ORIGINAL RESEARCH

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

Dementia is a major cause of disability in elderly people without available curative treatment.[1] Worldwide, there were ≈50 million people living with dementia in 2018, and this number is expected to increase because of population growth and aging.[2] 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.[3]

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the elderly population. AF was 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 dementia[5]; 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.[7] 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.[7] In this study, we aimed to use MR analysis to evaluate the causal association of AF with Alzheimer disease using MR analysis.

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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.[7] 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).[8,9] 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 ($P<5.0\times10^{-8}$). These locus index variants explained 4.6% of the variation in AF (*F* statistic=534, indicating sufficient strength of the instruments).[8] All these 111 SNPs were in different genomic regions and not in linkage disequilibrium ($r^2<0.10$).[8] 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 ($P<5.0\times10^{-8}$) 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, rs12604076, 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.[9] 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

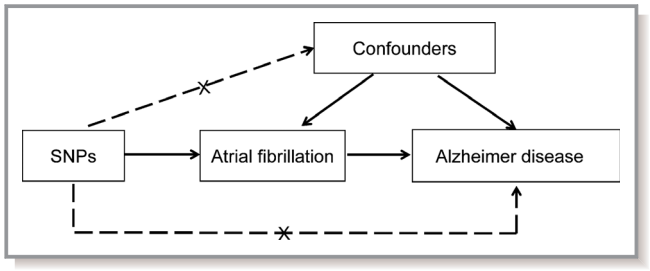

Figure 1. Conceptual framework for the Mendelian randomization analysis of atrial fibrillation and risk of Alzheimer disease. The design is under the assumption that the genetic variants are associated with atrial fibrillation, but not with confounders, and the genetic variants are not associated with 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	*ICD-10* code I48 or *ICD-9* code 427.3
deCODE	13 471/358 161	European	*ICD-10* code I48 or *ICD-9* code 427.3
Michigan Genomics Initiative	1226/11 049	European	*ICD-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 *ICD-10* I48
UK Biobank	14 820/380 919	European	*ICD-9* 427.3 or *ICD-10* I48
AFGen Consortium	15 979/102 776	European	Diagnosed according to *ICD-9*, *ICD-10*, or 12-lead ECG at the examinations
	641/5234	Black	
	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 with NINCDS-ADRDA criteria, DSM-IV criteria, the ADDTC's State of California criteria or DSM-III-R criteria
Alzheimer's Disease Sequencing Project [ADSP]	4114/3392	European	
UK Biobank	47 793/328 320	European	Self-report questionnaire administered during the in-person assessment and confirmed with *ICD-10* 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 inverse-variance 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]

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

SNP	Prioritized Genes	Position (hg19)	EA/OA	EAF	Effect on Atrial Fibrillation			Effect on AD		
					Beta	SE	*P* Value	Beta	SE	*P* Value
rs7529220	*HSPG2*	chr1:22282619	C/T	0.847	0.0621	0.0098	1.98×10^{-10}	0.0094	0.0029	0.001
rs11590635	*AGBL4*	chr1:49309764	A/G	0.024	0.1456	0.0248	4.12×10^{-9}	−0.0040	0.0079	0.616
rs146518726	*MIR6500*	chr1:51535039	A/G	0.033	0.1605	0.0207	8.27×10^{-15}	−0.0019	0.0072	0.795
rs1545300	*KCND3*	chr1:112464004	C/T	0.691	0.0558	0.0073	1.48×10^{-14}	0.0059	0.0024	0.013
rs4073778	*CASQ2*	chr1:116297758	A/C	0.564	0.0486	0.0067	4.96×10^{-13}	0.0028	0.0021	0.189
rs79187193	*GJA5*	chr1:147255831	G/A	0.943	0.1162	0.0153	3.15×10^{-14}	−0.0049	0.0054	0.363
rs11264280	*KCNN3*	chr1:154862952	T/C	0.333	0.1347	0.0071	3.07×10^{-79}	0.0000	0.0023	0.983
rs72700114	*LINC01142*	chr1:170193825	C/G	0.076	0.2021	0.013	3.29×10^{-54}	0.0006	0.0043	0.896
rs10753933	*PPFIA4*	chr1:203026214	T/G	0.448	0.0609	0.0067	9.84×10^{-20}	−0.0019	0.0021	0.381
rs7578393	*KIF3C*	chr2:26165528	T/C	0.796	0.0614	0.0088	2.42×10^{-12}	−0.0051	0.0062	0.405
rs11125871	*USP34*	chr2:61470126	C/T	0.605	0.0394	0.0068	6.42×10^{-9}	0.0003	0.0022	0.906
rs6747542	*GMCL1,ANXA4*	chr2:70106832	T/C	0.536	0.0554	0.0067	1.10×10^{-16}	−0.0006	0.0021	0.768
rs72926475	*REEP1*	chr2:86594487	G/A	0.877	0.0683	0.0102	2.37×10^{-11}	−0.0018	0.0032	0.575
rs28387148	*GYPC*	chr2:127433465	T/C	0.105	0.0741	0.0113	6.25×10^{-11}	−0.0051	0.0035	0.152
rs67969609	*TEX41*	chr2:145760353	G/C	0.071	0.0711	0.0126	1.71×10^{-8}	−0.0002	0.0037	0.951
rs56181519	*WIPF1*	chr2:175555714	C/T	0.732	0.0662	0.0077	6.46×10^{-18}	−0.0021	0.0024	0.371
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
rs3820888	*SPATS2L*	chr2:201180023	C/T	0.392	0.0684	0.0068	5.75×10^{-24}	−0.0005	0.0022	0.813
rs35544454	*ERBB4*	chr2:213266003	A/T	0.808	0.0589	0.0087	1.10×10^{-11}	0.0050	0.0028	0.071
rs7650482	*CAND2*	chr3:12841804	G/A	0.640	0.0711	0.007	1.79×10^{-24}	0.0030	0.0022	0.169
rs73041705	*THRB*	chr3:24463235	T/C	0.702	0.0443	0.0073	1.55×10^{-9}	−0.0016	0.0023	0.496
rs6790396	*SCN10A,SCN5A*	chr3:38771925	G/C	0.596	0.0627	0.0068	2.40×10^{-20}	−0.0012	0.0021	0.567
rs17005647	*FRMD4B*	chr3:69406181	T/C	0.364	0.0413	0.0069	2.70×10^{-9}	0.0026	0.0022	0.252
rs6771054	*EPHA3*	chr3:89489529	T/C	0.596	0.0457	0.0068	2.42×10^{-11}	0.0002	0.0022	0.925
rs10804493	*PHLDB2,PLCXD2*	chr3:111554426	A/G	0.651	0.0558	0.007	1.63×10^{-15}	−0.0003	0.0022	0.877
rs1278493	*PPP2R3A*	chr3:135814009	G/A	0.436	0.0389	0.0068	8.77×10^{-9}	0.0034	0.0021	0.105
rs7612445	*GNB4*	chr3:179172979	T/G	0.188	0.0493	0.0084	4.81×10^{-9}	0.0023	0.0026	0.372
rs60902112	*XXYLT1*	chr3:194800853	T/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
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

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Table 2. Continued

SNP	Prioritized Genes	Position (hg19)	EA/OA	EAF	Effect on Atrial Fibrillation			Effect on AD		
					Beta	SE	*P* Value	Beta	SE	*P* Value
rs6596717	*LOC102467213*	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	*SLC27A6*	chr5:128190363	G/A	0.790	0.0582	0.0094	4.92×10^{-10}	0.0029	0.0028	0.290
rs2040862	*WNT8A,NPY6R,MYOT,FAM13B*	chr5:137419989	T/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	*SLIT3*	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	*ATXN1*	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,PI16*	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	A/T	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	T/G	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	0.060	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	*XPO7*	chr8:21821778	G/T	0.885	0.0653	0.0104	3.55×10^{-10}	0.0047	0.0031	0.131
rs62521286	*FBXO32*	chr8:124551975	G/A	0.066	0.1202	0.0135	4.50×10^{-19}	−0.0004	0.0045	0.936
rs6994744	*PTK2*	chr8:141740868	C/A	0.495	0.0405	0.0066	1.10×10^{-9}	−0.0026	0.0021	0.212
rs10821415	*C9orf3*	chr9:97713459	A/C	0.413	0.0821	0.0067	2.92×10^{-34}	−0.0012	0.0021	0.574
rs2274115	*LHX3*	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	T/C	0.092	0.0707	0.013	4.87×10^{-8}	−0.0006	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	*NEURL1*	chr10:105342672	G/A	0.162	0.1537	0.009	8.95×10^{-66}	−0.0018	0.0028	0.514
rs10749053	*RBM20*	chr10:112576695	T/C	0.158	0.0555	0.0097	1.05×10^{-8}	−0.0065	0.0029	0.027
rs10741807	*NAV2*	chr11:20011445	T/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

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Table 2. Continued

SNP	Prioritized Genes	Position (hg19)	EA/OA	EAF	Effect on Atrial Fibrillation			Effect on AD		
					Beta	SE	*P* Value	Beta	SE	*P* Value
rs76097649	*KCNJ5*	chr11:128764570	A/G	0.093	0.1151	0.0124	1.26×10^{-20}	0.0038	0.0038	0.321
rs4963776	*LINC00477*	chr12:24779491	G/T	0.818	0.0913	0.0088	1.84×10^{-25}	−0.0016	0.0028	0.567
rs17380837	*SSPN*	chr12:26345526	C/T	0.693	0.0501	0.0072	4.80×10^{-12}	−0.0002	0.0023	0.927
rs12809354	*PKP2*	chr12:32978437	C/T	0.144	0.0718	0.0094	2.89×10^{-14}	0.0012	0.0029	0.667
rs2860482	*NACA*	chr12:57105938	A/C	0.274	0.054	0.0076	1.21×10^{-12}	0.0005	0.0024	0.835
rs71454237	*LRRC10*	chr12:70013415	G/A	0.791	0.062	0.0084	1.78×10^{-13}	0.0028	0.0026	0.293
rs12426679	*PHLDA1*	chr12:76237987	C/T	0.472	0.0391	0.0067	4.95×10^{-9}	0.0017	0.0021	0.416
rs883079	*TBX5*	chr12:114793240	T/C	0.707	0.0981	0.0074	2.84×10^{-40}	−0.0006	0.0023	0.782
rs10773657	*HIP1R*	chr12:123327900	C/A	0.138	0.0575	0.0103	2.54×10^{-8}	−0.0099	0.0031	0.002
rs6560886	*FBRSL1*	chr12:133150210	C/T	0.788	0.051	0.009	1.49×10^{-8}	−0.0060	0.0069	0.383
rs9506925	*LINC00540,LINC00621,SGCG*	chr13:23368943	T/C	0.267	0.0449	0.0075	2.72×10^{-9}	0.0002	0.0024	0.937
rs35569628	*CUL4A*	chr13:113872712	T/C	0.777	0.0452	0.008	1.38×10^{-8}	0.0039	0.0025	0.117
rs73241997	*CFL2*	chr14:35173775	T/C	0.142	0.0733	0.0093	2.94×10^{-15}	0.0018	0.0029	0.540
rs2738413	*SYNE2,MIR548AZ,ESR2,MTHFD1*	chr14:64679960	A/G	0.495	0.0778	0.0067	2.55×10^{-31}	0.0003	0.0021	0.895
rs74884082	*DPF3*	chr14:73249419	C/T	0.750	0.0493	0.0078	3.48×10^{-10}	0.0012	0.0025	0.632
rs10873298	*IRF2BPL*	chr14:77426525	C/T	0.366	0.0401	0.0069	7.07×10^{-9}	0.0004	0.0021	0.868
rs147301839	*GCOM1/MYZAP*	chr15:57924714	C/A	0.007	0.3328	0.0523	1.93×10^{-10}	0.0100	0.0173	0.565
rs7170477	*HERC1*	chr15:64103777	A/G	0.304	0.0393	0.0072	4.98×10^{-8}	0.0037	0.0023	0.108
rs74022964	*HCN4*	chr15:73677264	T/C	0.157	0.1132	0.009	3.51×10^{-36}	0.0008	0.0029	0.786
rs12908004	*ARNT2*	chr15:80676925	G/A	0.164	0.0732	0.009	4.12×10^{-16}	0.0007	0.0028	0.795
rs4965430	*IGF1R*	chr15:99268850	C/G	0.386	0.0441	0.0069	1.26×10^{-10}	0.0019	0.0022	0.370
rs140185678	*RPL3L*	chr16:2003016	A/G	0.035	0.1659	0.0218	2.43×10^{-14}	−0.0113	0.0068	0.097
rs2359171	*ZFHX3*	chr16:73053022	A/T	0.176	0.1746	0.0086	4.65×10^{-91}	0.0045	0.0028	0.101
rs7225165	*YWHAE,CRK,MYO1C*	chr17:1309850	G/A	0.887	0.0655	0.0111	3.20×10^{-9}	0.0020	0.0033	0.547
rs72811294	*MYOCD*	chr17:12618680	G/C	0.887	0.072	0.0106	9.67×10^{-12}	−0.0010	0.0033	0.772
rs11658278	*ZPBP2,GSDMB,ORMDL3*	chr17:38031164	T/C	0.479	0.0443	0.0067	3.47×10^{-11}	−0.0036	0.0021	0.089
rs1563304	*WNT3*	chr17:44874453	T/C	0.178	0.0644	0.0092	2.56×10^{-12}	0.0001	0.0029	0.979
rs8088085	*MEX3C*	chr18:48708548	A/C	0.535	0.0365	0.0067	4.79×10^{-8}	0.0012	0.0021	0.584
rs2834618	*LINC01426*	chr21:36119111	T/G	0.894	0.0944	0.0112	3.41×10^{-17}	−0.0024	0.0034	0.469
rs464901	*TUBA8*	chr22:18597502	T/C	0.665	0.0508	0.0072	1.53×10^{-12}	−0.0007	0.0022	0.761
rs133902	*MYO18B*	chr22:26164079	T/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.

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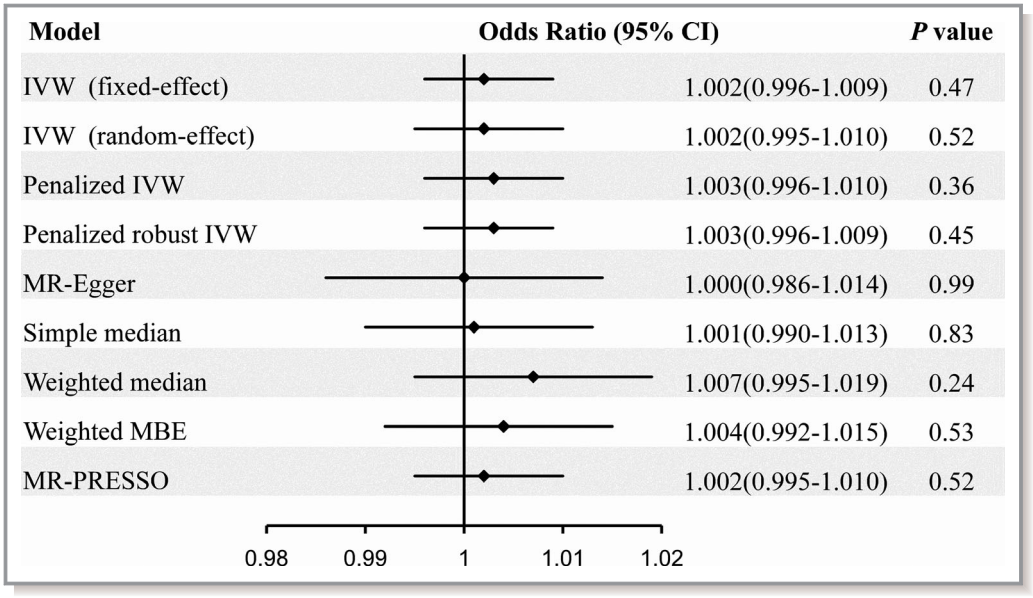

Figure 2. Risk of Alzheimer disease for genetically predicted atrial fibrillation. IVW indicates inverse-variance weighted; MBE, mode-based estimate; MR, Mendelian randomization; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier.

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

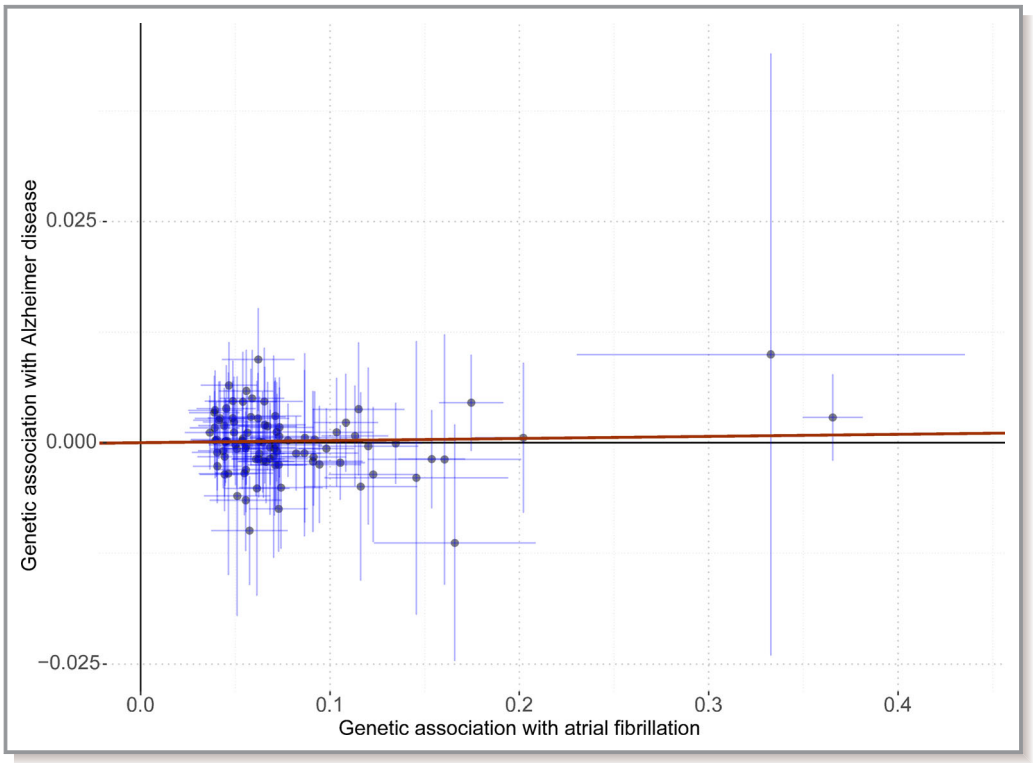

Figure 3. Associations of atrial fibrillation–related variants with risk of Alzheimer disease. The red line indicates the estimate of effect using inverse-variance weighted method. Circles indicate marginal genetic associations with atrial fibrillation and risk of Alzheimer disease for each variant.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

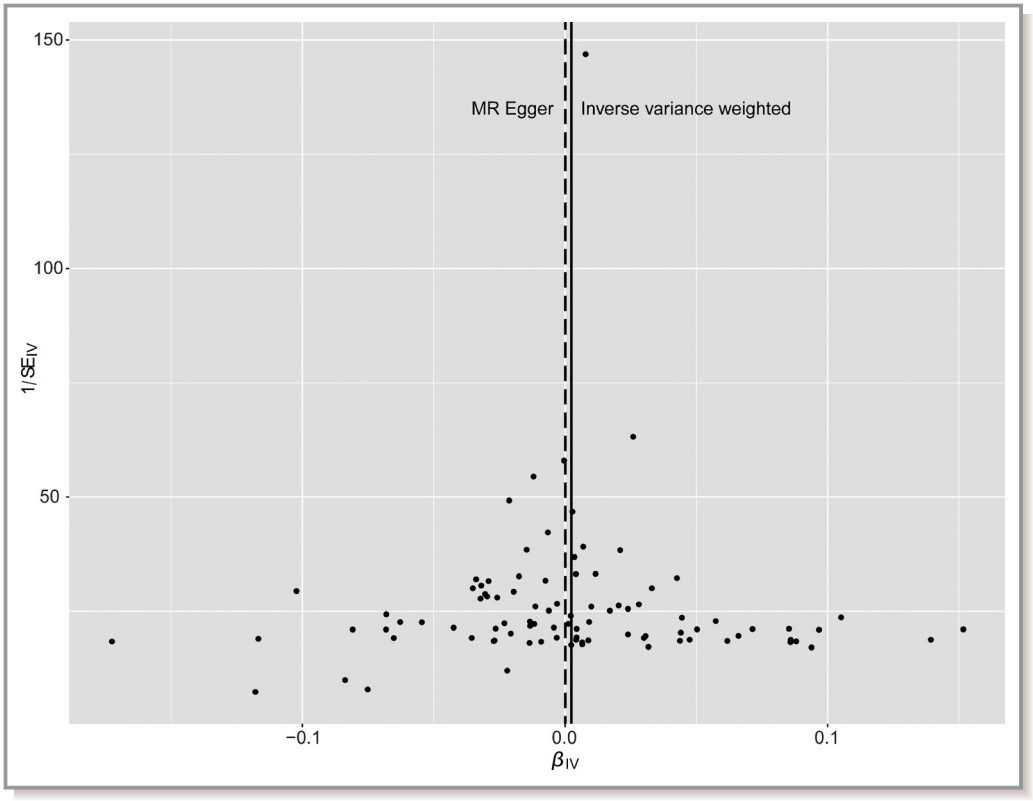

Figure 4. Funnel plot of the Mendelian randomization analysis for Alzheimer disease. Funnel plot evaluated the presence of possible heterogeneity across the estimates, which indicates the potential pleiotropic effects. The figure presents the observed causal effect of each of the 93 instrumental variables (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 I^2 index.[14] Potential pleiotropic effects were estimated by intercepts of the MR-Egger regression.[13] An I^2_{GX} statistic was calculated to test the presence of bias with MR-Egger because of measurement error; I^2_{GX} 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.

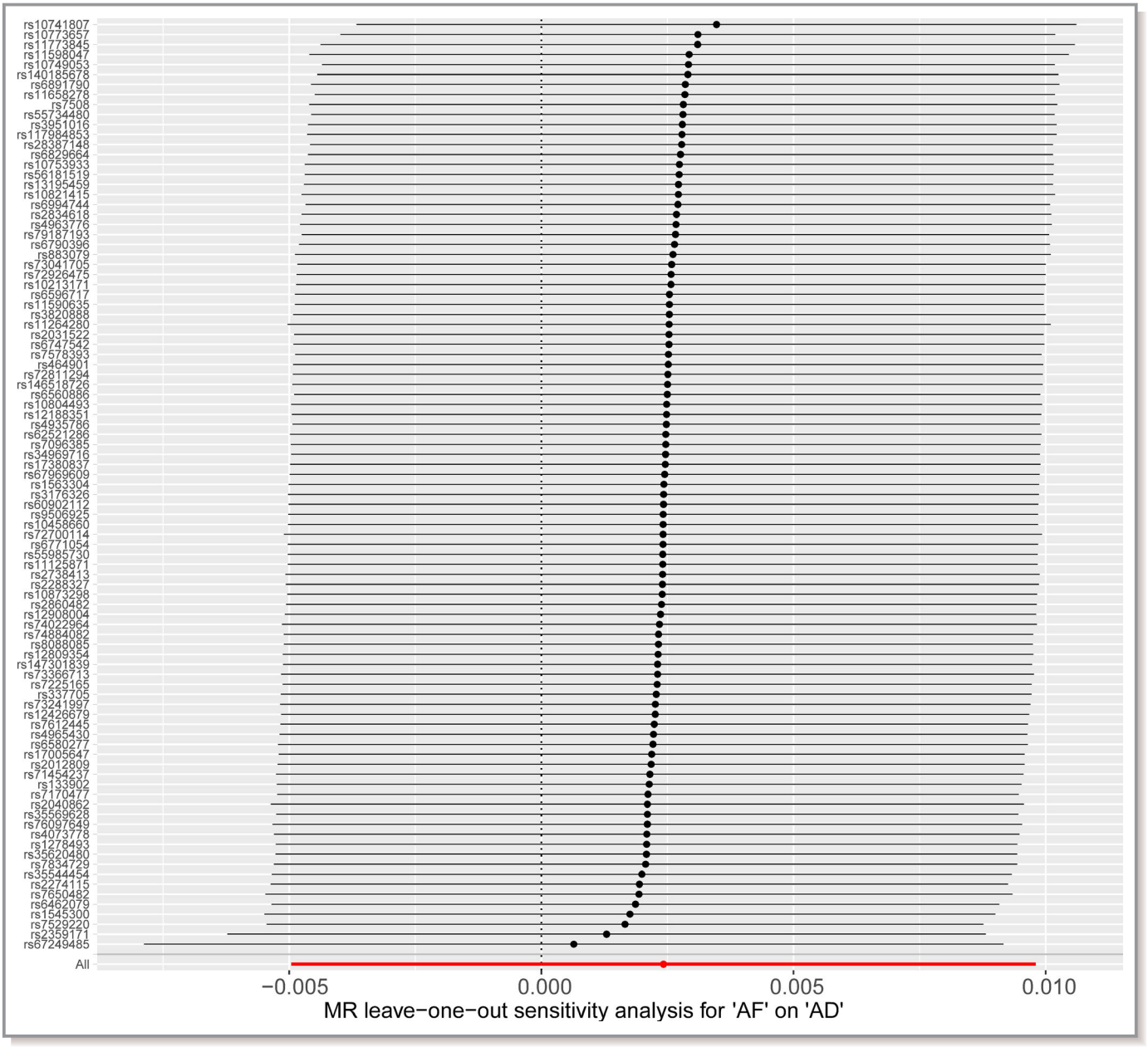

Figure 5. MR leave-1-out sensitivity analysis for atrial fibrillation on AD. Circles indicate MR estimates for atrial fibrillation on Alzheimer disease using inverse-variance weighted fixed-effect method if the SNP was omitted. The bars indicate the CI of MR estimates. AD indicates Alzheimer disease;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

There was no evidence of heterogeneity in the IVW analysis (Q=113.60, *P*=0.055; I^2=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 (I^2_{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 SNP-outcome were derived from 2 different populations. Third, estimates of SNP-AF association were derived from trans-ancestry 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-by-proxy 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-by-proxy, 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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