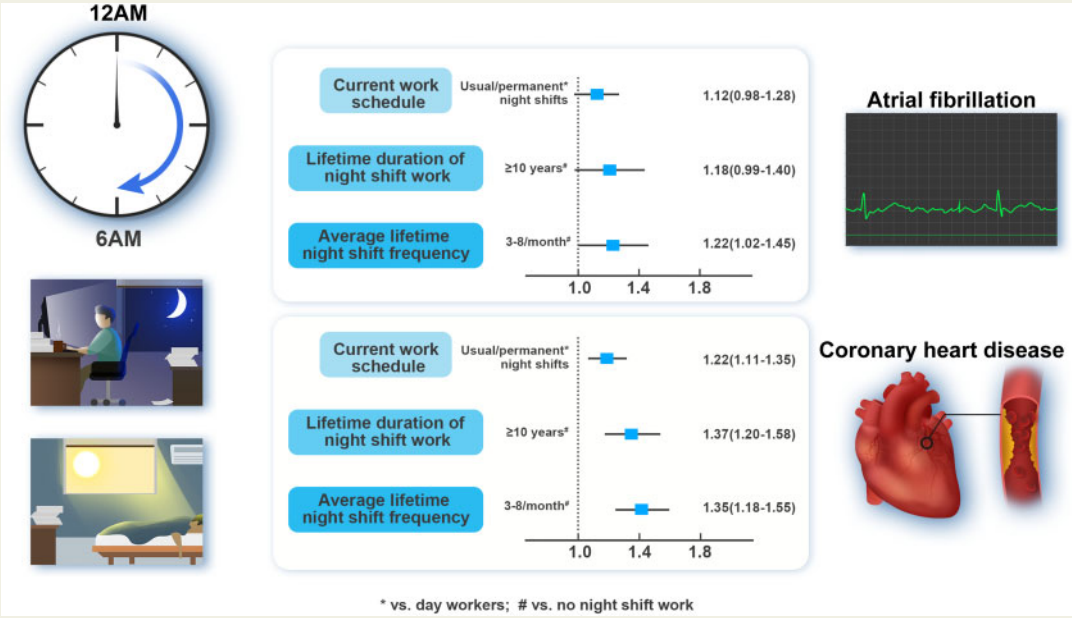
Graphical Abstract



This study demonstrates that both current and lifetime night shift exposures were associated with increased risk of atrial fibrillation and coronary heart disease.

Keywords Night shift • Lifestyle • Genetic risk • Atrial fibrillation • Coronary heart disease

Introduction

Atrial fibrillation (AF) is the most prevalent arrhythmia managed in clinical practice and often occurs as a cause or consequence of heart failure (HF).[1] The 2017 Global Burden of Disease Study showed that there were ~37.6 million individuals with AF worldwide, including 3 million people with new-onset AF and 287 000 people who died from AF in 2017.[2] The American Heart Association stated that the primary and secondary prevention of AF through intervention in lifestyle and risk factors was essential.[3] Several risk factors such as obesity, sleep apnoea, hypertension, diabetes and other modifiable lifestyle-related factors have been associated with the occurrence of AF.[4,5] Considering the increasing prevalence of AF, novel risk factors should be studied.

With the intensification of social production pressure and the refinement of the division of labour, shift work is gradually becoming common among employees in modern society.[6] According to the 6th European Working Conditions Survey, nearly 21% of the working population engaged in shift work, which is identified as an irregular working schedule outside the conventional daytime, often classified into daily, night, rotating and other types of shift work.[7] Growing evidence indicates that shift work, particularly night shift work, has an adverse impact on individual health and organ function.[8] Night shift work may break the body's circadian rhythm and affect metabolism and hormone secretion,[9] and the effect may be more significant with long-term night shift exposure. Several investigations have focused on the relationship of night shift work with metabolic and cardiovascular disease[10–12] and emphasize the important role of the lifetime duration of night shift work.[13] Thus, night shifts have been associated with various changes in metabolism and the autonomic system that are likely to be related to AF;[14,15] however, data on the association of night shifts with AF are lacking.

Besides environmental factors, genetic risk plays a role in the development of AF. A recent genome-wide association study identified ~140 loci associated with AF.[16] Genetic predisposition may modify the association between environmental factors and cardiometabolic diseases;[17] however, little is known about the potential interaction between genetic risk and night shift on AF risk.

Using this cohort of 283 657 participants from the UK Biobank (UKB), our objective was to test whether current night shift work was associated with AF. According to lifetime employment reports, we examined whether a longer duration of and more frequent night shift work were associated with a higher AF risk. We further analysed the effect of the interaction between night shift work and genetic AF predisposition on disease risk. In addition, the association between night shift exposure and cardiovascular diseases including coronary heart disease (CHD), stroke and HF was also measured as a secondary aim.

Materials and methods

Study design and population

The UKB is a prospective cohort study that included >500 000 community-dwelling adults aged 40–69 years across the UK between 2006 and 2010 (https://www.ukbiobank.ac.uk/, last accessed date 24 July 2021). Detailed information has been described previously.[18] We declare that all data are publicly available from the UKB repository.[18] The North West Multicentre Research Ethical Committee Study approved the UKB study, and all participants provided written informed consent.

Participants in paid employment or who were self-employed at baseline were included (n = 286 353). We excluded individuals with prevalent AF at baseline (n = 2696), and then, our sample consisted of 283 657 participants. Among those, 193 819 had genetic data. Moreover, 75 391 participants provided in-depth lifetime employment information by completing an online follow-up questionnaire in 2015, which was e-mailed to ∼330 000 UKB participants with known e-mail addresses, regardless of employment status and shift work at baseline;[19] a subgroup of 52 645 participants of European descent also had genetic data available (Supplementary material online, *Figure S1*). To broaden the scope of the research, we also sought to analyse the association between night shift exposure and other cardiovascular diseases including CHD, stroke, and HF as a secondary aim. There were 276 009 participants free of CHD, stroke and HF at baseline; and 73 986 participants had lifetime employment information (Supplementary material online, *Figure S1*).

Shift work assessment

Participants who indicated they were in paid employment or self-employed were asked whether their current work involved shift work. 'Shift work is a work schedule that falls outside of the normal daytime working hours of 9 a.m.–5 p.m. This may involve working afternoons, evenings or nights or rotating through these kinds of shifts'. The answers included 'never/rarely, sometimes, usually, and always' and additional options: 'prefer not to answer' and 'do not know'. Those who answered 'sometimes, usually, and always' were further asked whether their work involved night shift work that 'is a work schedule involving working through the normal sleeping hours, for instance working through the hours from 12 a.m. to 6 a.m.'. The answer options were the same as above. As suggested in previous studies,[12] current shift work status was categorized as 'day workers', 'shift but never/rarely night shifts', 'some night shifts', and 'usual/permanent night shifts'.

In the lifetime employment questionnaire, participants provided detailed information about each job ever worked, the number of years in each job, and the number of night shifts per month for each job. The lifetime employment information before the baseline in each participant was selected. Suggested by previous studies,[12] using that information, we calculated the duration (i.e. number of years working night shifts) and frequency (i.e. the average number of night shifts per month) of night shift work.

Ascertainment of atrial fibrillation

The outcome, incident AF (field ID 131351, ICD code I48), was extracted from the 'first occurrence of health outcomes defined by a three-character International Statistical Classification of Diseases and Related Health Problems 10th Revision code' (category ID in UKB 1712). The diagnosis of AF was obtained by using linkage with death register, primary care, and hospital inpatient records. Detailed information regarding the linkage procedure is available online (https://biobank.ctsu.ox.ac.uk/crystal/exinfo.cgi?src=diag_xtabs_HES, last accessed date 24 July 2021). How to ascertain CHD, stroke and HF is shown in the Supplementary material online.

Genetic risk score for atrial fibrillation

Detailed information on genotyping in the UKB was reported previously.[20] The weighted genetic risk score (GRS) was created for AF using single-nucleotide polymorphisms (SNPs) associated with AF at the genome-wide association significance in a meta-analysis of genome-wide association studies that did not include UKB participants.[16] Information on the 166 selected SNPs is listed in Supplementary material online, *Table S1*. Individual SNPs were coded as 0, 1, and 2 according to the number of risk alleles. The regression coefficient for each SNP was taken from the reported meta-analysis.[16] The GRS was formulated as the sum of the number of AF risk-increasing alleles at each locus multiplied by the respective regression coefficient.[21] We determined whether participants were at high (highest quartile), intermediate (mid two quartiles), or low (lowest quartile) genetic risk for AF.

Covariates

Three main groups of covariates were considered. One group was demographic information, including age, sex, ethnicity (white/others), education (university or college degree/others), and the Townsend index reflecting socioeconomic status (continuous).

The second group included seven ideal cardiovascular health metrics (ICVHMs) proposed by the American Heart Association, which are well-defined cardiometabolic health metrics and are potential confounders in the associations explored.[22] The ideal metrics were binomial variables including never or quit smoking, ideal body mass index (BMI <25.0 kg/m^2), physical activity goal (≥150 min/week of moderate intensity, ≥75 min/week of vigorous intensity, or an equivalent combination), dietary score ≥4 proposed in previous studies,[23] total cholesterol <5.18 mmol/L without using lipid-lowering medication, glycated haemoglobin <5.7% (39 mmol/mol), and no history of diabetes and blood pressure <120/<80 mmHg without using blood pressure-lowering medication.

The third group contained two sleep factors obtained from the self-reported sleep questionnaire including sleep duration (≤6, 7–8, and ≥9 h/day) and chronotype preference [morning type (a 'morning' person), intermediate type (more a 'morning' than 'evening' person, or more an 'evening' than 'morning' person), and evening type (an 'evening' person)].

Statistical analyses

Data analyses were performed using IBM SPSS Statistics, version 25 (IBM Corporation, Armonk, NY, USA). A P-value of <0.05 indicated statistical significance (two-sided). The baseline characteristics of the study population are reported as the means or percentages by current shift work status ('day workers', 'shift but never/rarely night shifts', 'some night shifts', and 'usual/permanent night shifts'). For lifetime employment, we examined the associations of cumulative night shift work duration (none, <10 and ≥10 years) and average monthly frequency of night shifts (none, <3 nights/month, 3–8 nights/month, or >8 nights/month) with AF risk. Cumulative cases of AF, CHD, stroke, and HF were calculated during follow-up visits. The follow-up time was determined from the baseline date (date of visiting the assessment centre) to the diagnosis of AF, CHD, stroke and HF, death, or censoring date (31 August 2019), whichever came first.

The a priori hypothesis was that current and past rotating night shift work increased AF risk. Thus, Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) in the association between current, lifetime duration and frequency of night shift and incident AF. Model 1 was adjusted for age and sex. Model 2 was further adjusted for ethnicity, education, and the Townsend index. Model 3 was adjusted for the terms in Model 2 and seven ICVHMs 'Day workers' were set as the reference. The P-value for trend was

calculated with continuous values of current night shift work, lifetime duration, and frequency categories. The association between night shift exposure and three cardiovascular diseases was also measured using the above final model. In preplanned secondary analyses, we tested whether sex, sleep duration, chronotype, and ICVHMs modified the association between current/lifetime shift work and the probability of type 2 diabetes using a log likelihood ratio test to compare models with and without cross-product interaction terms.

To estimate the population-level risk attributable to night shift work, the hypothetical population attributable risk (PAR%) was calculated. It is an estimate of the proportion of the incident AF in the study population during follow-up that theoretically would be prevented if all people were in the low-risk groups, assuming a causal relationship.[24]

We measured whether genetic susceptibility to AF modified the association between current and lifetime night shift work and AF risk. We first tested whether the weighted GRS (continuous) and GRS quartiles were positively associated with AF. Using the above interaction analysis based on a log likelihood ratio test comparing models with and without cross-product interaction terms, we calculated the *P*-values for interaction and stratified associations for those currently employed and those with lifetime employment information by GRS category [high (highest quartile), intermediate (mid two quartiles), and low (lowest quartile) AF risk group].

In the sensitivity analyses, we further adjusted sleep duration and chronotype category in the models. We also restricted subjects with incident AF ≥1 year from baseline to perform the regression.

Results

Table 1 presents the baseline characteristics of the study population according to current night shift status. Among 283 657 participants, 'day workers', 'shift but never/rarely night shifts', 'some night shifts', and 'usual/permanent night shifts' were found in 82.7%, 8.5%, 5.0%, and 3.9%, respectively. Compared with day workers, participants who engaged in night shift work more frequently were more likely to be men, have a higher Townsend deprivation index and lower education level, and work longer hours. In addition, they also tended to have shorter sleep durations and later chronotypes. The baseline characteristics of the study population according to lifetime night shift status are shown in Supplementary material online, *Tables S2* and *S3*.

Table 1 UK Biobank participants' characteristics by current night shift work exposure (*n* = 283 657)

	Current work schedule			
	Day workers	**Shift but never/rarely night shifts**	**Some night shifts**	**Usual/permanent night shifts**
n (%)	234 616 (82.7)	24 015 (8.5)	14 074 (5.0)	10 952 (3.9)
Age (years)	52.9 ± 7.1	52.5 ± 7.0	51.2 ± 6.8	51.3 ± 6.8
Male gender (%)	46.3	47.3	61.8	62.1
White (%)	95.2	90.9	87.9	86.7
Townsend deprivation index	-1.5 ± 2.9	-0.63 ± 3.2	-0.54 ± 3.3	-0.41 ± 3.3
University or college degree (%)	41.2	25.0	24.1	15.7
Sleep duration (%) (h/day)				
≤6	24.3	29.8	33.6	39.6
7–8	71.4	64.9	61.6	54.8
≥9	4.3	5.3	4.9	5.6
Chronotype (%)				
Morning	25.9	28.4	27.2	22.1
Intermediate	65.2	62.8	62.2	60.4
Evening	8.9	8.8	10.6	17.5
Drinks per week	8.4 ± 9.7	7.9 ± 10.5	8.7 ± 11.2	7.8 ± 10.6
Smoking, current/ever (%)	9.8/31.9	14.0/32.2	16.4/30.7	17.2/30.0
Body mass index (kg/m^2)	27.1 ± 4.6	27.8 ± 5.0	28.2 ± 4.9	28.4 ± 4.9
Diabetes	3.3	4.4	4.6	5.1
ICVHM (%)				
Non-smoking	90.2	86.0	83.6	82.8
Ideal body mass index	36.0	30.8	26.3	24.5
Physical activity at goal	49.9	56.3	59.8	59.9
Healthy diet	47.3	45.7	43.2	40.4
Ideal total cholesterol	25.0	25.5	26.8	28.1
Ideal fasting plasma glucose	86.6	85.2	85.4	83.5
Ideal blood pressure	16.1	15.7	14.6	13.5

Values are given as mean ± standard deviation for continuous variables and percentage for categorical variables.
ICVHM, ideal cardiovascular health metric.

Table 2 Current night shift work and atrial fibrillation in the UK Biobank ($n = 283\,657$)

	Current work schedule				*P* for trend
	Day workers	Shift but never/ rarely night shifts	Some night shifts	Usual/permanent night shifts	
Total cases	4748	508	290	231	
Total sample size	234 616	24 015	14 074	10 952	
Model 1	1.00	1.11 (1.01–1.22)	1.12 (1.00–1.26)	1.16 (1.02–1.32)	0.001
Model 2	1.00	1.10 (1.00–1.20)	1.12 (0.99–1.26)	1.15 (1.01–1.32)	0.003
Model 3	1.00	1.09 (0.99–1.19)	1.10 (0.97–1.24)	1.12 (0.98–1.28)	0.013

Data are hazards ratios (95% confidence interval). Model 1 adjusted for age and sex. Model 2 additionally adjusted for ethnicity (White/others), Townsend index (continuous), and education (university or college degree/others). Model 3 adjusted for terms in Model 2 and seven ideal cardiovascular health metrics included healthy diet, ideal body mass index, physical activity at goal, non-smoking, and ideal blood pressure, total cholesterol, and glycaemic status.

Table 3 Lifetime duration of night shift work involving night shifts and atrial fibrillation risk ($n = 75\,391$)

	Lifetime duration of night shift work			*P* for trend
	None	<10 years	≥10 years	
Total cases	995	158	148	
Total sample size	59 779	8749	6863	
Model 1	1.00	1.04 (0.88–1.24)	1.19 (1.00–1.42)	0.056
Model 2	1.00	1.05 (0.89–1.24)	1.20 (1.01–1.43)	0.046
Model 3	1.00	1.04 (0.88–1.23)	1.18 (0.99–1.40)	0.085

Data are hazards ratios (95% confidence interval). Model 1 adjusted for age and sex. Model 2 additionally adjusted for ethnicity (White/others), Townsend index (continuous), and education (university or college degree/others). Model 3 adjusted for terms in Model 2 and seven ideal cardiovascular health metrics included healthy diet, ideal body mass index, physical activity at goal, non-smoking, and ideal blood pressure, total cholesterol, and glycaemic status.

Subsamples with lifetime employment information seemed to have lower BMI than those without lifetime employment information, and the main characteristics were comparable between the samples with and without genetic samples (Supplementary material online, *Table S4*).

During a median follow-up of 10.4 years (~3.0 million person-years), a total of 5777 incident AF cases were observed. We first tested the association of current night shift work status and AF (*Table 2*). Compared with day workers, increasing categories of night shifts were associated with a higher risk of incident AF in age- and sex-adjusted models (*P* for trend 0.001), and rotating shifts with usual or permanent night shifts had the highest risk (HR 1.16, 95% CI 1.02–1.32). In addition, this association was still significant after adjusting for demographic variables including ethnicity, Townsend index, and education in Model 2. In the final model, multivariable adjustment for known AF risk factors including seven ICVHMs attenuated this estimate; nevertheless, a significant positive trend still existed between current night shift and AF risk (*P* for trend 0.013).

Across categories of lifetime years of rotating night shift work, we then examined associations between lifetime night shift duration and AF risk ($n = 75\,391$; 1301 cases) (*Table 3*). The results suggested that longer night shift work exposure was associated with a higher risk of AF in the final model (*P* for trend 0.085). The multivariable adjustment model showed a significant association between ≥10 years of night shift work exposure and AF risk (HR 1.18, 95% CI 0.99–1.40). When restricting participants with incident AF ≥1 year from the baseline, the above association was stronger (HR 1.21, 95% CI 1.01–1.45 for ≥10 years of night shift work) (Supplementary material online, *Table S5*).

Although the age- and sex-adjusted model suggested that more frequent night shift work exposure was associated with higher AF risk (*P* for trend 0.098) (*Table 4*), multivariable adjustment attenuated this association. In multivariate-adjusted models, only participants who worked an average of 3–8 nights/month had a significantly higher likelihood of AF than individuals who never worked night shifts (Model 3, HR 1.22, 95% CI 1.02–1.45) whereas the results were not significant in participants with <3 or >8 nights/month (HR 0.88, 95% CI 0.64–1.21 and HR 1.05, 95% CI 0.86–1.28, respectively).

The above associations in CHD, stroke, and HF are shown in *Figure 1*. Usual/permanent current night shifts were significantly associated with a higher risk of CHD (HR 1.22, 95% CI 1.11–1.35). There were also significant associations between ≥10 years and 3–8 nights/month of night shift work exposure and the risk of CHD (HR 1.37, 95% CI 1.20–1.58 and HR 1.35, 95% CI 1.18–1.55, respectively). Generally, these associations in stroke and HF were not significant.

Compared with no shift work, the PAR% of current shift work was 1.5% (95% CI 0.3–2.8) for AF and 2.6% (95% CI 1.5–3.7) for CHD, suggesting that, theoretically if causal, ~1.5% and 2.6% of the incident

Table 4 Association of average lifetime frequency of night shifts worked across all reported jobs and atrial fibrillation risk (n = 75 391)

	Average lifetime night shift frequency				*P* for trend
	None	<3/month	3–8/month	>8/month	
Total cases	995	39	152	115	
Total sample size	59 779	2305	7723	5584	
Model 1	1.00	0.88 (0.64–1.21)	1.23 (1.04–1.46)	1.07 (0.88–1.30)	0.098
Model 2	1.00	0.89 (0.64–1.22)	1.23 (1.04–1.47)	1.08 (0.89–1.31)	0.084
Model 3	1.00	0.88 (0.64–1.21)	1.22 (1.02–1.45)	1.05 (0.86–1.28)	0.147

Data are hazards ratios (95% confidence interval). Model 1 adjusted for age and sex. Model 2 additionally adjusted for ethnicity (White/others), Townsend index (continuous), and education (university or college degree/others). Model 3 adjusted for terms in Model 2 and seven ideal cardiovascular health metrics included healthy diet, ideal body mass index, physical activity at goal, non-smoking, and ideal blood pressure, total cholesterol, and glycaemic status.

AF and CHD in this cohort, respectively, will not have occurred if all participants had no shift work exposure. The PAR% of ≥10 years lifetime duration and ≥3 nights/month of night shift work was 1.7% (95% CI -0.2 to 3.6) and 2.7% (95% CI 0–5.4) for AF and 3.6% (95% CI 1.8–5.4) and 4.0% (95% CI 1.6–6.5) for CHD, respectively.

We further conducted stratified analyses by sex, sleep duration, chronotype preference and ICVHMs to evaluate whether there was a different association between current and lifetime night shift work and AF risk. A significant effect of the interaction between sex and lifetime duration of night shift work on AF ($P_{interaction}$ = 0.040) was observed: compared with day workers, for women, >10 years of night shift work significantly increased AF risk (HR 1.64, 95% CI 1.18–2.29), but this was not the case for men (HR 1.07, 95% CI 0.87–1.31). Moreover, the association between the lifetime duration and frequency of night shift work and AF risk was strengthened in individuals reporting non-ideal physical activity ($P_{interaction}$ = 0.045 and 0.022, respectively). However, associations between current and lifetime night shifts and AF did not differ by sleep duration, chronotype, or other ICVHMs (Supplementary material online, *Tables S6–S8*).

As expected, weighted GRS and weighted GRS quartiles were positively associated with AF risk, and participants with intermediate and high GRSs had a broadly higher risk for AF than those with a low genetic risk (HR 1.61, 95% CI 1.49–1.75 and HR 3.43 95% CI 3.16–3.73, respectively) (Supplementary material online, *Table S9*). Individuals with high genetic risk and usual/permanent night shifts, night shifts for ≥10 years, or medium frequency night shifts (3–8/month) had the highest risk of incident AF in the corresponding groups. Furthermore, we did not observe an interaction between the categories of GRS and current night shift status ($P_{interaction}$ = 0.704), lifetime duration ($P_{interaction}$ = 0.786), or frequency of night shift work ($P_{interaction}$ = 0.960) (Supplementary material online, *Table S10*).

In the sensitivity analyses, further adjusting sleep duration and chronotype category in the models and restricting subjects with incident AF ≥1 year from the baseline did not materially change the results (Supplementary material online, *Table S5*).

Discussion

In this large-scale cohort with a 10-year follow-up time, we found the following: (i) current night shift work was associated with increased risks of AF and in the multivariate-adjusted model. From 'day workers', 'shift but never/rarely night shifts', and 'some night shifts' to 'usual/permanent night shifts', there was a significant increasing trend in incident AF and CHD risk; (ii) longer lifetime durations of shift work exposure (i.e. ≥10 years) were significantly associated with higher AF and risks; (iii) an average 3–8 nights/month frequency of night shift work was associated with higher AF and risks; (iv) the positive association between current and lifetime night shift and AF held regardless of low, intermediate, or high genetic risk; and (v) night shift exposure was also significantly associated with CHD risk but not stroke or HF risk (*Graphical abstract*).

To the best of our knowledge, this was the first study to test the association between night shift work and AF. In a meta-analysis that evaluated 21 studies with a total of 173 010 participants, the authors highlighted that night shift workers had a 17% and 20% higher risk of cardiovascular disease events and mortality than day workers, respectively.[25] Our study extended those previous reports concerning cardiovascular health and focused on whether night shift work was a novel risk factor for AF. Besides CHD, we found the potential critical role of night shift work in current employment for AF. Compared with day workers, increasing more night shifts were significantly associated with elevated AF risk, and an evident positive trend still existed after adjusting for ICVHMs.

In addition, our findings based on a large number of lifetime employment reports focused on two aspects: duration and frequency of night shifts. The idea that a longer duration of working night shifts might be harmful to cardiovascular health has been suggested.[26] A prospective cohort of US female nurses found that 6 or more years of night shift work may increase the risk of CHD,[26] and another study found that the association between shift work and cardiovascular disease risk seemed to appear only after the first 5 years of exposure.[25] In line with this finding, we found a consistent linear relationship between lifetime duration of night shift and AF and CHD risks, and a duration of 10 or more years might be a risk factor. Regarding the frequency, we found that participants who worked an average of 3–8 nights/month, rather than >8 nights/month, had the highest likelihoods of AF. These non-linear associations were also observed in the CHD, stroke, and HF. Differences in study design, sample sizes, and changes in work intensity over time (healthy worker effect) may partly explain the non-linear relationship, which were also found in previous studies.[12,27] Few studies provide information on the association

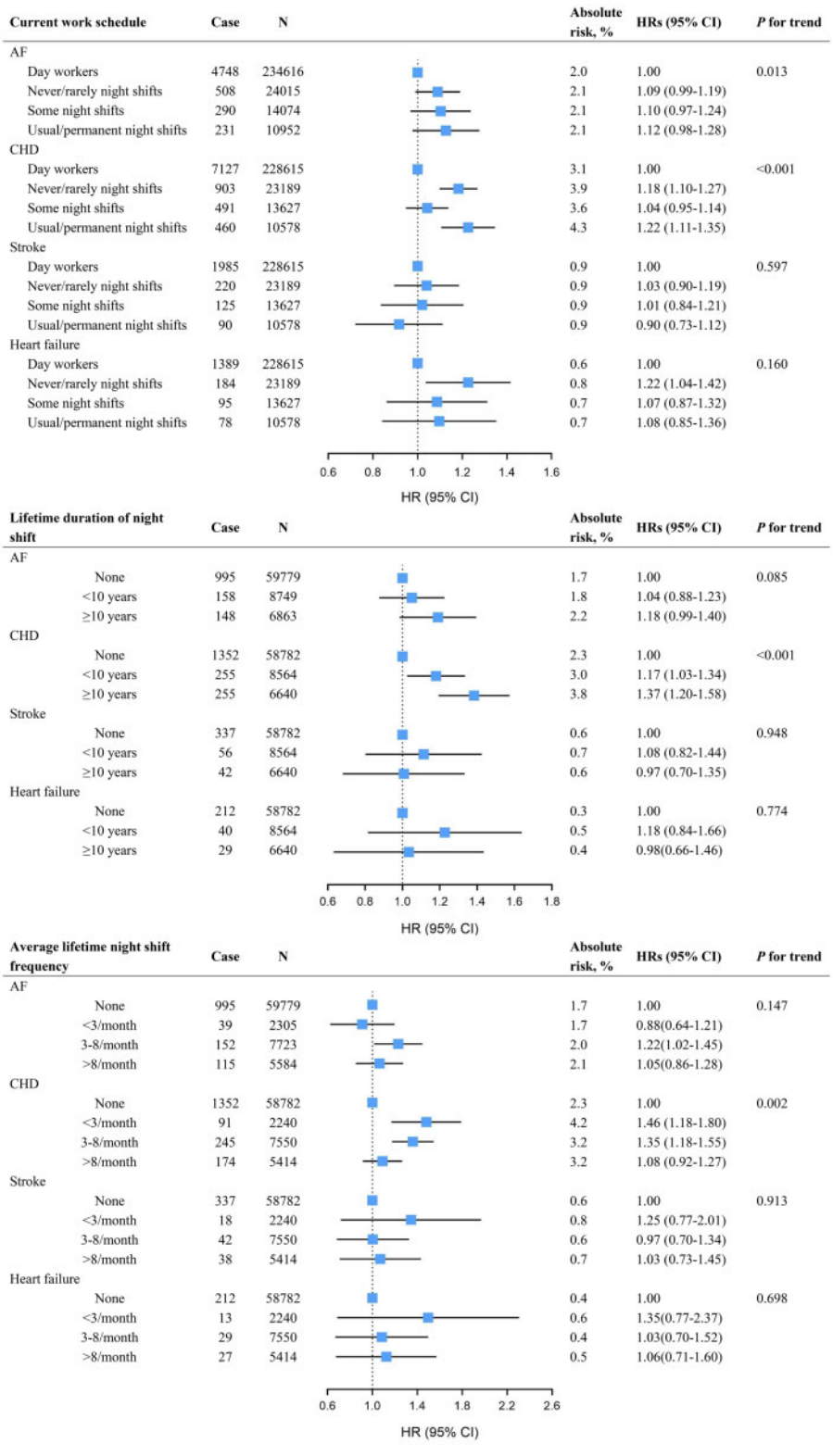


Figure 1 Multivariate hazard ratios of atrial fibrillation and three cardiovascular diseases when exposed to current and lifetime night shift work. The vertical line indicates the reference value of 1. A multivariable model was adjusted for age, sex, ethnicity (white/others), education (university or college degree/others), the Townsend index (continuous), and ideal cardiovascular health metrics (including healthy diet, ideal body mass index, physical activity goal, non-smoking, ideal blood pressure, total cholesterol, and glycaemic status). AF, atrial fibrillation; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio.

between lifetime night shift and AF risk. Future studies could systematically assess the duration and frequency of night shifts using objectively documented information.

In stratified analyses, significant interactions were found between sex and lifetime duration of night shift work and between physical activity and lifetime frequency and duration of night shift work. Prior evidence suggests that women are more susceptible to changes in circadian rhythms;[28,29] and in our study, women indeed had a stronger association between lifetime duration of night shift work and AF risk than men. In the UKB, participants with higher night shift frequency seem to have a higher prevalence of physical activity goals, which may be due to more physical activity from work. Nevertheless, the association between the duration and frequency of night shift work and AF was markedly stronger in individuals with a non-ideal amount of physical activity. We speculated that physical exercise might improve the body composition to adapt to changes in circadian rhythm. Overall, these secondary results require further exploration.

The potential mechanism by which rotating night shift work may increase the risk of AF and CHD is still unclear. Frequent rotating night shift work alters the circadian rhythm, causing significant adverse effects on biological functions.[30,31] After irregular work, disruption of the adaptability to environmental changes,[32] sympathetic nerve excitement, and excessive secretion of norepinephrine enhance myocardial contractility, increase conduction speed and oxygen consumption, and further aggravate the load on the heart.[33,34] Moreover, recent experiments related night shift work to increased cardiovascular inflammatory markers such as interleukin-6, C-reactive protein and tumour necrosis factor α.[35,36] The degree of oxidative stress damage was higher in night workers, which may lead to an increase in inflammatory factors.[37] Then, myocardial cells will also be adversely affected and link oxidative stress and inflammation to atrial electrical and anatomical remodelling caused by calcium overload and delayed after depolarizations, which is typically required for the initiation of AF.[38]

To the best of our knowledge, this is the first study to examine the effect of the interaction between night shift work and the GRS on incident AF. As expected, we observed that populations with high genetic risk and usual/permanent night shifts or lifetime durations over 10 years had the greatest AF risk. However, consistent with previous studies on diabetes,[12] low, intermediate, or high AF genetic predisposition did not significantly modify the association between current and lifetime night shift work and incident AF. This means that if the associations are causal, reducing night shift work frequency and duration might benefit AF risk regardless of the genetic predisposition to AF. In the low genetic risk group, the null association is likely to be because of the small size.

Our findings have public health implications for primary AF prevention. In fact, primary AF prevention seems to be not well mentioned in guidelines, indicating evidence lacking in this field.[39] A systematic review of 20 million participants explored whether 23 cardiovascular risk factors were also associated with AF.[40] Their findings suggest important differences in the risk factors for AF compared with other cardiovascular diseases. Therefore, in the primary prevention of AF, some strategy elements different from the current approaches for conventional cardiovascular diseases may be required. Our findings, together with previous studies such as Rauchenzauner *et al.*,[41] are consistent with suggestions that intervention in work schedules might be effective to improve arrhythmia. Because changes in shift work schedules could potentially reduce such risk and there is increasing prevalence of night shift work exposure in current society, it is important to consider and further explore the relationship between shift schedules and AF risk, even though the risk would be relatively small.

Our study has some strengths. First, this study has a large sample size of over 270 000 participants and detailed demographic and lifestyle information and medical history collected using a consistent method. Second, the novelty of this research is that for the first time, our investigation linked genetic and observational data in a large population with detailed current shift work and lifetime employment history. This employment information provides novel insight and a unique chance to examine the relation of night shift work to human health and thus provides valuable guidance for the future design of prevention strategies.

Some limitations also remained in our study. First, this is an observational study, and we cannot demonstrate the causal relationship between night shift work and incident AF and CHD. Second, there is the potential for undiagnosed AF events. However, only approximately one-tenth of AF was undiagnosed according to a previous study,[42] and the diagnosis of AF in our study was accurate, which was obtained by using medical records. Third, lifetime employment information was self-reported; and hence, it is likely to be prone to some degree of classification error. However, as mentioned in previous studies,[43] the true association could be towards the null and thus underestimated due to the presence of potential exposure misclassification resulting from such misclassifications. Fourth, the current and lifetime employment information was assessed at the baseline only, so this information might change over time during the follow-up. Fifth, although we carefully adjusted for various major confounders, bias from unknown and unmeasured confounding factors may still exist. Finally, this cohort included people of European descent, mostly White British, which limits the generalizability to other ethnicities, such as Asians and Blacks. The UKB aimed to be representative of the general population but was unrepresentative in terms of lifestyle because of a healthy volunteer selection bias.[44] Therefore, generalizing summary statistics to the general population should be done with caution.

Conclusions

In the UKB population, both current and lifetime night shift exposure were significantly associated with AF risk regardless of whether they had a high, intermediate, or low genetic risk. Night shift exposure also increased the risk of CHD but not stroke or HF. Whether decreasing night shift work frequency and duration might represent another avenue to improve heart health during working life and beyond warrants further study.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

This research has been conducted using the public UK Biobank Resource (www.ukbiobank.ac.uk/).

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