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Association of single and multiple cardiometabolic diseases with atrial fibrillation: a prospective cohort study

Qunyong Peng ,[1,2,3] Tianqi Ma,[2,3,4] Ming Gao,[1,2,3] Xuerui Wang,[1,2,3] Wei Pan[3,4]

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[1]Department of Geriatric Medicine, Xiangya Hospital, Central South University, Changsha, People's Republic of China
[2]Center of Coronary Circulation, Xiangya Hospital, Central South University, Changsha, People's Republic of China
[3]National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, People's Republic of China
[4]Department of Cardiovascular Medicine, Xiangya Hospital, Central South University, Changsha, People's Republic of China

Correspondence to
Dr Wei Pan; panwei1007@163.com

ABSTRACT

Background Individual cardiometabolic diseases (CMDs) increase atrial fibrillation (AF) risk; however, whether multiple CMDs exert a cumulative effect on AF risk remains unclear. Our objective was to examine the link between coexisting CMDs and AF, as well as their cumulative impact.

Methods This UK Biobank-based prospective cohort study included data from participants with information related to CMDs and AF. The assessment of CMDs and AF was based on participants' self-reported medical histories and electronic health records. Cox proportional hazard regression models were employed to analyse the link between the number of CMDs and AF and to determine the cumulative effect of multiple CMDs. Further, we performed stratified analyses and adjusted for confounding factors.

Results The study included 308 916 participants. The risk of AF was substantially associated with varying numbers of CMDs after multivariable adjustment in comparison to the reference group (all p<0.001). In the fully adjusted model, participants with 1, 2 and ≥3 CMDs exhibited elevated risks of 54% (HR: 1.54, 95% CI 1.48 to 1.59), 104% (HR: 2.04, 95% CI 1.94 to 2.15) and 212% (HR: 3.12, 95% CI 2.87 to 3.38), respectively. A significant cumulative dose-response relationship was noted between the number of CMDs and AF risk (HR: 1.45, 95% CI 1.42 to 1.48, p<0.001). A consistent dose-dependent cumulative relationship was observed in both stratified and sensitivity analyses.

Conclusions Multiple CMDs increased AF risk and exhibited a significant cumulative effect based on the number of CMDs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Individual cardiometabolic diseases (CMDs), including diabetes, hypertension, coronary artery disease and stroke, are strongly associated with an increased risk of developing atrial fibrillation (AF). However, the cumulative impact on AF risk when multiple CMDs coexist remains unclear.

WHAT DOES THIS STUDY ADD

⇒ In this study, we examined the relationship between varying numbers of CMDs and the risk of AF. The research findings demonstrate a significant increase in the risk of developing AF among patients with multiple CMDs, with a pronounced effect observed in females and younger individuals.

HOW MIGHT THIS IMPACT ON CLINICAL PRACTICE

⇒ Our study underscores the critical need for screening AF and implementing early preventive measures in patients with CMDs, especially those with multiple coexisting conditions.

INTRODUCTION

Atrial fibrillation (AF), the most frequent form of persistent arrhythmias in clinical practice, contributes significantly to cardiovascular diseases and mortality. It substantially elevates the likelihood of stroke, cognitive dysfunction, heart failure and hospitalisation.[1–3] It was estimated that the number of patients with AF reached 59.7 million globally in 2019.[4] It was projected to double by 2060,[5] resulting in a substantial disease burden on personal health and the global public health system. Additionally, AF frequently coexists with cardiometabolic diseases (CMDs), including diabetes, hypertension, stroke and coronary artery disease (CAD). Notably, 19% of patients with CAD also had AF.[6] Numerous studies have revealed that individual CMDs, such as diabetes, hypertension, CAD and stroke, are strongly linked to an increased risk of developing AF.[7–9] CMDs and AF may share common environmental and risk factors, such as inflammation and metabolic disorders,[7 8 10] and there may also be genetic similarities.[11]

As the global population ages, the concurrent presence of CMDs, known as cardiometabolic multimorbidity, has become a prevalent phenomenon.[12 13] Previous studies have increasingly suggested that cardiometabolic multimorbidity is associated with an elevated risk of adverse outcomes such as all-cause mortality,[14] depression[15] and cognitive impairment.[16] The cumulative effect on the risk of AF when multiple CMDs coexist remains unclear, even though existing research has confirmed the association between the occurrence of AF and individual CMDs. Therefore, this study, based on the prospective cohort of the UK Biobank, aimed to elucidate the relationship between cardiometabolic multimorbidity and AF risk and explore whether there is a cumulative effect of the coexistence of multiple CMDs.

METHODS

Study population and design

The UK Biobank is a large population-based prospective cohort that recruited over 500 000 participants between the ages of 37 and 73 during 2006–2010.[17] After obtaining written informed consent, the UK Biobank collected demographic, clinical and lifestyle information, as well as biological samples, from participants at 22 assessment centres across England, Scotland and Wales. The North West Multi-centre Research Ethics Committee has granted ethical sanction to the UK Biobank (updated ref 21/NW/0157, 18 June 2021).

The study acquired data from 502 359 participants. After excluding 8383 participants detected to have AF at baseline, 113 307 participants who developed additional CMDs during the follow-up period and 71 753 participants with missing covariate data, a total of 308 916 participants were included in the primary analysis (online supplemental figure 1).

Assessment of exposure

The exposure in this study was CMD status (diabetes, hypertension, stroke and CAD (including myocardial infarction and stable angina)). UK Biobank incorporated health outcome information from self-reported medical history, primary care records, hospital admission diagnoses and death records. The data were coded in accordance with the International Classification of Diseases version 10 (ICD-10). This study determined the occurrence and corresponding dates of individual CMDs: diabetes (E10-E14), hypertension (I10-I13, I15, O10), stroke (I60-I64) and CAD (I20-I25). To ascertain whether the disease was present prior to baseline or developed during the follow-up period, we compared the earliest diagnosis date with the recruitment date for participants with a specific disease. Participants were categorised based on the number of CMDs at recruitment (0–4). Due to the small number of participants with four coexisting CMDs (n=280), those with three and four diseases were consolidated into a single category of ≥3 CMDs.

Assessment of outcome

The primary study outcome was AF, defined according to the ICD-10 code I48 (online supplemental table 1) based on health outcome information obtained from the UK Biobank, which includes records of death registration, primary care, hospital admission diagnoses and self-report information. During the cohort recruitment phase, the follow-up period commenced from the participant's initial visit to the assessment centre during the cohort recruitment phase and continued until the occurrence of the study outcome, death, loss to follow-up or June 2023, whichever occurred first.

Assessment of covariates

This study involved demographic variables (age, sex, race, Townsend Deprivation Index, education degree and body mass index (BMI, kg/m^2)), lifestyle factors (smoking status, alcohol consumption frequency, healthy diet and physical activity level) and clinical factors (family history of cardiovascular disease (CVDs), history of chronic kidney disease (CKD), dyslipidaemia and depression). These covariates were determined using touchscreen-based questionnaires, interview records, anthropometric data and disease diagnosis information that were collected during baseline recruitment. Detailed definitions are available in the online supplemental table 2.

Statistical analyses

The population characteristics of the participants included in this investigation were described based on their CMD numbers at baseline. Categorical variables are expressed as numbers (percentages), while continuous variables are presented as means (SD).

In survival analysis, the Kaplan–Meier method was employed to assess the AF risk associated with CMD numbers with a log-rank test. Subsequently, Cox proportional hazards regression models were implemented to investigate the relationships between the number of CMDs and the AF risk. Three multivariable model parameters were implemented to adjust for probable confounding factors. Model 1 adjusted for age and sex, model 2 further adjusted for race, smoking status, Townsend Deprivation Index, BMI, alcohol consumption frequency, degree of education, healthy diet and physical activity level, while model 3 additionally adjusted for history of dyslipidaemia, family history of CVDs, history of depression and CKD. The reference group consisted of participants who did not have CMDs, and the results were expressed as HRs with 95% CIs.

We performed stratified analyses to identify subpopulations that were more susceptible to CMD-related risk of AF based on their age (<65 or ≥65 years) and sex (male or female). To determine whether the association between the number of CMDs and the risk of AF was altered by age or sex, we conducted a likelihood ratio test to compare the fully adjusted models with and without the interaction terms between stratification variables and CMD numbers.

We implemented numerous sensitivity analyses to evaluate the reliability of the results. First, there has been no agreement on the specific diseases that should be included in the definition of CMDs or cardiometabolic multimorbidity. Additionally, several previous studies that focused on cardiometabolic multimorbidity exclusively included CAD, diabetes and stroke.[18,19] Therefore, we restricted our analysis to these three diseases when assessing the number of CMDs. Second, we excluded participants with a follow-up period of <2 years to mitigate potential reverse

Table 1 Baseline characteristics overall and according to CMD numbers

Characteristics	Overall	0	1	2	≥3*
Participants, No. (%)	308 916	220 470 (71.4)	69 217 (22.4)	15 932 (5.1)	3297 (1.1)
Age (year), mean (SD)	56.1 (8.0)	54.7 (8.0)	59.1 (7.2)	61.2 (6.4)	62.2 (5.8)
Male, No. (%)	129 508 (41.9)	85 048 (38.6)	32 379 (46.8)	9747 (61.2)	2334 (70.8)
White, No. (%)	295 118 (95.5)	211 173 (95.8)	66 103 (95.5)	14 876 (93.4)	2966 (90.0)
TDI, mean (SD)	−1.5 (3.0)	−1.6 (2.9)	−1.5 (3.0)	−0.9 (3.3)	−0.1 (3.5)
Education degree, No. (%)					
High	159 238 (51.5)	119 873 (54.4)	31 866 (46.0)	6394 (40.1)	1105 (33.5)
Middle	55 366 (17.9)	39 295 (17.8)	12 811 (18.5)	2710 (17.0)	550 (16.7)
Low	94 312 (30.5)	61 302 (27.8)	24 540 (35.5)	6828 (42.9)	1642 (49.8)
BMI (kg/m^2), mean (SD)	26.9 (4.6)	26.1 (4.1)	28.5 (4.9)	30.3 (5.5)	31.5 (5.7)
Current smoking, No. (%)	280 702 (90.9)	199 807 (90.6)	63 644 (91.9)	14 373 (90.2)	2878 (87.3)
Alcohol consumption ≥3 times/week, No. (%)	169 891 (55.0)	120 595 (54.7)	37 245 (53.8)	9759 (61.3)	2292 (69.5)
Healthy diet, No. (%)	176 188 (57.0)	124 912 (56.7)	40 291 (58.2)	9174 (57.6)	1811 (54.9)
Meeting physical activity meeting guidelines, No. (%)	241 605 (78.2)	174 381 (79.1)	53 224 (76.9)	11 766 (73.9)	2234 (67.8)
Family history of CVDs, No. (%)	195 334 (63.2)	129 992 (59.0)	49 971 (72.2)	12 575 (78.9)	2796 (84.8)
CKD, No. (%)	28 361 (9.2)	16 054 (7.3)	8479 (12.2)	2884 (18.1)	944 (28.6)
Dyslipidaemia, No. (%)	40 201 (13.0)	11 585 (5.3)	17 557 (25.4)	8774 (55.1)	2285 (69.3)
Depression, No. (%)	28 702 (9.3)	19 152 (8.7)	6869 (9.9)	2069 (13.0)	612 (18.6)
Diabetes, No. (%)	13 008 (4.2)	0 (0.0)	2987 (4.3)	7306 (45.9)	2715 (82.3)
Hypertension, No. (%)	80 536 (26.1)	0 (0.0)	61 685 (89.1)	15 567 (97.7)	3284 (99.6)
Stroke, No. (%)	4431 (1.4)	0 (0.0)	1415 (2.0)	1845 (11.6)	1171 (35.5)
CAD, No. (%)	13 277 (4.3)	0 (0.0)	3130 (4.5)	7146 (44.9)	3001 (91.0)

*CMD number ≥3: since the small sample size of patients with concurrent four CMDs (n=280), conditions of three and four CMDs were analysed in combination as CMD number ≥3.
BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; CMDs, cardiometabolic diseases; CVDs, cardiovascular diseases; TDI, Townsend Deprivation Index.

causation. Subsequently, to enhance the reliability of the analysis results, we excluded participants with only self-reported AF history or only self-reported CMDs. Additionally, we included participants who developed new CMDs during the follow-up period in the analysis. Finally, to reduce the potential impact of secondary AF on the study results, we excluded participants with baseline cancer or any autoimmune diseases and those with baseline heart failure, valvular heart disease or myocarditis (disease definitions in online supplemental table 2) and reconducted the analyses. All statistical analyses were performed using the R software V.4.3.1. A two-sided p value of <0.05 was considered statistically significant.

RESULTS

Baseline patients' characteristics

Table 1 delineates the baseline characteristics of the study population. The study included 308 916 participants with an average age of 56.1 years. Among them, 129 508 (41.9%) were male and 295 118 (95.5%) were Caucasian. The absence of CMDs was observed in 220 470 participants (71.4%), while 69 217 (22.4%), 15 932 (5.1%) and 3297 (1.1%) had one, two or more diseases, respectively. In general, as the number of diseases increased, participants were more likely to be older, male, non-Caucasian, economically disadvantaged, less educated, have a higher BMI, consume more alcohol and engage in less physical activity. They were also more likely to have a family history of CVDs and a baseline history of CKD, dyslipidaemia and depression.

Association between CMDs and AF

A total of 16 490 participants developed AF during a median follow-up period of 14.18 years. Among participants without CMDs, 3.4% (7,425 individuals) developed AF; the incidence rates of AF for participants with one, two and three or more types of CMDs were 8.5% (5,897 individuals), 14.9% (2,371 individuals) and 24.2% (797 individuals), respectively. The relationship between the risk of AF and the number of CMDs was illustrated by plotting Kaplan–Meier survival curves, as illustrated in figure 1. The results suggested that participants with a higher number of CMDs exhibited a greater risk of developing AF.

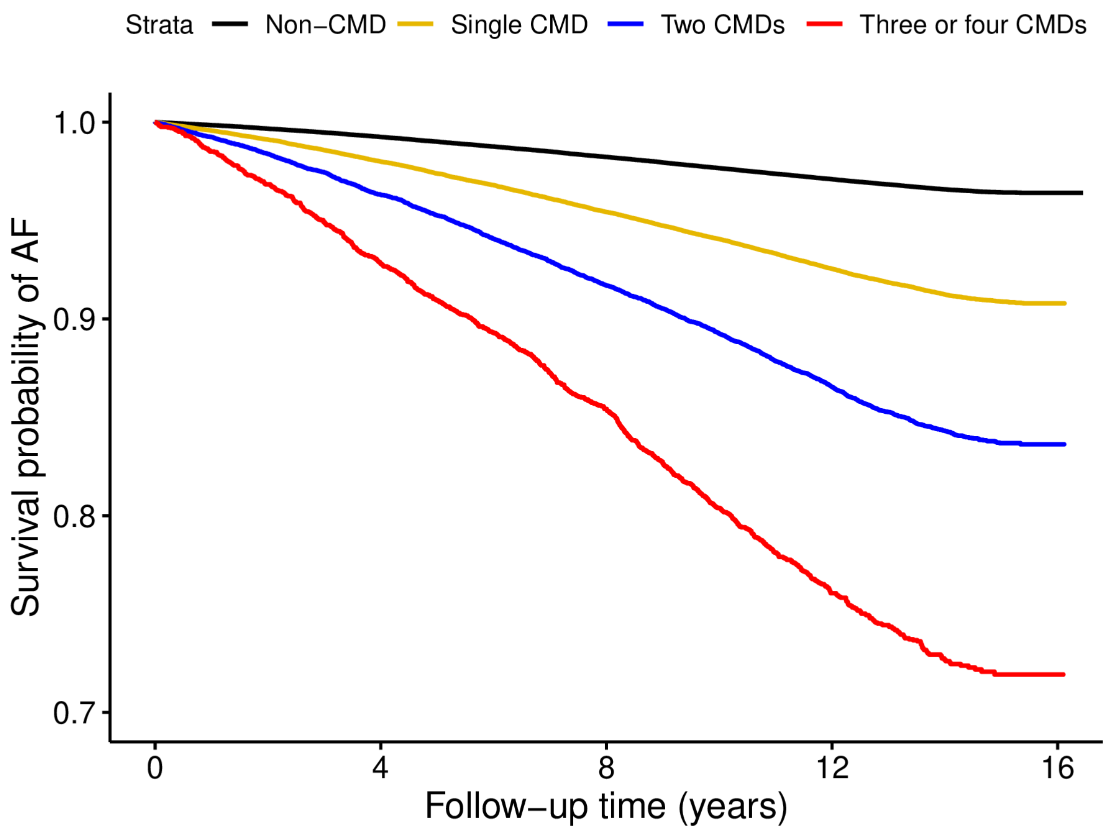

Figure 1 Survival probability of AF according to CMD numbers. According to the log-rank test, p<0.001. AF, atrial fibrillation; CMDs, cardiometabolic diseases.

Table 2 illustrates the correlation between the number of CMDs and the likelihood of AF. The incidence rate of AF among participants without CMDs was 2.44 per 1000 person-years, while it increased to 21.93 per 1000 person-years for those with three or more types of CMDs. In Model 1, after adjusting for age and sex, the number of CMDs and the AF risk were significantly positively correlated (all p<0.001), with a notable accumulative dose-response relationship (HR 1.62, 95% CI 1.59 to 1.65, p<0.001). In the fully adjusted model 3, compared with participants without CMDs at baseline, those with one, two and three or more types of CMDs had a 54% (HR: 1.54, 95% CI 1.48 to 1.59), 104% (HR: 2.04, 95% CI 1.94 to 2.15) and 212% (HR: 3.12, 95% CI 2.87 to 3.38) increased risk of developing AF during follow-up, respectively. The cumulative effect related to the number of CMDs was attenuated but remained significant (HR 1.45, 95% CI 1.42 to 1.48, p<0.001).

Stratified analyses and sensitivity analyses

As depicted in figure 2, we performed stratified analyses and discovered significant interactions of the number of CMDs with both age and sex ($P_{interaction}$<0.001). Particularly, female participants and those under the age of

Table 2 Associations of CMD numbers with risk of AF in the total population

		Model 1		Model 2		Model 3	
CMD numbers	Incident rate*	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
0	2.44	1 (reference)		1 (reference)		1 (reference)	
1	6.40	1.75 (1.69; 1.81)	<0.001	1.56 (1.50; 1.61)	<0.001	1.54 (1.48; 1.59)	<0.001
2	11.88	2.56 (2.44; 2.69)	<0.001	2.09 (1.99; 2.20)	<0.001	2.04 (1.94; 2.15)	<0.001
≥3	21.93	4.28 (3.97; 4.61)	<0.001	3.28 (3.04; 3.55)	<0.001	3.12 (2.87; 3.38)	<0.001
Accumulative dose effect	–	1.62 (1.59; 1.65)	<0.001	1.47 (1.44; 1.50)	<0.001	1.45 (1.42; 1.48)	<0.001

HRs were calculated in Cox proportional hazards model: model 1, adjustment for age, sex; model 2, further adjustment ethnicity, current smoking status, Townsend Deprivation Index, body mass index, alcohol consumption, education degree, healthy diet and physical activity based on model 1; model 3, further adjustment for dyslipidaemia, family history of cardiovascular diseases, depression and chronic kidney disease based on model 2.
*per 1000 person-year.
AF, atrial fibrillation; CMD, cardiometabolic diseases.

CMD numbers	Case/Number	HR (95%CI)	$P_{interaction}$
Age/years			<0.001
<65			
0	5269/196152	1 (Reference)	
1	3333/52847	1.86 (1.78, 1.95)	
2	1235/10495	2.89 (2.69, 3.10)	
≥3	397/2008	4.54 (4.05, 5.09)	
≥65			
0	2156/24318	1 (Reference)	
1	2564/16370	1.63 (1.54, 1.74)	
2	1136/5437	2.02 (1.86, 2.19)	
≥3	400/1289	3.20 (2.84, 3.60)	
Sex			<0.001
Male			
0	4074/85048	1 (Reference)	
1	3395/32379	1.44 (1.38, 1.52)	
2	1650/9747	1.94 (1.81, 2.07)	
≥3	590/2334	2.83 (2.57, 3.13)	
Female			
0	3351/135422	1 (Reference)	
1	2502/36838	1.65 (1.56, 1.75)	
2	721/6185	2.23 (2.03, 2.44)	
≥3	207/963	4.01 (3.45, 4.67)	

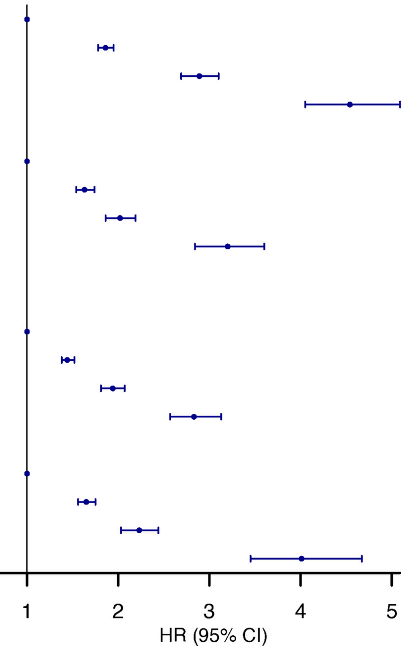

Figure 2 Associations of CMD numbers with risk of AF stratified by age and sex. HRs were calculated in Cox proportional hazards after adjusting for age, sex, ethnicity, current smoking status, Townsend Deprivation Index, body mass index, alcohol consumption, education degree, healthy diet, physical activity, dyslipidaemia, family history of cardiovascular diseases, depression and chronic kidney disease. The strata variable was not included in the model when stratifying by itself. AF, atrial fibrillation; CMDs, cardiometabolic diseases.

65 exhibited a more pronounced correlation between the number of CMDs and the risk of AF. Additionally, the number of CMDs exhibited an accumulative dose-response effect across all subgroups. Sensitivity analyses validated the reliability of the results, which remained consistent when we adjusted the definition of CMDs, included participants who developed new CMDs during the follow-up period and excluded participants with <2 years of follow-up, self-reported histories of AF or those with only self-reported CMDs, as well as excluded participants with baseline diseases who were susceptible for secondary AF (online supplemental table 3).

DISCUSSION

Main Findings

This prospective cohort study found that participants with CMDs exhibited a higher risk of developing AF compared with those without CMDs. After adjusting for potential confounding factors, a significantly dose-dependent cumulative association between the number of CMDs and AF persisted. Notably, this correlation was more pronounced among female participants and individuals younger than 65 years old.

Comparison with previous research

Our research findings indicate that patients with CMDs are at an increased risk of developing AF, which is consistent with previous research. A close association between CAD and AF has been demonstrated in previous research on specific CMDs.[8] Data indicates that 5.7% of acute coronary syndrome patients develop AF during hospitalisation,[20] while this percentage rises to 28% in acute myocardial infarction patients who concurrently experience reduced left ventricular ejection fraction.[21] A bidirectional Mendelian randomisation study also demonstrated that CAD elevated AF risk by 11%–14%.[22] Research also suggests a correlation between diabetes and an increased AF risk.[23 24] A 2011 meta-analysis, which encompassed seven prospective cohort studies and four case-control studies, revealed that patients with diabetes exhibit a 40% increased risk of developing AF compared with those without diabetes.[25] New genetic evidence supporting a causal relationship between type 2 diabetes and AF was collected in another Mendelian randomisation investigation.[26] The link between AF and stroke has been confirmed by numerous studies.[27–29] Interestingly, the probability of new-onset AF also increases following a haemorrhagic stroke.[30] Additionally, hypertension is identified as the most significant risk factor for AF occurrence. The Atherosclerosis Risk in Communities study revealed that 21.6% of AF cases could be attributed to hypertension.[31] The aforementioned studies all indicate that a history of specific CMD is a risk factor for new-onset AF. Nevertheless, there is currently no research examining whether the coexistence of multiple CMDs results in an additive increase in AF risk.

Cardiometabolic multimorbidity is currently afflicting approximately 10 million adults in the USA and Europe.[32 33] The cumulative effects of cardiometabolic multimorbidity on a series of adverse outcomes have been examined.[14 34] Patients with two CMDs have a threefold increased risk of mortality in comparison to those without CMDs, and this risk rises to nearly sevenfold for those with three conditions.[14] A cohort study reported that patients with cardiometabolic comorbidities possess a 73% increased risk of cognitive decline and an 86% elevated risk of dementia compared with patients without CMDs. Additionally, patients with three CMDs experienced cognitive decline and the onset of dementia 3.7 and 4.2 years earlier, respectively.[16] We assessed the correlation between the number of CMDs and the risk of AF in light of the increasing prevalence of cardiometabolic multi-morbidity. We found that an increase in the number of CMDs has a significant dose-dependent cumulative effect on AF risk. We associated the presence of adverse effects of concurrent CMDs with the occurrence of AF, aligning with the recent concept that AF is also a chronic disease based on cardiometabolic factors.[35 36] According to a recent multi-centre prospective cohort study among COVID-19 patients, the incidence of arrhythmias increased in tandem with the number of CMDs.[37] In summary, our results emphasise the necessity for early screening and AF prevention in patients with concurrent CMDs.

The observed accumulative association between the risk of AF and the coexistence of various CMDs in this study can be accounted for by a variety of mechanisms. First, CMDs and AF are associated with similar risk factors, including smoking, excessive alcohol consumption, sedentary lifestyle and obesity.[38] Second, CMDs are frequently observed in conjunction with chronic inflammation, alterations in neurohumoral regulation and cardiac structural remodelling.[39 40] These factors may lead to alterations in cardiac ion channels, atrial fibrosis and remodelling of cardiac electrical activity, thereby accelerating AF progression.[41] Additionally, psychosocial factors are significant modulators in AF development.[42] Patients with CMDs are usually affected by the chronic disease course, diminished physical function and economic burdens,[43 44] which negatively impact psychosocial factors and may accumulate with the cardiometabolic multimorbidity.[45]

Furthermore, in the age- and gender-stratified subgroup analyses, we noted a more pronounced dose-response effect linked to CMDs in females and younger individuals (<65 years). The association between the number of CMDs and AF is inconsistent among different subgroups, which may be attributed to the unique characteristics of specific subgroups. For instance, the AF risk is inherently higher in males and older subgroups,[46 47] potentially diluting the influence of CMDs, thereby resulting in a relatively stronger correlation in females and younger subgroups. The presence of a greater number of CMDs in younger individuals may suggest a less healthy lifestyle, a worse prognosis, a heavier economic burden and greater psychosocial stress, all of which could increase the risk of AF. Ningjian Wang *et al* also reported that most cardiometabolic factors and clinical comorbidities demonstrate significant interactions with age, and this association is generally more pronounced in younger populations.[48] As the results of subgroup analyses are provisional, additional research is required to validate the potential differences related to age and sex.

The cumulative impact of CMDs on AF is the primary finding of this investigation. The results indicate that patients with cardiometabolic multimorbidity, especially females and younger individuals, possess a higher risk of developing AF. Our research highlights the importance of screening for AF and early prevention in patients with CMDs, particularly in those with multiple comorbidities. Given the poor clinical prognosis linked to AF and cardiometabolic multimorbidity, as well as their combined presence,[14 38 49] it is imperative to implement a comprehensive biopsychosocial management strategy when diagnosing individuals with CMDs.[50] Chronic health issues and multimorbidity are becoming more prevalent as a result of the longer average lifespan and increased health awareness. Emphasis on cumulative effects can help us implement preventive and therapeutic measures in advance.

Strengths and limitations

Our research exhibits multiple advantages. First, we employed the extensive population data from the UK Biobank to conduct a prospective cohort analysis. This enabled us to stratify the number of CMDs within an adequately large sample and confirm the cumulative effects that may result from the coexistence of multiple diseases. Second, paroxysmal AF is frequently challenging to identify during medical appointments or self-monitoring. Our results indicate that the frequency of monitoring or screening should be increased in the presence of multiple CMDs, particularly among females and younger individuals. Third, we enhanced the definition of CMDs by incorporating diagnostic, medication and surgical information from self-reported medical histories, as well as diagnostic and surgical information from health-related records of hospitalised patients. This approach decreased the misclassification of patients with CMDs.

However, our study has several limitations. First, the participants in the UK Biobank are predominantly Caucasian, and there is evidence indicating that the incidence of AF is higher among Caucasians compared with other ethnic groups.[51] This restricts the generalisability of our findings to populations of other ethnicities and countries. Second, the maximum age of participants at recruitment in the UK Biobank was approximately 73 years, which may underestimate AF risk in individuals over the age of 65. Third, the potential for misclassification and biased results exists due to the fact that paroxysmal AF can be asymptomatic, which could have resulted in the omission of certain AF cases. Fourth, as this was

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an observational study, we cannot entirely rule out the possibility of residual confounding bias and reverse causality despite having adjusted for diverse confounding factors such as demographics, lifestyle and other clinical histories and conducted a series of sensitivity analyses. Lastly, we did not classify the specific types of AF, and there are numerous causes of secondary AF. Consequently, excluding all participants with common causes of secondary AF proved challenging. Although sensitivity analyses were performed after excluding participants with several common causes, the potential for overestimating the relationship between CMDs and the risk of AF remains.

Overall, the coexistence of multiple CMDs demonstrates a dose-dependent and cumulative relationship with increased AF risk. This correlation is more pronounced in individuals aged <65 years and females.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants but the UK Biobank has been approved by the North West Multi-centre Research Ethics Committee as a Research Tissue Bank, and separate ethical clearance is not required for researchers under this approval (updated ref 21/NW/0157, 18 June 2021). All participants of the UK Biobank have provided written informed consent.

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Data availability statement Data are available in a public, open access repository. Data may be obtained from a third party and are not publicly available. The data that support the findings of this study are available from the UK Biobank (approved project 84443) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the website https://www.ukbiobank.ac.uk/ upon reasonable request and with permission of UK Biobank.

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ORCID iD

Qunyong Peng http://orcid.org/0009-0007-2244-6336

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