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Causal relationship between type I diabetes mellitus and atrial fibrillation: A Mendelian randomization study

Yongkai Li [a,1], Shasha Liu [b,1], Yiming Dong [b,1], Jianzhong Yang [c,*], Yingping Tian [a,**]

[a] Emergency Department, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, China
[b] Emergency Department, The Fourth Hospital of Shijiazhuang, Shijiazhuang, China
[c] Emergency Trauma Center, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, China

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ABSTRACT

Background: Patients with type 1 diabetes mellitus have been at heightened risk for developing atrial fibrillation. We aimed to investigate whether this association is causal using Mendelian randomization.

Methods: Using publicly available genome-wide association studies data, we selected single nucleotide polymorphisms significantly associated with type 1 diabetes mellitus as instrumental variables. We employed inverse variance-weighted, weighted median, MR-Egger regression, simple mode, and weighted mode methods within a two-sample Mendelian randomization framework to assess the causal relationship between type 1 diabetes mellitus and atrial fibrillation. We evaluated the pleiotropy and heterogeneity levels of the included genetic instruments using MR-PRESSO, MR-Egger intercept test, Cochran's Q test, funnel plots, and leave-one-out plots.

Results: Causal impact of type 1 diabetes mellitus on atrial fibrillation: Inverse variance weighted (odds ratio [OR] = 0.996, 95 % confidence interval [CI]: 0.985–1.007, P = 0.498). MR-Egger (OR = 1.000, 95 % CI: 0.985–1.016, P = 0.963). Weighted median (OR = 0.985, 95 % CI: 0.973–0.998, P = 0.022). Simple mode (OR = 1.007, 95 % CI: 0.974–1.040, P = 0.698). Weighted mode (OR = 0.995, 95 % CI: 0.984–1.005, P = 0.298). MR-Egger intercept test (P = 0.437). There was no evidence of pleiotropy among the genetic instrumental variables included in the analysis.

Conclusions: In Mendelian randomization analysis, we did not find evidence of a causal relationship between genetically determined type 1 diabetes mellitus in European ancestry populations and atrial fibrillation.

1. Introduction

Type 1 diabetes mellitus (T1DM) is a common chronic autoimmune disease characterized by beta cells destruction leading to insufficient insulin secretion. However, its pathogenesis remains incompletely understood, likely involving interactions among susceptibility genes, autoantigens, and environmental factors[1]. Atrial fibrillation (AF) is a rapid and irregular atrial rhythm that is believed to result from chaotic re-entry involving multiple wavelets within the atria. Its incidence and prevalence are increasing both in the United States and globally[2]. In 2020, atrial fibrillation was estimated globally to affect 50 million individuals and is a leading cause of stroke-related disability and mortality [3]. In recent years, the incidence of T1DM has been steadily rising, imposing significant burdens on families and economies. Most existing data on the vicious cycle between AF and diabetes pertain to type 2 diabetes mellitus (T2DM), highlighting it as a key contributing factor to the occurrence of atrial fibrillation[2,4]. However, controversy remains regarding the relationship between T1DM and atrial fibrillation. Only a few clinical studies have demonstrated the independent role of T1DM as a risk factor for the development of atrial fibrillation, and this remains a topic of discussion. These findings are inconclusive, possibly confounded by other abnormalities associated with T1DM, including obesity and hypertension[5–7]. While the long-term macrovascular and microvascular complications of diabetes have been well-established, the relationship between T1DM and AF remains unclear, and causality has not been established.

* Corresponding author at: Emergency Trauma Center, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, China.
** Corresponding author at: Emergency Department, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, China.
E-mail addresses: yongkaiyaya@sina.com, 29405814@hebmu.edu.cn (Y. Li), sjhlssdyx@sina.com (S. Liu), 958111368@qq.com (Y. Dong), yjz6542@126.com (J. Yang), tianyingping2021@163.com (Y. Tian).
[1] These authors have contributed equally to this work.

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Mendelian randomization (MR) is a study design where random allocation of genetic variants at conception is used as instrumental variables to estimate the unconfounded causal effects of risk factors on disease[8]. Therefore, this study aims to investigate the causal association between T1DM and AF using Mendelian randomization, aiming to provide insights for clinical prevention and treatment strategies regarding T1DM and AF.

2. Methods

2.1. Study design

This study considers T1DM as the exposure factor and atrial fibrillation as the outcome variable, utilizing publicly available genome-wide association studies (GWAS) as the data source. We select single nucleotide polymorphisms (SNPs) significantly associated with T1DM as instrumental variables (IVs) for a two-sample Mendelian randomization analysis of the causal relationship between T1DM and AF. We employ Cochran's Q test to assess heterogeneity in the results and conduct sensitivity analyses to validate their reliability. To ensure effective IVs for causal association analysis in two-sample Mendelian randomization studies, this study establishes three core assumptions: 1) IVs are significantly associated with the exposure factor T1DM; 2) IVs are unrelated to all confounding factors of T1DM and the outcome variable AF; 3) IVs influence the outcome variable AF solely through the exposure factor T1DM and not through other pathways (Fig. 1), (Addi-tional file 1: Fig. S1).

Fig. 1 Study overview. GWAS, genome-wide association studies; T1DM, type 1 diabetes mellitus; AF; atrial fibrillation; SNPs, single nucleotide polymorphisms; MR, mendelian randomization; IVW, Inverse variance weighted; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; MR-Egger, Mendelian randomization-Egger.

2.2. Data sources

We obtained summary statistical data for T1DM and AF from the IEU Open GWAS project (https://gwas.mrcieu.ac.uk/). The GWAS ID for T1DM is ebi-a-GCST90014023, comprising 59,999,551 SNPs, with summary statistics for European ancestry including 18,942 cases and 520,580 controls[9]. This represents a comprehensive, interdisciplinary data resource spanning continents, still publicly accessible in the life sciences field. It is the largest and most recent GWAS study on T1DM. For atrial fibrillation, the GWAS ID is ebi-a-GCST006414, comprising 33,519,037 SNPs, with summary statistics for European ancestry including 60,620 cases and 970,216 controls[10]. All data were sourced from public databases and do not require additional ethical review.

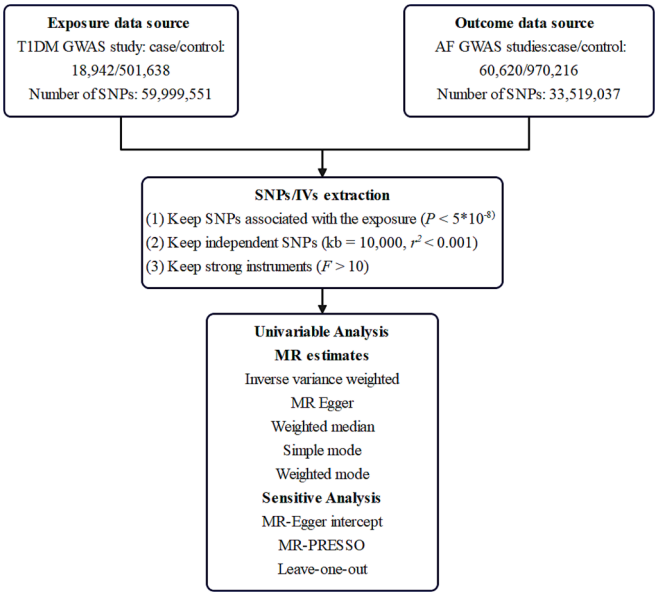

Fig. 1. Study overview. GWAS, genome-wide association studies; T1DM, type 1 diabetes mellitus; AF; atrial fibrillation; SNPs, single nucleotide polymorphisms; MR, mendelian randomization; IVW, Inverse variance weighted; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; MR-Egger, Mendelian randomization-Egger.

The selection of instrumental variables proceeded as follows: Firstly, SNPs closely associated with T1DM were screened with a threshold of $P < 5e\text{-}08$. Secondly, linkage disequilibrium (LD) was adjusted for; LD refers to non-random associations between alleles at different loci, indicating some degree of genetic linkage. Parameters were set at $r^2 = 0.001$ and kb = 10000 to ensure independence among genetic instruments. To assess the potential impact of weak instrumental variables, F-statistics were computed using the formula $F=R^2(N-2)/(1-R^2)$ [11]. SNPs with an F-statistic greater than 10 were deemed strongly associated with atrial fibrillation, while those with an F-statistic < 10 indicated possible weak instrumental variable bias and were therefore excluded to mitigate potential effects on results[12]. Finally, the PhenoScanner database was utilized to investigate secondary phenotypes associated with each SNP, removing any confounding factors related to the exposure and outcome variables.

2.3. Statistical analysis

We conducted a two-sample Mendelian randomization analysis using the TwoSampleMR package in R (v0.6.1; https://mrcieu.github.io/TwoSampleMR/) to assess the relationship between T1DM and AF. This study employed five Mendelian randomization methods to determine the causal relationship between T1DM and AF, including inverse variance weighted (IVW), weighted median (WM), Mendelian randomization-Egger (MR-Egger), simple mode, and weighted mode. The Mendelian randomization-Egger method assesses pleiotropy and adjusts for intercept presence in regression; convergence with IVW indicates minimal horizontal pleiotropy among instruments[13]. WM complements MR-Egger regression by providing consistent estimates if at least 50 % of weights originate from valid IVs[14]. Heterogeneity was assessed using Cochran's Q test, with a significance threshold of $P < 0.05$ indicating presence treated via random effects models; fixed effects models were used otherwise. Leave-one-out analysis evaluated individual SNP impacts on overall results, while scatter plots visualized SNP effects on exposure and outcomes. Forest plots depicted causal associations between exposure and outcomes, and funnel plots assessed selection bias per SNP. For sensitivity analysis, Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test identified horizontal pleiotropic outliers in multi-instrument summary-level Mendelian randomization[15]. All analyses were conducted using R 4.4.0.

Power calculations for Mendelian randomization were performed according to the formula proposed by Brion[16]. We estimated the minimum effect size to be able to observe the measured outcome (atrial fibrillation) using a total sample size of 1,030,836 with 60,620 cases of atrial fibrillation, an α threshold of 0.05, variance explained for each specific instrumental variable, and power > 80 %.

3. Results

3.1. Selection of SNPs

We ultimately selected 89 SNPs that met the criteria, all with F-values > 10, strongly associated with atrial fibrillation, and these instrumental variables only influence the outcome event of AF through the exposure factor of T1DM. Following harmonization with AF, the final Mendelian randomization analysis was conducted using 86 SNPs (Table 1).

Table 1
Instrumental variables associated with type I diabetes mellitus and atrial fibrillation.

SNPs	CHr	EA	NEA	βvalue	S. E.	*F* value
rs9517712	13	C	T	−0.102	0.741	41.701
rs9468618	6	T	C	−0.272	0.082	106.730
rs9385401	6	T	C	0.120	0.454	65.961
rs9260802	6	G	A	−0.356	0.035	72.925
rs855330	1	C	T	0.111	0.259	43.219
rs8046043	16	C	G	−0.085	0.392	31.070
rs78325861	10	G	C	−0.282	0.039	44.692
rs7795896	7	T	C	−0.135	0.692	68.065
rs7776597	7	G	A	0.244	0.959	45.156
rs7752257	6	G	T	−0.680	0.740	1677.550
rs7668577	4	C	A	0.094	0.312	37.947
rs7511678	1	A	G	0.094	0.229	30.650
rs73432769	6	T	C	0.335	0.020	53.693
rs7301381	12	C	T	−0.094	0.464	43.085
rs7237497	18	C	T	−0.220	0.839	139.966
rs722988	10	C	T	0.083	0.353	32.887
rs7130222	11	G	T	−0.092	0.308	32.324
rs7068821	10	T	G	−0.165	0.251	102.182
rs6908626	6	T	G	0.203	0.166	120.055
rs6908236	6	C	A	0.166	0.514	138.290
rs689	11	T	A	0.712	0.731	1476.890
rs6679677	1	A	C	0.642	0.114	939.332
rs663743	11	A	G	−0.100	0.349	43.872
rs6434435	2	A	G	−0.123	0.160	41.421
rs61839660	10	T	C	−0.357	0.085	188.999
rs61759532	17	T	C	0.118	0.235	40.563
rs607703	11	T	C	0.092	0.484	41.520
rs601338	19	A	G	0.127	0.479	77.695
rs574384	1	A	C	−0.134	0.895	31.311
rs57209021	17	T	C	0.101	0.226	30.286
rs56994090	14	C	T	−0.134	0.431	84.627
rs55993634	16	G	C	0.219	0.085	80.970
rs55893453	2	G	A	0.095	0.202	29.866
rs4820827	22	C	T	−0.130	0.621	82.590
rs4548024	6	C	T	−0.096	0.234	32.853
rs4490209	2	G	C	−0.085	0.360	29.901
rs41295159	10	G	C	−0.700	0.009	60.079
rs3802214	8	C	T	−0.107	0.799	30.735
rs35327136	17	A	C	−0.119	0.156	39.448
rs34593439	15	A	G	−0.218	0.108	81.748
rs34536443	19	C	G	−0.385	0.043	100.073
rs3184504	12	C	T	−0.231	0.533	270.096
rs3087243	2	A	G	−0.199	0.422	196.595
rs3024493	1	A	C	−0.164	0.154	69.597
rs28752526	6	G	A	0.630	0.357	1569.786
rs28648882	2	A	G	0.099	0.224	30.686
rs2611211	4	T	C	−0.144	0.824	59.248
rs2543537	22	T	C	−0.083	0.460	33.971
rs2493411	1	C	T	0.127	0.132	32.364
rs2429557	6	A	T	1.021	0.011	308.356
rs238873	6	G	A	0.793	0.015	221.481
rs238265	13	G	T	−0.091	0.695	35.903
rs231972	16	C	A	0.171	0.118	65.750
rs229527	22	A	C	0.104	0.416	54.192
rs2188962	5	T	C	0.079	0.404	31.776
rs2111485	2	G	A	0.128	0.604	77.960
rs202535	20	A	C	−0.141	0.828	58.748
rs1947178	8	G	A	−0.103	0.792	36.325
rs1881146	2	T	A	−0.095	0.311	29.892
rs1808094	18	C	T	−0.114	0.524	58.180
rs1794269	6	T	C	1.594	0.432	8073.918
rs17623914	1	C	T	−0.135	0.100	33.282
rs17323934	7	G	C	−0.130	0.223	59.440
rs17106304	14	G	C	0.115	0.656	60.648
rs1701704	12	G	T	0.244	0.339	281.025
rs1611236	6	A	G	−0.260	0.299	223.172
rs1574285	9	T	G	−0.127	0.591	79.746
rs1350275	14	G	T	−0.094	0.698	37.561
rs13259300	8	C	A	−0.092	0.598	39.498
rs13147049	4	G	A	−0.110	0.641	55.593
rs12927355	16	T	C	−0.204	0.316	180.198
rs12742756	1	G	A	−0.083	0.428	30.384
rs12644686	4	G	C	−0.108	0.194	31.104
rs12464462	2	G	A	−0.088	0.410	37.615
rs12257077	10	T	C	0.231	0.032	39.156
rs12128789	1	C	T	0.127	0.132	34.762
rs114378220	5	T	C	0.178	0.070	34.147
rs113374757	19	T	C	−0.171	0.163	68.009
rs112733823	6	T	C	0.383	0.142	362.648
rs11203203	21	A	G	0.144	0.349	99.657
rs10844597	12	A	G	−0.090	0.506	41.461
rs10801128	1	G	A	0.096	0.717	37.536
rs10751776	1	C	A	0.078	0.510	30.935
rs1050979	6	G	A	0.106	0.515	56.493
rs10275896	7	C	T	−0.121	0.232	53.488
rs10224046	7	G	T	0.086	0.324	30.904

3.2. Analysis of the Mendelian randomization method

Our analysis revealed the following results: The Inverse variance weighted (IVW) method showed no statistically significant difference (OR = 0.996, 95 % CI: 0.985–1.007, $P = 0.498$). Similarly, the MR Egger method also showed no statistically significant difference (OR = 1.000, 95 % CI: 0.985–1.016, $P = 0.963$). In contrast, the Weighted median method demonstrated a statistically significant difference (OR = 0.985, 95 % CI: 0.973–0.998, $P = 0.022$). Both the Simple mode (OR = 1.007, 95 % CI: 0.974–1.040, $P = 0.698$) and Weighted mode methods (OR = 0.995, 95 % CI: 0.984–1.005, $P = 0.298$) showed no statistically significant differences. Among these methods, the IVW method, which assumes no pleiotropy and does not account for intercept presence in regression, is considered the primary analysis method[17]. Therefore, it can still be concluded that there is no causal relationship between the exposure factor and the outcome, indicating that T1DM does not increase the risk of AF occurrence (Table 2, Figs. 2, 3).

3.3. Heterogeneity and pleiotropy

Heterogeneity assessed by IVW method analysis indicated Cochran's Q = 175.747, $P < 0.05$. Similarly, MR-Egger method analysis showed Cochran's Q = 174.482, $P < 0.05$. Both methods revealed heterogeneity among individual SNPs. MR-PRESSO results in Global Test $P < 0.001$; however, MR-PRESSO results in the Distortion test, $P = 0.922$, indicated no difference in outlier values affecting the outcomes, thus a random effects model was employed. Pleiotropy analysis showed MR-Egger intercept = -0.001, $P = 0.437$, indicating no horizontal pleiotropy and robust results. Funnel plot results indicated a symmetric distribution of causal effect estimates of included SNPs, suggesting no bias and stable outcomes (Fig. 4).

3.4. Sensitivity analysis

Using the "Leave-one-out plot" to assess the influence of each SNP on the Mendelian randomization analysis results, no sensitive SNPs were identified (Fig. 5).

Table 2
Causal relationship between T1DM and AF.

Method	Odds Ratio (*OR*)	95 % Confidence Interval (*CI*)	*P* value
Inverse Variance Weighted (IVW)	0.996	0.985–1.007	0.498
MR Egger	1.000	0.985–1.016	0.963
Weighted Median	0.985	0.973–0.998	0.022
Simple Mode	1.007	0.974–1.040	0.698
Weighted Mode	0.995	0.984–1.005	0.298

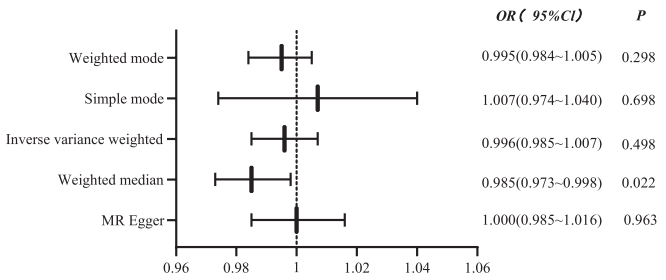

Fig. 2. MR results between T1DM and AF.

4. Discussion

In current studies, T1DM has been identified as a potential independent risk factor for AF. However, in the current Mendelian randomization study involving over one million individuals of European ancestry, there is no convincing evidence to suggest a causal relationship between T1DM and AF. Our study findings indicate no evidence of a causal relationship between T1DM and AF, underscoring the need for further clinical research to consolidate existing conclusions.

AF and diabetes mellitus (DM) are two common comorbidities in Western countries. The prevalence of AF among adults in Europe, the United States, and Australia is reported to range from 1 % to 4 %[18]. The association between diabetes and AF occurrence is primarily observed in populations diagnosed with diabetes, suggesting that prolonged exposure to high blood glucose may increase the risk of AF. While the mechanisms underlying this association and other potential pathways remain hypothetical, there is scarce supportive functional data. However, our study findings indicate that genetic T1DM is not associated with AF, suggesting that these disruptions in glucose metabolism are not causative factors for AF. A Mendelian randomization study has indicated no causal relationship between T2DM or glucose abnormalities and the risk of AF[19]. Some studies have shown an association between the two, with one potential explanation being that diabetes-related comorbidities such as hypertension and obesity contribute to the causal link between diabetes and AF. Indeed, recent Mendelian randomization analyses have demonstrated a causal relationship between BMI and the incidence of AF[20]. A plausible mechanism may involve the comorbid conditions associated with Type 1 diabetes (T1D), specifically hypertension and obesity, which could mediate the pathophysiological link between T1D and atrial fibrillation (AF).

A Swedish population-based cohort study employed Cox proportional hazards models to assess the relationship between blood glucose status and atrial fibrillation. In models adjusted for age and sex, significant correlations were observed between blood glucose status and AF incidence across all groups except for impaired glucose tolerance, with the diabetes group showing the strongest correlation ($P < 0.001$). However, in models further adjusted for factors including gender, age, systolic blood pressure, BMI, antihypertensive medications, cholesterol, alcohol consumption, smoking, education level, marital status, and physical activity, no significant association was found between blood glucose status and AF. These findings suggest that after adjusting for potential confounders, the association between blood glucose status and AF diminishes. Diabetes and prediabetes do not appear to be

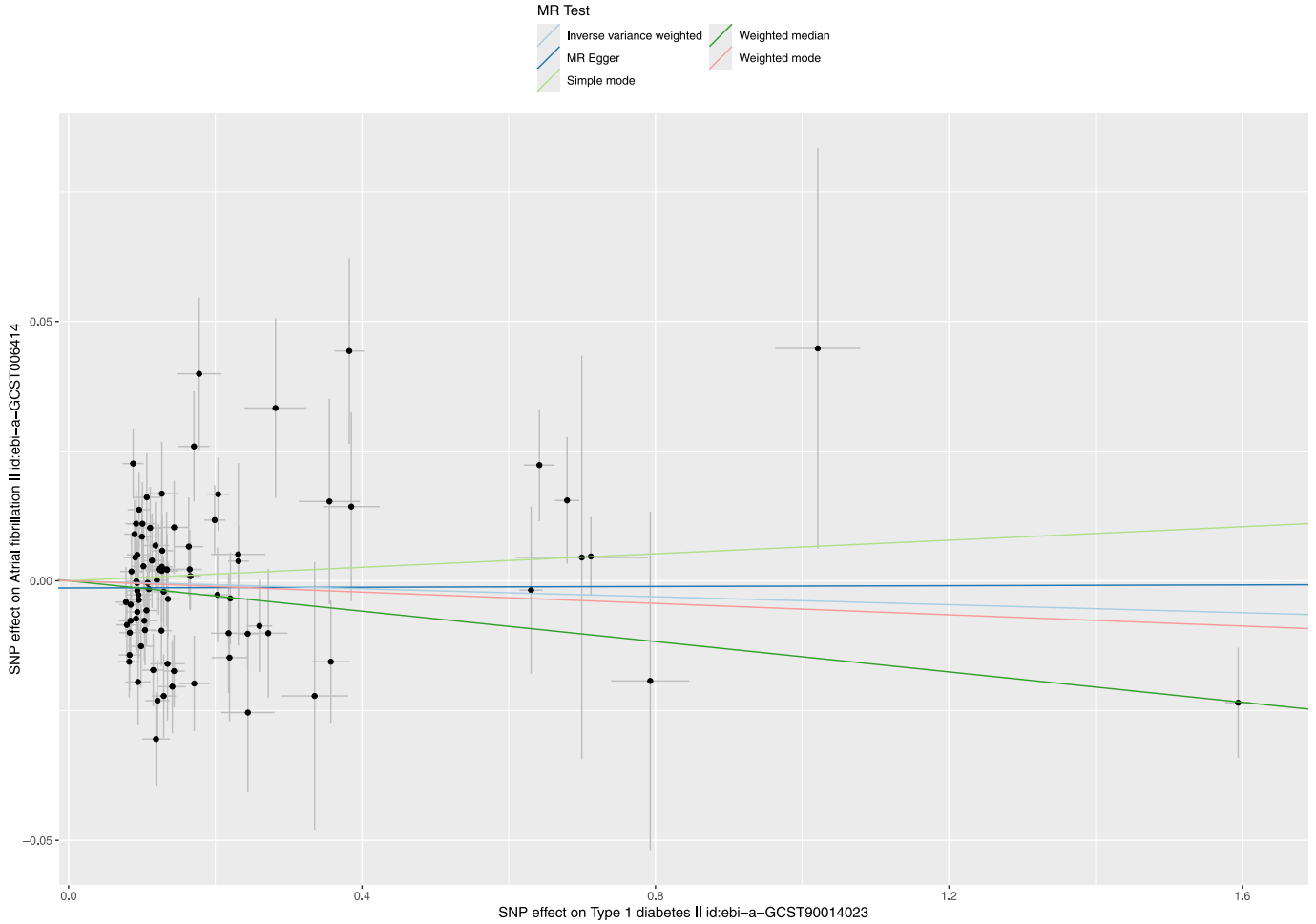

Fig. 3. Causal relationship between T1DM and AF.

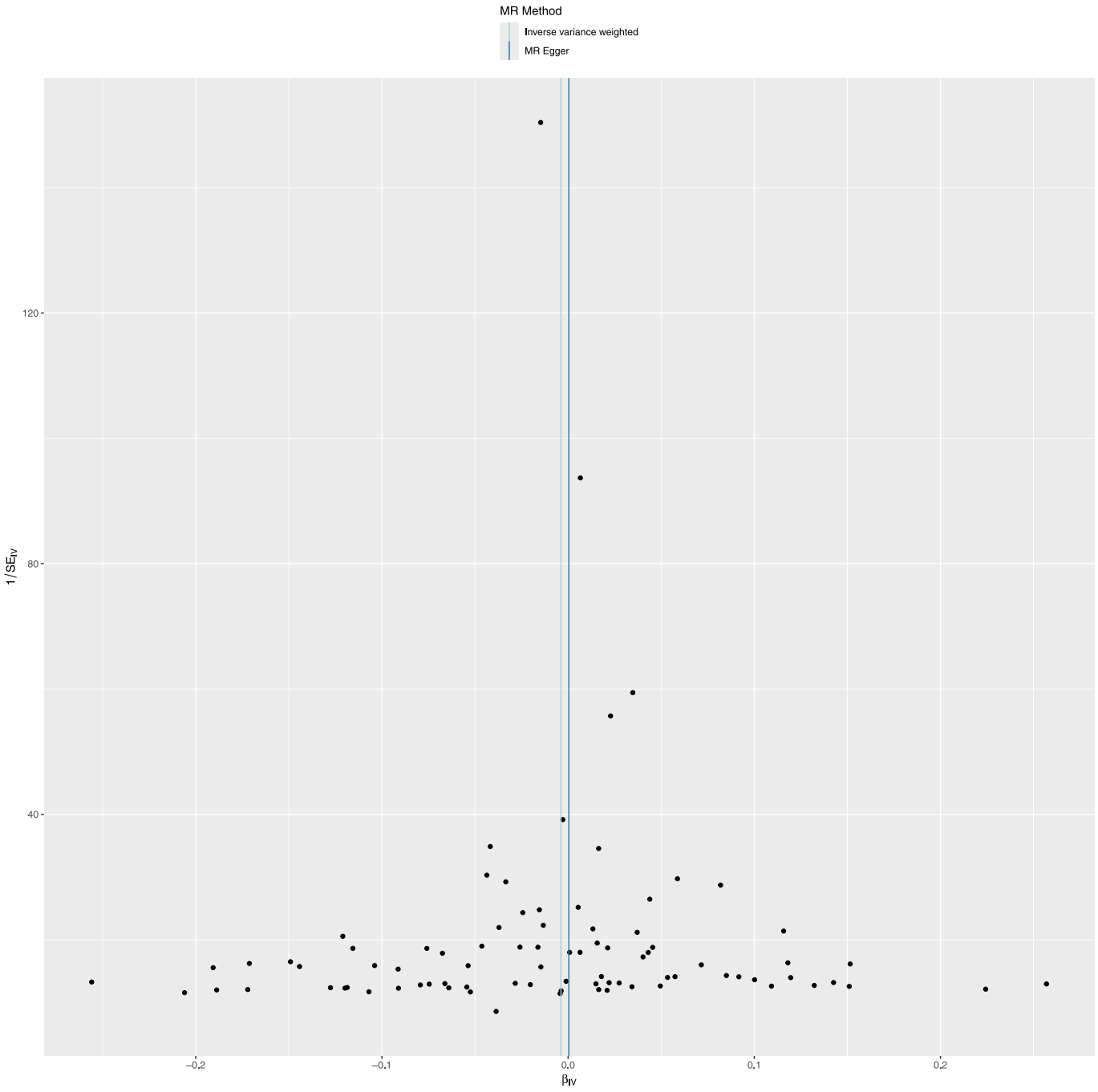

Fig. 4. Funnel plot of the two-sample mendelian randomization.

independent risk factors for AF. The increased risk of AF observed in patients with diabetes and prediabetes may be related to the high prevalence of other risk factors[21]. Conversely, a study in Korea reported results contradicting those of the Swedish study. They found that the hazard ratio (HR, 95 % CI) for AF occurrence in the T1DM group compared to the non-diabetes group was 1.748 (1.534–1.993). However, the article also acknowledged the limitations of the study, noting that the observed HRs ranging from 1.608 (for AF) to 2.105 (for heart failure hospitalization) in the T1DM group compared to the T2DM group could only be explained by an unmeasured confounding factor related to diabetes type, which poses a higher risk than or equal to the confounding factors measured in their study. This confounding factor may influence the final results, highlighting the study's limitations. Finally, the article cautioned about extrapolating results to different racial groups due to all subjects being Korean, underscoring the study's inherent limitations in generalizability[7].

A *meta*-analysis has indicated that diabetes is associated with an increased likelihood of non-paroxysmal atrial fibrillation rather than paroxysmal atrial fibrillation[22]. This systematic review provides a comprehensive summary of the evidence linking diabetes with different types of atrial fibrillation. However, it does not establish causality between diabetes and atrial fibrillation types. It underscores the need for future studies to appropriately adjust for confounding factors, use Cox models with time-varying covariates to consider the onset of diabetes, and conduct high-quality research to examine causality, elucidate the exact mechanisms linking diabetes with non-paroxysmal atrial fibrillation, and assess the potential predictive value of diabetes in predicting non-paroxysmal atrial fibrillation. In a Mendelian randomization study

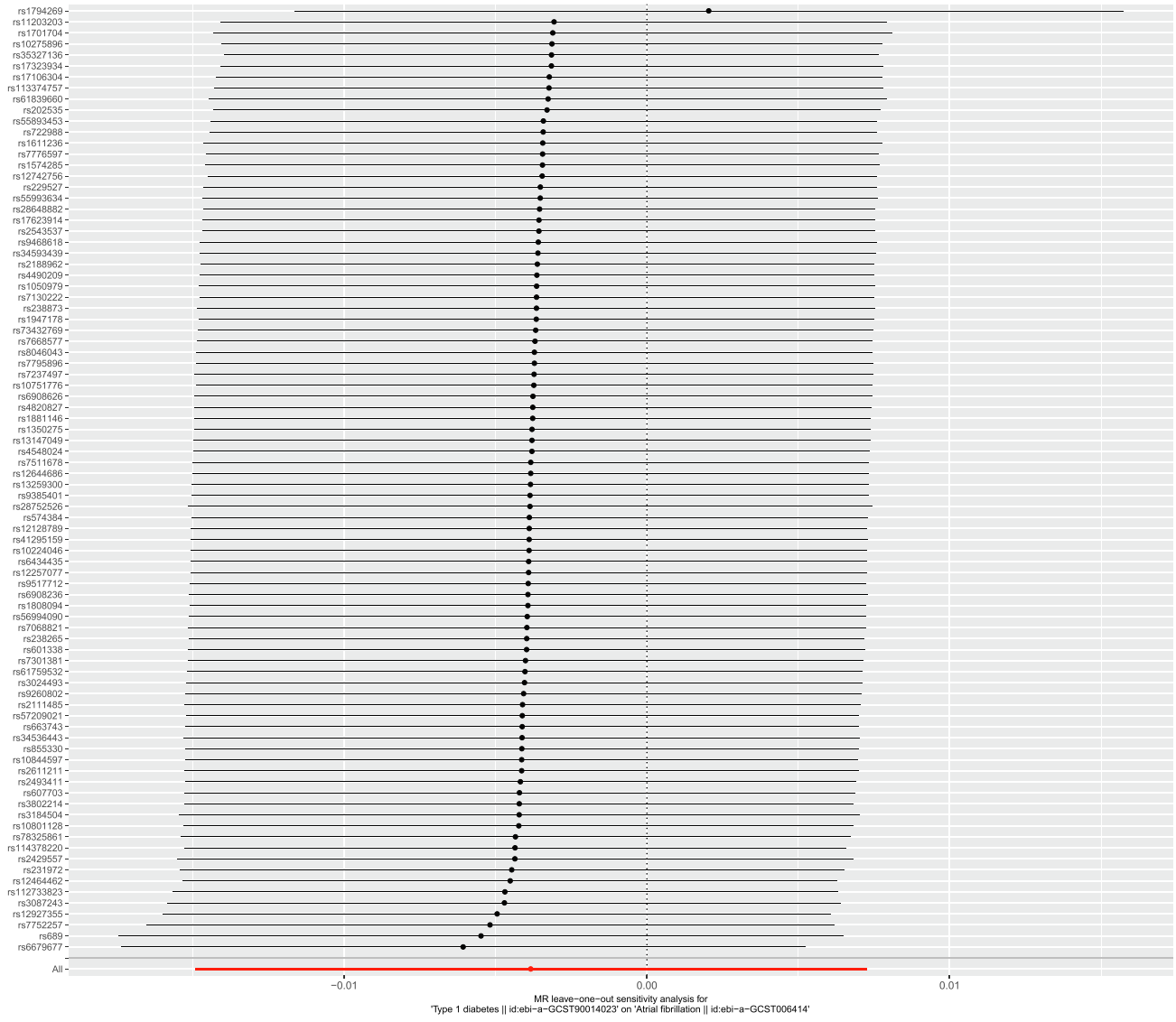

Fig. 5. The leave-one-out plots of the sensitivity analysis.

investigating the causal relationship between T1DM and cardiovascular diseases, it was noted that no significant causal relationship was found between T1DM and AF. The study only provided evidence supporting a causal relationship between T1DM and peripheral arterial disease and coronary artery disease[23].

Compared to traditional epidemiological studies, this study has several strengths: it utilizes two-sample Mendelian randomization to explore the causal relationship between T1DM and AF. This method leverages genotypes randomly allocated in nature as instrumental variables to infer the impact of exposures on outcomes, thereby largely mitigating issues related to reverse causation and confounding factors. We validated our hypothesis using the latest AF genome-wide association study data. Moreover, the study employed multiple Mendelian randomization analysis methods to ensure the reliability and stability of the results. However, this study also has its limitations: In the present dataset, the diagnostic information for atrial fibrillation (AF) was acquired from registry databases, the accuracy and reliability of which may be subject to multiple confounding factors. It relies on summary data from European populations, thus the conclusions may lack generalizability and should be complemented by data from diverse ethnic groups. Finally, the study solely explores the relationship between T1DM and AF from a genetic perspective, leaving the specific mechanisms requiring further validation through additional research. Future studies should incorporate longitudinal data from prospective cohort studies to elucidate the mechanistic pathways through which disease progression trajectories influence the clinical course of atrial fibrillation. Although MR analysis revealed no direct causal association between T1DM and AF, preclinical evidence suggests that chronic hyperglycemia and oxidative stress—hallmarks of T1DM—may promote progressive atrial structural remodeling. Such remodeling likely initiates decades prior to AF symptom onset, a dynamic pathophysiological process inherently undetectable by MR methodologies, which rely on genetic variants as static proxies. Future investigations should integrate advanced imaging biomarkers (e.g., left atrial strain quantification) and mediator analyses (e.g., inflammatory cytokine trajectories) to delineate the temporal cascade linking T1DM-driven subclinical changes to AF manifestation.

5. Conclusion

In the current Mendelian randomization study, we did not find evidence of a causal relationship between genetically determined T1DM in European ancestry populations and atrial fibrillation. The question of whether T1DM leads to atrial fibrillation remains difficult to answer

definitively to date, given the challenges posed by cardiovascular complications, active management of risk factors, and the relatively lower incidence rate of T1DM. In clinical research, emphasis should be placed on understanding the impact of confounding factors on study outcomes, enhancing study rigor, and improving accuracy.

CRediT authorship contribution statement

Yongkai Li: Writing – original draft, Software, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Shasha Liu:** Data curation. **Yiming Dong:** Data curation. **Jianzhong Yang:** Writing – review & editing, Writing – original draft. **Yingping Tian:** Writing – review & editing, Writing – original draft.

Funding

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics approval and consent to participate

All data were sourced from public databases and do not require additional ethical review.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2025.101643.

Data availability

Data will be made available on request.

All data generated or analyzed during this study are included in this article and its supplementary information files.

References

[1] F.Z. Syed, Type 1 Diabetes Mellitus, Ann. Intern. Med. 175 (3) (2022) Itc33-itc48, https://doi.org/10.7326/aitc202203150.
[2] J.A. Joglar, M.K. Chung, A.L. Armbruster, et al., 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, Circulation 149 (1) (2024) e1–e156, https://doi.org/10.1161/cir.0000000000001193.
[3] C.W. Tsao, A.W. Aday, Z.I. Almarzooq, et al., Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association, Circulation 147 (8) (2023) e93–e621, https://doi.org/10.1161/cir.0000000000001123.
[4] A.M. Gillis, A Sober Reality? Alcohol, Abstinence, and Atrial Fibrillation, N. Engl. J. Med. 382 (1) (2020) 83–84, https://doi.org/10.1056/NEJMe1914981.
[5] S. Dahlqvist, A. Rosengren, S. Gudbjörnsdottir, et al., Risk of atrial fibrillation in people with type 1 diabetes compared with matched controls from the general population: a prospective case-control study, Lancet Diabetes Endocrinol. 5 (10) (2017) 799–807, https://doi.org/10.1016/s2213-8587(17)30262-0.
[6] S.C. Larsson, A. Wallin, N. Håkansson, et al., Type 1 and type 2 diabetes mellitus and incidence of seven cardiovascular diseases, Int. J. Cardiol. 262 (2018) 66–70, https://doi.org/10.1016/j.ijcard.2018.03.099.
[7] Y.B. Lee, K. Han, B. Kim, et al., Risk of early mortality and cardiovascular disease in type 1 diabetes: a comparison with type 2 diabetes, a nationwide study, Cardiovasc. Diabetol. 18 (1) (2019) 157, https://doi.org/10.1186/s12933-019-0953-7.
[8] C.J. O'donnell, M.S. Sabatine, Opportunities and Challenges in Mendelian Randomization Studies to Guide Trial Design, JAMA Cardiol. 3 (10) (2018) 967, https://doi.org/10.1001/jamacardio.2018.2863.
[9] J. Chiou, R.J. Geusz, M.L. Okino, et al., Interpreting type 1 diabetes risk with genetics and single-cell epigenomics, Nature 594 (7863) (2021) 398–402, https://doi.org/10.1038/s41586-021-03552-w.
[10] J.B. Nielsen, R.B. Thorolfsdottir, L.G. Fritsche, et al., Biobank-driven genomic discovery yields new insight into atrial fibrillation biology, Nat. Genet. 50 (9) (2018) 1234–1239, https://doi.org/10.1038/s41588-018-0171-3.
[11] N. Papadimitriou, N. Dimou, K.K. Tsilidis, et al., Physical activity and risks of breast and colorectal cancer: a Mendelian randomisation analysis, Nat. Commun. 11 (1) (2020) 597, https://doi.org/10.1038/s41467-020-14389-8.
[12] E. Sanderson, W. Spiller, J. Bowden, Testing and correcting for weak and pleiotropic instruments in two-sample multivariable Mendelian randomization, Stat. Med. 40 (25) (2021) 5434–5452, https://doi.org/10.1002/sim.9133.
[13] J. Bowden, G. Davey Smith, S. Burgess, Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression, Int. J. Epidemiol. 44 (2) (2015) 512–525, https://doi.org/10.1093/ije/dyv080.
[14] S. Burgess, J. Bowden, T. Fall, et al., Sensitivity Analyses for Robust Causal Inference from Mendelian Randomization Analyses with Multiple Genetic Variants, Epidemiology 28 (1) (2017) 30–42, https://doi.org/10.1097/ede.0000000000000559.
[15] M. Verbanck, C.Y. Chen, B. Neale, et al., Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases, Nat. Genet. 50 (5) (2018) 693–698, https://doi.org/10.1038/s41588-018-0099-7.
[16] M.J. Brion, K. Shakhbazov, P.M. Visscher, Calculating statistical power in Mendelian randomization studies, Int. J. Epidemiol. 42 (5) (2013) 1497–1501, https://doi.org/10.1093/ije/dyt179.
[17] S. Burgess, F. Dudbridge, S.G. Thompson, Combining information on multiple instrumental variables in Mendelian randomization: comparison of allele score and summarized data methods, Stat. Med. 35 (11) (2016) 1880–1906, https://doi.org/10.1002/sim.6835.
[18] F. Rahman, G.F. Kwan, E.J. Benjamin, Global epidemiology of atrial fibrillation, Nat. Rev. Cardiol. 11 (11) (2014) 639–654, https://doi.org/10.1038/nrcardio.2014.118.
[19] H. Harati, D. Zanetti, A. Rao, et al., No evidence of a causal association of type 2 diabetes and glucose metabolism with atrial fibrillation, Diabetologia 62 (5) (2019) 800–804, https://doi.org/10.1007/s00125-019-4836-y.
[20] N.A. Chatterjee, F. Giulianini, B. Geelhoed, et al., Genetic Obesity and the Risk of Atrial Fibrillation: Causal Estimates from Mendelian Randomization, Circulation 135 (8) (2017) 741–754, https://doi.org/10.1161/circulationaha.116.024921.
[21] C. Johansson, L. Örtendahl, M.M. Lind, et al., Diabetes, prediabetes, and atrial fibrillation-A population-based cohort study based on national and regional registers, J. Intern. Med. 294 (5) (2023) 605–615, https://doi.org/10.1111/joim.13688.
[22] F. Alijla, C. Buttia, T. Reichlin, et al., Association of diabetes with atrial fibrillation types: a systematic review and meta-analysis, Cardiovasc. Diabetol. 20 (1) (2021) 230, https://doi.org/10.1186/s12933-021-01423-2.
[23] Z. Liu, H. Wang, Z. Yang, et al., Causal associations between type 1 diabetes mellitus and cardiovascular diseases: a Mendelian randomization study, Cardiovasc. Diabetol. 22 (1) (2023) 236, https://doi.org/10.1186/s12933-023-01974-6.