Cardiovascular Diabetology

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Circulating mediators linking cardiometabolic diseases to HFpEF: a mediation Mendelian randomization analysis

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Abstract

Background Heart failure with preserved ejection fraction (HFpEF) is an increasingly prevalent clinical syndrome with high morbidity and mortality. Although HFpEF frequently coexists with cardiometabolic diseases, the causal mechanisms and potential mediators remain poorly understood.

Objectives This study aimed to identify cardiometabolic risk factors specifically driving HFpEF and to determine their underlying circulating mediators.

Methods We used two-sample Mendelian Randomization (MR) to analyze the effects of obesity, Type 2 diabetes, hypertension, chronic kidney disease (CKD), and dyslipidemia on HFpEF and heart failure with reduced ejection fraction (HFrEF) in large European-ancestry GWAS datasets. We then performed mediation MR to identify plasma proteins and metabolites that mediate the transition from each cardiometabolic disease to HFpEF, respectively. We applied multivariable MR to assess the impact of risk confounding on the results. Bioinformatic analyses were conducted to delineate mechanisms.

Results Cardiometabolic diseases had heterogeneous effects on HFpEF and HFrEF. Obesity and type 2 diabetes showed adjusted causal effects with HFpEF, hypertension showed potential relevance to HFpEF, whereas dyslipidemia and CKD did not. MR analysis identified 5 proteins that mediate obesity to HFpEF; 5 proteins that mediate type 2 diabetes to HFpEF. Further mediation MR analysis of obesity and T2D on HFrEF revealed heterogeneity in circulating mediators between metabolic HFpEF and HFrEF. Comprehensive bioinformatics analyses showed that IL1R1, together with other proteins such as TP53 and FGF19, orchestrates the inflammatory and fibrotic processes underlying HFpEF.

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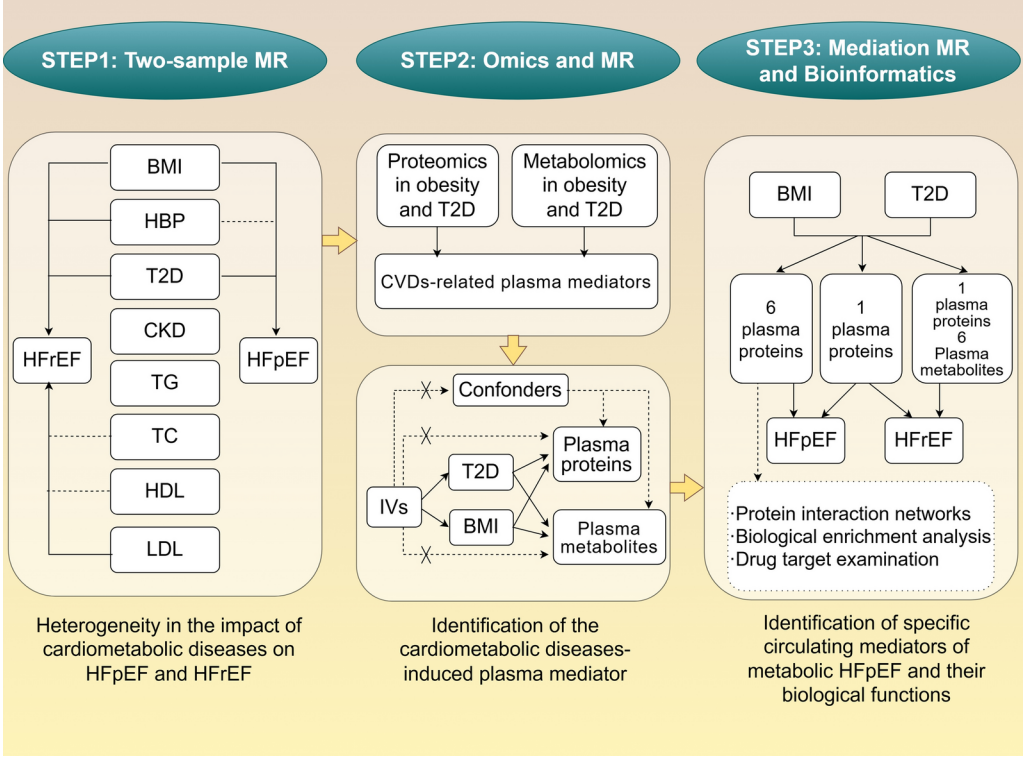
Conclusions These findings suggest that metabolic HFpEF has distinct etiological features compared with HFrEF and is driven by complex, condition-specific mediators. IL1R1 mediates HFpEF in multiple metabolic risk states, suggesting a potential therapeutic target. Further translational studies are warranted to evaluate anti-inflammatory strategies targeting IL1R1 in HFpEF.

Keywords HFpEF, Cardiometabolic diseases, Circulating mediators, Type 2 diabetes, IL1R1

Graphical Abstract



Research insights

What is currently known about this topic?

HFpEF prevalence is rising worldwide.
Cardiometabolic diseases are related to HFpEF.
Metabolic HFpEF involves complex regulatory mechanisms.

What is the key research question?

How do cardiometabolic diseases specifically drive HFpEF via circulating mediators?

What is new?

Metabolic HFpEF and HFrEF are heterogeneous.
Specific circulating mediators link cardiometabolic diseases to HFpEF.
IL1R1 may be a key target in metabolic HFpEF.

How might this study influence clinical practice?

Targeting IL1R1-related pathway may benefit HFpEF management.

Introduction

Heart failure is one of the leading causes of mortality, hospitalizations, and marked decline in quality of life among patients with cardiovascular diseases (CVDs) [1]. Heart failure can be classified into heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF). Although they share similar clinical symptoms, there are significant differences in underlying pathophysiology and patient characteristics [2]. Patients with HFpEF exhibit typical signs and symptoms of heart failure despite having a normal or near-normal left ventricular ejection fraction (usually ≥ 50%), whereas patients with HFrEF have an LVEF < 40% [1]. From a pathophysiological perspective, HFrEF is largely driven by the loss of cardiomyocytes (e.g., following myocardial infarction), resulting in systolic dysfunction. HFpEF, by contrast, is characterized by preserved systolic function, impaired diastolic filling,

and increased chamber stiffness. Globally, HFpEF currently accounts for about half of all heart failure cases [3]. Over the past few decades, although HFrEF incidence has declined, HFpEF incidence has increased. Compared to HFrEF patients, those with HFpEF are generally older and have a history of multiple cardiometabolic conditions [3]. Despite their differences, both HFpEF and HFrEF have high morbidity and mortality rates. However, research on HFpEF has lagged behind that of HFrEF, resulting in significant gaps in understanding and treatment. Historically, many pivotal heart failure trials have focused on HFrEF, yielding multiple effective therapies (e.g., β-blockers and RAAS inhibitors) [4]. By contrast, HFpEF has long been considered an "orphan" disease, with only a few therapies (e.g., sodium-glucose cotransporter 2 (SGLT2) inhibitors) recently showing clear benefits [5]. Conventional HFrEF treatments fail to improve outcomes in HFpEF, underscoring the complex and heterogeneous nature of HFpEF pathogenesis. Previous observational studies have shown that HFpEF has a high comorbidity rate with multiple cardiometabolic diseases, especially hypertension, type 2 diabetes (T2D), and obesity [6–9]. However, the specific contribution and molecular mechanisms of various cardiometabolic diseases to HFpEF need further study.

HFpEF is primarily driven by systemic metabolic factors [10]. Circulating mediators in plasma (e.g., proinflammatory cytokines, adipokines, fibrosis markers, and metabolic byproducts) can reflect the critical pathological processes linking metabolic conditions to cardiac remodeling [11]. Modern high-throughput omics approaches have greatly advanced this research. Proteomic studies have shown that patients with HFrEF and HFpEF exhibit distinct proteomic signatures, each enriched in different biological pathways [12]. Likewise, metabolomic studies have uncovered differences in circulating metabolites between HFpEF and HFrEF, further underscoring the biological heterogeneity and complexity of HFpEF [13]. Therefore, it is important to study the specific cardiometabolic diseases-induced HFpEF through these circulating factors. As it helps identify the mechanistic pathways driving the disease and may uncover potential therapeutic targets or biomarkers. Mendelian randomization (MR) and other genetics-based methods have emerged as powerful tools to test causal hypotheses regarding biomarkers and risk factors [14]. MR uses genetic variants as instrumental variables to infer causality in risk-outcome relationships, helping to address confounding factors present in observational studies [15]. In HFpEF research, MR can help pinpoint which plasma proteins or metabolites are not only associated with HFpEF but also potentially mediate its development in a cardiometabolic environment. This approach may uncover new pathophysiological insights and therapeutic targets for HFpEF [16]. In this study, we first used two-sample Mendelian randomization analyses to verify the heterogeneous effects of cardiometabolic conditions, including obesity, T2D, dyslipidemia, hypertension, and chronic kidney disease (CKD) on HFpEF and HFrEF. Next, we performed a two-step MR analysis and identified circulating mediators that link these cardiometabolic diseases to HFpEF. Our findings include 5 plasma proteins mediating the effect of obesity to HFpEF, 5 plasma proteins mediating the effect of T2D on HFpEF. We focused on circulating mediators that mediate metabolic HFpEF, with the goal of discovering independent mechanisms of HFpEF. Using protein–protein interaction analyses and mediation effect estimates, we found that IL1R1 is a key circulating mediator that underlies HFpEF induced by cardiometabolic conditions. Unlike previous studies that primarily described associations between metabolic dysfunction and HFpEF, we found that specific cardiometabolic diseases had adjusted causal effects on HFpEF. Our study describes plasma mediators linking cardiometabolic diseases to specific pathogenesis in HFpEF. We identified previously unrecognized pathways and key regulatory molecules mediating these interactions, providing a more complete understanding of disease mechanisms. Furthermore, our findings pave the way for innovative strategies for the prevention, diagnosis, and treatment of HFpEF by highlighting potential therapeutic targets and biomarkers that can be exploited for precision medicine approaches .

Methods

Data sources for instrumental variables

All genetic instrumental variable data for cardiometabolic traits and heart failure were obtained from public datasets (Table S1). To minimize potential bias due to population stratification, we used data from individuals of European ancestry only. Genome-wide association study (GWAS) summary statistics for BMI (as an indicator of obesity) [17], T2D [18, 19], hypertension [20], eGFR [21] and dyslipidemia (including high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), and total cholesterol (TC) were obtained from the large cohorts such as UK Biobank (UKB) [22, 23]. The BMI meta-analysis included association results from 125 studies with up to 339,224 individuals, of which 82 studies had GWAS results (n = 322,154). The T2D-related GWAS data were from 659,316 individuals of European ancestry. The hypertension-related GWAS data were from 152,249 UK Biobank participants, and the eGFR GWAS meta-analysis included 54 cohorts of European ancestry (n = 567,460), and the major lipid GWAS data were from 393,193 to 441,016 UK Biobank participants. Genetic data for heart failure were from the Million Veterans Program (MVP) for individuals of European ancestry, including 187,840 controls and 23,363 heart failure

patients [24]. Details of these traits are provided in Supplementary Table S1. Relevant SNPs reaching genome-wide significance ($P < 5 \times 10^{-8}$) were considered as candidate instrumental variables (IVs). Next, we removed single-nucleotide polymorphisms (SNPs) in linkage disequilibrium ($r^2 < 0.001$ within a 10,000 kb range) or those with palindromic alleles of intermediate allele frequency. We also excluded SNPs unavailable in the outcome dataset or those with only proxy SNPs. We calculated the F statistic to evaluate the strength of IV-exposure associations. Only SNPs with an F statistic > 10 were considered valid and reliable IVs (Table S1).

To obtain genetic instruments for target plasma proteins, we accessed genetic summary data from the deCODE database, which included 35,559 participants [25]. This dataset provides genetic associations for 4,907 circulating proteins, validated extensively through protein quantitative trait loci (pQTL) analysis [26]. For each circulating protein, we selected independent and significant pQTLs according to a standardized protocol ($P < 5 \times 10^{-8}$, $r^2 < 0.0001$) to remove linkage disequilibrium, with clumping performed using the European 1000 Genomes reference panel. Similarly, we calculated the F statistic for each instrument and deemed only those with an F statistic > 10 to be valid and reliable IVs, thereby minimizing weak-instrument bias. All data used in this study were from publicly available GWAS summary-level datasets, requiring no further ethical approval. Data on plasma metabolomics were derived from summary-level GWAS findings on 1,091 circulating metabolites and 309 metabolite ratios [27]. We applied the same instrument selection criteria as above. We screened for highly relevant genetic instruments for all cardiometabolic factors. All data used in this study were from publicly available GWAS summary-level datasets that required no additional ethics approval.

Multi-omics analysis

We obtained proteomics data that differed in plasma between healthy people and obese or T2D patients from the Human Protein Atlas (https://www.proteinatlas.org/) [28]. We matched CVDs-related proteins that were differentially expressed in plasma of T2D or obesity from and MalaCards databases [29]. We integrated data from two large clinical metabolomics cohorts to obtain metabolites that were potentially related to T2D and obesity [30, 31].

MR analysis

In order for the results of MR to be valid, three core assumptions must be met [32]. First, the genetic instrumental variables must be strongly correlated with the risk factors, and second, the genetic variants should not be associated with confounding factors; in addition, the genetic variants should only affect the outcomes through risk factors, that is, the correlation assumption, the independence assumption, and the exclusion of restriction assumptions. To this end, after screening the genetic instrumental variables according to the above criteria, we performed relevant MR analysis as well as rigorous sensitivity analysis and horizontal pleiotropy tests to ensure the reliability of our MR results [15].

We employed two-sample MR and mediation MR approaches to investigate the causal effects of circulating mediators in cardiometabolic HFpEF. In the initial analysis, we used data from two European-ancestry datasets and applied the random-effects inverse variance weighting (IVW) method to estimate the causal effects of all cardiometabolic diseases on the two heart failure subtypes [33]. To assess the causal effects of multiple exposure factors on the outcomes, we further adopted MVMR, which allows multiple exposure factors to be included in the same model simultaneously to adjust for potential confounding effects between them, thereby more accurately assessing the causal relationship of a single exposure [32]. We included the exposure factors that showed positive results in the MR analysis as independent variables and performed multivariate analysis in the same model. The statistical significance of the *P* value after Bonferroni correction was set at 0.0031 (8 exposure factors and 2 outcomes). *P* values between 0.05 and 0.0031 were considered suggestive evidence of a potential causal relationship [34]. The mediation MR approach provided evidence for the mediating role of each circulating factor in the exposure-outcome relationship. We extracted the instrumental variables for mediators found significant in the first step to determine the causal influence of these mediators on heart failure. Effect sizes were expressed as odds ratios (OR) with 95% confidence intervals (CIs). Using genetic instruments for cardiometabolic diseases, we evaluated the causal influence of these diseases on candidate mediators. Next, we quantified the proportion of the effect mediated by each candidate by dividing the indirect effect by the total effect. Bootstrap methods were used to estimate the confidence intervals. Moreover, to ensure robust results from the IVW method, we performed complementary analyses: weighted median and MR-Egger. Because the Bonferroni correction is too stringent and leads to a steep increase in the risk of false negatives in large-scale omics analyses, we used the Benjamini–Hochberg method to correct *P* values for false discovery rate (FDR). When the IVW adjusted *P* value was < 0.1, all methods showed consistent effect directions, and no horizontal pleiotropy was detected, we considered the findings statistically significant [35–37]. This threshold helps maintain statistical power while controlling type I error.

To ensure the reliability of the genetic IVs we selected for predicting causal effects and to adjust for potential biases and other confounding factors, we performed sensitivity tests on all MRs. We used MR-Egger regression and MR-PRESSO to detect and correct potential horizontal pleiotropy. A non-zero MR-Egger intercept may indicate directional pleiotropy, while MR-PRESSO can identify and remove outlier IVs. We used the Cochran's Q statistic to assess heterogeneity among SNP effect estimates in each MR association. If the intercept of the MR-Egger model does not deviate significantly from 0, it means that the SNPs are unlikely to have horizontal pleiotropy. Using MR-PRESSO to remove abnormal SNPs helps us further evaluate whether the causal effect of MR is still robust after removing genetic overlapping genetic instrumental variables. All MR studies followed the STROBE-MR guidelines [38]. Finally, we visualized the results using heat maps, forest plots, and tables. All analyses were performed in R version 4.4.2 using the packages "TwoSampleMR (version 0.6.8)", "MRInstruments (version 0.3.2)", "MendelianRandomization (version 0.10.0)", "VariantAnnotation (version 1.50.0)", "MVMR (version 0.4)", "ieugwasr (version 1.0.3)", "gwasglue (version 0.0.0.9000)", "gwasvcf (version 0.1.2)", "forestploter (version 1.1.2)", and "ComplexHeatmap (version 2.15.4)".

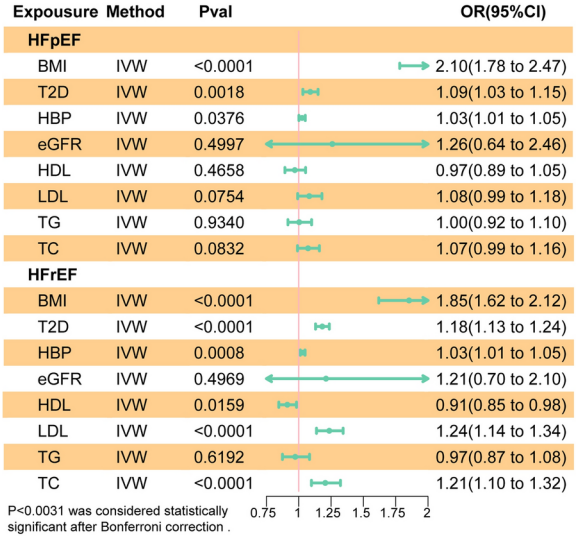


Fig. 1 Effects of cardiometabolic diseases on HFpEF and HFrEF IVW were used to investigate the association between cardiometabolic diseases and Heart failure. When the OR value is greater than 1, we believe that this exposure is acting as a risk factor and has a causal effect. If it is less than 1, it may act as a protective factor. BMI: body mass index; T2D: type 2 diabetes mellitus; HBP: high blood pressure; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides; TC: total cholesterol; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; OR: Odds ratio; IVW, Inverse-variance weighting; 95% CI, 95% confidence interval. *P* value < 0.05 was considered statistically significant

Protein–protein interaction network analysis

The Search Tool for the Retrieval of Interacting Genes (STRING) is an online resource for assessing protein–protein interaction (PPI) networks [39]. We used STRING (version 12.5) to evaluate the potential PPIs among these differentially expressed genes (DEGs). The confidence score threshold was set to ≥ 0.4, and the maximum number of interactors was limited to ten. The resulting PPI network was constructed and visualized using Cytoscape 3.6.0 [40].

Gene enrichment analysis

To explore potential biological processes in which the circulating mediators may be involved, we used the R package "ClusterProfiler" to perform Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses on the target interaction network. GO analysis was used to annotate biological processes, molecular functions, and cellular components. KEGG was used to annotate gene pathways. Enrichment was deemed significant if adjusted $P < 0.05$. We then used the "enrichplot (version 1.10.1)" package in R 4.4.2 to visualize enrichment results.

Drug-target prediction analysis

We used the following online resources to assess the druggability of candidate circulating mediators: Therapeutic Target Database [41], Drug-Gene Interaction Database [42], DrugBank [43]. We also explored the potential ligand-receptor pairs from CellChatDB [44]. Each database reported drug-gene pairs for both approved and unapproved drugs.

Results

Effects of cardiometabolic diseases on HFpEF and HFrEF

To investigate the causal relationships of each cardiometabolic disease with the two heart failure subtypes, we conducted two-sample MR. The exposures included BMI (as an obesity measure), T2D, hypertension, eGFR (as a measure of CKD), and dyslipidemia (including HDL, LDL, TG, TC). We then examined HFpEF and HFrEF as outcomes. Using stringent statistical filtering based on the standard methodology described earlier, we ultimately selected 541 exposure-related IVs, all of which had an F statistic > 10. Among them, 30 were strongly associated with BMI, 106 with T2D, 21 with hypertension, 53 with eGFR, and 255 with dyslipidemia (87 for HDL, 44 for LDL, 58 for TC, 66 for TG). In the two-sample MR analysis using HFpEF as the outcome, IVW estimates showed positive causal associations of BMI (OR = 2.10, 95% CI = 1.78–2.47, $P < 0.0001$), T2D (OR = 1.09, 95% CI = 1.03–1.15, $P = 0.0018$), hypertension (OR = 1.03, 95% CI = 1.01–1.05, $P = 0.0376$) with HFpEF (Fig. 1). To ensure the reliability of the causal relationship, we performed a

Bonferroni correction test (the significance threshold was 0.0031). After correction, BMI and T2D remained statistically significant. This indicates that obesity and T2D have positive causal effect in HFpEF as risk factors. However, hypertension was no longer significant, suggesting that this potential causal relationship may be affected by other exposure factors. Weighted median similarly showed significant positive effects of these exposures on HFpEF, strengthening the causal inference. MR-Egger intercept tests did not indicate directional pleiotropy. Although IVW heterogeneity testing yielded $P<0.05$, MR-PRESSO indicated that removing outliers did not bias the final estimates, suggesting that heterogeneity did not compromise our results. Leave-one-out analyses confirmed that no single extreme SNP drove the overall effect, supporting the robustness of our findings (Table S3). We observed no causal effects for eGFR (OR = 1.26, 95% CI = 0.64–2.46, $P=0.4997$) or dyslipidemia (HDL (OR = 0.97, 95% CI = 0.89–1.05, $P=0.4658$), LDL (OR = 1.08, 95% CI = 0.99–1.18, $P=0.0754$), TG (OR = 1.00, 95% CI = 0.92–1.10, $P=0.9340$), TC (OR = 1.07, 95% CI = 0.99–1.16, $P=0.0832$)) on HFpEF. Although these metabolic conditions frequently coexist with HFpEF, our analysis does not support the conclusion that CKD or dyslipidemia alone causes HFpEF.

In contrast, when considering HFrEF as the outcome in our MR analysis, we observed positive causal relationships for BMI (OR = 1.85, 95% CI = 1.62–2.12, $P<0.0001$), T2D (OR = 1.18, 95% CI = 1.13–1.24, $P<0.0001$), hypertension (OR = 1.03, 95% CI = 1.01–1.05, $P=0.0008$), and dyslipidemia (LDL (OR = 1.24, 95% CI = 1.14–1.34, $P<0.0001$), TC (OR = 1.21, 95% CI = 1.10–1.32, $P<0.0001$)) with HFrEF. Each of these cardiometabolic traits raised the risk of HFrEF. The inverse causal relationship with HFrEF in HDL (OR = 0.91, 95% CI = 0.85–0.98, $P=0.0159$). After Bonferroni correction test, the causal effects of BMI, T2D, hypertension, LDL and TC on HFrEF remained statistically significant, whereas the results for HDL were no longer significant. Furthermore, we found no evidence of a causal association for eGFR (OR = 1.21, 95% CI = 0.70–2.10, $P=0.4969$) or TG (OR = 0.97, 95% CI = 0.87–1.08, $P=0.6192$) with HFrEF (Table S3) Weighted median also demonstrated significant positive effects of these exposures, further confirming the causal relationships. The MR-Egger intercept test provided no evidence of directional pleiotropy. Thus, strong causal evidence supports substantial heterogeneity in the circulating microenvironment mechanisms linking cardiometabolic diseases to HFpEF versus HFrEF.

Because the genetic tools of obesity and T2D may overlap, we further performed MVMR analyses to assess whether each exposure still directly causes HFpEF after adjusting for the genetic correlations between these risk factors. MVMR confirmed that obesity ($P<0.0001$) and T2D ($P=0.0006$) retained significant causal associations with HFpEF (Table S3). The MVMR results showed that after adjusting for other risk factors, the causal effects of T2D or BMI on HFpEF remained significant.

In HFrEF, we also performed MVMR analyses to assess whether each exposure still causes HFrEF after adjusting for the genetic correlations between these risk factors (Table S3). MVMR confirmed that BMI ($P<0.0001$), T2D ($P=0.0001$), hypertension ($P=0.0034$) and LDL ($P<0.0001$) remained significant. However, TC ($P=0.478$) lost significance, this suggests that his causal effect is confounded.

Identification of the cardiometabolic diseases-induced plasma mediator

Both BMI and T2D lead to an increased risk of HFpEF and HFrEF. We found plasma proteins that were differentially expressed in T2D and obesity in the large human proteomics database (www.proteinatlas.org) (Table S3-S5), and compared them with disease-related protein databases (www.malacards.org) to find potential CVDs-related proteins [29]. Through plasma metabolomics of two large clinical cohorts, we screened metabolites associated with cardiometabolic diseases (Table S6-S7). We then identified genetic IVs that were strongly associated with plasma proteins and metabolites. Among them, proteins and metabolites with no significant associated instrumental variables were excluded through the instrumental variable screening method mentioned in the method. After FDR correction, we included 42 CVDs-related proteins and 168 metabolites (or metabolite ratios) differentially expressed in obese patients and 54 CVDs-related proteins and 172 metabolites (or metabolite ratios) differentially expressed in T2D for further causal effect inference.

We performed two sample MR to determine whether there is a direct causal relationship between BMI, T2D, and these circulating mediators, rather than just coexistence (Fig.2). IVW analysis systematically evaluated the potential causal effects of BMI and T2D on plasma protein and metabolite levels (Table S8-S11). We then performed multiple testing corrections to verify the reliability of our causal inferences. The results showed that BMI significantly affected the levels of 21 plasma proteins, while T2D also showed a causal effect on the levels of 16 plasma proteins. In addition, we identified a causal relationship between BMI and 5 metabolites or metabolic ratios, while T2D also had a significant causal association with 24 metabolites or metabolic ratios. In order to verify the robustness of the results obtained by the IVW method, we further used MR Egger and Weighted Median method for supplementary analysis. The results showed that these methods were consistent with the

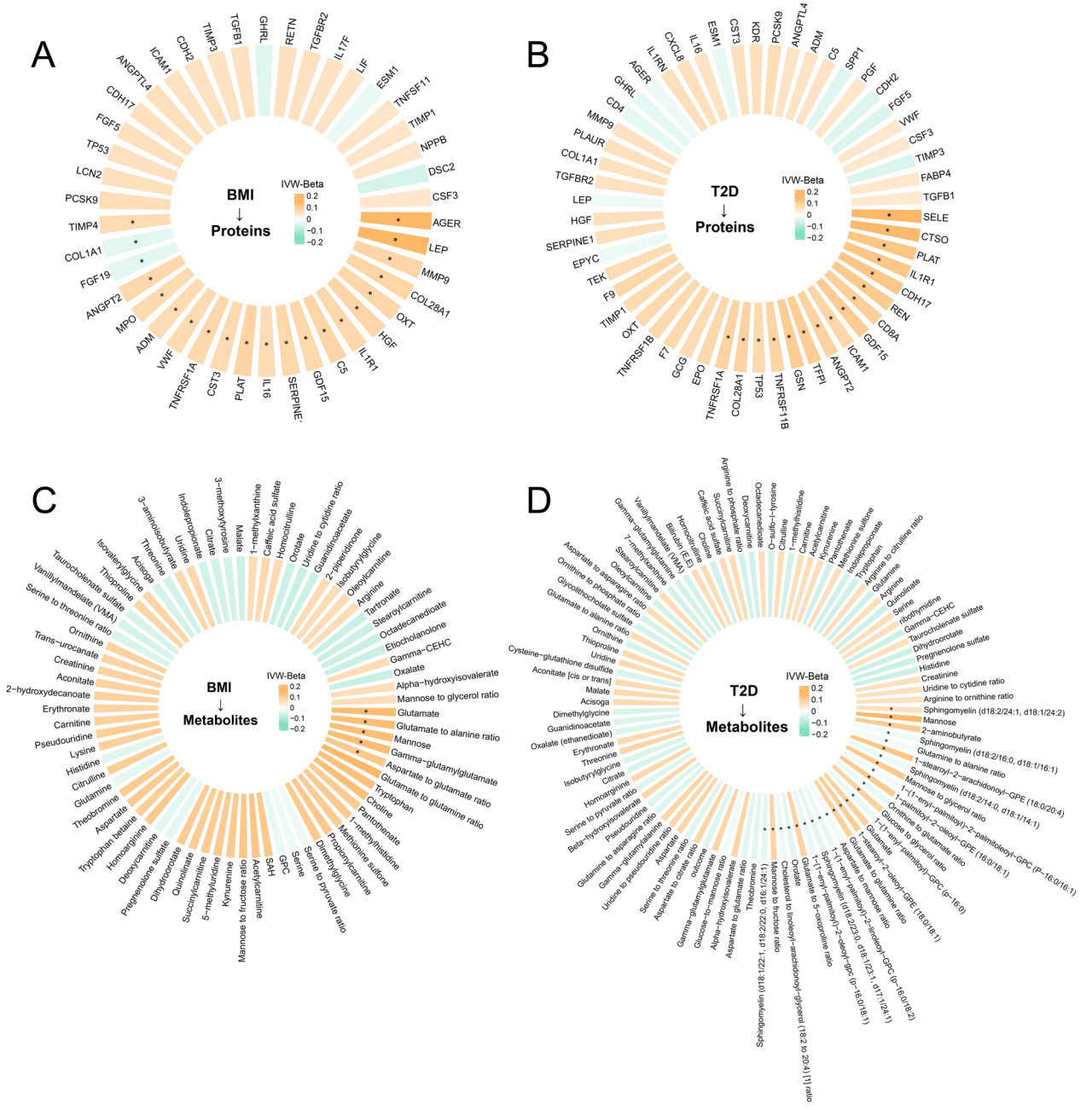


Fig. 2 Cardiometabolic disease-induced plasma mediator heatmaps show the impact of cardiometabolic disease to plasma proteins and plasma metabolites. When the IVW beta value > 0, it indicates a positive causal relationship, and when the IVW beta value < 0, it indicates a negative causal relationship, "*" indicates that the IVW analysis results are statistically significant: (**A**): Effect of plasma protein expression and concentrations by BMI. (**B**): Effects of plasma protein expression and concentrations by T2D. (**C**): Effects of plasma metabolites expression and concentrations by BMI. (**D**): Effects of plasma metabolites expression and concentrations by T2D

IVW analysis in the direction of effect, further enhancing the reliability of the research conclusions.

Identification of causal mediators in HFpEF or HFrEF

We further explored the potential roles of these cardiometabolic diseases-induced proteins in the risk of HFpEF and HFrEF and analyze their differences in the pathogenic mechanisms of the two heart failure subtypes. To this end, we used mediation MR analysis to evaluate the mediating role of these proteins in the pathogenesis of HFpEF and HFrEF (Fig. 3). After FDR correction, we identified cardiometabolic diseases-induced proteins with significant causal associations with HFpEF, including TIMP4 (OR = 0.91, 95% CI = 0.86–0.97, *P(adj)* = 0.0411), COL28A1 (OR = 1.32, 95% CI = 1.08–1.61, *P(adj)* = 0.0063), C5 (OR = 1.22, 95% CI = 1.04–1.44,

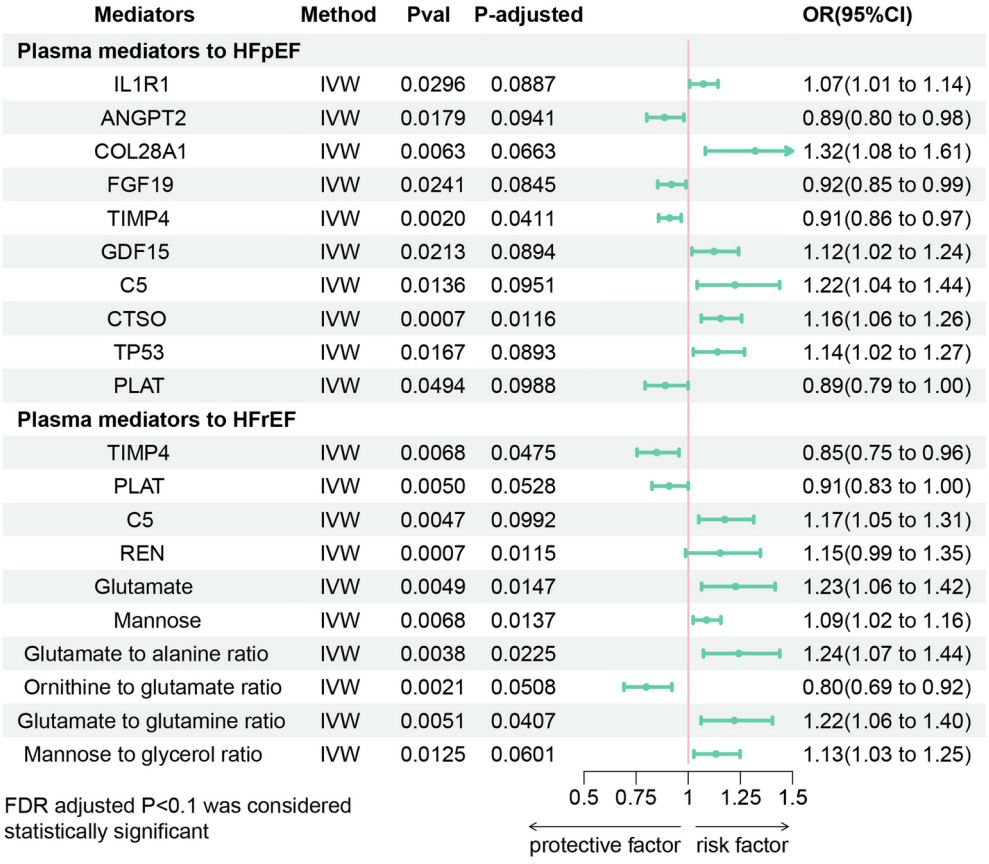


Fig. 3 Identification of causal mediators in HFpEF or HFrEF Forest plot of plasma mediators with causal effects on HFpEF or HFrEF. When the OR value is greater than 1.0, we believe that this medium is acting as a risk factor and has a causal effect. If it is less than 1.0, it may act as a protective mediator. The FDR adjusted $P < 0.1$ indicates causal effect is significant

P(adj) = 0.0951), ANGPT2 (OR = 0.89, 95% CI = 0.80–0.98, *P(adj)* = 0.0941), GDF15 (OR = 1.12, 95% CI = 1.02–1.24, *P(adj)* = 0.0894), FGF19 (OR = 0.92, 95% CI = 0.85–0.99, *P(adj)* = 0.0845), IL1R1 (OR = 1.07, 95% CI = 1.01–1.14, *P(adj)* = 0.0887), CTSO (OR = 1.16, 95% CI = 1.06–1.24, *P(adj)* = 0.0116),, TP53 (OR = 1.14, 95% CI = 1.02–1.27, *P(adj)* = 0.0893), PLAT (OR = 0.89, 95% CI = 0.79–1.00, *P(adj)* = 0.0988). Among them, TIMP4, C5, and FGF19 serve as circulating mediators of obesity-induced HFpEF; CTSO, TP53, and PLAT serve as circulating mediators of T2D-induced HFpEF; in addition, COL28A1, ANGPT2, GDF15, and IL1R1 serve as circulating mediators of both obesity- and T2D-induced HFpEF (Table S12-S13).

We also found some cardiometabolic diseases-induced proteins were also causally associated with the risk of HFrEF, including TIMP4 (OR = 0.85, 95% CI = 0.75–0.96, *P(adj)* = 0.0068), C5 (OR = 1.17, 95% CI = 1.05–1.31, *P(adj)* = 0.0992) and PLAT (OR = 0.91, 95% CI = 0.83–1.00, *P(adj)* = 0.0528) REN (OR = 1.15, 95% CI = 1.05–1.20, *P(adj)* = 0.0115) (Fig.3). Among them, TIMP4, C5 and PLAT serve as circulating mediators of obesity-induced HFrEF; REN serve as circulating mediators of T2D-induced HFrEF. Except for REN, the remaining proteins have causal effects on both HFpEF and EFrEF (Table S14-S15). This study identified CTSO, COL28A1, TP53, ANGPT2, GDF15, IL1R1, and FGF19 as circulating mediators that specifically mediate HFpEF but not HFrEF. Considering the potential role of hypertension in the pathogenesis of HFpEF, we further performed MR analysis on the causal relationship between hypertension and these proteins. The results showed that only IL1R1 (OR = 1.02, 95% CI = 1.01–1.03, *P(adj)* = 0.0475) remained potential relevance (Table S16), suggesting that IL1R1 may serve as a core circulating mediator that plays a key mediating role between multiple cardiometabolic diseases (including BMI, T2D, and hypertension) and HFpEF.

Using the same method, we performed mediation MR to explore the relationship between metabolites or ratios and the onset of heart failure (Tables S17-S18). For HFpEF, all metabolites lost significance after *P*-value correction. Glutamate to alanine ratio (OR = 1.24, 95% CI = 1.07–1.44, *P(adj)* = 0.0225), Glutamate (OR = 1.23, 95% CI = 1.06–1.42, *P(adj)* = 0.0147), Ornithine to glutamate ratio(OR = 0.80, 95% CI = 0.69–0.92, *P(adj)* = 0.0508), Glutamate to alanine ratio(OR = 1.24, 95% CI = 1.07–1.44,

P(adj) = 0.0451), Glutamate to glutamine ratio, (OR = 1.22, 95% CI = 1.07–1.44, *P(adj)* = 0.0407) Mannose(OR = 1.09, 95% CI = 1.02–1.16, *P(adj)* = 0.0409), Mannose to glycerol ratio (OR = 1.13, 95% CI = 1.03–1.25, *P(adj)* = 0.0601) maintained a causal relationship with HFrEF (Fig.3) (Table S19-S20). Among them, Glutamate, Glutamate to alanine ratio, mannose are mediators of obesity-induced HFrEF, Glutamate to alanine ratio, mannose, Ornithine to glutamate ratio, Glutamate to glutamine ratio, Mannose, Mannose to glycerol ratio are mediators of T2D-induced HFrEF.

Mediation effect estimates and sensitivity analyses

MR-Egger regression is a method for detecting and adjusting the overlap of multiple genetic effects. This method provides more robust causal inference by estimating the overall effects of genetic instrumental variables and multiple exposure factors and performing weighted average [15]. In this study, we applied MR-Egger regression and MR-PRESSO methods to evaluate the robustness of mediation MR analysis (Tables S21). The results of the MR-Egger intercept term did not show significant horizontal pleiotropy, and the IVW estimates under the weighted median analysis remained consistent in the direction of the effect. However, we observed that the MR results of COL28A1, GDF15, and C5 failed the horizontal pleiotropy test. Although C5 and GDF15 cannot exclude the interference of horizontal pleiotropy in sensitivity analysis, we further applied the MR-PRESSO method to detect and correct for potential pleiotropic effects. Notably, the causal effect remained significant under the MR-PRESSO outlier test, further supporting the robustness of our findings. In addition, except for individual metabolites that could not be evaluated due to too few SNPs available for pleiotropy testing, the MR-PRESSO analysis of most proteins did not show significant outliers or horizontal pleiotropy after removing suspicious SNPs.

Using two-step MR and bootstrap methods, we investigated each circulating factor's mediation effect (Fig. 4). We calculated the proportion mediated by dividing the factor's indirect effect by the total effect of each cardiometabolic disease on HFpEF. During mediation analysis, we noted that COL28A1, TIMP4, PLAT, Glutamate to alanine ratio, the confidence intervals for the mediating effects of these plasma proteins and metabolites on the association between cardiometabolic diseases and heart failure exceeded zero, so they could not be identified as significant mediators and may also be the result of interactions with other risk factors (Table S22).

For the remaining mediators, the proportion of HFpEF risk due to BMI that was mediated by each factor was as follows: C5(6.68%), IL1R1 (3.84%), GDF15(3.47%), FGF19 (1.29%). Elevated ANGPT2 in plasma conferred a compensatory protective mediation effect of 3.37% in BMI-driven HFpEF. In addition, we noted that although FGF19 was negatively correlated with susceptibility to HFpEF, the metabolic environment of obesity reduced the content of FGF19, which was equivalent to weakening the protective effect of FGF19, so changes in its levels still served as a risk mediator. In T2D-driven HFpEF, GDF15(7.21%), IL1R1 (5.11%), TP53 (4.38%), CTSO (3.34%) served as risk mediators, while ANGPT2 again acted in a compensatory factor (5.81%) (Fig. 5). The proportion of HFrEF risk due to BMI that was mediated by each factor was as follows: C5(6.38%), Glutamate to alanine ratio (6.57%). The proportion of HFrEF risk due to T2D that was mediated by each factor was as follows: REN (6.81%), Ornithine to glutamate ratio (10.59%), Mannose (9.09%), Glutamate to glutamine ratio (8.50%), Mannose to glycerol ratio (7.86%).

As a conclusion, we found that IL1R1, GDF15, FGF19, C5 were risk mediators of BMI-induced HFpEF; IL1R1, CTSO, GDF15, and TP53 were risk mediators of T2D-induced HFpEF, and ANGPT2 was a compensatory protective mediator of both BMI and T2D that induced HFpEF. REN, Glutamate, Glutamate to alanine ratio Mannose were risk mediators of BMI-induced HFrEF; REN, Ornithine to glutamate ratio, Glutamate to alanine ratio, Glutamate to glutamine ratio, Mannose, and Mannose to glycerol ratio were risk mediators of T2D-induced HFrEF.

Protein–protein interaction and pathway enrichment analyses

To investigate how circulating mediators link cardiometabolic diseases to HFpEF, we selected plasma proteins that mediate HFpEF and performed PPI network analysis and mapped the interactions between these proteins (Fig. 6). Interacting proteins mediating the effect of BMI on HFpEF were identified, involving interleukin-1 receptor activity, fibroblast growth factor receptor binding, and growth factor receptor binding. IL-1 receptor activity promotes inflammatory activation in the heart, driving microvascular dysfunction and impaired myocardial contraction, which in turn fosters collagen secretion and ventricular remodeling. Ultimately, this leads to diastolic dysfunction and, consequently, HFpEF. The IL-1 receptor pathway was enriched among the mediating proteins linking several cardiometabolic diseases to HFpEF, suggesting a central role in metabolic HFpEF. The fibroblast growth factor receptor pathway, meanwhile, promotes collagen fiber formation, decreasing ventricular compliance and exacerbating diastolic dysfunction. Cytokine-mediated signaling can activate MAPK and NF-κB, further driving cardiac and vascular inflammation and fibrosis, thereby worsening HFpEF pathophysiology. We also identified T2D-induced HFpEF mediators and their

A

Exposure	Outcome	Protein Mediators	Mediator Effect Proportion	95% Confidence Interval
BMI	HFpEF	C5	6.68%	(0.88%,15.37%)
	HFpEF	IL1R1	3.84%	(1.09%,6.76%)
	HFpEF	GDF15	3.46%	(0.43%, 7.84%)
	HFpEF	ANGPT2	-3.37%	(-8.13%, -0.31%)
	HFpEF	FGF19	1.29%	(0.02%,6.07%)
T2D	HFpEF	GDF15	7.21%	(0.77%,14.85%)
	HFpEF	ANGPT2	-5.81%	(-20.30%, -0.48%)
	HFpEF	IL1R1	5.11%	(0.41%,17.51%)
	HFpEF	TP53	4.38%	(0.16%,15.90%)
	HFpEF	CTSO	3.34%	(1.63%,55.12%)

B

Exposure	Outcome	Metabolites Mediators	Mediator Effect Proportion	95% Confidence Interval
BMI	HFrEF	C5	6.38%	(1.54%,13.50%)
	HFrEF	Glutamate	9.87%	(2.10%,21.55%)
	HFrEF	Glutamate to alanine ratio	6.57%	(1.98%-11.07%)
	HFrEF	Mannose	3.70%	(0.62%,8.43%)
T2D	HFrEF	REN	6.81%	(0.40%,12.37%)
	HFrEF	Ornithine to glutamate ratio	10.59%	(2.45%,23.14%)
	HFrEF	Glutamate to glutamine ratio	8.50%	(1.43%,19.79%)
	HFrEF	Mannose	9.09%	(2.17%,19.37%)
	HFrEF	Mannose to glycerol ratio	6.87%	(0.31%,24.41%)

Fig. 4 The mediated effect of circulating mediators (**A**): Bootstrap method to calculate the mediator effect proportion of plasma mediators between BMI, T2D and HFpEF. (**B**): Bootstrap method to calculate the mediator effect proportion of plasma mediators between BMI, T2D and HFrEF

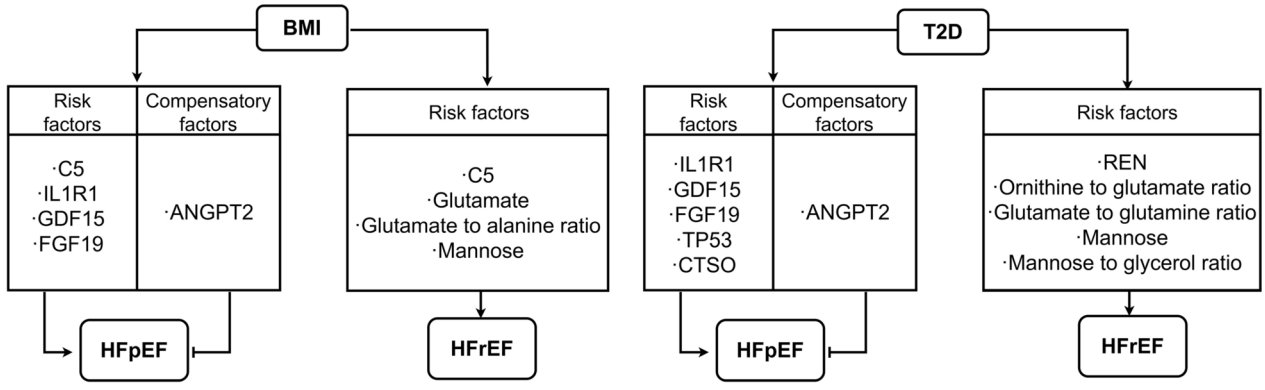


Fig. 5 Circulating mediators in HFpEF Circulating mediators mediate HFpEF and HFrEF in BMI and T2D, playing both promoting and compensatory protective roles

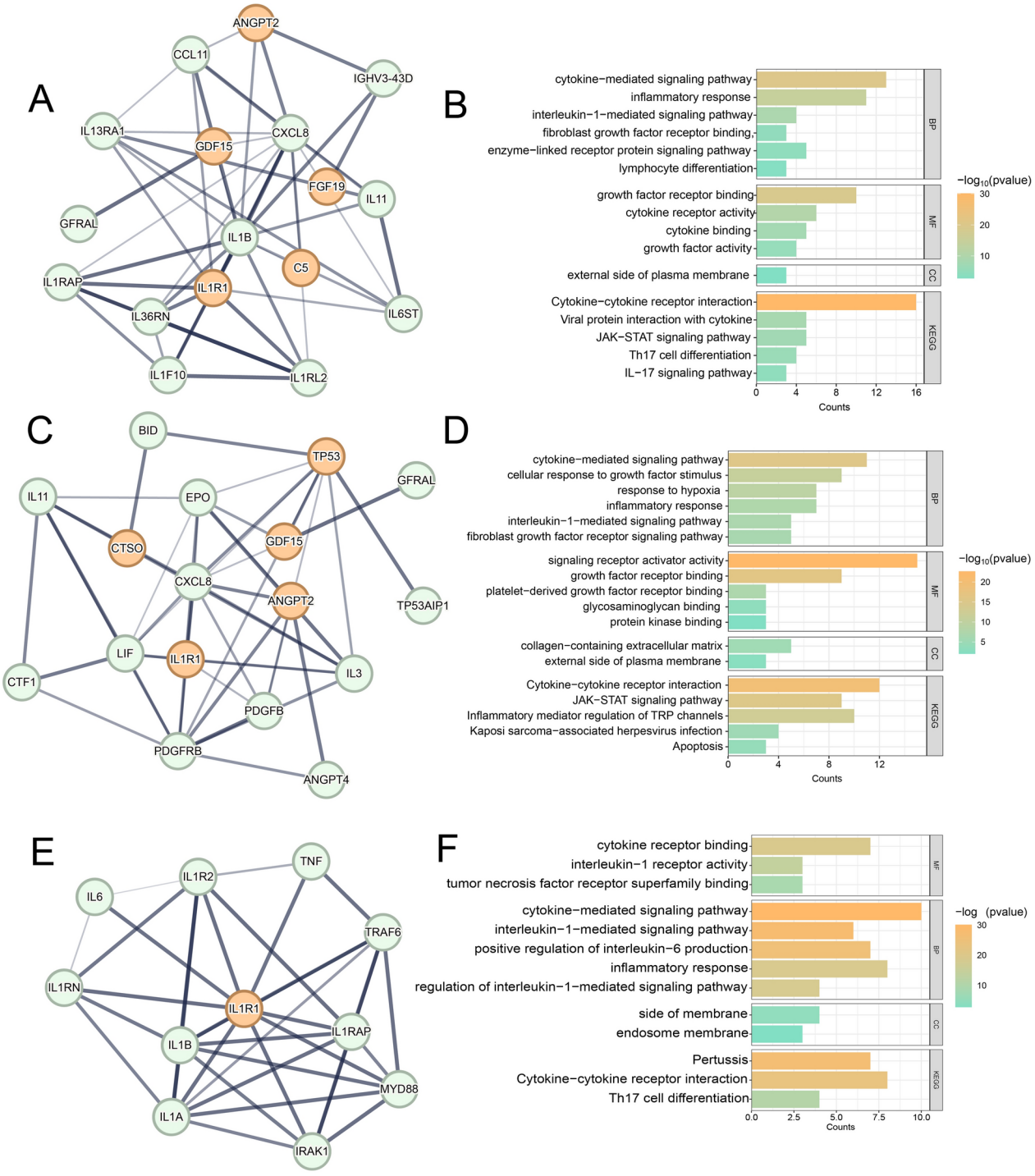


Fig. 6 Protein–Protein Interaction and Pathway Enrichment Analyses Discover the causal mediators' interaction networks and biological functions: (**A**): Protein–protein-metabolite interaction network of BMI circulating mediators with causal effects on HFpEF; (**B**): GO enrichment analysis and KEGG pathway enrichment analysis of causal circulating mediators and their interacting proteins. (**C**): Protein–protein-metabolite interaction network of T2D circulating mediators with causal effects on HFpEF; (**D**): GO enrichment analysis and KEGG pathway enrichment analysis of causal circulating mediators and their interacting proteins. (**E**): Protein–protein-metabolite interaction network of key IL1R1 with causal effects on HFpEF; (**F**): GO enrichment analysis and KEGG pathway enrichment analysis of causal circulating mediators and their interacting proteins. MF: Molecular function. BP: Biological process. CC: Cellular component. KEGG: Kyoto Encyclopedia of Genes and Genomes

interacting proteins, encompassing IL-1 receptor activity, growth factor receptor binding, and IL-1-mediated signaling pathways. Beyond the IL-1 receptor pathway, the others also implicate inflammatory processes and collagen fiber production in the heart. In addition, we discovered IL1R1-interacting proteins implicated in HFpEF, encompassing cytokine receptor binding, interleukin-1 receptor activity, and tumor necrosis factor receptor superfamily binding. These also regulate inflammatory signaling. In sum, within cardiometabolic HFpEF, circulating mediators and their networks broadly contribute to cardiac inflammation and fibrosis, promoting HFpEF through cytokine binding, response to hypoxia, and related processes.

Potential translational values of IL1R1

We found that IL1R1 simultaneously mediates multiple metabolic risk factors in the progression of heart failure, suggesting it may be a key molecule in cardiometabolic diseases. We therefore performed a protein interaction analysis, gene enrichment analysis, and druggability assessment. Our PPI analysis revealed a network of 10 proteins or chemical substances interacting with IL1R1, implicating cytokine-mediated signaling pathways associated with interleukin-1 and the inflammatory response. Using DrugBank, Drug-Gene Interaction Database, Therapeutic Target Database, and CellChatDB, we investigated potential drug targets in IL1R1 and its ligand-receptor pairs (Table S23). The Therapeutic Target Database highlights several related receptors that are either in clinical trials or approved for clinical use. The Therapeutic Target Database, Drug-Gene Interaction Database, and DrugBank collectively report 108 drug-target pairs involving IL1R1 and its reported ligands (Table S24-S26). We found that the current indications for IL1R1-related drug development are mainly for systemic inflammatory diseases (such as rheumatoid arthritis) or tumor-related diseases, involving the targeting of inflammatory or immune phenotypes. We have not yet found relevant applications in CVDs. These findings illustrate the translational potential of these IL1R1 signaling pathways, although more rigorous mechanistic studies are needed to validate the potential pathways.

Discussion

In this study, we combined mediation MR with bioinformatic approaches to identify key circulating mediators responsible for HFpEF under cardiometabolic diseases. First, we identified which cardiometabolic diseases cause HFpEF in a large European cohort and identified heterogeneity in the effects of these diseases on HFpEF or HFrEF. These results provide additional causal evidence to complement previous observational studies [10]. We identified only obesity and T2D as causal factors for HFpEF, with hypertension as a potential risk factor for HFpEF. We then used multi-omics integrating MR to identify the causal effects from BMI and T2D to plasma proteins and plasma metabolites. Mediation MR identified key circulating mediators of obesity-induced or T2D-induced HFpEF and HFrEF. Using various bioinformatics analyses, we identified circulating mediators and signaling networks associated with metabolic HFpEF, but also found that IL1R1 mediates HFpEF caused by multiple metabolic diseases, suggesting that it is a key target for metabolic HFpEF. Our findings provide important insights into the underlying mechanisms of metabolic HFpEF and potential prevention and treatment strategies.

Unlike HFrEF, where pathogenesis typically involves neurohormonal overactivation after myocardial injury, HFpEF features disturbances across multiple systems beyond the neurohormonal axis [45]. Previous research has shown that inflammation, oxidative stress, comorbidity-driven endothelial dysfunction, and fibrosis act synergistically in HFpEF. Cardiometabolic risk factors, such as obesity, diabetes, and hypertension, frequently coexist and collectively contribute to HFpEF. HFpEF is even described by some as a “cardiometabolic syndrome” [46]. Obesity is one of the most critical risk factors for HFpEF; surveys indicate that over 80% of HFpEF patients are overweight or obese [47]. In a pooled analysis of four longitudinal studies, each standard deviation increase in BMI was associated with a 34% higher HFpEF risk and an 18% higher HFrEF risk [48]. Our results similarly found a strong causal link between BMI and HFpEF. Excess adipose tissue in obese individuals is metabolically active and triggers chronic low-grade inflammation, as adipocytes and macrophages secrete proinflammatory cytokines (e.g., TNF-α, IL-6) and adipokines, contributing to cardiac fibrosis and microvascular dysfunction [47]. Activation of the mediator IL-1R1 perpetuated this inflammatory environment, increasing immune cell infiltration and cytokine production, which in turn leads to tissue damage, fibrosis, and further decline in cardiac function [49]. GDF15 is a stress response protein that belongs to the classic myocardial fibrosis family: the TGF-β superfamily. Clinical studies have shown that elevated plasma GDF15 levels are significantly associated with an increased risk of HFpEF, and its concentration is associated with decreased cardiac compliance, left ventricular hypertrophy, and reduced exercise tolerance [37]. However, some other studies have revealed a protective role in metabolic diseases [50]. In our study, elevated GDF levels promote the increased risk of HFpEF. It meanstha further mechanistic studies are required to determine its exact role. After being activated, C5 splits into C5a (proinflammatory factor) and C5b (component of the membrane attack complex, MAC). C5a has a strong proinflammatory

effect and may be involved in the inflammatory process of HFpEF [51, 52]. FGF19 is closely linked to cardiac metabolism and influences HFpEF onset and progression by modulating energy metabolism, vascular function, and extracellular matrix remodeling [53, 54]. In our study, we found that the metabolic environment of obesity led to a decrease in FGF19 levels, which may have weakened this protective effect and led to heart failure. No metabolite had a direct causal effect on HFpEF, indicating that the metabolic regulation of HFpEF involves a complex metabolic interaction network rather than being driven by a single metabolite. Therefore, compared with HFrEF, HFpEF may be more dependent on systemic metabolic imbalances at the multi-omics level rather than the individual effects of specific metabolites.

T2D and insulin resistance frequently coexist with obesity in HFpEF and exert profound cardiac effects. Approximately 40–50% of HFpEF patients have diabetes, a much higher prevalence than in HFrEF cohorts [55]. Our MR analyses support a causal role for T2D in HFpEF. Diabetes induces various cardiovascular changes, collectively termed "diabetic cardiomyopathy." Chronic hyperglycemia promotes oxidative stress through the accumulation of advanced glycation end products (AGEs) in myocardial tissue, crosslinking collagen and increasing myocardial stiffness [55]. It also triggers oxidative stress and disrupts calcium handling in cardiomyocytes. Clinical observations, however, indicate that strict glycemic control alone exerts only modest effects on HFpEF outcomes [56]. This supports the view that T2D, as a systemic metabolic disease, leads to complex metabolic alterations that drive HFpEF, rather than hyperglycemia alone being the primary culprit. Our research identified circulating mediators that link T2D to HFpEF. Beyond IL1R1, T2D enhances TP53 activity, increasing cardiomyocyte apoptosis, fibrosis, and incomplete repair, thus exacerbating diastolic dysfunction and contributing to cardiac remodeling [57, 58]. BMI and T2D share multiple circulating mediators, indicating similarities in the metabolic environment of the two diseases. Combined with our protein interaction and biological enrichment analyses, inflammatory responses may be an important target for inhibiting metabolic HFpEF. Previous studies have shown that dysregulation of CTSO may increase the risk of metabolic-related diseases [59]. Our study also shows its role as a risk mediator. CTSO may increase cardiac stiffness through myocardial ECM remodeling and increased interstitial fibrosis, leading to HFpEF. However, there is a lack of research on CTSO in the CVDs, and its function needs to be further clarified.

Epidemiologically, about 75% of HFpEF patients have a history of hypertension [56]. In contrast, while hypertension is also common in HFrEF, it is generally not the primary cause but rather a contributing factor in the presence of ischemic or valvular disease. In HFpEF, especially when long-standing and poorly controlled, hypertension is often a major driver of heart failure through increased afterload and concentric remodeling (wall thickening with normal chamber size), preserving systolic function but amplifying diastolic stiffness [46]. Recent studies indicate that the hemodynamic overload triggered by hypertension stimulates inflammatory cell infiltration in the myocardium, activating inflammatory pathways and collagen deposition that increase stiffness. Previous studies have shown that blood pressure has effect on heart failure risk [3]. However, our MR results did not statistically support this causal inference. Combined with previous studies and considering that other risk factors could confound this relationship, the high incidence of HFpEF in hypertensive patients may involve more complex multiple effects in metabolic syndrome.

In our study, we did not observe a causal relationship between CKD or dyslipidemia and HFpEF, despite observational research showing CKD is a common comorbidity in HFpEF. CKD and HFpEF share several risk factors (hypertension, diabetes, aging, obesity) and downstream mechanisms (volume overload, RAAS activation, oxidative stress) [60]. Because of shared risk factors and intertwined downstream processes that worsen both CKD and HFpEF, the complexity and confounding inherent to CKD may obscure any direct causal effect of CKD on HFpEF. This aligns with conclusions from prior MR studies [61, 62]. Similarly, we found no independent causal link from dyslipidemia to HFpEF. Because of its overlap with metabolic syndrome and CAD, many HFpEF patients exhibit dyslipidemia or receive lipid-lowering therapy. Prior studies suggest that genetically mediated CAD risk (through high LDL or low HDL) is not a principal driver of HFpEF: Genetic risk scores for CAD do not predict HFpEF incidence, even though they strongly predict HFrEF [63]. In other words, genetically conferred susceptibility to dyslipidemia elevates the risk of HFrEF (often via myocardial infarction) but does not similarly increase HFpEF risk. This reinforces the notion that HFpEF is more closely tied to microvascular and metabolic inflammation rather than lipid abnormalities alone. In summary, dyslipidemia appears more auxiliary in HFpEF pathogenesis. Low HDL and high triglycerides, associated with insulin resistance and a proinflammatory milieu, may contribute to HFpEF, but the direct pathophysiological drivers in HFpEF are likely metabolic and inflammatory pathways rather than dyslipidemia itself [46, 48].

Our multiple bioinformatics analyses highlighted the major role of inflammation and fibrosis in the pathogenesis of HFpEF [11]. Previous studies have shown that IL-1β-IL1R1 signaling is critical in inflammatory diseases and that inhibition of IL1R1 can significantly reduce

organ fibrosis [64, 65]. Our results suggest that IL1R1, C5, TP53 and other mediators may play a role in the inflammation and fibrosis-related pathways of metabolic HFpEF. In addition, future integrated metabolomics and proteomics analyses may reveal whether the inflammatory signals mediated by circulating mediators such as IL1R1, C5, TP53 are regulated upstream or downstream by specific metabolic abnormalities, such as free fatty acids and insulin resistance-related metabolites. Further exploration of the hierarchical relationship between these multi-omics results will help deepen the understanding of the molecular mechanisms of HFpEF. IL1R1, as a central inflammatory mediator, may be a key molecular bridge for the above-mentioned metabolic diseases to cause HFpEF. These circulating mediators may also explain the high incidence of HFpEF in women. First, sex hormones play a key role in regulating cardiovascular function and metabolic adaptation. The decline in estrogen levels after menopause may lead to vascular dysfunction, reduced cardiac compliance, and a chronic inflammatory state, thereby promoting the occurrence of HFpEF [66]. Second, sex differences in metabolic and inflammatory pathways may affect the pathogenesis of HFpEF [67]. Women are more sensitive to IL1R1-mediated inflammatory signals, and obesity and insulin resistance further exacerbate this effect. In addition, sex-specific changes in cardiac structure and function, such as women being more susceptible to diastolic dysfunction and men being more susceptible to left ventricular remodeling and impaired systolic function, also explain the gender distribution differences in HF types to a certain extent [68]. In future mechanistic studies and clinical interventions for HFpEF, gender factors should be fully considered to explore the role of IL1R1-mediated inflammatory pathways in different genders and optimize individualized treatment strategies. HFrEF is mainly related to ischemic heart disease, cardiomyopathy, and myocardial fibrosis, while HFpEF is more likely to be driven by metabolic disorders and inflammatory imbalances. Therefore, based on IL1R1-mediated inflammatory regulation, future treatment strategies may include targeted intervention of IL1-related pathways to alleviate the inflammatory response induced by metabolic abnormalities, thereby improving the clinical outcomes of HFpEF patients. Currently, IL1R1-targeted therapies are being investigated clinically [69]. For example, canakinumab, a monoclonal antibody targeting IL-1β-IL1R1 signaling, has been approved for the treatment of diseases such as systemic juvenile idiopathic arthritis and rheumatic diseases, showing effective anti-inflammatory responses [70, 71]. In addition, the IL-1 receptor antagonist anakinra has shown efficacy in other inflammation-related diseases [72, 73]. However, its definitive role in cardiac inflammation or myocardial fibrosis remains to be investigated, and its efficacy in HFpEF requires further clinical trials. According to our drug target screening, a variety of targeted drugs targeting the IL1β-IL1R1 pathway are currently undergoing clinical trials, although they have not yet specifically targeted metabolic HFpEF and their effectiveness remains to be further elucidated.

In this study, we integrated mediation MR with bioinformatic analyses to identify key plasma proteins and metabolites that mediate HFpEF complications arising from cardiometabolic diseases. Our findings hold meaningful clinical potential for the early detection, personalized treatment, and refined risk stratification of patients with metabolic HFpEF. Nonetheless, our study has certain limitations: 1. It is restricted to individuals of European ancestry, and marked differences in genetic background or environmental exposures in other populations could introduce heterogeneity in causal inferences. 2. Due to limited available GWAS summary statistics, our study did not explicitly investigate sex-specific effects. Future studies should explore whether the identified mediating proteins and metabolites exhibit sex-specific associations. 3. We used a two-step MR approach, which inevitably incorporates some residual confounding, including environmental factors (e.g., diet, exercise, medications) and potential gene-environment interactions. 4. FDR < 0.1 standard in this study is widely accepted in large-scale omics studies, it helps to control the false positive rate while maintaining sufficient detection sensitivity. At a more stringent threshold (FDR < 0.05), almost all previous identified mediators lost their statistical significance for metabolic HFpEF. This result also emphasizes the trade-off between multiple hypothesis correction and statistical power in omics studies, especially in the context of building complex causal inference models. It is necessary to further confirm these findings in larger sample sizes or independent validation cohorts in the future. 5. These circulating mediators still need to be further validated through preclinical experiments. In future studies, more extensive upstream and downstream studies will need to be conducted using multi-omics technologies.

Conclusions

Our findings suggest that metabolic HFpEF has distinct etiological features compared with HFrEF and is driven by complex, condition-specific mediators. IL1R1 mediates HFpEF in multiple metabolic risk states, suggesting a potential therapeutic target. Further translational studies are warranted to evaluate anti-inflammatory strategies targeting IL1R1 in HFpEF.

Abbreviations

BMI	Body mass index
BP	Biological process
CC	Cellular component
CI	Confidence interval

CVD	Cardiovascular disease
CKD	Chronic kidney disease
DEGs	Differentially expressed genes
eGFR	Estimated glomerular filtration rate
FDR	False discovery rate
GO	Gene ontology
GWAS	Genome-wide association analyses
HBP	High blood pressure
HDL	High-density lipoprotein
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
IVs	Instruments variables
IVW	Inverse variance weighting
KEGG	Kyoto Encyclopedia of Genes and Genomes
LDL	Low-density lipoprotein
MF	Molecular function
MR	Mendelian randomization
MVP	Million Veteran Program
OR	Odds ratios
PPI	Assessing protein–protein interaction
pQTL	Protein quantitative trait loci
SGLT2	Sodium-glucose cotransporter 2
SNP	Single-nucleotide polymorphisms
T2D	Type 2 diabetes mellitus
TC	Total cholesterol
TG	Triglycerides
UKB	The UK Biobank

Supplementary Information

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Additional file1 (XLSX 300 kb)

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Author contributions
Pengyu Jia, Mingzhi Lin, Jiuqi Guo and Hongqian Tao, conceived, designed and drafted the manuscript. Pengyu Jia, Mingzhi Lin, Jiuqi Guo, Dalin Jia and Yingxian Sun revised it for important intellectual content. Hongqian Tao, Zhilin Gu, Wenyi Tang, Fuliang Zhou, Yanling Jiang and Ruyi Zhang. made contributions to drafted and revised the manuscript. All authors approved the final version of the manuscript.

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Availability of data and materials
The datasets used in this study are publicly available summary datasets and can be found in cited papers, in the IEU OpenGWAS Project repository (https://gwas.mrcieu.ac.uk/) or in the GWAS Catalogue repository (https://www.ebi.ac.uk/gwas/home), There are no restrictions on data availability other than those imposed by the corresponding data committee. The full summary level association GWAS in the MVP are from dbGaP (https://www.ncbi.nlm.nih.gov/gap, accession number phs001672). Other datasets used or analysed during the current study are available from the corresponding author on reasonable request. All data analyses in this study used existing public R packages. The following are the R packages used in this study and their corresponding version information and download links: TwoSampleMR (version 0.6.8): https://github.com/MRCIEU/TwoSampleMR/releases/tag/v0.6.8; MRInstruments (version 0.3.2): https://github.com/MRCIEU/MRInstruments/releases/tag/0.3.2; MendelianRandomization (version 0.10.0): https://cran.r-project.org/web/packages/MendelianRandomization/index.html; VariantAnnotation (version1.50.0): https://www.bioconductor.org/packages/release/bioc/html/VariantAnnotation.html; MVMR (version 0.4): https://github.com/WSpiller/MVMR; ieugwasr (version 1.0.3): https://github.com/MRCIEU/ieugwasr/releases/tag/v1.0.3; gwasglue (version 0.0.0.9000): https://github.com/MRCIEU/gwasglue; gwasvcf (version 0.1.2): https://github.com/MRCIEU/gwasvcf/releases/tag/v0.1.2; forestploter (version 1.1.2): https://github.com/adayim/forestploter/releases/tag/v1.1.2; ComplexHeatmap (version 2.15.4): https://github.com/jokergoo/ComplexHeatmap.

Declarations

Ethics approval and consent to participate
Summary-level GWAS statistics used in this study is publicly available and no specific ethical approval was required.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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