

Investigation of Causal Effect of Atrial Fibrillation on Alzheimer Disease: A Mendelian Randomization Study

Yuesong Pan, PhD; Yilong Wang, MD, PhD; Yongjun Wang, MD

Background—Atrial fibrillation (AF) has been shown to be associated with an increased risk of dementia as well as Alzheimer disease in observational studies. Whether this association reflects causal association is still unclear. The purpose of this study was to examine the causal association of AF with Alzheimer disease.

Methods and Results—We used a 2-sample Mendelian randomization approach to evaluate the causal effect of AF on Alzheimer disease. Summary data on the association of single nucleotide polymorphisms with AF were obtained from a recently published genome-wide association study with up to 1 030 836 individuals and data on single nucleotide polymorphism-Alzheimer disease association from another genome-wide association study with up to 455 258 individuals. AF was mainly diagnosed according to International Classification of Diseases, Ninth Revision (ICD-9 or ICD-10) and Alzheimer disease was mainly diagnosed according to clinical criteria (eg, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA] criteria). Effect estimates were calculated using the inverse-variance weighted method. The Mendelian randomization analysis showed nonsignificant association of genetically predicted AF with risk of Alzheimer disease (odds ratio=1.002, 95% CI: 0.996–1.009, P=0.47) using 93 single nucleotide polymorphisms as the instruments. Mendelian randomization-Egger indicated no evidence of genetic pleiotropy (intercept=0.0002, 95% CI: -0.001 to 0.001, P=0.70).

Conclusions—This Mendelian randomization analysis found no evidence to support causal association between AF and Alzheimer disease. (J Am Heart Assoc. 2020;9:e014889. DOI: 10.1161/JAHA.119.014889.)

Key Words: Alzheimer disease • atrial fibrillation • causal association • genetics • Mendelian randomization

mentia is a major cause of disability in elderly people without available curative treatment. Worldwide, there were ≈ 50 million people living with dementia in 2018, and this number is expected to increase because of population growth and aging. Although the pathophysiologic mechanism of dementia is largely unknown, there has been increasing evidence that vascular risk factors and vascular diseases may contribute to cognitive decline and dementia.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the elderly population. AF was

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associated with an increased risk of ischemic stroke, which may further cause cognitive decline and dementia.4 It was well established that AF may increase vascular dementia⁵; however, the relationship between AF and degenerative dementia such as Alzheimer disease was still controversial. There were growing evidences indicating that the presence of AF might increase the risk of cognitive decline and dementia even in patients without prior stroke.⁶ Recently, several longitudinal studies have suggested that AF not only contributed to vascular dementia, but also to Alzheimer disease. 5,6 However, observational studies might be confounded by potential biases and reverse causation. Whether the association between AF and Alzheimer disease observed in observational studies reflects causal association required further investigation.

Mendelian randomization (MR) analysis can avoid potential unmeasured confounders and reverse causation by using genetic variants as instrumental variables and make stronger causal inferences between an exposure and risk of disease. In this study, we aimed to use MR analysis to evaluate the causal association of AF with Alzheimer disease using MR analysis.

Clinical Perspective

What Is New?

- The relationship between atrial fibrillation and degenerative dementia such as Alzheimer disease is still unclear.
- The causal association of atrial fibrillation with Alzheimer disease was examined using a 2-sample Mendelian randomization analysis using summary data from recently published genome-wide association studies.

What Are the Clinical Implications?

 This study did not provide convincing evidence to support a causal association between atrial fibrillation and Alzheimer disease.

Methods

Study Design and Data Sources

We designed a 2-sample MR approach to evaluate the causal effect of AF on Alzheimer disease (Figure 1). The MR design is under the assumption that the genetic variants are associated with AF, but independent of confounders and risk of Alzheimer disease conditional on AF and confounders. Based on this design, MR analysis can control potential confounders and reverse causation and make stronger causal inferences. Data on the association of single nucleotide polymorphisms (SNPs) with AF and the association of SNPs with Alzheimer disease were obtained from recently published genome-wide association studies (GWAS). The protocol and data collection of the original studies were approved by the ethics committee of participating sites and informed consent was obtained from all participants. All data generated or analyzed during this study are included in this published article.

Selection of Genetic Variants

We used previous published genetic variants associated with AF from a recent published GWAS. That study tested association between 34 740 186 genetic variants and AF with a total of 60 620 cases and 970 216 controls from 6 contributing studies. Table 1 shows the characteristics of the contributing studies of the GWAS. The majority (98.6%) of individuals were of European ancestry. AF was mainly diagnosed according to *International Classification of Diseases, Ninth Revision (ICD-9* or *ICD-10*). In that study, 111 genetic loci with at least 1 genetic variant associated with AF were identified ($P < 5.0 \times 10^{-8}$). These locus index variants explained 4.6% of the variation in AF (F statistic=534, indicating sufficient strength of the instruments). All these 111 SNPs were in different genomic regions and not in

linkage disequilibrium $(r^2 < 0.10)$. We performed a look-up of the 111 SNPs in Phenoscanner (a curated database holding publicly available results from large-scale GWAS with >65 billion associations and >150 million unique genetic variants; accessed on October 27, 2019) to evaluate whether these SNPs were associated with other traits at genome-wide significance level ($P < 5.0 \times 10^{-8}$) that may affect our results.¹⁰ We found that 9 SNPs (rs284277, rs1458038, rs60212594, rs422068, rs2540949, rs9899183, rs35005436, rs10006327, and rs12245149) were also associated with systolic blood pressure or self-reported hypertension and 7 SNPs (rs7789146, rs2885697, rs9953366, rs4951258, rs 12604076, rs56201652, and rs34080181) were also associated with whole body water mass, fat-free mass, or fat percentage. After exclusion of these 16 SNPs and 2 SNPs (rs12648245 and rs11156751) not found in outcome data sets, we used the remaining 93 SNPs as the instrument in the MR analysis. Table 2 shows the characteristics and associations of the 93 included SNPs with AF.

Outcomes

Summary statistics for the associations between the 93 SNPs related to AF and Alzheimer disease were obtained from the recently published genome-wide meta-analysis. In that study, genome-wide meta-analysis was performed through 3 phases including 71 880 Alzheimer disease cases and 383 378 controls (Table 1). Phase 1 involved a genome-wide meta-analysis for clinically diagnosed Alzheimer disease (eg, according to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA] criteria) case—control status using data from 3 independent consortia with 79 145 individuals of European ancestry and 9 862 738 genetic variants. Phase 2 involved a GWAS using 376 113 individuals of European ancestry from UK Biobank with

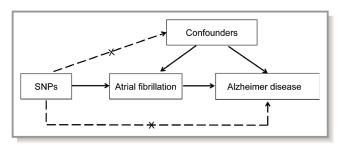


Figure 1. Conceptual framework for the Mendelian randomization analysis of atrial fibrillation and risk of Alzheimer disease. The design is under the assumption that the genetic variants are associated with atrial fibrillation, but not with confounders, and the genetic variants are not associated with risk of Alzheimer disease conditional on atrial fibrillation and confounders. SNP indicates single nucleotide polymorphism.

Table 1. Description of Contributing Studies

Contributing Studies	Sample Size (Cases/Controls)	Ancestry	Diagnosis of Diseases
GWAS for atrial fibrillation	60 620/970 216		
The Nord-Trøndelag Health Study	6493/63 142	European	/CD-10 code 48 or /CD-9 code 427.3
deCODE	13 471/358 161	European	/CD-10 code I48 or /CD-9 code 427.3
Michigan Genomics Initiative	1226/11 049	European	/CD-9 code 427.31
DiscovEHR Collaboration Cohort	6679/41 803	European	At least 1 electronic health record problem list entry or at least 2 diagnosis code entries for 2 separate clinical encounters on separate calendar days for <i>ICD-10</i> I48
UK Biobank	14 820/380 919	European	/CD-9 427.3 or /CD-10 I48
AFGen Consortium	15 979/102 776	European	Diagnosed according to ICD-9, ICD-10, or 12-lead ECG at
	641/5234	Black	the examinations
	837/3293	Japanese	
	277/3081	Hispanic	
	197/758	Brazilian	
GWAS for Alzheimer disease	71 880/383 378		
Alzheimer's disease working group of the Psychiatric Genomics Consortium [PGC-ALZ]	2965/14 512	European	According to the recommendations from the NIA/AA, NINCDS-ADRDA criteria or the ICD-10 research criteria
International Genomics of Alzheimer's Project [IGAP]	17 008/37 154	European	Autopsy- or clinically confirmed Alzheimer Disease cases wit NINCDS-ADRDA criteria, DSM-IV criteria, the ADDTC's State
Alzheimer's Disease Sequencing Project [ADSP]	4114/3392	European	of California criteria or DSM-III-R criteria
UK Biobank	47 793/328 320	European	Self-report questionnaire administered during the in-person assessment and confirmed with <i>ICD-10</i> codes (G30, F00) in national medical records

ADDTC indicates Alzheimer's Disease Diagnostic and Treatment Centers; DSM-III-R, DSM-Third Edition, Revised; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition*; GWAS, genome-wide association studies; *ICD, International Classification of Diseases*; NIA/AA, National Institute on Aging-Alzheimer's Association; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.

parental Alzheimer disease status weighted by age to construct an Alzheimer disease-by-proxy status assessed as part of the self-report questionnaire administered during the in-person assessment and additional information obtained from medical records. All individuals of phase 1 and phase 2 were meta-analyzed together in phase 3. The associations between each SNP related to AF and Alzheimer disease are presented in Table 2.

Statistical Analysis

We used 2-sample MR approaches to compute estimates of the effect of AF on Alzheimer disease using summarized data of the SNP-AF and SNP-Alzheimer disease associations. We performed both fixed-effect and random-effect inversevariance weighted (IVW) MR analysis in which the effect estimate was the IVW mean of ratio estimates from 2 or more instruments using first-order weights, assuming all SNPs were valid instruments. ¹¹ In sensitivity analyses, we also conducted penalized IVW, penalized robust IVW, MR-Egger, simple

median, weighted median, weighted mode-based estimate (MBE), and Mendelian Randomization Pleiotropy Residual Sum and Outlier (MR-PRESSO) methods of MR analyses. The penalized methods improved the robustness by penalizing the weights of instruments with pleiotropic effect with heterogeneous ratio estimates in the weighted regression model and the robust method can provide robust estimates both to outliers and to data points with high leverage by performing robust regression. 12 The MR-Egger method was performed by weighted linear regression of the associations of SNP with Alzheimer disease on the associations of SNP with AF using the inverse-variance of SNP-Alzheimer disease estimate as weights. The MR-Egger method may provide robust estimates to potential violations of the standard instrumental variable assumptions because of directional pleiotropy (a genetic variant affects the Alzheimer disease via a different biological pathway from AF). 13 The weighted median method may provide robust estimates against invalid instruments (even if up to 50% of genetic variants are invalid instruments) using the inverse of the variance of the ratio estimates as weights. 14

Continued

Table 2. Characteristics of the 93 SNPs Associated With Atrial Fibrillation

SMP Description Grows Character metry Sh. OA Ehr. OA C 00244 O 10249 1 184 x 10 x 10 O 10244 O 10244 O 10244 O 10244 O 10244 O 10249 1 184 x 10 x 10 O 10244 O 10249 O 10249 1 184 x 10 x 10 O 10244 O 10249 O 10249 O 10249 O 10244 O 10249 O 10249 <th></th> <th></th> <th></th> <th></th> <th></th> <th>Effect on Atrial Fibrillation</th> <th>al Fibrillation</th> <th></th> <th>Effect on AD</th> <th></th> <th></th>						Effect on Atrial Fibrillation	al Fibrillation		Effect on AD		
KPP022 ChT1.22226619 CTT 0.847 0.0024 0.1456 0.0028 1.38 × 10 · 10 6 AGBRA ChT1.25282619 AGC 0.024 0.1456 0.0248 4.12×10 · 3 6 AGBRA ChT1.2526039 AGC 0.024 0.0268 0.0273 142×10 · 3 6 AGMROSO ChT1.112464004 CT 0.0681 0.0073 142×10 · 14 6 AGRAC CHT1.112464004 CT 0.0684 0.0073 148×10 · 14 6 AGRAC CHT1.112464004 CT 0.0589 0.0163 3.15×10 · 14 6 AGG CHT1.112464004 CT 0.0583 0.1162 0.0153 3.15×10 · 14 6 AGG CHT1.112464004 CG 0.0786 0.0164 0.0017 3.07×10 · 14 6 AGG CGG CGG 0.0786 0.0064 0.0017 3.07×10 · 12 6 AGG CGG CGG 0.0786 0.0064 0.0063 2.42×10 · 12	SNP	Prioritized Genes	Position (hg19)	EA/0A	EAF	Beta	SE	P Value	Beta	SE	P Value
6 MMPRSOD ChT-48209764 AG 0.024 0.1456 0.0248 4.12×10 ° 6 MMPRSOD ChT-15153099 AG 0.033 0.1605 0.0207 8.27×10 ° 6 CAROZ ChT-11240044 CT 0.684 0.0659 0.0077 148×10 ° 6 CARSZ ChT-11240044 CT 0.684 0.0667 0.0077 148×10 ° 1 GARS ChT-1140049 CT 0.684 0.0667 0.0077 148×10 ° 1 GARS ChT-1140049 CT 0.069 0.0077 3.07×10 ° 1 CARONS ChT-1170193825 CG 0.076 0.0207 3.05×10 ° 1 CARONS ChT-1170193825 CG 0.076 0.0071 3.07×10 ° 1 CARONS ChT-1170193825 CG 0.076 0.0071 3.07×10 ° 1 CARONS ChT-1170193825 CG 0.076 0.0071 3.08×10 ° 1 CARONS C	rs7529220	HSPG2	chr1:22282619	C/T	0.847	0.0621	0.0098	1.98×10^{-10}	0.0094	0.0029	0.001
6 MINRESOR ChT:5153639 AG 0.033 0.1605 0.0207 8.27 × 10 − 15 CARD23 ChM23 ChM23 ChM24 0.0486 0.0073 1.48 × 10 − 14 CARD23 ChM24 ChM25 ChM25 0.0073 1.48 × 10 − 14 CARD24 ChM25 ChM25 0.0073 0.0073 1.48 × 10 − 14 CARD25 ChM25 ChM25 0.0073 0.0073 1.48 × 10 − 14 CAGM2 ChM25 ChM25 0.0075 0.0173 0.0077 1.48 × 10 − 14 CAGM2 ChM27 ChM27 0.0077 </td <td>rs11590635</td> <td>AGBL4</td> <td>chr1:49309764</td> <td>A/G</td> <td>0.024</td> <td>0.1456</td> <td>0.0248</td> <td>4.12×10^{-9}</td> <td>-0.0040</td> <td>0.0079</td> <td>0.616</td>	rs11590635	AGBL4	chr1:49309764	A/G	0.024	0.1456	0.0248	4.12×10^{-9}	-0.0040	0.0079	0.616
KOND3 Chri.112464004 CT 0.694 0.0558 0.0073 148×10 ⁻¹⁴ CAS2Z Chri.11629768 AC 0.564 0.0466 0.0067 4,96×10 ⁻¹³ AGAS Chri.14023768 AC 0.564 0.0466 0.0067 4,96×10 ⁻¹³ ACAD Chri.1701382625 TG 0.033 0.0147 3,07×10 ⁻¹³ AMD Chri.17013825 TG 0.048 0.0067 340×10 ⁻²⁰ AMD Chri.2701428 TG 0.048 0.0067 340×10 ⁻²⁰ AMD Chri.2701428 TG 0.796 0.0077 340×10 ⁻²⁰ AMD Chri.27014825 TG 0.796 0.0067 340×10 ⁻²⁰ AMD Chri.2701482 TG 0.796 0.0067 340×10 ⁻²⁰ AMD Chri.2701482 TG 0.796 0.0067 340×10 ⁻²⁰ AMD Chri.2701482 TG 0.796 0.0067 1.10×10 ⁻¹² AMD Chri.2701482 TG 0.796 0.0564	rs146518726	MIR6500	chr1:51535039	A/G	0.033	0.1605	0.0207	8.27×10^{-15}	-0.0019	0.0072	0.795
CASS22 Chr.1.16297758 AC 0.564 0.0486 0.0067 4.96×10 ⁻¹³ KCMM3 Chr.1.147258831 GA 0.943 0.1162 0.0153 3.15×10 ⁻¹⁴ KCMM3 Chr.1.70193825 T/C 0.333 0.1347 0.0071 3.07×10 ⁻⁷³ LMC07142 Chr.1.20192825 T/C 0.736 0.0067 9.84×10 ⁻⁷³ MADAZ Chr.2.2616528 T/C 0.736 0.0614 0.0067 9.84×10 ⁻⁷³ MADAZ Chr.2.2616528 T/C 0.736 0.0614 0.0067 9.84×10 ⁻⁷³ MADAZ Chr.2.2016528 T/C 0.736 0.0654 0.0067 1.10×10 ⁻¹⁶ MADAZ Chr.2.2165285 T/C 0.736 0.0654 0.0067 1.10×10 ⁻¹⁶ MADAZ Chr.2.21665283 G/C 0.074 0.01067 1.10×10 ⁻¹⁶ MADAZ Chr.2.14733465 T/C 0.736 0.074 0.1136 1.71×10 ⁻¹⁶ MADAZ Chr.2.14810403 G/C 0.071 0.071	rs1545300	KCND3	chr1:112464004	C/T	0.691	0.0558	0.0073	1.48×10^{-14}	0.0059	0.0024	0.013
6.M65 CHT:147258831 G/A 0.943 0.1162 0.0153 3.15×10 ⁻¹⁴ MCOM/142 CHT:154862962 T/C 0.333 0.1347 0.0071 3.05×10 ⁻⁷⁷ MCOM/142 CHT:124862962 T/C 0.076 0.0069 0.0067 3.28×10 ⁻⁵⁴ MCACATACA CHT:120402624 T/C 0.076 0.0064 0.0068 2.42×10 ⁻⁵² MCACA CHT:2040202614 T/C 0.056 0.0064 0.0068 2.42×10 ⁻⁵² MCACA CHT:20402026 CT 0.056 0.0064 0.0068 2.42×10 ⁻⁵² MCACA CHT-2040202 T/C 0.056 0.0064 0.0068 2.42×10 ⁻⁵² MCACA CHT-2040202 T/C 0.056 0.0064 0.0068 2.42×10 ⁻⁵² MCACA CHT-204032 T/C 0.056 0.0077 1.00 1.00 MCACA CHT-204032 T/C 0.074 0.017 1.01 1.00 MCACA CHT-204032 T/C 0.078	rs4073778	CASQ2	chr1:116297758	A/C	0.564	0.0486	0.0067	4.96×10^{-13}	0.0028	0.0021	0.189
KOMN2 ChT:154862822 T/C 0.333 0.1347 0.0071 3.07×10 ⁻⁷⁹ IMOD1/42 ChT:170193825 C/G 0.076 0.2021 0.013 3.29×10 ⁻⁵⁴ IMOD1/42 ChT:1203026214 T/G 0.078 0.0609 0.0067 98×10 ⁻⁷⁰ IMOD2/44 ChT:1203026214 T/G 0.796 0.0614 0.0068 2.42×10 ⁻¹⁵ IMOD2/4MA ChT:2203026214 T/G 0.796 0.0644 0.0068 2.42×10 ⁻¹⁵ IMOD2/AMA ChT:2203026214 T/G 0.796 0.0644 0.0068 6.42×10 ⁻¹⁶ IMOD2/AMA ChT:2203026214 T/G 0.796 0.0649 0.0068 6.42×10 ⁻¹⁶ IMMP ChT:220302636 T/G 0.105 0.0102 2.37×10 ⁻¹¹ IMMP ChT:2203026003 T/G 0.105 0.0102 2.37×10 ⁻¹¹ IMMP ChT:217326003 T/G 0.105 0.013 1.10×10 ⁻¹⁶ IMMP ChT:217326003 CT 0.392 0.0683 0.001	rs79187193	G.M5	chr1:147255831	G/A	0.943	0.1162	0.0153	3.15×10^{-14}	-0.0049	0.0054	0.363
MIGNOTIAR2 ChT:170193825 C/G 0,076 0,02021 0,013 329×10 ⁻⁵⁴ M/32C ChT:203026214 T/G 0,448 0,0609 0,0067 9;84×10 ⁻²⁰ M/32C ChT:203026214 T/G 0,748 0,0609 0,0067 9;84×10 ⁻²⁰ L/873A ChT 0,695 0,0094 0,0068 2,42×10 ⁻¹² L/873A ChT 0,695 0,0068 6,42×10 ⁻⁹ CMX21,AWA4 ChT:2450483 T/C 0,636 0,0067 1,10×10 ⁻¹⁶ CMA21,AWA4 ChT:24734365 T/C 0,071 0,0102 2,42×10 ⁻¹⁷ CMA21,AWA4 ChT:24736353 T/C 0,071 0,010 2,27×10 ⁻¹⁸ TEAT TRAT ChT 0,035 0,007 1,11×10 ⁻¹⁸ TRAT ChT 0,035 0,007 1,11×10 ⁻¹⁸ SPATS2L ChT 0,732 0,066 1,10×10 ⁻¹¹ CAMD2 ChR24 0,640 0,071 0,013 1,10×10 ⁻¹¹ THR	rs11264280	KCNN3	chr1:154862952	1/0	0.333	0.1347	0.0071	3.07×10^{-79}	0.000	0.0023	0.983
HPFRA4 Chr1.203026214 T/G 0.448 0.0609 0.0067 9.84×10 ⁻²⁰ M/32C Chr2.2616528 T/C 0.796 0.0614 0.0068 2.42×10 ⁻¹² L/672A Chr2.24 Chr2.1470126 CT 0.665 0.0674 0.0068 6.42×10 ⁻¹² G/MCZ J.AUXA4 Chr2.7106832 T/C 0.655 0.054 0.0067 1.10×10 ⁻¹⁶ AREPT Chr2.7106832 T/C 0.653 0.054 0.0067 1.10×10 ⁻¹⁶ AREPT Chr2.17433465 T/C 0.077 0.0741 0.0128 1.77×10 ⁻⁸ MPF Chr2.174341665 G/A 0.772 0.0663 0.0077 6.48×10 ⁻¹⁶ T/M/MRS48/L/RPP/T/M-AS7 Chr2.17366033 G/C 0.071 0.071 1.10×10 ⁻¹¹ AMPS Chr2.17841665 G/A 0.772 0.0663 0.725 1.17×10 ⁻⁸ AMD2 Chr2.17841665 G/A 0.772 0.0673 1.77×10 ⁻⁸ AMD2 Chr2.2463255 T/C 0.392 <td>rs72700114</td> <td>LINC01142</td> <td>chr1:170193825</td> <td>5/0</td> <td>0.076</td> <td>0.2021</td> <td>0.013</td> <td>3.29×10^{-54}</td> <td>9000.0</td> <td>0.0043</td> <td>968.0</td>	rs72700114	LINC01142	chr1:170193825	5/0	0.076	0.2021	0.013	3.29×10^{-54}	9000.0	0.0043	968.0
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LGP34 ChT 0.605 0.0394 0.0068 642×10 ⁻⁹ CMMC1/AWA44 Cht2710106832 T/C 0.536 0.0654 0.0067 1.10×10 ⁻¹⁶ In REP1 Cht2710106832 T/C 0.536 0.0054 0.0007 1.10×10 ⁻¹⁶ In REP1 Cht2127433465 T/C 0.105 0.0102 2.37×10 ⁻¹¹ In Rep1 Cht2127433465 T/C 0.105 0.0102 2.37×10 ⁻¹¹ In Rep1 Cht2.1765033 G/C 0.071 0.013 6.25×10 ⁻¹¹ In MIPST Cht2.176411665 G/C 0.071 0.010 1.71×10 ⁻⁸ In MIPST Cht2.176411665 G/A 0.0662 0.0077 6.46×10 ⁻¹⁸ In MIPST Cht2.13266003 AT 0.808 0.0089 7.26×10 ⁻²⁵ In MBS Cht2.13266003 AT 0.808 0.008 1.10×10 ⁻¹¹ In MBS Cht2.23266003 AT 0.808 0.008 1.10×10 ⁻¹¹ In MBS Cht2.22610 0.072 0.043 <td>rs7578393</td> <td>KIF3C</td> <td>chr2:26165528</td> <td>1/C</td> <td>0.796</td> <td>0.0614</td> <td>0.0088</td> <td>2.42×10^{-12}</td> <td>-0.0051</td> <td>0.0062</td> <td>0.405</td>	rs7578393	KIF3C	chr2:26165528	1/C	0.796	0.0614	0.0088	2.42×10^{-12}	-0.0051	0.0062	0.405
GMOZ 1, AMX44 Ch02-70106832 T/C 0.536 0.0564 0.0067 1.10×10 ⁻¹⁶ REEP7 CHPC Ch2863487 G/A 0.877 0.0683 0.0102 2.37×10 ⁻¹¹ CHPC CHPC CHPC CHPC 0.105 0.0741 0.0113 6.25×10 ⁻¹¹ H CHPC CHPC CHPC 0.077 0.077 6.46×10 ⁻¹⁶ H CHPC CHPC 0.077 0.077 6.46×10 ⁻¹⁶ H CHPC CHPC 0.077 0.077 6.46×10 ⁻¹⁶ H CHPC CHPC 0.071 0.071 0.077 6.46×10 ⁻¹⁶ H VMPFT CHPC CHPC 0.075 0.0689 0.077 6.46×10 ⁻¹⁶ CHBS4 CHPC CHPC 0.732 0.0689 0.0077 1.70×10 ⁻²⁶ CHBS4 CHPC CHPC 0.732 0.0689 0.0077 1.70×10 ⁻²⁶ CHBS4 CHPC CHPC 0.732 0.0689 0.077 1.70×1	rs11125871	USP34	chr2:61470126	C/T	0.605	0.0394	0.0068	6.42×10^{-9}	0.0003	0.0022	906.0
GFP7 ChR2.86594487 G/A 0.877 0.0683 0.0102 2.37×10 ⁻¹¹ GPPC ChR2.127433465 T/C 0.105 0.0741 0.0113 6.25×10 ⁻¹¹ INTATIONALIZATION CHR2.145760353 G/C 0.071 0.0711 0.0126 1.77×10 ⁻⁸ INTAMIRS-48V,FGBP7,TTM-ASY Chr2.175655714 C/T 0.732 0.0662 0.0077 6.46×10 ⁻¹⁸ INTAMIRS-48V,FGBP7,TTM-ASY Chr2.175660033 A/T 0.808 0.0684 0.0068 7.75×10 ⁻²⁴ INTARS-AND CHR2.213266003 A/T 0.808 0.0073 1.75×10 ⁻²⁴ INMAR ChR3.22463235 T/C 0.702 0.043 0.0073 1.55×10 ⁻²⁴ INMAR ChR43 ChR3.22463235 T/C 0.596<	rs6747542	GMCL1,ANXA4	chr2:70106832	1/C	0.536	0.0554	0.0067	1.10×10^{-16}	900000-	0.0021	0.768
GPPC Chr2.127433465 T/C 0.105 0.0741 0.0113 6.25×10 ⁻¹¹ INPPT Chr2.1274560353 G/C 0.071 0.0711 0.0126 1.77×10 ⁻⁸ INPPT Chr2.145760353 G/C 0.077 0.0862 0.0077 6.46×10 ⁻¹⁸ INPPT Chr2.175555714 C/T 0.732 0.0862 0.0077 6.46×10 ⁻¹⁸ INPPT Chr2.213266003 C/T 0.392 0.0869 0.0087 7.28×10 ⁻²⁴ INPBB4 Chr2.213266003 A/T 0.808 0.0589 0.0087 1.10×10 ⁻¹¹ INPBB4 Chr2.12463235 T/C 0.392 0.0687 1.0007 1.79×10 ⁻²⁴ INPBB4 Chr3.12463235 T/C 0.396 0.0077 1.79×10 ⁻³ 1.75×10 ⁻³ INRBBA Chr3.2463235 T/C 0.702 0.0443 0.0068 2.40×10 ⁻³ SCNIOA,SUSA Chr3.38771925 G/C 0.596 0.0627 0.0068 2.70×10 ⁻⁹ PHDB2, PLXOZ Chr3.38771925	rs72926475	REEP1	chr2:86594487	G/A	0.877	0.0683	0.0102	2.37×10^{-11}	-0.0018	0.0032	0.575
TEK41 Chr2:145760353 G/C 0.0711 0.0126 1.71×10 ⁻⁸ WIPPT Chr2:17555574 CT 0.732 0.0662 0.0077 6.46×10 ⁻¹⁸ TTM MIRSASWI, FKBPT, TTM-AS7 Chr2:179411665 G/A 0.156 0.0919 0.0089 7.26×10 ⁻²⁸ SPATS2L Chr2:21180023 CT 0.392 0.0684 0.0068 5.75×10 ⁻²⁴ GAND2 Chr2:213266003 AT 0.389 0.0087 1.70×10 ⁻¹¹ GAND2 Chr3:12841804 G/A 0.640 0.0711 0.007 1.79×10 ⁻²⁴ THBB Chr3:12841804 G/A 0.640 0.0711 0.007 1.79×10 ⁻¹¹ GAND2 Chr3:12841804 G/A 0.640 0.0711 0.007 1.79×10 ⁻²⁴ FRMD48 Chr3:12841804 G/C 0.596 0.0627 0.0068 2.40×10 ⁻²⁰ FPHAD3 Chr3:111554426 A/G 0.656 0.043 0.0068 2.42×10 ⁻¹¹ FPHAD82 CKAD2 Chr3:179172979 T/G <	rs28387148	СИРС	chr2:127433465	1/C	0.105	0.0741	0.0113	6.25×10^{-11}	-0.0051	0.0035	0.152
WIPFT Chr2:175555714 CT 0.732 0.0662 0.0077 6.46×10 ⁻¹⁸ T71I,MMR548I/FKBP7,T7I/-AS7 Chr2:179411665 G/A 0.156 0.0919 0.0089 7.26×10 ⁻²⁶ FRB84 Chr2:201180023 C/T 0.392 0.0684 0.0068 5.75×10 ⁻²⁴ CAND2 Chr2:13266003 A/T 0.808 0.0689 0.0087 1.10×10 ⁻¹¹ CAND2 Chr3:12841804 G/A 0.640 0.0711 0.007 1.79×10 ⁻²⁴ THRB Chr3:12841804 G/A 0.640 0.0711 0.007 1.79×10 ⁻¹¹ SCNIOA,SCN/54 Chr3:1841804 G/A 0.640 0.0713 1.05×10 ⁻⁹ FRMD4B Chr3:89406181 T/C 0.596 0.0627 0.0068 2.42×10 ⁻⁹ PHLDB2, PLXD2 Chr3:89489529 T/C 0.596 0.0457 0.0068 8.77×10 ⁻⁹ Chr3 G/M84 Chr3:194800853 T/C 0.596 0.0457 0.0068 8.77×10 ⁻⁹ Chr3 Chr3 <	rs67969609	TEX41	chr2:145760353	g/C	0.071	0.0711	0.0126	1.71×10^{-8}	-0.0002	0.0037	0.951
TTN MIR548V, FABPT, TTN-AS7 chr2.17941665 G/A 0.156 0.0919 0.0089 7.26×10 ⁻²⁵ SPATS2L chr2.201180023 C/T 0.392 0.0684 0.0068 5.75×10 ⁻²⁴ ERB84 chr2.213266003 A/T 0.808 0.0689 0.0087 1.10×10 ⁻¹¹ in CAND2 chr3.12841804 G/A 0.640 0.0711 0.0073 1.75×10 ⁻²⁴ in THBB chr3.2463235 T/C 0.702 0.0443 0.0073 1.75×10 ⁻⁹ in THRB chr3.2463235 T/C 0.702 0.0443 0.0073 1.55×10 ⁻⁹ in SCNITOA,SCNSA chr3.89406181 T/C 0.364 0.0443 0.0068 2.40×10 ⁻⁹ EPHA3 chr3.89489529 T/C 0.364 0.0457 0.0068 2.70×10 ⁻⁹ in PHLDB2, PLCX02 chr3.135814009 G/A 0.436 0.0568 0.0078 1.72×10 ⁻⁹ in ANB4 chr3.194800853 T/C 0.226 0.0445	rs56181519	WIPF1	chr2:175555714	C/T	0.732	0.0662	0.0077	6.46×10^{-18}	-0.0021	0.0024	0.371
SPATS2L Chr2:201180023 C/T 0.392 0.0684 0.0068 5.75×10 ⁻²⁴ FBB94 Chr2:213266003 A/T 0.808 0.0589 0.0087 1.10×10 ⁻¹¹ CAMD2 Chr3:12841804 G/A 0.640 0.0711 0.007 1.79×10 ⁻²⁴ In TABB Chr3:12841804 G/A 0.640 0.0711 0.007 1.79×10 ⁻²⁴ Chr3:128463235 T/C 0.702 0.0443 0.0073 1.55×10 ⁻⁹ Chr3:128463235 T/C 0.596 0.0627 0.0068 2.40×10 ⁻⁹ Chr3:128480529 T/C 0.596 0.0457 0.0068 2.42×10 ⁻¹¹ PHDB2,PLXD2 Chr3:135814009 G/A 0.651 0.0457 0.0068 8.77×10 ⁻⁹ Chr3:135814009 G/A 0.651 0.0457 0.0068 8.77×10 ⁻⁹ Chr3:179172979 T/G 0.226 0.0445 0.0079 1.72×10 ⁻⁸ Chr4x1 Chr4x111448656 G/A 0.0565 0.0076 1.92×10 ⁻¹⁴³ Ch	rs2288327	TTN,MIR548N,FKBP7,TTN-AS1	chr2:179411665	G/A	0.156	0.0919	0.0089	7.26×10^{-25}	0.0004	0.0028	0.891
CAND2 Chr2:13266003 AT 0.808 0.0589 0.0087 1.10×10 ⁻¹¹ CAND2 Chr3:12841804 G/A 0.640 0.0711 0.007 1.79×10 ⁻²⁴ FINBS Chr3:24463235 T/C 0.702 0.0443 0.0073 1.55×10 ⁻⁹ FINDAB Chr3:89406181 T/C 0.364 0.0043 0.0068 2.40×10 ⁻⁹ FPHAB Chr3:89489529 T/C 0.366 0.0457 0.0068 2.42×10 ⁻¹¹ PHLDB2,PLCX02 Chr3:11554426 A/G 0.651 0.0558 0.007 1.63×10 ⁻⁹ PHLDB2,PLCX02 Chr3:135814009 G/A 0.436 0.0058 8.77×10 ⁻⁹ ChNB4 Chr3:135814009 G/A 0.188 0.0084 4.81×10 ⁻⁹ PHZDB2,PLCX02 Chr3:135814009 G/A 0.188 0.0084 4.81×10 ⁻⁹ ChNB4 Chr3:111699685 T/A 0.199 0.3655 0.0076 1.92×10 ⁻⁴³ CAMM2D Chr4:11448656 G/A 0.061 0.091 0.0	rs3820888	SPATS2L	chr2:201180023	C/T	0.392	0.0684	0.0068	5.75×10^{-24}	-0.0005	0.0022	0.813
CAND2 Chr3:12841804 G/A 0.640 0.0711 0.007 1.79×10 ⁻²⁴ FHBB Chr3:2463235 T/C 0.702 0.0443 0.0073 1.55×10 ⁻⁹ FHBB Chr3:2463235 T/C 0.702 0.0443 0.0073 1.55×10 ⁻⁹ FHMD4B Chr3:69406181 T/C 0.596 0.0627 0.0668 2.40×10 ⁻²⁰ FPHA3 Chr3:89489529 T/C 0.596 0.0457 0.0668 2.42×10 ⁻¹¹ FPHA3 Chr3:11155426 A/G 0.651 0.058 0.0068 2.72×10 ⁻¹⁹ FPHA3 Chr3:1155426 A/G 0.651 0.058 0.0068 8.77×10 ⁻⁹ FPHA3 Chr3:135814009 G/A 0.436 0.0088 8.77×10 ⁻⁹ Chr3:144800853 T/G 0.188 0.0045 0.0079 1.72×10 ⁻⁸ FMX2 Chr4:111699685 T/A 0.199 0.3655 0.0076 1.92×10 ⁻¹³ Chr4:1448656 G/A 0.061 0.0134 0.0134 1.32×10	rs35544454	ERBB4	chr2:213266003	AT	0.808	0.0589	0.0087	1.10×10^{-11}	0.0050	0.0028	0.071
THRB chr3:24463235 T/C 0.702 0.0443 0.0073 1.55×10 ⁻⁹ SCNIOA,SCNSA chr3:38771925 G/C 0.596 0.0627 0.0068 2.40×10 ⁻²⁰ FRIMDAB chr3:69406181 T/C 0.364 0.0413 0.0069 2.70×10 ⁻⁹ FPHA3 chr3:89489529 T/C 0.596 0.0457 0.0068 2.42×10 ⁻¹¹ FPHA3 chr3:11155426 A/G 0.651 0.0558 0.007 1.63×10 ⁻¹⁵ GNIB4 chr3:135814009 G/A 0.436 0.0084 8.77×10 ⁻⁹ chr3:13684 chr3:136814009 G/A 0.436 0.0068 8.77×10 ⁻⁹ chr3:13684 chr3:136814009 G/A 0.226 0.0045 1.72×10 ⁻⁹ chr3:14486685 T/A 0.226 0.0455 0.0079 1.72×10 ⁻⁹ chr4:11448656 G/A 0.265 0.0076 1.92×10 ⁻¹³ chr4:1448656 G/A 0.061 0.091 0.0134 1.32×10 ⁻¹¹	rs7650482	CAND2	chr3:12841804	G/A	0.640	0.0711	0.007	1.79×10^{-24}	0.0030	0.0022	0.169
SCNYOA,SCNSA chr3:88771925 G/C 0.596 0.0627 0.0068 2.40×10 ⁻²⁰ FRMDAB chr3:69406181 T/C 0.364 0.0413 0.0069 2.70×10 ⁻⁹ FPHA3 chr3:69406181 T/C 0.364 0.0413 0.0069 2.70×10 ⁻⁹ FPHA3 chr3:11554426 A/G 0.651 0.0558 0.007 1.63×10 ⁻¹⁵ FPHDB2,PLCXD2 chr3:11554426 A/G 0.651 0.0589 0.007 1.63×10 ⁻¹⁵ GMB4 chr3:135814009 G/A 0.188 0.0084 4.81×10 ⁻⁹ GMB4 chr3:179172979 T/G 0.266 0.0445 0.0079 1.72×10 ⁻⁸ PTXZ PTXZ chr4:111699685 T/A 0.199 0.3655 0.0076 1.92×10 ⁻¹³ GAMK2D chr4:11448656 G/A 0.061 0.0134 1.32×10 ⁻¹¹³	rs73041705	THRB	chr3:24463235	2/1	0.702	0.0443	0.0073	1.55×10^{-9}	-0.0016	0.0023	0.496
FPMDAB Chr3:69406181 T/C 0.364 0.0413 0.0069 2.70×10 ⁻⁹ FPMA3 Chr3:89489529 T/C 0.596 0.0457 0.0068 2.42×10 ⁻¹¹ PHLDB2, PLCXD2 chr3:11554426 A/G 0.651 0.0558 0.007 1.63×10 ⁻¹⁵ PPP2R34 chr3:135814009 G/A 0.436 0.0389 0.0068 8.77×10 ⁻⁹ GNB4 chr3:179172979 T/G 0.188 0.0493 0.0084 4.81×10 ⁻⁹ HYXZ chr3:194800853 T/C 0.226 0.0445 0.0079 1.72×10 ⁻⁸ HYXZ chr4:11448656 G/A 0.262 0.0556 0.0076 1.92×10 ⁻¹³ CAMM2D chr4:1448656 G/A 0.061 0.014 0.0134 1.32×10 ⁻¹¹	rs6790396	SCN10A,SCN5A	chr3:38771925	0/5	0.596	0.0627	0.0068	2.40×10^{-20}	-0.0012	0.0021	0.567
EPHA3 Chr3:89489529 T/C 0.596 0.0457 0.0068 2.42×10 ⁻¹¹ PHLDB2,PLCXD2 chr3:111554426 A/G 0.651 0.0558 0.007 1.63×10 ⁻¹⁵ PPP2R34 chr3:135814009 G/A 0.436 0.0389 0.0068 8.77×10 ⁻⁹ chr3:179172979 T/G 0.188 0.0084 4.81×10 ⁻⁹ chr3:179172979 T/G 0.226 0.0445 0.0079 1.72×10 ⁻⁸ chr4:11699685 T/A 0.199 0.3655 0.0076 1.92×10 ⁻¹³ chr4:11448656 G/A 0.061 0.091 0.0134 1.32×10 ⁻¹¹	rs17005647	FRMD4B	chr3:69406181	2/1	0.364	0.0413	6900:0	2.70×10^{-9}	0.0026	0.0022	0.252
PHLDB2,PLCXD2 Chr3:11554426 A/G 0.651 0.0558 0.007 1.63×10 ⁻¹⁵ PPP2R34 Chr3:135814009 G/A 0.436 0.0389 0.0068 8.77×10 ⁻⁹ GNIB4 Chr3:179172979 T/G 0.188 0.0493 0.0084 4.81×10 ⁻⁹ NXYLT7 Chr3:194800853 T/C 0.226 0.0445 0.0079 1.72×10 ⁻⁸ PITX2 Chr4:111699685 T/A 0.199 0.3655 0.0076 1.92×10 ⁻¹³ CAMM2D Chr4:11448656 G/A 0.061 0.091 0.0134 1.32×10 ⁻¹¹	rs6771054	ЕРНАЗ	chr3:89489529	1/C	0.596	0.0457	0.0068	2.42×10^{-11}	0.0002	0.0022	0.925
PPP2R34 Chr3:135814009 G/A 0.436 0.0389 0.0068 8.77×10 ⁻⁹ CMB4 Chr3:179172979 T/G 0.188 0.0084 4.81×10 ⁻⁹ CMB4 Chr3:194800853 T/C 0.226 0.0445 0.0079 1.72×10 ⁻⁸ PITX2 Chr4:111699685 T/A 0.199 0.3655 0.0081 7.32×10 ⁻⁴⁴³ CAMM2D Chr4:114448656 G/A 0.065 0.0076 1.92×10 ⁻¹³ ARHGAP10 Chr4:148937537 G/C 0.061 0.091 0.0134 1.32×10 ⁻¹¹	rs10804493	PHLDB2, PLCXD2	chr3:111554426	A/G	0.651	0.0558	0.007	1.63×10^{-15}	-0.0003	0.0022	0.877
GNIB4 Chr3:179172979 T/G 0.188 0.0493 0.0084 4.81×10 ⁻⁹ XXYLT Chr3:194800853 T/C 0.226 0.0445 0.0079 1.72×10 ⁻⁸ PITX2 Chr4:111699685 T/A 0.199 0.3655 0.0081 7.32×10 ⁻⁴⁴³ CAMM2D Chr4:114448656 G/A 0.262 0.0556 0.0076 1.92×10 ⁻¹³ ARHGAP10 Chr4:148937537 G/C 0.061 0.091 0.0134 1.32×10 ⁻¹¹	rs1278493	PPP2R34	chr3:135814009	G/A	0.436	0.0389	0.0068	8.77×10^{-9}	0.0034	0.0021	0.105
XXYLT7 Chr3:194800853 T/C 0.226 0.0445 0.0079 1.72×10 ⁻⁸ PITX2 Chr4:111699685 T/A 0.199 0.3655 0.0081 7.32×10 ⁻⁴⁴³ CAMM2D Chr4:114448656 G/A 0.262 0.0556 0.0076 1.92×10 ⁻¹³ ARHGAP10 Chr4:148937537 G/C 0.061 0.091 0.0134 1.32×10 ⁻¹¹	rs7612445	GNB4	chr3:179172979	9/1	0.188	0.0493	0.0084	4.81×10^{-9}	0.0023	0.0026	0.372
PITX2 CAMM2D Chr4:11699685 T/A 0.199 0.3655 0.0081 7.32×10 ⁻⁴⁴³ ARHGAP10 Chr4:11448656 G/A 0.262 0.0556 0.0076 1.92×10 ⁻¹³ Chr4:148937537 G/C 0.061 0.091 0.0134 1.32×10 ⁻¹¹	rs60902112	XXXLT1	chr3:194800853	1/C	0.226	0.0445	0.0079	1.72×10^{-8}	0.0001	0.0025	0.967
	rs67249485	PITX2	chr4:111699685	T/A	0.199	0.3655	0.0081	7.32×10^{-443}	0.0029	0.0025	0.250
ARHGAP10 chr4:148937537 G/C 0.061 0.091 0.0134 1.32×10 ⁻¹¹	rs6829664	CAMK2D	chr4:114448656	G/A	0.262	0.0556	0.0076	1.92×10^{-13}	-0.0030	0.0025	0.217
	rs10213171	ARHGAP10	chr4:148937537	g/C	0.061	0.091	0.0134	1.32×10^{-11}	-0.0021	0.0041	0.605

Table 2. Continued

					Effect on Atrial Fibrillation	iai ribiliatiori		Effect on AD		
SNP	Prioritized Genes	Position (hg19)	EA/0A	EAF	Beta	SE	P Value	Beta	SE	P Value
rs6596717	L0C102467213	chr5:106427609	C/A	0.395	0.0404	0.0068	3.00×10^{-9}	-0.0011	0.0022	0.617
rs337705	KCNN2	chr5:113737062	G/T	0.375	0.0564	0.0068	1.63×10^{-16}	0.0012	0.0021	0.592
rs2012809	SLC2746	chr5:128190363	G/A	0.790	0.0582	0.0094	4.92×10^{-10}	0.0029	0.0028	0.290
rs2040862	WNT8A,NPY6R,MY0T,FAM13B	chr5:137419989	1/C	0.178	0.1084	0.0087	1.08×10 ⁻³⁵	0.0023	0.0028	0.420
rs6580277	NR3C1	chr5:142818123	G/A	0.237	0.067	0.0079	1.64×10^{-17}	0.0019	0.0025	0.456
rs12188351	SL/T3	chr5:168386089	A/G	0.056	0.0865	0.0145	2.52×10^{-9}	-0.0012	0.0048	0.807
rs6891790	NKX2-5	chr5:172670745	G/T	0.717	0.0729	0.0076	4.53×10^{-22}	-0.0025	0.0023	0.278
rs73366713	ATXW1	chr6:16415751	G/A	0.860	0.1035	0.0099	1.53×10^{-25}	0.0012	0.0031	0.700
rs34969716	KDM1B,DEK	chr6:18210109	A/G	0.305	0.0702	0.0078	1.60×10^{-19}	-0.0015	0.0058	0.791
rs3176326	CDKN1A,PANDAR,P116	chr6:36647289	G/A	0.802	0.0626	0.0085	1.42×10^{-13}	0.0001	0.0026	0.958
rs2031522	CGA	chr6:87821501	A/G	0.624	0.0436	0.0068	1.47×10^{-10}	-0.0009	0.0022	0.677
rs3951016	SLC35F1,PLN	chr6:118559658	ΑΤ	0.459	0.0648	0.0067	2.15×10^{-22}	-0.0021	0.0021	0.328
rs13195459	HSF2	chr6:122403559	G/A	0.638	0.0623	0.007	4.15×10^{-19}	-0.0018	0.0022	0.402
rs117984853	UST	chr6:149399100	1/6	0.101	0.1228	0.012	1.34×10^{-24}	-0.0036	0.0039	0.357
rs55734480	DGKB	chr7:14372009	A/G	0.249	0.0548	0.0078	2.20×10^{-12}	-0.0034	0.0024	0.155
rs6462079	CREB5	chr7:28415827	A/G	0.721	0.0466	0.0076	8.79×10^{-10}	0.0065	0.0025	0.009
rs11773845	CAV1, CAV2	chr7:116191301	A/C	0.586	0.1054	0.0067	2.39×10^{-55}	-0.0022	0.0021	0.295
rs55985730	OPN1SW,CALU	chr7:128417044	G/T	090.0	0.0867	0.0149	5.24×10^{-9}	0.0006	0.0049	0.907
rs35620480	GATA4	chr8:11499908	C/A	0.157	0.054	0.0092	5.15×10 ⁻⁹	0.0046	0.0029	0.107
rs7508	ASAH1	chr8:17913970	A/G	0.711	0.0711	0.0075	1.69×10^{-21}	-0.0025	0.0024	0.292
rs7834729	XP07	chr8:21821778	G/T	0.885	0.0653	0.0104	3.55×10^{-10}	0.0047	0.0031	0.131
rs62521286	FBX032	chr8:124551975	G/A	990.0	0.1202	0.0135	4.50×10^{-19}	-0.0004	0.0045	0.936
rs6994744	PTK2	chr8:141740868	C/A	0.495	0.0405	9900:0	1.10×10^{-9}	-0.0026	0.0021	0.212
rs10821415	C9ort3	chr9:97713459	A/C	0.413	0.0821	0.0067	2.92×10^{-34}	-0.0012	0.0021	0.574
rs2274115	ТНЖЗ	chr9:139094773	G/A	0.700	0.0487	0.0076	1.69×10^{-10}	0.0047	0.0023	0.042
rs7096385	SIRT1, MYPN	chr10:69664881	1/C	0.092	0.0707	0.013	4.87×10^{-8}	900000—	0.0039	0.868
rs10458660	C10orf11	chr10:77936576	G/A	0.173	0.0537	0.0087	6.78×10^{-10}	0.0002	0.0028	0.932
rs11598047	NEURL 1	chr10:105342672	G/A	0.162	0.1537	600.0	8.95×10^{-66}	-0.0018	0.0028	0.514
rs10749053	RBM20	chr10:112576695	1/C	0.158	0.0555	0.0097	1.05×10^{-8}	-0.0065	0.0029	0.027
rs10741807	NAV2	chr11:20011445	1/C	0.245	0.0729	0.0079	1.59×10^{-20}	-0.0075	0.0025	0.003
rs4935786	SORL1	chr11:121661507	T/A	0.267	0.0463	0.0079	4.85×10^{-9}	-0.0035	0.0058	0.551

Table 2. Continued

SNP Prioritized Genes rs76097649 KCNU5 rs4963776 LINC20477 rs17380837 SSPN rs12860482 NACA rs71454237 LRRC10 rs12426679 PHLD41 rs83079 TBX5 rs6560886 FBRSL1 rs6560886 FBRSL1 rs5569628 CUL44 rs35569628 CUL4A rs73241997 CRL2 rs738413 SYNEZ, MIR548AZ, ESRZ, MTHFD rs74884082 DPF3 rs10873298 IRF2BPL		chr12:24764570 chr12:24779491 chr12:26345526 chr12:32978437 chr12:57105938 chr12:70013415 chr12:76237987 chr12:14793240 chr12:133150210 chr12:133150210	EA/OA A/G G/T C/T C/T A/C G/A C/T C/T C/T C/T C/T C/T C/T C	0.093 0.818 0.693 0.144 0.274 0.791 0.707 0.707 0.788	0.0913 0.0913 0.0501 0.054 0.062 0.0391 0.0981 0.0575 0.051	0.0124 0.0088 0.0088 0.0094 0.0076 0.0084 0.0067	P Value 1.26×10^{-20} 1.84×10^{-25} 4.80×10^{-12} 2.89×10^{-14} 1.21×10^{-12} 1.78×10^{-13}	0.0038 -0.0016	SE 0.0038 0.0028	P Value 0.321
		chr11:128764570 chr12:24779491 chr12:2634526 chr12:32978437 chr12:70013415 chr12:70013415 chr12:714793240 chr12:123327900 chr12:133150210 chr13:1333527902	6/T 6/T 6/T 6/T 6/A 6/A 6/A 7/C C/T 7/C C/A	0.093 0.818 0.693 0.144 0.274 0.791 0.707 0.138	0.0151 0.0913 0.0501 0.0718 0.062 0.082 0.0391 0.0981 0.0575	0.0028 0.0088 0.0072 0.0094 0.0076 0.0084 0.0067	1.26×10 ⁻²⁰ 1.84×10 ⁻²⁵ 4.80×10 ⁻¹² 2.89×10 ⁻¹⁴ 1.21×10 ⁻¹² 1.78×10 ⁻¹³	0.0038	0.0038	0.321
		chr12:24779491 chr12:26345526 chr12:32978437 chr12:57105938 chr12:76237987 chr12:114793240 chr12:123327900 chr12:133150210 chr13:13372712	G/T C/T C/T A/C G/A C/T T/C C/A C/A	0.818 0.693 0.144 0.274 0.791 0.472 0.707 0.708	0.0913 0.0501 0.0718 0.054 0.0391 0.0391 0.0575 0.0575	0.0088 0.0072 0.0094 0.0076 0.0084 0.0067	1.84×10 ⁻²⁵ 4.80×10 ⁻¹² 2.89×10 ⁻¹⁴ 1.21×10 ⁻¹² 1.71×10 ⁻¹³	-0.0016	0.0028	
		chr12:2634556 chr12:32978437 chr12:57105938 chr12:70013415 chr12:76237987 chr12:114793240 chr12:123327900 chr12:133150210 chr13:13386943	C/T C/T A/C G/A C/T T/C C/A C/T	0.693 0.144 0.274 0.791 0.472 0.707 0.138	0.0501 0.0718 0.054 0.062 0.0391 0.0981 0.0575	0.0072 0.0094 0.0076 0.0084 0.0067	4.80×10 ⁻¹² 2.89×10 ⁻¹⁴ 1.21×10 ⁻¹² 4.80×10 ⁻¹⁴ 1.21×10 ⁻¹²			0.567
		chr12:32978437 chr12:57105938 chr12:70013415 chr12:76237987 chr12:123327900 chr12:133150210 chr12:133150210 chr13:23368943	C/T A/C G/A C/T T/C C/A C/A	0.144 0.274 0.791 0.472 0.707 0.138	0.054 0.062 0.0391 0.0981 0.0575 0.0549	0.0094 0.0076 0.0084 0.0067 0.0074	2.89×10 ⁻¹⁴ 1.21×10 ⁻¹² 1.78×10 ⁻¹³	-0.0002	0.0023	0.927
		chr12:57105938 chr12:70013415 chr12:76237987 chr12:114793240 chr12:123327900 chr12:133150210 chr13:13368943	6/A 6/A C/T T/C C/A C/T	0.274 0.791 0.472 0.707 0.138	0.054 0.062 0.0391 0.0981 0.0575 0.0549	0.0076 0.0084 0.0067 0.0074	1.21×10 ⁻¹²	0.0012	0.0029	0.667
		chr12:70013415 chr12:76237987 chr12:114793240 chr12:123327900 chr12:133150210 chr13:23368943	G/A C/T T/C C/A C/T	0.791 0.472 0.707 0.138 0.788	0.062 0.0391 0.0981 0.0575 0.051	0.0084	1 79 ~ 10-13	0.0005	0.0024	0.835
		shr12:76237987 shr12:114793240 shr12:123327900 shr12:133150210 shr13:23368943	C/T 1/C C/A C/T	0.472 0.707 0.138 0.788	0.0391 0.0981 0.0575 0.051	0.0067	01.707.1	0.0028	0.0026	0.293
		shr12:114793240 shr12:123327900 shr12:133150210 shr13:23368943	T/C C/A C/T	0.707	0.0981 0.0575 0.051	0.0074	4.95×10 ⁻⁹	0.0017	0.0021	0.416
		chr12:123327900 chr12:133150210 chr13:23368943 chr13:113872712	C/A	0.138	0.0575		2.84×10^{-40}	9000:0-	0.0023	0.782
		chr12:133150210 chr13:23368943 chr13:113872712	C/T	0.788	0.051	0.0103	2.54×10^{-8}	-0.0099	0.0031	0.002
		chr13:23368943		730.0	0.0449	600.0	1.49×10 ⁻⁸	-0.0060	6900.0	0.383
		shr13:113872712	1/C	0.20/		0.0075	2.72×10^{-9}	0.0002	0.0024	0.937
			1/C	0.777	0.0452	0.008	1.38×10^{-8}	0.0039	0.0025	0.117
		chr14:35173775	T/C	0.142	0.0733	0.0093	2.94×10^{-15}	0.0018	0.0029	0.540
	1	chr14:64679960	A/G	0.495	0.0778	0.0067	2.55×10^{-31}	0.0003	0.0021	0.895
		chr14:73249419	C/T	0.750	0.0493	0.0078	3.48×10^{-10}	0.0012	0.0025	0.632
	0	chr14:77426525	C/T	0.366	0.0401	0.0069	7.07×10^{-9}	0.0004	0.0021	0.868
rs147301839 <i>GCOM1/MYZAP</i>		chr15:57924714	C/A	0.007	0.3328	0.0523	1.93×10^{-10}	0.0100	0.0173	0.565
rs7170477 <i>HERC1</i>		chr15:64103777	A/G	0.304	0.0393	0.0072	4.98×10^{-8}	0.0037	0.0023	0.108
rs74022964 HCN4	0	chr15:73677264	1/C	0.157	0.1132	600.0	3.51×10^{-36}	0.0008	0.0029	0.786
rs12908004 <i>ARNT2</i>	0	chr15:80676925	G/A	0.164	0.0732	600.0	4.12×10^{-16}	0.0007	0.0028	0.795
rs4965430 <i>IGF1R</i>	0	chr15:99268850	C/G	0.386	0.0441	0.0069	1.26×10^{-10}	0.0019	0.0022	0.370
rs140185678 <i>RPL3L</i>	0	chr16:2003016	A/G	0.035	0.1659	0.0218	2.43×10^{-14}	-0.0113	0.0068	0.097
rs2359171 <i>ZFHX3</i>)	chr16:73053022	A/T	0.176	0.1746	0.0086	$ 4.65\times10^{-91}$	0.0045	0.0028	0.101
rs7225165 <i>YWHAE, CRK, MYO1C</i>	0	chr17:1309850	G/A	0.887	0.0655	0.0111	$3.20{\times}10^{-9}$	0.0020	0.0033	0.547
rs72811294 <i>MYOCD</i>	0	chr17:12618680	C/C	0.887	0.072	0.0106	9.67×10^{-12}	-0.0010	0.0033	0.772
rs11658278 <i>ZPBP2, GSDMB, ORMDL3</i>		chr17:38031164	1/C	0.479	0.0443	0.0067	3.47×10^{-11}	-0.0036	0.0021	0.089
rs1563304 <i>WWT3</i>	0	chr17:44874453	1/C	0.178	0.0644	0.0092	2.56×10^{-12}	0.0001	0.0029	0.979
rs8088085 <i>MEX3C</i>		chr18:48708548	A/C	0.535	0.0365	0.0067	4.79×10^{-8}	0.0012	0.0021	0.584
rs2834618 <i>LINC01426</i>		chr21:36119111	1/6	0.894	0.0944	0.0112	3.41×10^{-17}	-0.0024	0.0034	0.469
rs464901 <i>TUBA8</i>		chr22:18597502	1/C	0.665	0.0508	0.0072	1.53×10^{-12}	-0.0007	0.0022	0.761
rs133902 <i>MYO18B</i>	0	chr22:26164079	1/C	0.427	0.0419	0.0068	9.14×10^{-10}	0.0028	0.0021	0.194

AD indicates Alzheimer disease; EA, effect allele; EAF, effect allele frequency; OA, other allele; SE, standard error; SNP, single nucleotide polymorphism.

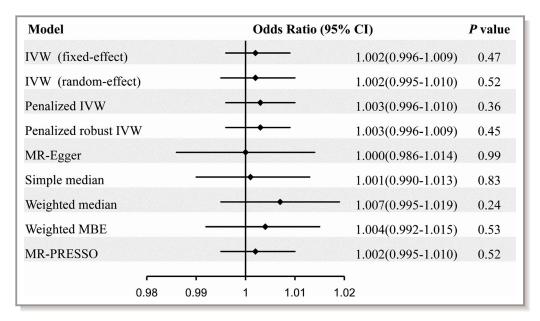


Figure 2. Risk of Alzheimer disease for genetically predicted atrial fibrillation. IVW indicates inverse-variance weighted; MBE, mode-based estimate; MR, Mendelian randomization; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier.

The weighted MBE method used the mode of the IVW empirical density function as the weighted MBEs and obtained a causal effect estimate robust to horizontal pleiotropy. ¹⁵ The

MR-PRESSO approach was used to detect and correct for horizontal pleiotropic outliers through outlier removal in multi-instrument summary-level MR testing. ¹⁶ These methods had

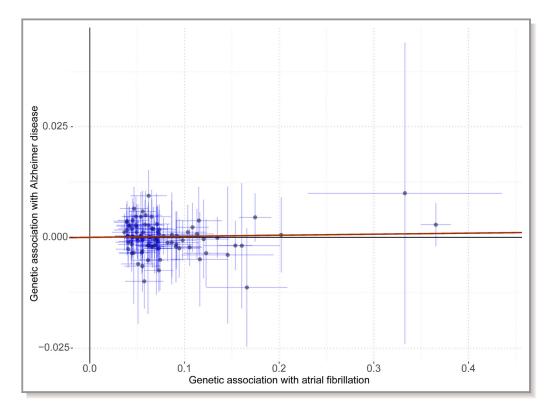


Figure 3. Associations of atrial fibrillation—related variants with risk of Alzheimer disease. The red line indicates the estimate of effect using inverse-variance weighted method. Circles indicate marginal genetic associations with atrial fibrillation and risk of Alzheimer disease for each variant. Error bars indicate 95% Cls.

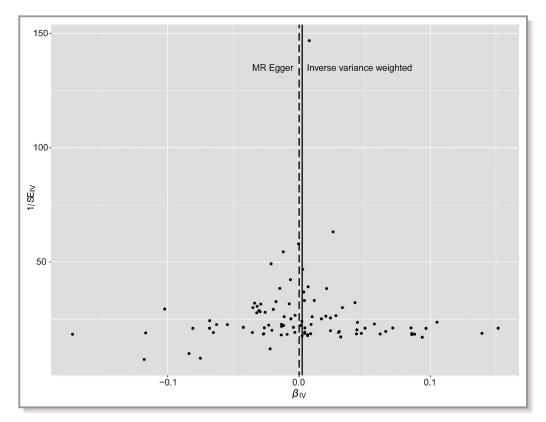


Figure 4. Funnel plot of the Mendelian randomization analysis for Alzheimer disease. Funnel plot evaluated the presence of possible heterogeneity across the estimates, which indicates the potential pleiotropic effects. The figure presents the observed causal effect of each of the 93 instrumental variables (IVs) by dots, and the averaged causal effect of all IVs combined (β_{IV}) using inverse variance weighted (solid line) and MR-Egger (dashed line) method on *x*-axis. *Y* axis presents the inverse standard error of the estimated causal effect for each of the single nucleotide polymorphisms (IVs).

been demonstrated to be more robust to the inclusion of pleiotropic and/or invalid instruments and provide a consistent estimate of the causal effect. The second-order weights were used in the weighted MBE method and first-order weights were used for all other methods. Heterogeneity between SNPs in the IVW analysis was estimated by Q statistic and I² index. 14 Potential pleiotropic effects were estimated by intercepts of the MR-Egger regression. 13 An I $_{\rm GX}^2$ statistic was calculated to test the presence of bias with MR-Egger because of measurement error; I $_{\rm GX}^2$ statistic >0.90 was considered no obvious violation of "NO Measurement Error" assumption and sufficient for instruments in the MR-Egger analyses. 17 We also performed a leave-1-out analysis in which 1 SNP was excluded in turn to estimate the influence of outlying and/or pleiotropic SNPs. 18

The associations between genetically predicted AF and Alzheimer disease were presented as odds ratios (ORs) with their 95% CIs per 1-unit-higher log-odds of AF. The association of each genetic variant with AF was further plotted against its effect for the risk of Alzheimer disease.

A power analysis using a web-based application (http://cnsgenomics.com/shiny/mRnd/) was conducted to estimate

the minimum detectable magnitude of association in terms of OR per log odds of AF. Based on the sample size of 1 030 836, our MR analysis has 80% power at an alpha rate of 5% to detect an OR of 1.055 per log odds of AF.

An observed 2-sided P<0.05 was considered as significant evidence for a causal association. All analyses were conducted with R 3.5.3 (R Development Core Team).

Results

The MR analysis showed nonsignificant association of genetically predicted AF with risk of Alzheimer disease using 93 SNPs as the instruments (Figure 2). The fixed-effect and random-effect IVW methods showed that genetically predicted AF was not associated with the risk of Alzheimer disease (OR=1.002, 95% CI: 0.996–1.009, P=0.47; OR=1.002, 95% CI: 0.995–1.010, P=0.52). Similar results were observed using the penalized IVW, penalized robust IVW, MR-Egger, simple median, weighted median, weighted MBE, and MR-PRESSO methods. Association between each variant with AF and risk of Alzheimer disease are displayed in Figure 3.

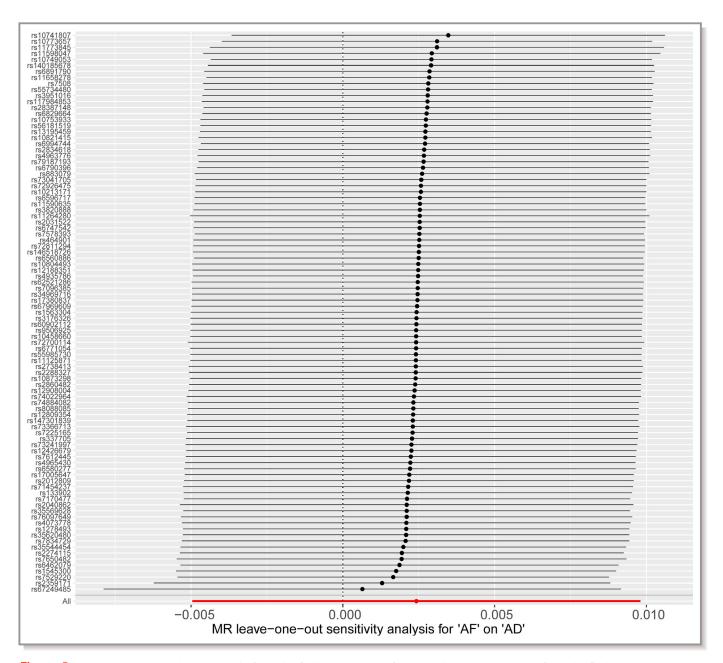


Figure 5. MR leave-1-out sensitivity analysis for atrial fibrillation on AD. Circles indicate MR estimates for atrial fibrillation on Alzheimer disease using inverse-variance weighted fixed-effect method if the SNP was omitted. The bars indicate the CI of MR estimates. AD indicates Alzheimer disease; AF, atrial fibrillation; MR, Mendelian randomization.

There was no evidence of heterogeneity in the IVW analysis (Q=113.60, P=0.055; I²=19%). MR-Egger regression showed no evidence of directional pleiotropy for the association of the included SNPs with risk of Alzheimer disease (intercept=0.0002, 95% CI: -0.001 to 0.001, P=0.70). There was a low risk of bias with MR-Egger because of measurement error (I²_{GX} statistic=96.6%). Funnel plot also showed no evidence of obvious heterogeneity across the estimates, indicating absence of the potential pleiotropic effects (Figure 4). The results of leave-1-out sensitivity analysis showed that the negative association between AF and Alzheimer

disease was not substantially driven by any individual SNP (Figure 5).

Discussion

Using 2-sample MR analysis based on data from large-scale GWAS studies, our study demonstrated that genetically predicted AF had no causal effect on the risk of Alzheimer disease. The findings were robust in sensitivity analyses with different instruments and statistical models.

AF and dementia are frequent diseases that predominantly affect elderly people. There were several assumed mechanisms that contribute to AF-related cognitive decline and dementia, including occurrence of AF-related (clinically overt or silent) strokes, systemic inflammation, and chronic hypoperfusion of the brain.^{3,19} Strong evidences from many prospective studies have been established that AF was associated with cognitive impairment, cognitive decline, and dementia. 3,6,19-23 However, most studies included all-cause dementia without separate investigation of vascular dementia and Alzheimer disease. 19-23 In the past decades, accumulating observational evidence has demonstrated that AF was also associated with degenerative dementias such as Alzheimer disease. 3,6,24 In the prospective Intermountain Heart Collaborative Study with 37 025 patients and 5-year follow-up, AF was independently associated with all forms of dementia, including Alzheimer disease.²⁴ In the Korea National Health Insurance Service-Senior cohort with 262 611 participants, incident AF was associated with an increased risk of both Alzheimer and vascular dementia.6 Longitudinal association was observed between prevalent AF and all-cause dementia, but the association was nonsignificant between either incident or prevalent AF and Alzheimer disease in the Rotterdam Study.²⁵ However, these studies still cannot control the influence of unmeasured confounders because of the nature of observational study. The present study provides evidence supporting a negative causal effect of genetically predicted AF on risk of Alzheimer disease using an MR approach, and this method may control unmeasured confounders and reverse causation.²⁶

Our findings demonstrated that the causal role of AF on Alzheimer disease could be different from that on vascular dementia. The lack of causal association of AF with the risk of Alzheimer disease in our study suggests that the association of AF with Alzheimer disease risk observed in observational cohort studies may be confounded by other risk factors rather than indicate a causal relationship. It was perhaps unsurprising because dementia and AF share numerous common vascular risk factors, such as hypertension, heart failure, diabetes mellitus, lipid disorders, age, obesity, and physical inactivity. 3,27,28 The co-occurrence of AF and Alzheimer disease might be explained by the existence of these common factors. Another potential explanation was that AF probably increased the risk of Alzheimer disease only when AF started in middle age and with a longer duration of AF as neuropathology of underlying dementia gradually developed over many years.3 There was only indirect evidence in observational studies that anticoagulation in AF was associated with a preventive effect on cognitive impairment and dementia development. 4,6 However, these studies did not separately analyze the dementia subtypes and may be confounded by other treatments (ie, patients with anticoagulation may also have a high compliance with treatment targeting other risk factors, such as hypertension, heart failure, diabetes mellitus, and lipid disorders).

The strength of the study is the design of MR analysis based on AF-related SNPs and effects of SNP-Alzheimer disease from large-scale GWAS studies. Using the 2-sample MR approach, we were able to investigate the effect of AF based on data with large sample sizes (60 620 AF cases and 970 216 controls; 71 880 Alzheimer disease cases and 383 378 controls). Compared with traditional observational study, MR analysis is less prone to potential unmeasured confounding and also to avoid reverse causation since genetic variation is allocated at conception, and thus can strengthen the evidence for causal inference. ¹¹

Our study has several limitations. First, it is difficult to completely avoid the influence of potential horizontal pleiotropy (a genetic variant affects the outcome via a different biological pathway from the exposure), which may lead to biased causal effect estimates. 13 However, pleiotropic effect was not observed in MR-Egger regression or heterogeneity test, and similar results were observed in sensitivity analyses using several other robust models. Second, the findings were limited since data of associations of SNP-exposure and SNPoutcome were derived from 2 different populations. Third, estimates of SNP-AF association were derived from transancestry studies, which may cause bias because of population admixture. The same genetic variant could exhibit different pleiotropic effects in different populations. However, we note that this might have subtle influences on the effect estimates because the majority of individuals were of European ancestry and merging studies showed the genetic architecture for common diseases was likely similar across ethnic groups.²⁹ Fourth, measurement error may exist as Alzheimer disease-byproxy was used in UK Biobank in phase 2 of GWAS of Alzheimer disease. This measurement error would likely bias results towards the null. However, a strong genetic correlation (0.81) between Alzheimer disease status and Alzheimer disease-byproxy, and substantial concordance in the individual SNP effects were observed in the original study. ⁹ Finally, there were some overlapping samples between the AF and Alzheimer disease GWAS data set (38.4% in the AF GWAS data set and 82.6% in the Alzheimer disease GWAS data set), which could inflate MR estimates.³⁰ However, this would only affect the study by producing a false positive result and our study observed only negative results.

Conclusions

Our 2-sample MR analysis did not provide convincing evidence to support a causal effect of AF on risk of Alzheimer disease.

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Disclosures

None.

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