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ORIGINAL RESEARCH

Neuroticism and the Risk of Atrial Fibrillation

An Observational Epidemiologic and Mendelian Randomization Study

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ABSTRACT

BACKGROUND The association between neuroticism and atrial fibrillation (AF) remains unknown.

OBJECTIVES This study aimed to assess the epidemiological and causal relationships between neuroticism and AF.

METHODS Individuals without AF history were selected From the UK Biobank nationwide prospective cohort study. Participants were divided into 2 groups (high and low) based on the median summary score from a self-questionnaire of 12 neurotic behavior domains. The 10-year AF risk was compared between the neuroticism score groups using inverse probability of treatment weighting. The causal relationship between neuroticism and AF was evaluated using a 2-sample summary-level Mendelian randomization with the inverse variance–weighted method.

RESULTS Of 394,834 participants (mean age 56.3 ± 8.1 years, 45.9% male), AF occurred in 23,509 (6.0%) during a 10-year follow-up. The risk of incident AF significantly increased in the high neuroticism score group (score ≥4) (inverse probability of treatment weighting–adjusted HR: 1.05; 95% CI: 1.02-1.09; $P = 0.005$) compared with the low neuroticism group. In the subgroup analysis, younger age, lower body mass index, or nonsmoker/ex-smoker participants were particularly susceptible to increased AF risk due to high neuroticism scores. A Mendelian randomization analysis showed a significant causal relationship between an increase in neuroticism score and increased risk of AF (OR by inverse variance–weighted method 1.06; 95% CI: 1.02-1.11; $P = 0.007$) without evidence of reverse causality.

CONCLUSIONS There was a significant longitudinal and causal relationship between neuroticism and AF. An integrated care including active mental health screening and management may benefit in high-risk populations.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Atrial fibrillation (AF) is associated with an increased risk of morbidity and mortality.[1] Given its increasing prevalence in the aging population,[2] the significance of early detection and prevention is emphasized in recent guideline.[3] AF is influenced by various factors, including comorbid conditions, such as hypertension, diabetes, and heart failure, as well as by lifestyle factors, such as smoking and alcohol consumption.[2,4] Although somewhat neglected in cardiological clinics, psychological factors (eg, stress, job strain, and traumatic life events such as child loss) are also well recognized to be associated with increased AF risks.[5-7] Hence, the management of comorbidities, lifestyle factors, and psychological morbidity is recommended as part of a holistic or integrated care approach to AF care,[8,9] given the improved outcomes of such an approach.[10]

Neuroticism, 1 of the 5 personality traits, is characterized by a tendency to experience negative emotions, such as anxiety, depression, fear, irritability, and worry, in response to stress and to reinforce these emotions.[11,12] While neuroticism is known to correlate with mental traits, cardiovascular disease, and cardiometabolic risk factors,[13,14] the association between neuroticism and AF has not been established. To address this, we used the UK Biobank, a nationwide population-based prospective cohort study, to investigate the epidemiological and causal relationships between neuroticism and AF.

METHODS

STUDY PARTICIPANTS. The UK Biobank is a large nationwide cohort designed to investigate the health and lifestyle habits of over 500,000 people between 40 and 69 years of age who were enrolled in the National Health Service and lived within 25 miles of the study assessment center. All protocols were previously published elsewhere.[15] Data were collected between 2006 and 2010, and the study was approved by the North West Multi-Centre Research Ethics Committee and the National Health Service National Research Ethics Service. The present study was approved by the UK Biobank Review Committee under application number 76593. To gather clinical information, we used self-report questionnaires, anthropometric measures, lifestyle data, and information on diagnosed diseases from the hospital and death registries. A total of 394,834 participants were analyzed after excluding those with: 1) missing values for the neuroticism score; and 2) a history of AF (**Figure 1**). Ethical approval for this study was obtained from the general ethical approval for UK Biobank studies from the National Health Service National Research Ethics Service on 17 June 2011 (Ref 11/NW/0382) and extended to 10 May 2016 (Ref 16/NW/0274). All the participants provided written informed consent.

ASSESSMENT OF NEUROTICISM AND DEFINITION OF GROUPS BY NEUROTICISM SCORE. In the present study, the summarized form of the revised Eysenck Personality Questionnaire (EPQ-N) was utilized to assess the degree of neuroticism among the participants.[16,17] The 12-item scale, which was derived from the summarized form of the EPQ-N, was used to gather data through a computerized touchscreen interview as part of the baseline assessment of the UK Biobank. The participants were asked to respond to each item with either "yes" or "no," and the responses were recorded as 1 or 0, respectively. The responses were then aggregated to calculate a total score ranging from 0 to 12, which demonstrated reliable consistency and validity according to previous studies.[16,18] In this study, the participants were classified into 2 groups based on their neuroticism scores: high ($\geq$4) and low ($<$4), with the median score used as the cutoff point.

DEFINITIONS OF COVARIATES AND OUTCOMES. Definitions of the covariates and outcomes used in this study are provided in Supplemental Table 1. Demographic information, anthropometric measurements, lifestyle factors, and cardiometabolic risk factors were used as potential confounding factors. The primary outcome, AF, was determined using inpatient hospital and death registry data linked to the UK Biobank and was defined using the International Classification of Diseases-10th Revision code I48. Participants were followed-up until the earliest occurrence of the primary outcome, death, or the end of the 10-year follow-up period, at which point they were censored.

STATISTICAL ANALYSIS. For categorical variables, the data were presented as numbers and relative frequencies (percentages), and for continuous variables, the data were presented as mean $\pm$ SD. The chi-square test and independent-samples *t*-test were used for comparisons, as appropriate. A density distribution plot of neuroticism scores as a continuous variable and a restricted cubic spline curve illustrating the adjusted 10-year risk of AF based on neuroticism scores were drawn. Kaplan-Meier censoring estimates and the log-rank test were used to compare the cumulative event rates between the high and low neuroticism score groups. The multivariable Cox proportional hazards models generated

ABBREVIATIONS AND ACRONYMS

ANS = autonomic nervous system

EPQ-N = Eysenck Personality Questionnaire

GWAS = genome-wide association study

IPTW = inverse probability of treatment weighting

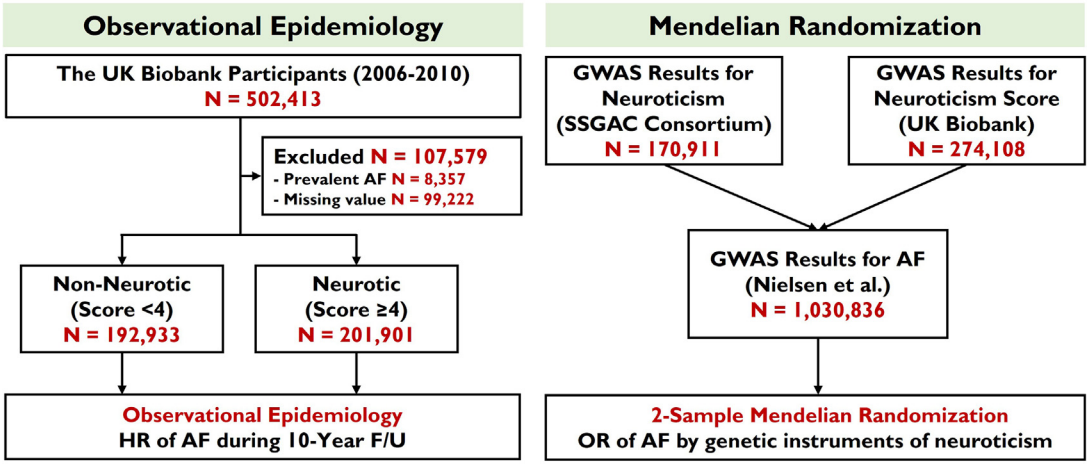
IVW = inverse variance weighted

MR = Mendelian randomization

SNP = single nucleotide polymorphism

SSGAC = Social Science Genetic Association Consortium

FIGURE 1 Study Flow



The flow diagram of the present study is shown. AF = atrial fibrillation; GWAS = genome-wide association study; SSGAC = Social Science Genetic Association Consortium.

adjusted HRs with 95% CIs, with age, sex, enrollment center, ethnicity, Townsend deprivation index, income level, body mass index, current smoking, daily drinking, moderate-to-vigorous physical activity, diabetes mellitus, hypertension, dyslipidemia, and Charlson comorbidity index as covariates. We tested the proportional hazards assumption using a log-minus-log plot and the goodness-of-fit test. We utilized the rms package in R version 4.1.2 (R Foundation for Statistical Computing), employing 4 default knots for the neuroticism score on the x-axis. As previously mentioned, we designated the median value of the neuroticism score (score 4) as the reference point for the curve. To adjust for imbalanced baseline features, multivariable Cox regression and inverse probability of treatment weighting (IPTW) were used. For the IPTW analysis, a multivariable logistic regression model was established to calculate propensity scores indicating the likelihood of belonging to the high neuroticism score group using the aforementioned covariates. The output of the Cox proportional hazards regression model was weighted using the inverted value of the propensity score. The balance between the 2 groups was determined before and after the IPTW adjustment by calculating the standardized mean differences of the covariates. Subgroup analyses were performed based on age (median), sex, ethnicity, Townsend deprivation index (median), body mass index (median), current smoking, daily drinking, moderate-to-vigorous physical activity, diabetes mellitus, and hypertension. Results were validated using sensitivity analyses based on various follow-up durations, lag periods, and subpopulations. All *P* values were 2-tailed, and a *P* value <0.05 was considered statistically significant. Statistical analyses were conducted using Stata (version 17.0, StataCorp) and R.

SUMMARY-LEVEL 2-SAMPLE MENDELIAN RANDOMIZATION. The genetic instrument used in this study has been previously published.[19] The summary statistics for the Social Science Genetic Association Consortium (SSGAC) genome-wide association study (GWAS) for neuroticism measurements are publicly accessible,[20] as are the summary statistics for the neuroticism score trait from the UK Biobank GWAS.[21] Summary statistics for the AF trait from the GWAS meta-analysis are available at GWAS catalog.[22] Two-sample Mendelian randomization (MR) was performed using summary-level data, and causal relationships between neuroticism and AF were established. Palindromic variants were excluded during the harmonization of summary statistics in the summary-level MR.[23] The main MR method utilized was the fixed-effects inverse variance-weighted (IVW) method and additional sensitivity MR analyses were conducted: 1) the weighted median method was applied, which provides valid causal estimates even in the presence of invalid instruments[24]; and 2) MR-PRESSO (Mendelian Randomization Pleiotropy RESidual Sum and Outlier) was executed to detect and correct the effects of outliers, resulting in causal estimates that are robust to heterogeneity.[25]

TABLE 1 Baseline Characteristics Before and After IPTW Adjustment

	Before IPTW				After IPTW			
	High Neuroticism Score (≥4) (n = 201,901)	Low Neuroticism Score (<4) (n = 192,933)	ASD	*P* Value	High Neuroticism Score (≥4) (n = 163,518)	Low Neuroticism Score (<4) (n = 163,538)	ASD	*P* Value
Age, y	55.6 ± 8.1	57.0 ± 8.0	−0.176	<0.001	56.1 ± 8.0	56.1 ± 8.2	<0.001	0.97
Male	39.4 (79,477)	52.8 (101,814)	−0.26	<0.001	47.6 (78,265)	47.6 (77,335)	<0.001	0.95
Ethnicity			−0.005	<0.001			0.001	0.862
Asian	1.7 (3,524)	1.8 (3,466)			1.7 (2,754)	1.9 (3,013)		
Black	1.2 (2,468)	1.6 (3,021)			1.1 (1,816)	1.6 (2,585)		
White	95.4 (192,651)	95.1 (183,532)			95.5 (157,097)	95.2 (154,736)		
Mixed	0.6 (1,235)	0.5 (1,043)			0.6 (1,002)	0.5 (877)		
Others	1.0 (2,023)	1.0 (1,871)			1.1 (1,793)	0.9 (1,377)		
Townsend deprivation index	−1.2 ± 3.1	−1.6 ± 2.9	0.103	<0.001	−1.5 ± 3.0	−1.5 ± 3.0	0.001	0.821
Household income before tax, pound			−0.097	<0.001			0.001	0.866
<£18,000	20.6 (41,531)	16.1 (31,074)			19.6 (32,179)	16.0 (26,028)		
£18,000-£30,999	21.7 (43,779)	21.5 (41,575)			22.5 (36,917)	21.4 (34,748)		
£31,000-£51,999	22.6 (45,720)	23.4 (45,236)			24.3 (40,006)	24.0 (38,963)		
£52,000-£100,000	17.2 (34,808)	20.1 (38,867)			19.5 (32,080)	20.9 (34,017)		
>£100,000	4.1 (8,326)	6.2 (11,956)			4.9 (8,086)	6.4 (10,478)		
Body mass index, kg/m^2	27.4 ± 5.0	27.4 ± 4.6	0.003	0.006	27.3 ± 4.7	27.3 ± 4.6	0.001	0.81
Current smoker	11.6 (23,493)	9.2 (17,800)	0.076	<0.001	10.1 (16,561)	10.0 (16,315)	0.001	0.745
Daily drinking	20.0 (40,319)	21.7 (41,958)	−0.039	<0.001	21.5 (35,362)	21.5 (34,961)	<0.001	0.993
Moderate-to-vigorous physical activity	52.4 (86,991)	56.8 (93,109)	−0.089	<0.001	54.7 (90,022)	54.7 (88,998)	<0.001	0.995
Diabetes mellitus	5.3 (10,685)	5.1 (9,826)	0.008	0.005	5.0 (8,220)	5.0 (8,120)	<0.001	0.961
Hypertension	30.0 (60,548)	27.7 (53,365)	0.05	<0.001	28.1 (46,207)	28.1 (45,634)	0.001	0.86
Dyslipidemia	19.0 (38,278)	18.9 (36,508)	−0.003	0.77	18.5 (30,481)	18.5 (30,119)	<0.001	0.946
Charlson comorbidity index	1.4 ± 1.2	1.5 ± 1.2	<0.001	<0.001	1.4 ± 1.2	1.4 ± 1.2	<0.001	0.977
Neuroticism score	6.8 ± 2.3	1.4 ± 1.1	2.965	<0.001	6.7 ± 2.3	1.4 ± 1.1	2.922	<0.001

Values are mean ± SD or % (n).
ASD = absolute standardized difference; IPTW = inverse probability of treatment weighting.

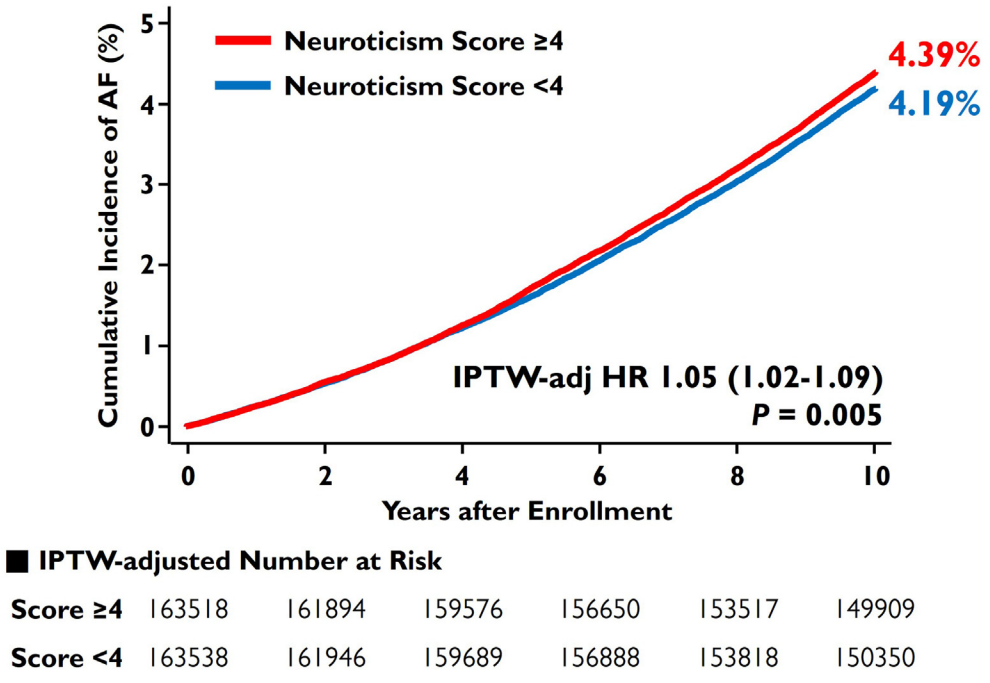
To evaluate the possibility of reverse causality, the causal relationship between the AF genetic instrument and neuroticism traits was evaluated using the IVW method. Summary-level MR analysis was performed using the TwoSampleMR package in R.

RESULTS

We studied 394,834 eligible participants (mean age of 56.3 ± 8.1 years; 54.1% female), whereby during follow-up, 6.0% (n = 23,509) developed AF. Participants were divided into 2 groups based on their neuroticism score (≥4 vs <4), and the baseline statistics before and after IPTW adjustment are shown in **Table 1**. The mean neuroticism score was 6.8 ± 2.3 in the high-score group and 1.4 ± 1.1 in the low-score group. The high neuroticism score group had a younger population, more women, and greater socioeconomic deprivation. There were also differences in lifestyle and comorbidities, with a higher proportion of current smokers, and those with hypertension in the high-score group and a higher proportion of frequent alcohol drinkers and participants with moderate-to-vigorous physical activity in the low-score group. After IPTW adjustment, the standardized mean differences were within ±0.1 across all covariates, indicating successful balance achievement between the 2 groups.

LONGITUDINAL ASSOCIATION OF NEUROTICISM SCORE WITH ATRIAL FIBRILLATION. The distribution of neuroticism scores (median 4.0; Q1-Q3: 1.0-6.0) is shown in Supplemental Figure 1A. A significant association was observed between increasing neuroticism scores and an increased 10-year AF risk (Supplemental Figure 1B). The IPTW-adjusted 10-year cumulative incidence of AF was 4.4% in the high neuroticism score group compared with 4.2% in the low neuroticism score group (log-rank P = 0.005) (**Figure 2**). **Table 2** demonstrates that the risk of AF was significantly higher in the high neuroticism score group than in the low neuroticism score group in

FIGURE 2 Cumulative Atrial Fibrillation Incidence Difference Among Neuroticism Score Groups



The Kaplan-Meier curves depict the cumulative incidence of atrial fibrillation (AF) in the high vs low neuroticism score group up to 10 years of follow-up. IPTW = inverse probability of treatment weighting.

the IPTW-adjusted model (IPTW-adjusted HR: 1.05; 95% CI: 1.02-1.09; $P = 0.005$). This result was consistent across the 3 different multivariable Cox regression models, demonstrating an increased risk of AF by 7% to 11% in the high neuroticism score group (all $P < 0.001$). The Cox regression model fulfilled the proportional hazards assumption.

SUBGROUP ANALYSIS. The findings of the exploratory subgroup analysis are shown in Supplemental Figure 2. The elevated risk of AF was particularly evident among individuals of younger age (P for interaction = 0.040), nonobese individuals ($P = 0.025$), and nonsmokers or ex-smokers ($P = 0.036$). In all subgroups, except for age, body mass index, and smoking history, a higher risk of AF was consistently associated with a high neuroticism score (all P for interaction > 0.05).

SENSITIVITY ANALYSIS FOR LONGITUDINAL ASSOCIATION ANALYSIS. The results of the sensitivity analyses, outlined in Supplemental Table 2, were consistent with the primary results. Regardless of the duration of follow-up (8 and 12 years), the risk of AF was

TABLE 2 Adjusted Risk of Atrial Fibrillation in High Neuroticism Score Group

Risk of 10-Year AF in High Neuroticism Score Group (vs Low Neuroticism Score Group)	Adjusted HR (95% CI)	*P* Value
IPTW model[a]	1.05 (1.02-1.09)	0.005
Multivariable Cox proportional hazards models		
Model 1 : Age, sex, enrollment center, ethnicity, Townsend deprivation index, and income level	1.11 (1.08-1.14)	<0.001
Model 2 : Model 1 + BMI, current smoking, daily drinking, and moderate-to-vigorous physical activity	1.10 (1.07-1.14)	<0.001
Model 3 : Model 2 + DM, hypertension, dyslipidemia, and Charlson comorbidity index	1.07 (1.03-1.11)	<0.001

[a]The IPTW model used propensity score generated by logistic regression model including age, sex, enrollment center, ethnicity, Townsend deprivation index, income level, BMI, current smoking, daily drinking, moderate-to-vigorous physical activity, DM, hypertension, dyslipidemia, and Charlson comorbidity index as covariates.

AF = atrial fibrillation; BMI = body mass index; DM = diabetes mellitus; IPTW = inverse probability of treatment weighting.

significantly higher in the high neuroticism score group, with increased risks of 5% and 6%, respectively. The results were not affected by changes in the lag periods of 1 and 2 years, with a 5% increased risk of AF in all models. The results were similar across various subpopulations, as shown in Supplemental Table 3.

A higher risk of AF in the high neuroticism score group was observed in populations of White ethnicity (n = 376,183), without a prior history of major cardiovascular disease, including myocardial infarction, stroke, or heart failure (n = 379,928), or without a history of major depression, schizophrenia, or bipolar disorder (n = 372,072).

MENDELIAN RANDOMIZATION RESULTS FROM SUMMARY-LEVEL DATA. For the summary-level MR analysis, 8 single nucleotide polymorphisms (SNPs) from the SSGAC Consortium GWAS results and 56 SNPs from the UK Biobank database were utilized as genetic instruments for neuroticism measurements and scores. The results indicated that a genetically predicted increase in the neuroticism measurement and score was significantly associated with an elevated risk of AF, and the causal estimates were confirmed to be statistically significant using the IVW, weighted median, and MR-PRESSO methods (**Table 3**). The results of the sensitivity analysis were consistent with those of the leave-one-out analysis of causal estimates from the 2-sample MR (Supplemental Figure 3). To exclude the possibility of reverse causality, a genetic instrument for AF (109 common SNPs from the SSGAC Consortium GWAS and 111 common SNPs from the UK Biobank GWAS) was used to evaluate neuroticism measurements and scores. The IVW MR analysis did not yield any significant causal estimates between AF and neuroticism measurements or scores (Supplemental Table 4).

TABLE 3 Causal Relationship Between Neuroticism and AF Assessed by 2-Sample Mendelian Randomization

	Outcome: AF (n = 1,030,836)[a]	
2-Sample Mendelian Randomization	OR (95% CI)	*P* Value
Exposure: neuroticism (SSGAC Consortium, n = 170,911)		
IVW	1.57 (1.01-2.44)	0.046
Weighted median	1.57 (1.15-2.14)	0.005
MR-PRESSO	1.05 (1.01-1.09)	0.029
Exposure: neuroticism score (UK Biobank, n = 274,108)		
IVW	1.06 (1.02-1.11)	0.007
Weighted median	1.06 (1.01-1.12)	0.023
MR-PRESSO	1.45 (1.18-1.79)	0.018

[a]Nielsen et al.[19]

AF = atrial fibrillation; IVW = inverse-variance weighted; MR-PRESSO = Mendelian Randomization Pleiotropy RESidual Sum and Outlier; SSGAC = Social Science Genetic Association Consortium.

DISCUSSION

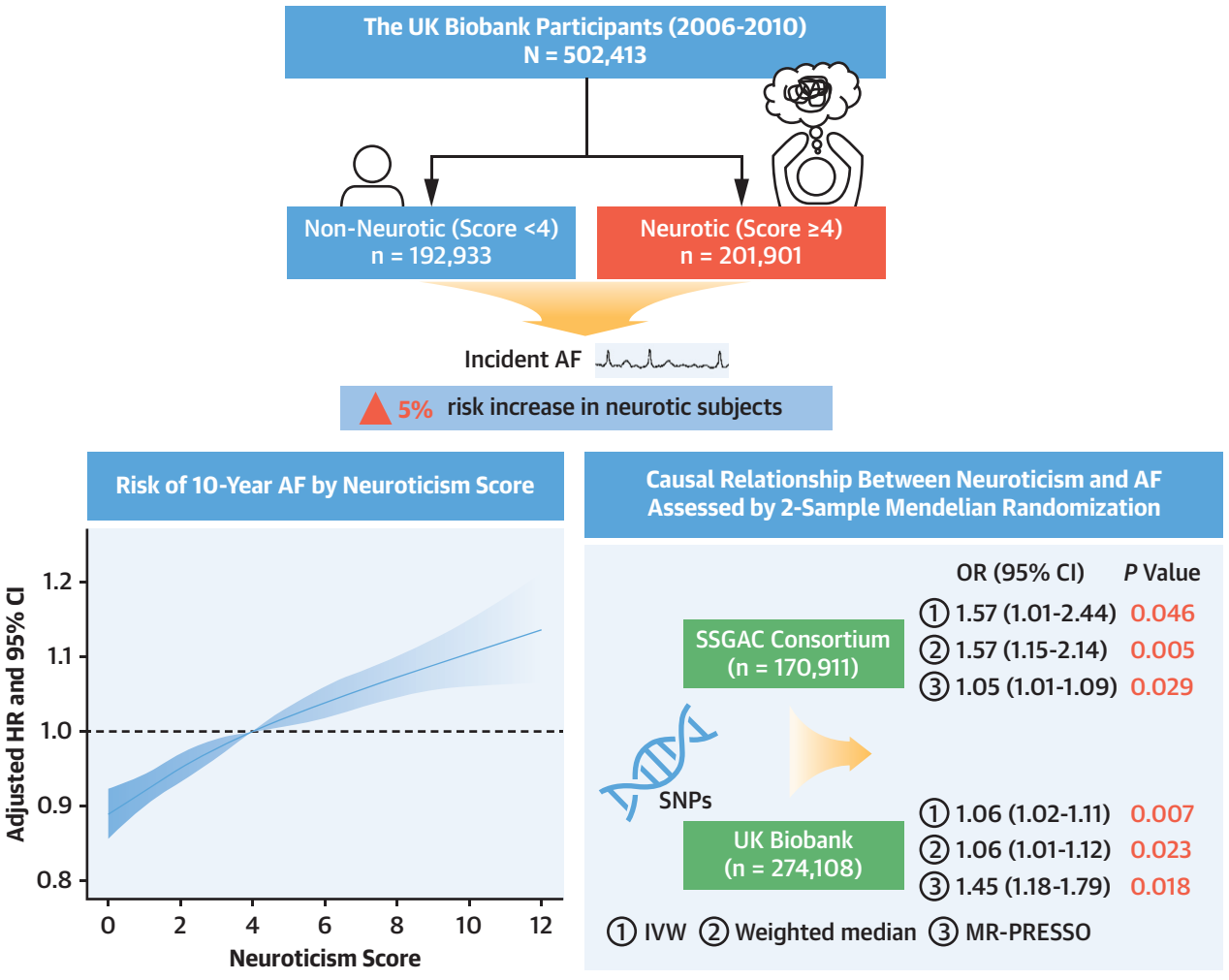
In this large longitudinal cohort study from the UK Biobank, our principal findings were as follows: 1) there was a significant association between increased neuroticism scores and an increased risk of AF at 10 years; 2) the elevated risk of AF was particularly pronounced among young, nonobese individuals and among nonsmokers or ex-smokers, and the increased risk of AF in the high neuroticism score group was observed consistently across different subpopulations and various follow-up or lag periods; and 3) the results of the summary-level 2-sample MR analysis further confirmed the causal association between a genetically predicted increase in neuroticism and an elevated risk (**Central Illustration**).

NEUROTICISM AND THE RISK OF AF. Whether psychological factors increase the risk of AF has been controversial among previous studies.[26-29] In the recent meta-analyses, the risk of AF was increased by anxiety, anger, depression, antidepressant use, and work stress.[30,31] These studies focused on the psychological traits that seem to be the result of neuroticism coping with the outer stimulus and not neuroticism itself. Previous studies have focused chiefly on the effect of AF on patients' quality of life via neuroticism and not vice versa.[32,33] In addition, these studies did not include comprehensive information on the neuroticism phenotype and were insufficient to prove a causal relationship.

Our study used a large, well-phenotyped UK Biobank database and identified significant associations between neuroticism and AF, although the effect was modest, even after adjusting for confounding factors. These results were consistent with the sensitivity analyses of various subpopulations and subgroup analyses, supporting the robustness of the association. Furthermore, the causal relationship between neuroticism and AF was identified using genotype data provided by the UK Biobank.

CAUSAL RELATIONSHIPS BETWEEN NEUROTICISM AND AF. The MR study approach has frequently been used to prove causal relationships between various psychological factors and cardiovascular disease. For example, neuroticism scores did not show a causal genetic association with coronary artery disease.[34] However, the genetic liability of depression is

CENTRAL ILLUSTRATION **Causal Link Between Neuroticism and AF Risk in the UK Biobank**



Rhee T-M, et al. JACC: Asia. 2024;4(2):138–147.

Among UK Biobank participants, those with a neuroticism score ≥4 showed an increased atrial fibrillation (AF) risk (inverse probability of treatment weighting-adjusted HR: 1.05; 95% CI: 1.02-1.09; $P = 0.005$). Increasing neuroticism scores showed a significant association with an increased 10-year AF risk. The causal relationship was consistent in 2-sample Mendelian randomizations. IVW = inverse variance weighted; MR-PRESSO = Mendelian Randomization Pleiotropy RESidual Sum and Outlier; SNP = single nucleotide polymorphism; SSGAC = Social Science Genetic Association Consortium.

associated with a higher risk of coronary artery disease and myocardial infarction.[35] Individuals with higher levels of neuroticism also showed an increased risk of heart failure and myocardial infarction in another MR study.[36] Genetically predicted well-being spectra have also reported controversial results on myocardial infarction and heart failure.[37,38]

In previous studies using MR, the association between psychological factors and AF was insignificant.[35-37] Only one study showed that genetically predicted neuroticism using 27 SNPs was causally associated with AF (OR: 1.20; 95% CI: 1.04-1.39, $P = 0.015$).[38] However, the study did not include data on individual neuroticism scores. Our study provides novel data showing an association between higher neuroticism scores and an increased risk of AF as well as a causal relationship between neuroticism and AF.

Possible mechanisms may explain the increased AF observed in participants with higher neuroticism scores. A high level of neuroticism is related to the

upregulation of inflammatory agents such as interferon γ and interleukin-6,[39,40] and an increase in inflammatory biomarkers is associated with an increased risk of AF.[41,42] Autonomic nervous system (ANS) dysregulation may be another mechanism underlying the association between neuroticism and AF, as higher neuroticism is associated with ANS imbalance.[43] An imbalance of the cardiac ANS due to simultaneous sympathetic and parasympathetic activity in a canine model is a trigger for AF.[44]

CLINICAL IMPLICATIONS. The causal relationship between neuroticism and AF proven in this study has several implications. As neuroticism increases the risk of AF, mental health screening in large populations using neuroticism score assessment tools such as the Eysenck Personality Questionnaire-Revised (EPQ-R) might be beneficial. In addition, early interventions, including lifestyle modifications (eg, alcohol and smoking) and AF risk factor management among high-risk neurotic subgroups (young, lower body mass index, nonsmoker/ex-smoker), may potentially be an effective preventive strategy for reducing incident AF and AF-related complications.[2,4] In addition, mental health management, including physical activity to reduce stress levels, may be helpful. However, further clinical studies are needed to determine the benefits of mental health care in reducing the risk of AF in neurotic patients.

STUDY LIMITATIONS. First, the relatively low incidence of overall cardiovascular diseases in the general population of the UK Biobank may have resulted in limited statistical power and may limit the extrapolation of our results on the population with high cardiovascular risk. Second, the absence of a validation cohort restricts the generalizability of the findings, and further evaluation of the results in other ethnicities and populations is required. Third, the exposure used in this study was based on subjective measures that may not apply to all individuals. Hence, clinicians should carefully consider the subjective nature of neurotic traits in light of the individual's specific circumstances. Fourth, considering that the diagnosis of AF was established based on inpatient hospital records and death registry data, individuals with asymptomatic AF who did not seek hospital care might have been omitted.

CONCLUSIONS

There was a significant longitudinal and causal relationship between neuroticism and the incidence of AF. Active mental health screening and management of AF, as part of an integrated care approach, are needed in this high-risk population.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Neuroticism might need to be considered as a new risk factor of AF.

COMPETENCY IN PATIENT CARE: The high-risk patients of neuroticism should be made aware that active mental health screening and AF management may be beneficial for AF prevention.

TRANSLATIONAL OUTLOOK: The impact of neuroticism score change over time should further be explored. The beneficial effect of active mental health management accompanying reduction of neuroticism score should be investigated.

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KEY WORDS atrial fibrillation, Mendelian randomization, neuroticism, outcome

APPENDIX For supplemental tables and figures, please see the online version of this paper.