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EVIDENCE-BASED MEDICINE

Mendelian randomization provides evidence for a causal effect of serum insulin-like growth factor family concentration on risk of atrial fibrillation

Sha Lin, Jie Tang, Xing Li, Gang Wu, Yi-Fei Lin, Yi-Fei Li

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Abstract

BACKGROUND

Atrial fibrillation (AF) is one of the most common persistent arrhythmias among adult cardiovascular diseases. It is important to identify potential risk factors for AF. Members of the insulin-like growth factor (IGF) family exert a variety of effects on various cell types in the context of the pathogenesis of cardiovascular diseases, and previous population-based studies indicate associations between IGF family members and AF. However, the causal effects of IGF family members in AF have not been evaluated.

AIM

In the current study two-sample Mendelian Randomization (MR) was used to assess genetic relationships between IGF family members and AF.

METHODS

MR was performed based on genome-wide association study (GWAS) datasets, and concentration levels of 14 IGF family members were retrieved. An initial MR analysis was conducted to identify single nucleotide polymorphisms potentially associated with IGF serum concentrations. A GWAS meta-analysis including 60620 AF cases and 970216 control participants of European ancestry was then conducted to identify AF causal effects. Two-sample MR packages were used to perform MR analysis in R. MR-Egger, weighted median (WM), and inverse variance weighted (IVW) methods were used.

RESULTS

In two-sample MR assessments there were lower levels of circulating IGF binding protein 3 in both WM [odds ratio (OR) 0.964, 95% confidence interval (CI) 0.940–0.960, P = 0.006] and IVW (OR 0.968, 95%CI: 0.947–0.987, P = 0.001) analyses. Higher serum levels of IGF2 receptor were associated with AF (OR 1.045, 95%CI: 1.016–1.076, P = 0.039). In reverse MR analysis conducted to investigate casual effects, elevated levels of circulating CYR61 were associated with AF (OR 1.060, 95%CI: 1.005–1.119, P = 0.031).

CONCLUSION

The results of the present study provide novel insights into the pathogenesis of AF, and the implications of serum IGF family member concentrations when assessing the risk of AF. The study generated evidence on the potential roles of developmental pathological effects in the pathogenesis of AF. Further observational and experimental studies are critically needed.

Key Words: Atrial fibrillation; Genome-wide association study; Insulin-like growth factor binding protein 3; Insulin-like growth factor family; Mendelian randomization

Core Tip: Due to the high prevalence of atrial fibrillation (AF), and adverse outcomes related to it, it is important to identify risk factors associated with development of the condition. Insulin-like growth factor (IGF) family members exert a variety of effects on various cell types in the context of the pathogenesis of cardiovascular diseases, and previous population-based studies indicate associations between IGF family members and AF. However, the causal effects of IGF family members in AF have not been evaluated. The results of the current study provide novel insights on the pathogenesis of AF, and implications of serum IGF family member concentrations when assessing the risk of AF. The study generated evidence on the potential roles of developmental pathological effects in the pathogenesis of AF. Further observational and experimental studies are critically needed.

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INTRODUCTION

Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice worldwide. It recently ranked as the persistent arrhythmia with the highest prevalence in the elderly population. The risk of AF increases with age, with a sharp increase between the ages of 60 and 69 years, and progressive increases from 70–79 years and 80–89 years. The phenotypes of AF are heterogeneous[1], and it is a major public health problem in both developing and developed countries.

Heart failure and metabolic disorders such as diabetes and obesity have been identified as contributing to the pathogenesis of AF, and these associations have been extensively documented. With regard to the exact mechanisms underlying AF, predominant theories center on structural remodeling induced by external stressors, including hemodynamic stressors and inflammation. Structural remodeling is commonly recognized as comprising three key components; fibroblast activation, myocardial fibrosis, and collagen deposition[2]. Given the fundamental pathophysiological mechanisms involved in AF development, which include hemodynamic stress, inflammation, and myocardial fibrosis, numerous studies have explored potential associations between biomarkers reflecting pathobiological processes and AF onset. A relationship between circulating natriuretic peptide (NP) concentrations and incident AF has been well-established in various cohorts, including the Framingham Offspring Study, Cardiovascular Health Study, and the CHARGE-AF Consortium, among others[3-5]. In addition to NPs, C-reactive protein has been recognized for its significant role in systemic inflammation and the prediction of AF[5,6]. Furthermore, several biomarkers associated with fibrosis have been investigated as potential indicators of the onset of incident AF[7-9].

Developmental aspects of AF have been documented in clinical and translational studies. Early myocardium development and its interaction with large vessels, particularly pulmonary veins, has been considered a major contributor to AF onset. Atrial fibrosis is regarded as another of the primary mechanisms underlying AF. Localized atrial fibrosis leads to abnormal calcium processing in atrial myocardium, thereby inducing re-entry and electrical disturbances, establishing a molecular and mechanical basis for AF. Thus, factors present in circulation that are implicated in atrial myocardial fibrosis should be regarded as potential contributors to AF.

The peptidic hormone insulin-like growth factor (IGF) family comprises two ligands (IGF1 and IGF2), two receptors (IGF1R and IGF2R), seven high-affinity binding proteins (IGFBPs 1–7), a substantial group of IGFBP proteases, and a novel category of proteins known as low-affinity IGFBP-related proteins (IGFBP-rPs). It has been well established that the

family plays pivotal roles in growth and development, regulating processes such as proliferation, differentiation, metabolism, and cell survival in various tissues. It is also associated with metabolic disorders, including hypertension, obesity, and stroke. Recent research indicates that reduced IGF1 Levels are linked to an elevated risk of cardiovascular disease-associated mortality. To date no population-based study has investigated associations between AF morbidity and members of the IGF family, such as IGF1 and IGFBP3[10]. In experimental rat models Wang *et al*[3] demonstrated that IGF1 was associated with atrial fibrosis and participated in AF. It has also been reported that IGF1 and IGFBPs are involved in diabetes, which exacerbates interstitial fibrosis in the atria. These associations have been seen in both animal studies[11,12] and human studies[13].

The above-described associative observations were primarily derived from conventional observational studies, which are susceptible to sample size limitations, reverse causation bias, and confounding factors[14]. It is often challenging to draw definitive conclusions given these considerations and the inherent heterogeneity between different studies, rendering it difficult to conduct causal effect analyses based on these prior studies. Additionally, conventional studies often have limitations with respect to the number of variables that can be observed. Consequently, investigations into the causal effects of all members of the IGF family on the risk of AF are limited.

To mitigate the influences of reverse causality and potential confounding factors from environmental and social sources, the current study used a Mendelian randomization (MR) methodology. The approach relies on genetic variants strongly and exclusively associated with the phenomenon of interest, so-called instrumental variables, to establish causal associations. Two-sample MR analysis was conducted to investigate genetic relationships between IGF family members and AF. The aim was to determine whether IGF family members could be considered contributors to AF.

MATERIALS AND METHODS

Study design

This study was design to assess the causal effects of IGF family members in the risk of AF. The related traits of IGF family members had been identified, and fourteen IGF family members traits included: IGF1, IGF1-sR, IGF-IIR, IGFBP1, IGFBP2, IGFBP3, IGFBP4, IGFBP5, IGFBP6, IGFBP7, IGF-LR1, CTGF, WISP1 and CYR61. Besides, three traits had been retrived for genetic association of AF, including ebi-a-GCST006414, UKB-b-536, and finn-b-I9_AF. First, the effects of fourteen IGF family members and their serum concentration were evaluated to identify the potential single nucleotide polymorphisms (SNPs) as one sample MR analysis. Then two-sample MR analysis had been completed among AF traits to measure the causa effects of IGF family members in AF pathogensis in the largest sample size trait (ebi-a-GCST006414). Then, further confirmation had been performed among three AF traits to validate the results. After that, the reverse MR analysis to rule out the bias in analysis to evaluate the causal effects of AFs in regulating the expression of circulating IGF family members' proteins. And there was no existed protocol.

Genome-wide association studies summary data of AF and IGF family

We acquired the genome-wide association studies (GWAS) summary data for AF from a comprehensive combination of sources, including the Nord-Trøndelag Health Study, the deCODE cohort, the MGI cohort, the DiscovEHR collaboration cohort, the AFGen Consortium, and the United Kingdom Biobank resource[15]. This dataset encompassed a total of 60620 AF cases and 970216 control participants. The identification of atrial fibrillation events within the summary dataset was based on diagnostic codes, self-reports, operation codes, or causes of death. Additionally, we utilized GWAS summary datasets from the FinnGen Biobank and the UK Biobank as duplications.

To identify SNPs associated with IGF family members, we extracted and selected data from the latest and largest genome-wide association studies (GWAS) available in the UK Biobank resource, the KORA cohorts[16], and the INTERVAL study[17]. These genetic associations were adjusted for age, sex, and body mass index. All the GWAS datasets we selected are presented in Table 1.

Genetic correlation analysis

We utilized LDSC (v1.0.1, https://github.com/bulik/Ldsc) software to assess the genetic correlations between AF and each member of the IGF family. LDSC is a robust approach for conducting genetic correlation analyses of complex diseases or traits. It allows for the discrimination between true polygenetic effects and potential mixed biases, encompassing implicit associations and demographic stratification. When a genetic association demonstrates both statistical and quantitative significance, it provides confirmation that the overall phenotypic association is not solely attributable to environmental confounding factors. In this study, we examined the linkage disequilibrium (LD) between AF and each IGF family member, employing the European 1000 G reference panel as the reference dataset. To establish statistical significance, we applied a stringent Bonferroni correction, setting the significant association threshold at $P > 0.00357$ (0.05/14). P values falling within the range of 0.00357 to 0.05 were considered suggestive of significance[18].

Mendelian randomization analysis

In the present study, we employed MR analysis to assess the potential causal relationship between each member of the IGF family and AF. We conducted the analysis using the inverse variance weighted (IVW) method and initially identified significant IGF family members through ldSC analysis, which were subsequently included in further analyses. For each IGF family member, we selected SNPs strongly predictive of exposure at the genome-wide significance level ($P < 5 \times 10^{-8}$). To minimize potential pleiotropy, we excluded SNPs associated with multiple cytokines. Additionally, we retained SNPs

Table 1 All genome-wide association study datasets selected in this article

Trait	GWAS id	Sample size	Number of SNPs
Atrial Fibrillation	ebi-a-GCST006414	1030836	33519037
Atrial Fibrillation	ukb-b-536	337199	10894596
Atrial Fibrillation	finn-b-I9_AF	-	16379794
IGF-1	prot-c-2952_75_2	-	501428
IGF-I sR	prot-c-4232_19_2	-	501428
IGF-IIR	prot-c-3676_15_3	-	501428
IGFBP-1	prot-c-2771_35_2	-	501428
IGFBP-2	prot-c-2570_72_5	-	501428
IGFBP-3	prot-c-2571_12_3	-	501428
IGFBP-4	prot-c-2950_57_2	-	501428
IGFBP-5	prot-c-2685_21_2	-	501428
IGFBP-6	prot-c-2686_67_2	-	501428
IGFBP-7	prot-c-3320_49_2	-	501428
IGF-LR1	prot-a-1455	3301	10534735
CTGF	prot-c-2975_19_2	-	501428
WISP-1	prot-c-3057_55_1	-	501428
CYR61	prot-a-758	3301	10534735

GWAS: Genome-wide association study; SNPs: Single nucleotide polymorphisms.

with low linkage disequilibrium ($r^2 < 0.1$) to avoid the confounding effects of correlated SNPs. However, it should be noted that despite these efforts, none of the SNPs associated with IGF family members showed significant associations with AF in the harmonized GWAS datasets. Consequently, we adopted a more stringent cutoff ($P < 1 \times 10^{-5}$) to select SNPs predicting IGF family members. We reported the number of included SNPs, along with effect estimates, confidence intervals, and *P* values.

MR estimates were derived using the IVW method and the MR-Egger method, both implemented under a random-effects model. To assess the robustness of our IVW results, we conducted tests for heterogeneity, multiple validity tests, and sensitivity analyses using weighted median estimation and MR–Egger regression. The TwoSampleMR packages[19] (version 0.5.6) in R (version 4.0.4) were utilized for performing the MR analysis. The statistical significance level was set at $P < 0.05$.

RESULTS

Causal effects of serum IGF family member concentrations on the risk of AF

Fourteen molecules were included in the first one-sample MR to identify SNPs potentially influencing their serum concentrations; IGF1 (prot-c-2952_75_2), IGF1-sR (prot-c-4232_19_2), IGF2R (prot-c-3676_15_3), IGFBP1 (prot-c-2771_35_2), IGFBP2 (prot-c-2570_72_5), IGFBP3 (prot-c-2571_12_3), IGFBP4 (prot-c-2950_57_2), IGFBP5 (prot-c-2685_21_2), IGFBP6 (prot-c-2686_67_2), IGFBP7 (prot-c-3320_49_2), IGF-LR1 (prot-a-1455), CTGF (prot-c-2975_19_2), WISP1 (prot-c-3057_55_1), and CYR61 (prot-a-758). Of the 14 IGF family members with serum concentrations reported in published studies, 13 were associated with more than one genomewide significant SNP site. Detailed information after clumping of LD-independent SNPs as exposure are presented in Supplementary material. All F-statistics were above 10, indicating that the results were less likely to be affected by weak instrument bias.

In the first one-step MR analysis the MR-Egger method and the IVW method were used. More than one significant SNP was identified at the genome-wide level ($P < 0.001$), and these SNPs were used to calculate causal associations with AF. In pooled data analysis three molecules were associated with AF. Lower levels of circulating IGF1 were negatively associated with AF onset [odds ratio (OR) 0.918, 95% confidence interval (CI) 0.849–0.993, MR-Egger analysis]. IGFBP3 was negatively correlated with AF prevalence in both WM analysis (OR 0.964, 95%CI: 0.940–0.960, $P = 0.006$) and IVW analysis (OR 0.968, 95%CI: 0.947–0.987, $P = 0.001$). Higher serum IGF2R was positively correlated with AF pathogenesis in MR-Egger analysis (OR 1.045, 95%CI: 1.016–1.076, $P = 0.039$). Other IGF family members were not significantly associated with the risk of AF (Figure 1).

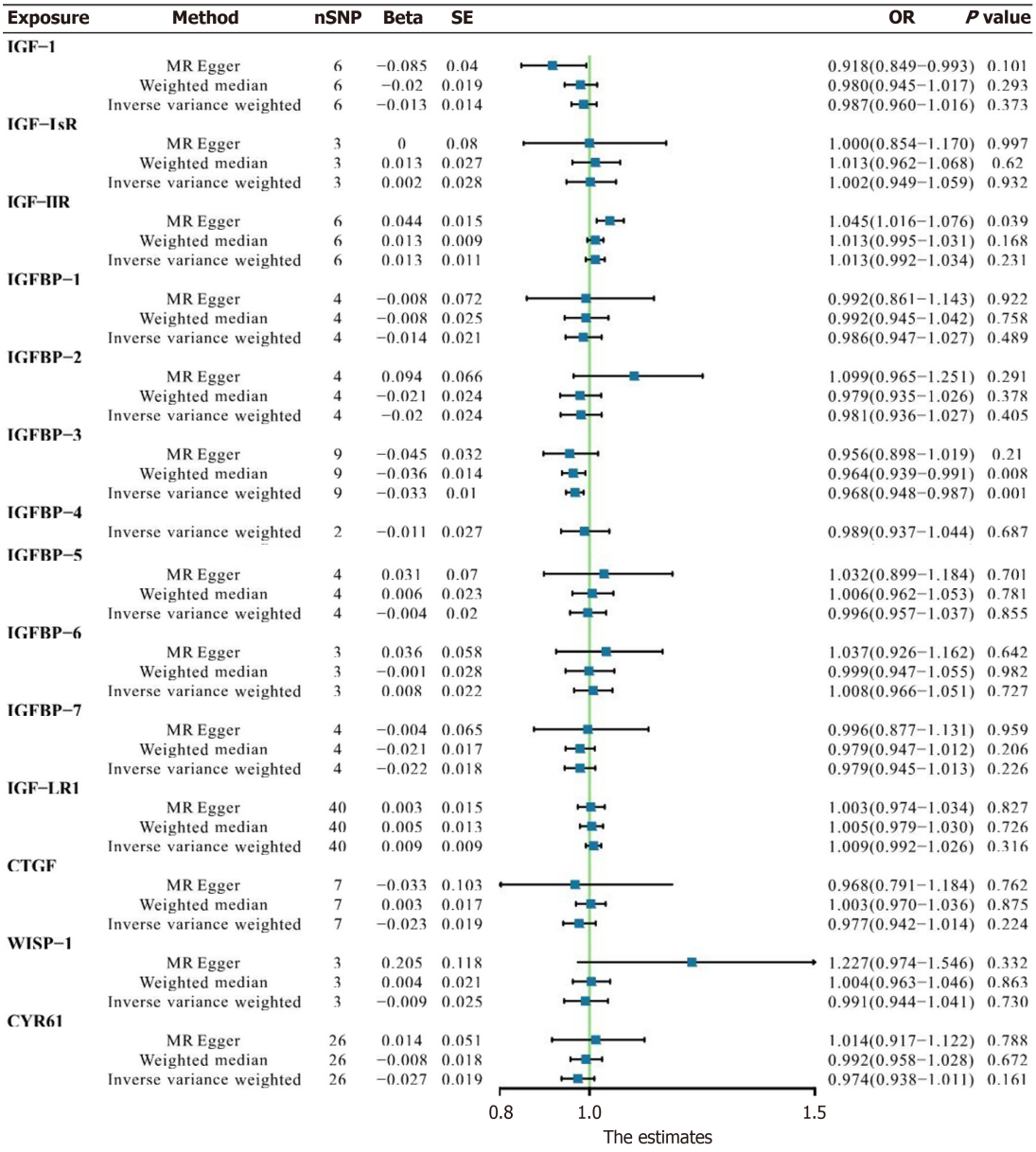

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Figure 1 Causal effect estimates of insulin-like growth factor family members on atrial fibrillation outcomes.

In IGF1 and IGF2R assessments, neither finn-b-19_AF (OR 0.873, 95%CI: 0.652–1.169, P = 0.414 and OR 0.976, 95%CI: 0.912–1.045, P = 0.528, respectively) nor ukb-b-964 (OR 0.994, 95%CI: 0.988–0.999, P = 0.154 and OR 1.000, 95%CI: 1.000–1.001, P = 0.167, respectively) yielded any significant results in MR-Egger or IVW analyses. The significant negative correlation between IGFBP3 and AF was confirmed in finn-b-19_AF trait analysis (OR 0.950, 95%CI: 0.907–0.955, P = 0.029), indicating that lower serum IGFBP3 contributes to AF (Figure 2).

Evaluation of causal effects of IGF family member expression on AF

Analyses were conducted to identify causal associations between serum IGF family member levels and AF. There was no convincing evidence of genetic associations between IGF family member expression and AF. In basic IVW analysis based on the ebi-a-GCST006414 trait, CYR61 was significantly positively correlated with AF (OR 1.060, 95%CI: 1.005–1.119, P = 0.031, Figure 3). In a more detailed validation test however, CYR61 was not positively correlated with finnb19_AF or ukb-b-964 traits as determined *via* any analysis methods (Figure 4).

DISCUSSION

In this study two-sample MR analyses using multiple GWAS datasets was conducted to assess relationships between individual IGF family members and AF. Results indicated that genetically determined lower levels of IGF1 and IGFBP3, as well as genetically determined higher levels of IGF2R, contribute to increased risk of AF. The presence of AF was

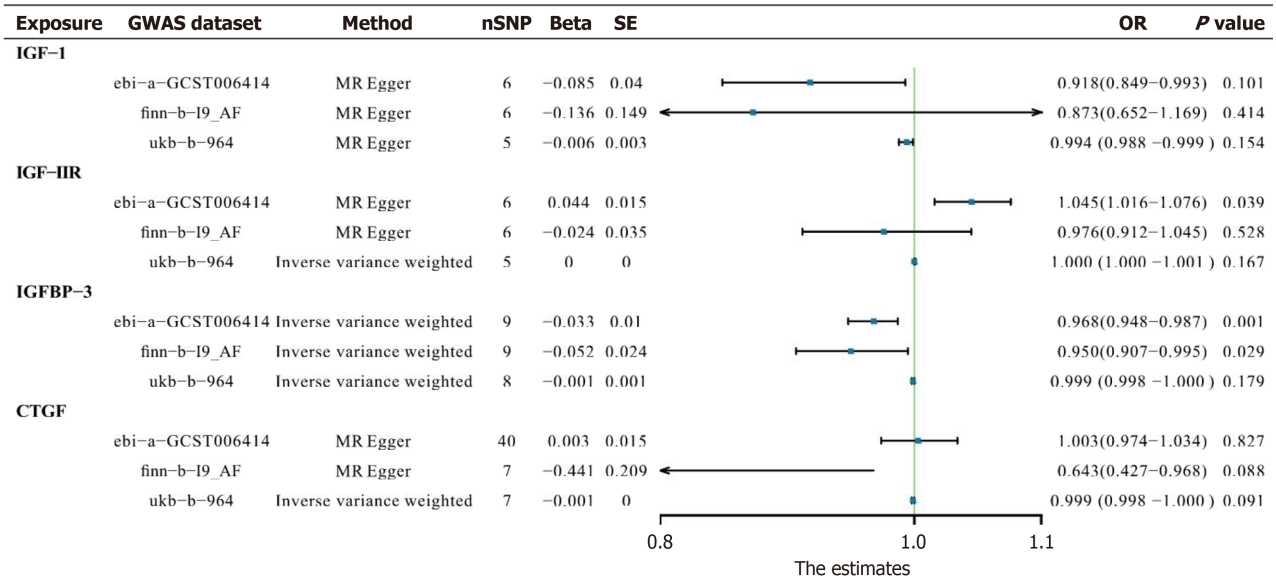

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Figure 2 Detected associations between genetically predicted insulin-like growth factor family members and risk of atrial fibrillation in different genome-wide association study datasets.

genetically associated with elevated CYR61 levels. To the best of our knowledge the current study is the first comprehensive MR analysis systematically investigating associations between multiple IGF family members and AF.

In the present study a genetically determined decrease in circulating IGF1 was associated with an increased incidence of AF, a finding consistent with previously published MR analyses[20] and observational trials[10,21]. IGF1, a 70-amino acid peptide, is primarily synthesized in the liver and regulated by hypothalamic growth hormone-releasing hormone and pituitary growth hormone[22]. Notably IGFBP3—the most abundant binding partner of IGF1—was significantly positively associated with AF. Numerous studies have identified effects of IGF1 on the cardiovascular system, linking abnormalities in IGF1 levels to elevated risks of cardiovascular diseases, including atherosclerosis, hypertension, and coronary artery disease. Furthermore, IGF1 levels are age-dependent, peaking during puberty and declining throughout the remainder of life. IGFBP3, like IGF1, exhibits growth hormone-dependent regulation. Recent *in vivo* studies indicate that fetal growth restriction in mice leads to IGF1 deficiency and an increased risk of adult cardiovascular diseases. Moreover, intrauterine administration of additional IGF1 can mitigate the risk of adult cardiovascular diseases in a mouse fetal growth restriction model[23]. These effects are reportedly mediated by a deficiency in the mTORC1 pathway[24], a downstream component of the IGF1 pathway[25]. Studies in elderly populations have revealed significantly lower mean serum levels of IGF1 (P = 0.02) and IGFBP3 (P = 0.03) in AF patients than in non-AF participants[21]. A population-based study yielded similar results, further suggesting that low IGF1/IGFBP3 ratios are associated with a higher prevalence of AF[10]. Therefore our findings align with previous research suggesting that insufficient levels of IGF1 and IGFBP3 throughout life, particularly during periods of higher circulating IGF1 and growth hormone, significantly contribute to the onset of AF. These biomarkers hold potential for the prevention of AF.

In addition to IGF1 and IGFBP3, in the current study elevated levels of IGF2R were associated with AF. IGF2R, also known as the cation-independent mannose-6-phosphate receptor, comprises a substantial N-terminal extracellular region, a single membrane-spanning region, and a small cytoplasmic tail. Its primary role is to regulate circulating and tissue levels of IGF2 by targeting it for lysosomal degradation, thereby modulating IGF2 activity[26]. Both IGF2 and IGF2R have been implicated in placental and fetal growth and development. SNPs within IGF2R have been linked to increased risks of growth abnormalities, reduced growth rates during the first 3 years of life, and certain cancers[27-29]. Recent research suggests that an unfavorable intrauterine environment can induce epigenetic changes in the IGF2/H19 and IGF2R genes, subsequently altering the expression of IGF2 and IGF2R[30,31]. In animal studies fetal myocardial levels of IGF2 and IGF2R increased in response to reduced placental substrate supply in lambs[32]. In mice inactivation of the maternal IGF2R allele resulted in excessive growth and perinatal lethality, a phenotype that could be rescued with an IGF2 null allele[33]. Notably, protein abundance was inversely associated with relative left ventricle weight in models with reduced placental function, whereas it exhibited a positive correlation in the control group. This suggests that the IGF2R signaling pathway may be pathologically activated, leading to ventricular hypertrophy[32].

Previous reports have discussed the potential benefits of suppressing the IGF2R signaling pathway, such as protecting against myocardial cell apoptosis and preventing the progression of heart failure[34]. The present study provides the first indication of a potential correlation between IGF2R and AF, underscoring the potential for fetal pathological effects on the occurrence of adult cardiovascular diseases, including AF. Notably however, our literature review did not identify any observational studies investigating relationships between IGF2R and AF. Further research is therefore warranted, to investigate IGF2R as a potential biomarker of AF, and to deepen our understanding of its role in AF pathogenesis.

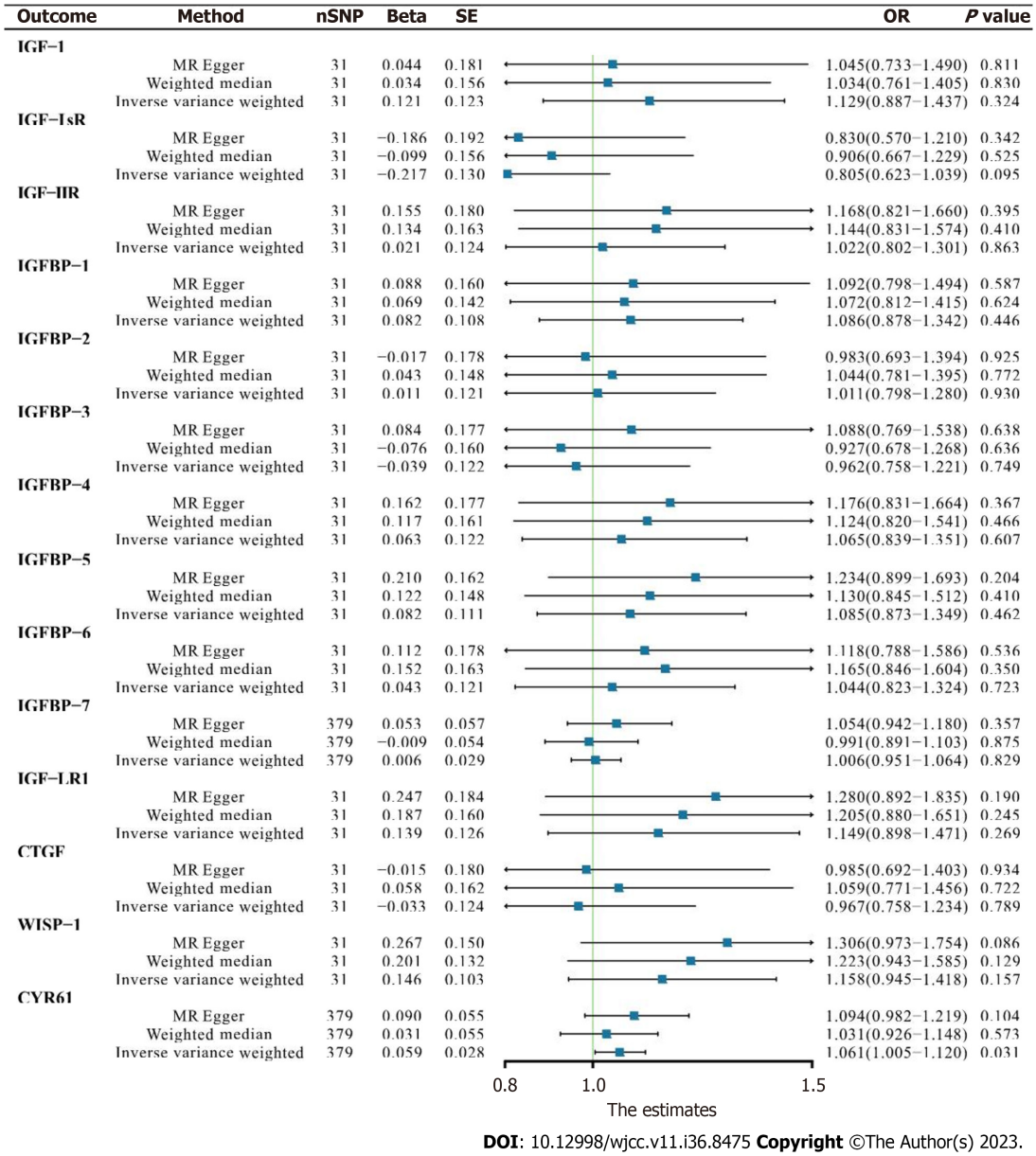

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Figure 3 Causal effect estimates of atrial fibrillation on insulin-like growth factor family members outcomes.

In the present study there was a correlation between AF and alterations in CYR61 Levels in circulation. CYR61, also known as cellular communication network factor 1 (CCN1), belongs to the CCN family of matricellular proteins and plays pivotal roles in angiogenesis, inflammation, and the repair of fibrotic tissue[35-37]. Observational studies have consistently indicated significant increases in CYR61 within atherosclerotic lesions rich in vascular smooth muscle cells. Such studies have also identified CYR61 increases in the cardiomyocytes of individuals with ischemic cardiomyopathy, and STelevation in myocardial infarction patients[38-40]. Furthermore, the addition of CYR61 to the reference GRACE risk score led to improved risk stratification for all-cause mortality, surpassing the predictive capacity of high-sensitivity troponin T in subsequent analyses[40]. In the current study a preliminary CYR61-related result suggested that AF may induce increased CYR61 expression, but more detailed investigations did not confirm this. Thus a causal association between AF and CYR61 was not convincingly demonstrated. Notably however, levels of circulating CYR61 may assist the functional assessment of cardiovascular diseases.

The present study investigated associations between fourteen IGF family members and AF, and identified potential relationships with respect to three of them. Bidirectional analysis indicated that AF may influence CYR61. The use of MR analysis and large European GWAS datasets in the study conferred a substantial advantage with respect to reduced susceptibility to inverse causality, confounding, and biases inherent in the use of small sample sizes. The study also had some limitations. Primarily, the use of a higher significance threshold ($P < 1 \times 10^{-5}$) for SNP selection from GWAS datasets on IGF family members was necessitated by the limited number of IGF family members that yielded at least one genome-wide significant SNP when using the conventional threshold of $P < 5 \times 10^{-8}$. Thirteen IGF family members exhibited multiple genome-wide significant SNPs under the $P < 1 \times 10^{-5}$ threshold. A combined GWAS dataset was used for AF and atrial flutter, precluding distinction between these two arrhythmia subtypes. Due to unavailability of relevant datasets for

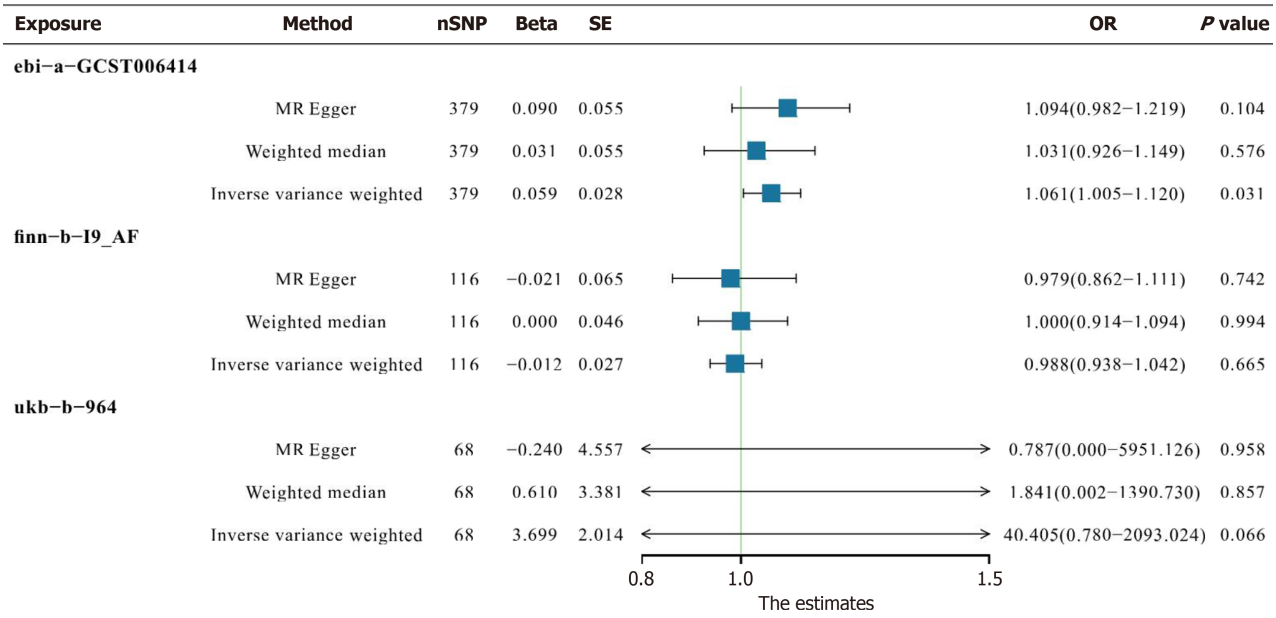

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Figure 4 Associations between genetically predicted CYR61* and risk of atrial fibrillation in different genome-wide association study datasets. *CYR61: Cysteine rich angiogenic inducer 61; AF: Atrial fibrillation.

each specific AF subtype, the study focused solely on associations between IGF family members and AF onset. We were unable to stratify our results based on different AF phenotypes. Given the multifaceted nature of AF pathogenesis, ascertaining the precise roles played by the identified IGF family members in AF pathogenesis remains elusive. The results of the current study emphasize the urgent need for further observational and experimental studies.

CONCLUSION

Based on GWAS summary datasets derived from AF and circulating IGF family members, we identified causal relationships between three IGF family members and AF *via* MR analysis. IGFBP3 was negatively correlated with AF prevalence in both WM analysis and IVW analysis. The study results provide novel insights into AF pathogenesis and the implications of serum IGF family member concentrations with respect to AF risk. Further observational and experimental studies are critically required.

ARTICLE HIGHLIGHTS

Research background

The etiology of atrial fibrillation is still unknown, and insulin-like growth factor had been suspected to be involved in atrial fibrillation.

Research motivation

The relationship between insulin-like growth factor and atrial fibrillation had not be well addressed.

Research objectives

This study was carried out to evaluate the causal effect of serum insulin-like growth factor family concentration on risk of atrial fibrillation.

Research methods

Mendelian Randomization analysis was performed based on genome-wide association study datasets of insulin-like growth factor family concentration and atrial fibrillation.

Research results

Lower levels of circulating insulin-like growth factor binding protein 3 was associated with atrial fibrillation.

Research conclusions

The study generated evidence on the potential roles of developmental pathological effects in the pathogenesis of atrial fibrillation.

Research perspectives

Further observational and experimental studies are critically needed.

FOOTNOTES

Co-corresponding authors: Yi-Fei Li and Gang Wu.

Author contributions: Lin S, Tang J and Li X collected the data; Lin S performed the MR analysis; Wu G, Lin YF and Li YF conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content; Wu G, Lin YF and Li YF were responsible for the revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

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