scientific reports

Check for updates

OPEN

Blood metabolites mediate effects of breakfast skipping on heart failure via Mendelian randomization analysis

Luo Lv[1,4], Yuli Guo[2,4], Zhongyi Zheng[3] & Bao Li[1]✉

Numerous observational studies have suggested a potential causal relationship between skipping breakfast and cardiovascular diseases, including heart failure (HF). However, these studies are susceptible to inherent confounders and the challenge of reverse causation, and the underlying metabolic factors are not yet clear. Therefore, our aim is to assess the causal impact of breakfast skipping on HF and the role of potential mediating metabolic products from a genetic perspective, by conducting Mendelian Randomization (MR) studies and mediation analysis. We leveraged summary data from the most extensive genome-wide association studies to date on breakfast skipping (with 193,860 participants), blood metabolites (with 118,461 participants), and HF (involving 47,309 cases and 930,014 controls). To explore the causal relationship between breakfast skipping and HF, as well as the role of 249 potential blood metabolite mediators, we conducted bidirectional MR and mediation MR analyses. We primarily employed the Inverse Variance Weighted (IVW) method, complemented by various other techniques to ensure the comprehensiveness and reliability of our analysis. Our research confirms a causal association between breakfast skipping and an increased risk of HF (odds ratio [OR]: 1.378, 95% confidence interval [CI]: 1.047–1.813; $p = 0.022$). Furthermore, our research findings demonstrate that breakfast skipping is positively correlated with 6 blood metabolites and negatively correlated with 2 others. Notably, our mediation MR analysis further reveals that three blood metabolites act as mediators in the relationship between breakfast skipping and the risk of HF. Specifically, the mediating effects are attributed to the ratio of docosahexaenoic acid (DHA) to total fatty acids (proportion mediated = 9.41%, 95% CI: 2.10–28.61%), glucose (proportion mediated = 6.17%, 95% CI: 0.97–28.53%), and glycoprotein acetyls (GlycA) (proportion mediated = 5.68%, 95% CI: 0.94–21.62%). The combined mediating effects of these three factors total 20.53% (95%CI: 8.59–91.06%). Our research confirms the causal relationship between genetically instrumented breakfast skipping and HF, underscoring the potential mediating roles played by three key blood metabolites: ratio of DHA to total fatty acids, glucose and GlycA. This discovery offers valuable perspectives for clinical strategies targeting HF.

Heart failure (HF) remains a significant and escalating global health challenge, affecting millions worldwide and leading to substantial health and economic burdens[1]. HF is a complex clinical syndrome caused by various factors that impair the heart's ability to efficiently pump blood, thus failing to meet the body's metabolic demands[2]. Despite advancements in treatment and management strategies, the incidence and mortality of HF continue to rise, highlighting the urgent need for prevention strategies targeting modifiable risk factors[1]. Among these, dietary habits, particularly breakfast consumption, have emerged as potential influencers of cardiovascular health[3,4].

Breakfast is often celebrated as the most crucial meal of the day across various cultures, essential for distributing energy and regulating metabolism[5]. Despite this, there is an increasing global trend of breakfast skipping[6]. Research has shown that breakfast skipping increases the risk of cardiovascular diseases (CVD) and all cause mortality[7]. Moreover, research underscores the significance of maintaining optimal dietary practices, including

[1]Department of Cardiology, The Second Hospital of Shanxi Medical University, School of Medicine, Shanxi Medical University, Taiyuan, China. [2]Department of Cardiology, The Frist Hospital of Shanxi Medical University, School of Medicine, Shanxi Medical University, Taiyuan, China. [3]Department of Urology, The First Hospital of Shanxi Medical University, School of Medicine, Shanxi Medical University, Taiyuan, China. [4]These authors contributed equally: Luo Lv and Yuli Guo. ✉email: libao_medical@163.com

limiting breakfast skipping to fewer than three times per week, late-night dinners to less than three times per week, and bedtime snacking to less than three times per week. Deviating from these dietary guidelines significantly correlates with an elevated risk of myocardial infarction, angina, and HF[8]. Notably, prospective studies indicate that eating cereals for breakfast can decrease the risk of HF[9]. Moreover, studies have shown that breakfast skipping leads to elevated levels of specific bioactive metabolites in the bloodstream, such as low-density lipoprotein (LDL)[3] and glucose[10], which are intimately associated with HF. For instance, a systematic review and meta-analysis encompassing 77 prospective studies revealed that heightened glucose levels significantly augment the risk of HF[11]. Additionally, a study involving 40,607 myocardial infarction patients demonstrated that lowering LDL cholesterol substantially reduces the rate of hospitalizations for HF[12]. Consequently, we posit that breakfast skipping represents a risk exposure that indirectly heightens the risk of HF outcomes by influencing the levels of potential mediators, such as LDL and glucose, key bioactive metabolites. However, the current understanding of the relationships between breakfast skipping and HF, as well as between breakfast skipping and blood metabolites, and between blood metabolites and HF, is primarily based on observational studies. These studies are constrained by limited sample sizes and numerous confounding factors. This methodological limitation poses significant challenges in eliminating the possibility of reverse causality, thus hindering the ability to establish definitive causal links.

Mendelian randomization (MR), an innovative epidemiological approach, utilizes genetic variants tied to specific exposures as instrumental variables (IVs) to explore their causal effects on health outcomes[13]. This methodology offers a robust defense against the biases stemming from confounding factors and reverse causation, issues prevalent in traditional observational studies, by leveraging the inherent randomness and permanence of genetic variants from conception[14]. Esteemed for its capacity to mitigate bias and strengthen the validity of its conclusions, MR is instrumental in probing the links between risk factors and disease development[15]. We conducted a bidirectional MR study and implemented a two-step MR approach, utilizing summary data from the most comprehensive and recent genome-wide association studies (GWAS) on skipping breakfast, blood metabolites, and HF, to explore the relationships among them.

Materials and methods

Study design

In this study, we employed a two-step MR approach for an in-depth mediation analysis, as shown in Fig. 1. Our aim was to ascertain the relationship between skipping breakfast and the genetically predicted risk of HF, and whether blood metabolite signatures could mediate this association. First, we assessed the effects of breakfast skipping on HF, and then analyzed the potential mediating effects through two-step MR approach. In the first step, we evaluated the causal effects of breakfast skipping on potential mediating factors; in the second step, we analyzed the causal impact of these potential mediating factors on HF. The MR methodology utilized in this study adheres to three essential criteria for accurate causal inference: (1) There must be a robust association between the IVs and the exposure. (2) The IVs should not be linked with any confounders that could affect the relationship between the genetic variants and HF outcomes. (3) The impact of the IVs on HF outcomes should be mediated exclusively through their connection with the exposure, without any alternative indirect pathways[16].

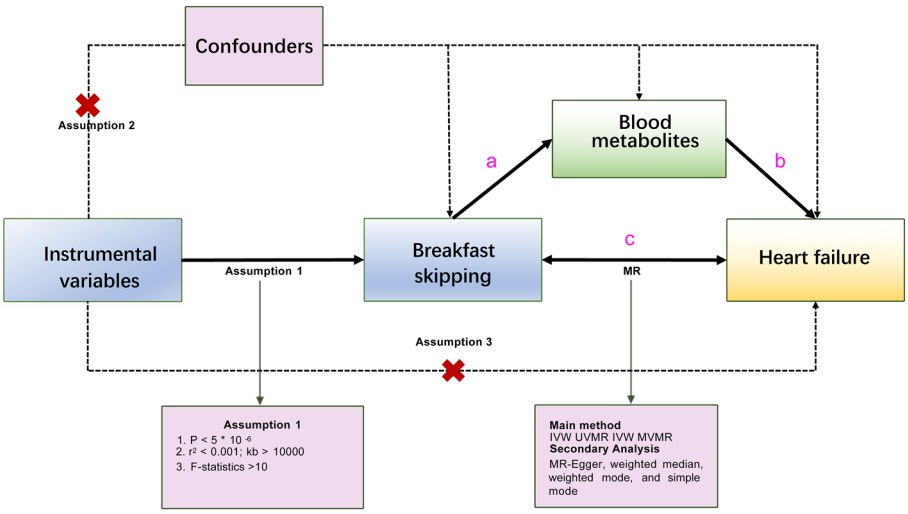

Figure 1. The study design. The study design is divided into three parts. The first part assesses the causal relationship between breakfast skipping and heart failure (**c**). The second part examines the causal link of breakfast skipping on blood metabolites (**a**). The third part evaluates the causal relationship of blood metabolites associated with breakfast skipping on heart failure (**b**). *IVW* Inverse Variance Weighted, *UVMR* Univariable Mendelian Randomization, *MVMR* Multivariable Mendelian Randomization.

Data sources

In our MR analysis, we used datasets from publicly accessible GWASs, thus obviating the need for ethical approval[17]. The datasets employed are complete with no missing values for the key variables used, eliminating the need for employing methods to handle missing data such as multiple imputation or weighting and modeling methods[18,19]. Additionally, when the exposure SNPs were not available in the outcome dataset, we chose not to use proxy SNPs by default. Details of the GWAS data sources used are provided in Supplementary Table S1. The dataset related to breakfast skipping was obtained from a comprehensive study, providing detailed genetic variation maps for 193,860 individuals of European ancestry[20]. This survey utilized the Oxford WebQ to systematically collect dietary data, where participants retrospectively reported their food and beverage intake over the previous 24 h. Based on up to five dietary recalls per participant and their responses, breakfast consumption was estimated and categorized into "never eat breakfast," "sometimes skip breakfast," and "regular breakfast consumers".

The GWAS dataset for blood metabolites was derived from an expansive metabolomics dataset recently made available by the UK Biobank[21]. Employing nuclear magnetic resonance spectroscopy technology, researchers analyzed non-fasting EDTA plasma samples from a randomly selected group of 118,461 UK Biobank participants. This analysis resulted in the quantification of 249 metabolic traits, comprising 168 absolute concentrations and 81 ratios. These metabolic traits cover a broad spectrum, including various lipoprotein lipids, fatty acids and their subclasses, along with a multitude of low-molecular-weight metabolites such as amino acids, ketone bodies, and metabolites related to glycolysis, all measured in molar concentrations.

The HF dataset was acquired from the HERMES Consortium, which includes data on 47,309 cases and 930,014 controls[22]. The cases consist of individuals who have been clinically diagnosed with HF from any etiology, without any selection criteria based on the left ventricular ejection fraction.

Instrumental variable selection

In our research, we initially set a genome-wide significance threshold of $p < 5 \times 10^{-8}$ to pinpoint single nucleotide polymorphisms (SNPs) significantly correlated with breakfast skipping. However, the number of SNPs that met this criterion was insufficient for conducting MR analysis. Consequently, we relaxed this threshold to $p < 5 \times 10^{-6}$, similar to previous MR studies[23]. For the selection of genetic IVs related to blood metabolites and HF, we applied the same genome-wide significance threshold of $p < 5 \times 10^{-6}$. Afterwards, independent SNPs were obtained by linkage disequilibrium (LD) clumping with a threshold $r^2 < 0.001$ and an allele distance > 10,000 kb. To mitigate the risk of horizontal pleiotropy in our analysis, we employed the PhenoScanner v2 database (http://www.phenoscanner.medschl.cam.ac.uk) to meticulously evaluate the phenotypes associated with each SNP. Furthermore, we systematically excluded SNPs associated with recognized confounders such as smoking, alcohol consumption, diabetes, body mass index, coronary artery disease, cardiomyopathy, hypertension, and obesity[24–26]. Additionally, all palindromic SNPs were excluded. The strength of the association between these genetic instruments and breakfast skipping was quantified by calculating the R^2-values. To evaluate the potential for weak instrument bias, the F-statistic was calculated. An F-value exceeding 10 suggested the lack of such bias, thus strengthening the credibility of our causal inferences[27].

Multivariable Mendelian randomization analysis and MR mediation analysis

First, we identified key metabolites that had MR causal support for both breakfast skipping on the mediators and the mediators on the HF. Subsequently, we conducted multivariable Mendelian randomization (MVMR) mediation analysis to explore the degree to which these characteristics mediate the effect of genetically predicted breakfast skipping on the risk of HF. In MVMR, the total effect of each exposure is decomposed into direct and indirect effects. This allows for the estimation of potential mediating effects and the proportion of the main exposure's effect on the outcome mediated through other considered exposures. We use the following formula to calculate the proportion of the effect mediated by any potential mediator (E%): $E\ (\%) = (\Sigma \text{ from } k = 1 \text{ to } K \text{ of } \beta_1 \times \beta_{2k}) / (\Sigma \text{ from } k = 1 \text{ to } K \text{ of } (\beta_3 + \beta_1 \times \beta_{2k}))$[28]. In this equation: β_1 represents the MR effect of the exposure (e.g., breakfast skipping) on the mediator (e.g., glucose). β_{2k} represents the MR effect of mediator k (e.g., a specific metabolite like glucose) on the outcome (e.g., HF), adjusted for genetically determined breakfast skipping. β_3 is the direct MR effect of the exposure (breakfast skipping) on the outcome (HF), adjusted for genetically determined potential mediators. The summation (Σ) over k indicates that the calculation is done for each mediator and then summarized to consider all potential mediators. This method quantifies the portion of the relationship between exposure and outcome explained by mediators, helping to understand potential biological pathways. All regression coefficients (β) are derived using the inverse variance weighted (IVW) method from MR tool analysis.

Sensitivity analysis

In this study, we employed the IVW method as our principal analytical approach. This method assumes that each SNP, serving as an IV, has a uniform causal effect on the exposure variable[29]. To further enhance the robustness of our analysis, we incorporated the weighted median method, simple mode method, and weighted mode method estimations. The weighted median method provides a robust estimate of the causal effect by calculating the median estimate across all IVs, effectively reducing the impact of potentially invalid IVs[30]. The simple mode and weighted mode method strengthen the analysis by identifying the most common causal effect estimate, making it particularly useful in the presence of significant heterogeneity among IVs. For the evaluation of heterogeneity between IVs, Cochran's Q test was utilized. Simultaneously, the intercepts from MR Egger and MR-PRESSO method regressions were used to measure horizontal pleiotropy[31,32]. A p-value greater than 0.05 indicates no horizontal pleiotropy in our study outcomes. Throughout the analysis, considerable emphasis was placed on performing a leave-one-out analysis to ascertain whether any single SNP had a disproportionate impact on the overall findings, ensuring our conclusions were not skewed by any individual SNP.

In our analysis, we used the mRnd tool (http://shiny.cnsgenomics.com/mRnd/) to assess the ability to detect true causal relationships. This tool applies the non-centrality parameter of the two-sample MR method to binary outcomes. This advanced computation takes into account the variance explained by the IVs, the odds ratio (OR) of the exposure effect on the outcome, the proportion of cases in the outcome, and the total sample size, providing a rigorous estimate of our study's capability to determine significant results[33]. Additionally, the issue of multiple testing correction was addressed through the application of the Bonferroni correction procedure[34]. After adjustment, *P* values were defined as statistically significant, where the significance threshold between breakfast skipping and HF was set at 0.025 (0.05/2), between breakfast skipping and blood metabolites at 0.0001 (0.05/249/2), and between blood metabolites related to breakfast skipping and HF at 0.0031 (0.05/8/2). *P* values less than 0.05 were considered to have suggestively significant associations. All these analyses were conducted using the TwoSampleMR, Mendelian Randomization, and MR-PRESSO packages in The R Project for Statistical Computing version 4.3.1, along with the URL https://www.r-project.org/.

Ethical approval

Our study utilizes publicly accessible GWAS datasets, which have already undergone rigorous ethical review and approval, ensuring participant consent and data anonymization. Consequently, MR analyses using these data typically do not require separate ethical approval[17]. We maintain high ethical standards in our research by verifying data source compliance, adhering strictly to data security measures, and ensuring transparency in our data usage.

Results

Genetic causality between breakfast skipping and HF

In this research, based on the established criteria for selecting IVs, we incorporated 24 independent SNPs as IVs for breakfast skipping (Supplementary Table S2). The R^2 value for breakfast skipping is 0.002, and the median F-statistic is 17.1 (range 14.9–22.8), suggesting robust IVs. Our analysis shows a power of 0.96, indicating a high likelihood of accurately detecting a causal effect of breakfast skipping on HF, highlighting the strength of our results. Employing the IVW method as the primary method of analysis, findings reveal a causal connection of breakfast skipping on the risk of HF (OR: 1.378, 95% confidence interval [CI]: 1.047–1.813; $p = 0.022$), achieving statistical significance. The primary results of our MR study are presented in Fig. 2 and further detailed in Supplementary Table S3. The Cochran Q test detected no heterogeneity within our analysis (Supplementary Table S6), and the MR-Egger intercept test and MR-PRESSO analysis showed no evidence of horizontal pleiotropy (Supplementary Table S7). Additionally, the visualized results of our findings are presented in Supplementary Fig. S1, which includes forest plots, scatterplots, and leave-one-out sensitivity analysis plots.

Furthermore, we conducted a reverse MR analysis. We included 43 independent SNPs as IVs for HF, as shown in Supplementary Table S2. The R^2 value for HF is 0.039, and the median F-statistic is 744.5 (range 629.4–2426.3), indicating strong instrument validity. Figure 2 and Supplementary Table S3 showed that no significant causal effect of HF on skipping breakfast was found (OR = 1.018, 95% CI [0.997, 1.040], $p = 0.101$). No heterogeneity and horizontal pleiotropy were discovered (Supplementary Table S6 and S7). Similarly, the visualization of the results is displayed in Supplementary Fig. S1.

Association of breakfast skipping with blood metabolites

In our study examining the relationship between breakfast skipping and 249 metabolic markers in blood, we utilized the IVW method as our principal analysis technique. The findings demonstrated a positive correlation between breakfast skipping and 6 metabolic markers, alongside a negative correlation with 2 markers (Fig. 3, Supplementary Table S4). Among these, we identified a statistically significant causal relationship for ratio of docosahexaenoic acid (DHA) to total fatty acids (Beta: − 0.303, 95% CI: − 0.451– to 0.155; $p = 0.00006$). However, after applying the Bonferroni correction for multiple comparisons, the other associations were not statistically significant. These markers are primarily involved in several crucial biochemical pathways such as glucose metabolism, ketone body formation, lipid metabolism, and amino acid metabolism. In the reverse MR analysis, all IVW *p*-values of casual effect of the 8 metabolites on breakfast skipping were greater than 0.05, indicating no

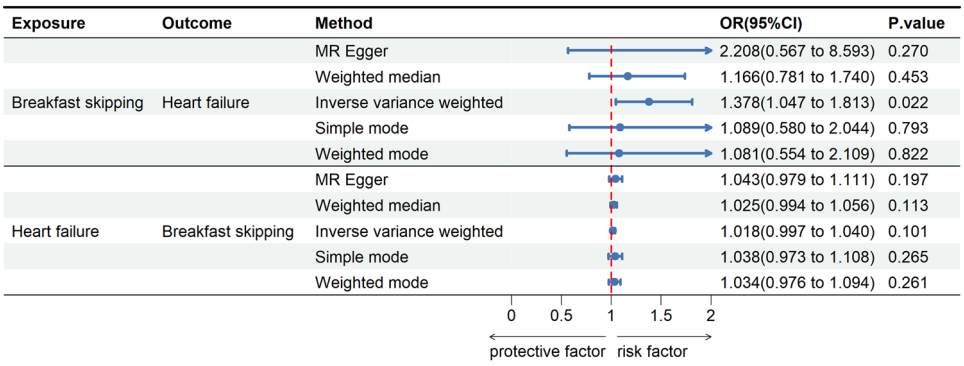

Figure 2. The forest plot of the causal relationship between breakfast skipping and heart failure.

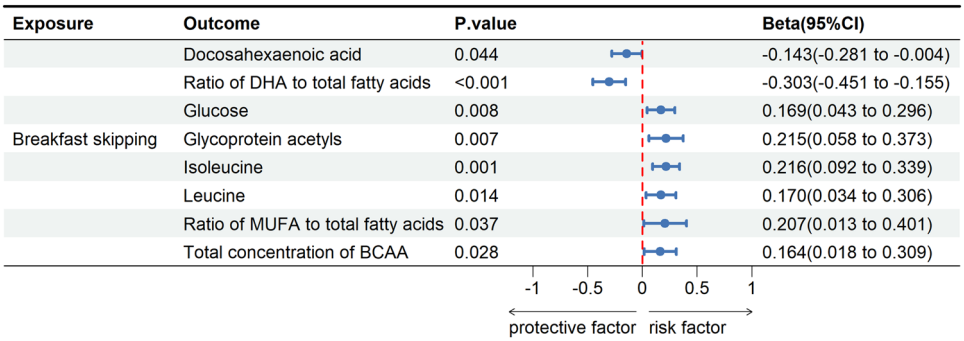

Figure 3. The forest plot of the causal relationship of breakfast skipping on blood metabolites in IVW method. *IVW* Inverse Variance Weighted, *DHA* docosahexaenoic acid, *MUFA* monounsaturated fatty acids, *BCAA* branched-chain amino acids.

association (Supplementary Table S4). Using Cochran's Q statistic, MR-Egger intercept test, and MR-PRESSO analysis, we confirmed no significant heterogeneity or horizontal pleiotropy in this MR analysis, as detailed in Supplementary Tables S6 and S7. Furthermore, the visual representations of our findings can be found in Supplementary Fig. S2, featuring forest plots, scatterplots, and leave-one-out sensitivity analysis plots.

Association of blood metabolites with HF

In our previous research, we identified the potential impact of breakfast skipping on 8 blood metabolic traits. Building on this discovery, we further investigated the potential causal effects of these metabolites on HF. The study selected 506 SNPs as IVs for blood metabolites (Supplementary Table S2). For these blood metabolites, the R^2 value ranges from 0.010 to 0.070, and the median F-statistic is 24.8 (range 16.6–3929.5). Utilizing MR analysis, we discovered suggestive associations between the ratio of DHA to total fatty acids (OR: 0.877, 95% CI: 0.776–0.992, $p = 0.036$), glucose (OR: 1.116, 95% CI: 1.013–1.230, $p = 0.026$), and glycoprotein acetyls (GlycA) (OR: 1.077, 95% CI: 1.005–1.155, $p = 0.035$) with HF (Fig. 4 and Supplementary Table S5). Furthermore, our power analysis when HF is the outcome shows that the power for the ratio of DHA to total fatty acids is 0.91, for glucose is 0.91, and for GlycA is 0.93. All these power values are greater than 0.9, demonstrating the high statistical efficacy of our analysis. However, these associations did not reach statistical significance after Bonferroni correction. Similarly, the reverse MR analysis did not yield suggestively significant p-values between HF and the 3 blood metabolites (IVW $p > 0.05$) (Supplementary Table S5). Notably, the analysis did not reveal any significant heterogeneity or horizontal pleiotropy, enhancing the stability and credibility of the results (Supplementary Table S6 and S7). Moreover, the graphical depictions of our findings are illustrated in Supplementary Fig. S3, which includes forest plots, scatterplots, and leave-one-out sensitivity analysis plots.

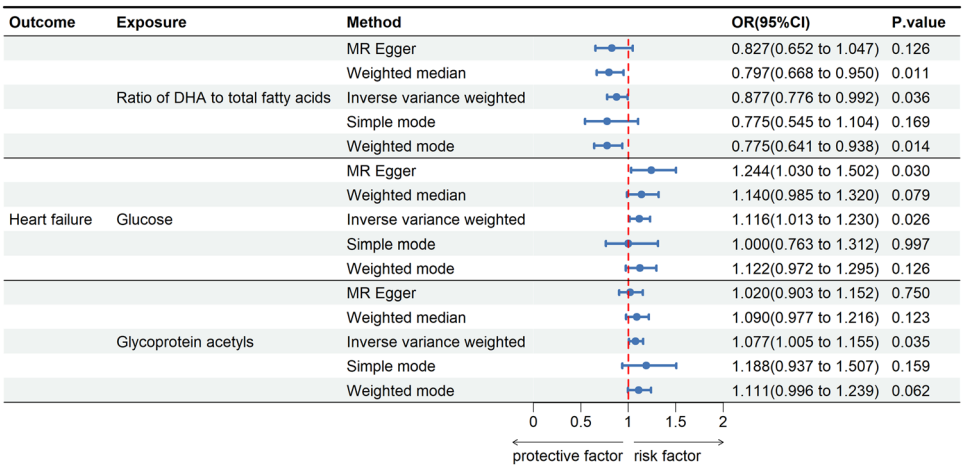

Figure 4. The forest plot of the causal relationship of blood metabolites associated with breakfast skipping on heart failure. *DHA* docosahexaenoic acid.

Mediation effect of blood metabolites

First, we explored those key metabolites that had causal support from MR for both an effect of exposure on mediators and of the mediators on outcome: ratio of DHA to total fatty acids, glucose, and GlycA. Accordingly, we confirmed 3 important metabolites, with their contributing to mediation of breakfast skipping on HF. The detrimental effect, i.e., direct effect, of genetically predicted breakfast skipping on HF risk attenuated from OR 1.378 (95% CI 1.047–1.813) in IVW univariable analysis to OR 1.291 (95% CI 1.007–1.656), 1.314 (95% CI 1.019–1.693), and 1.331 (95% CI 1.043–1.698) after adjusting for ratio of DHA to total fatty acids, glucose, and GlycA, respectively, and to 1.206 (95% CI 0.967–1.503) after adjusting for them three in MVMR analysis (Supplementary Table S8). Then, the proportion of the effect of genetically predicted breakfast skipping mediated through genetically predicted ratio of DHA to total fatty acids, glucose, and GlycA individually, as well as them together was estimated to be 9.41% (95% CI 2.10–28.61%), 6.17% (95% CI 0.97–28.53%), 5.68% (95% CI 0.94–21.62%), and 20.53% (95% CI 8.59–91.06%), respectively (Table 1).

Discussion

In our mediation MR study, we found a significant causal association between breakfast skipping and the risk of HF. According to the mediation MR findings, the ratio of DHA to total fatty acids, glucose, and GlycA could respectively account for 9.41%, 6.17%, and 5.68% of the effect of skipping breakfast on the risk of HF. Combined, these three metabolites accounted for 20.53% of the effect.

A meta-analysis has shown that breakfast skipping is associated with an increased risk of heart disease[35]. Furthermore, a comprehensive systematic review has reinforced the benefits of regularly consuming breakfast for cardiovascular health, indicating that individuals who eat breakfast more than three times a week have a reduced risk of CVDs, type 2 diabetes, hypertension, and cardiovascular mortality compared to those who eat breakfast three times a week or less[36]. Consistently, a prospective study has linked not eating breakfast with a significant increase in mortality from CVDs[37]. Beyond heart disease, numerous studies have associated breakfast skipping with an increased risk of various health issues, including hypertension[38], diabetes[10], obesity[39], and an elevated risk of coronary heart disease[40]. Overall, these conditions are recognized risk factors for HF.

DHA and eicosapentaenoic acid (EPA) represent crucial forms of omega-3 polyunsaturated fatty acids (PUFAs), playing a vital role in maintaining cardiovascular health[41]. The ratio of DHA to total fatty acids, as a composite biomarker, may more accurately reflect the impact of dietary habits on lipid metabolism. Regularly breakfast skipping can affect metabolic stress responses and disrupt circadian rhythms, leading to compensatory increases in energy intake and changes in food choices[42,43]. This dietary pattern may not only indirectly cause a daily deficiency in the intake of DHA-rich foods like deep-sea fish but also disrupt lipid balance, leading to changes in the ratio of DHA to total fatty acids. Besides, poor dietary habits are typically linked to an overall unhealthy lifestyle, which may lead low intake of DHA[44]. Breakfast skipping may exacerbate chronic inflammation, potentially impacting the metabolism of fatty acids such as DHA[45]. Studies have shown that these fatty acids can reduce the risk of CVD through various mechanisms, including enhancing the electrophysiological properties of the heart, reducing inflammatory responses, and optimizing lipid profiles[46]. Notably, DHA preferentially incorporates into cell membranes over EPA[47], significantly influencing calcium and potassium channels that are crucial in regulating heart rate and myocardial contractility[48]. Additionally, DHA and EPA effectively suppress the nuclear factor κB (NF-κB) pathway, ameliorating cardiac inflammation and oxidative stress, thereby averting pathological cardiac remodeling[49]. Omega-3 PUFAs also rectify mitochondrial dysfunction[50], boosting the energy metabolism of cardiac cells, which further supports cardiac function. Moreover, omega-3 PUFAs ameliorate lipid profiles by reducing plasma triglyceride levels[51], contributing to the alleviation of arteriosclerosis, and thereby indirectly enhancing the cardiac function and overall health of HF patients. Empirical evidence supports that exogenous supplementation of DHA and EPA has been proven to significantly decrease hospitalization rates and mortality risk in patients with HF, thereby improving their prognosis[52]. Furthermore, omega-3 PUFAs are particularly beneficial for patients with HF, as they can reduce ventricular remodeling and myocardial fibrosis, and improve the contractile and relaxation functions of the ventricles[53]. Multiple studies have confirmed the positive impact of omega-3 PUFAs on the prognosis of HF[54–56]. Therefore, incorporating DHA and EPA into the diet or through supplementation is essential for cardiovascular health, particularly in the management and prognosis of HF.

Consuming breakfast is crucial for promoting normal insulin secretion, which helps maintain stable blood glucose levels. Conversely, breakfast skipping can disrupt our circadian clock and the expression of its regulatory

	OR	95% CI	*p* value	Mediation effect (%)
MR-IVW regression, crude	1.378	1.047, 1.813	0.022	
Multivariable model				
(1) Adjusted for ratio of DHA to total fatty acids	1.291	1.007, 1.656	0.044	9.41 (2.10–28.61)
(2) Adjusted for glucose	1.314	1.019, 1.693	0.035	6.17 (0.97–28.53)
(3) Adjusted for GlycA	1.331	1.043, 1.698	0.021	5.68 (0.94–21.62)
(4) Adjusted for ratio of DHA to total fatty acids, glucose, and GlycA	1.206	0.967, 1.503	0.096	20.53 (8.59–91.06)

Table 1. Multiple separate-sample MR analysis of causal effect of breakfast skipping on HF risk based on IVW MVMR model. *DHA* docosahexaenoic acid, *GlycA* glycoprotein acetyls.

genes, leading to changes in circadian rhythms and abnormalities in glucose metabolism, resulting in increased postprandial blood sugar levels in both healthy individuals and diabetes patients[57]. Furthermore, breakfast skipping can lead to unstable insulin responses and decreased insulin sensitivity, thereby increasing blood sugar levels[58]. It may also cause excessive hunger at lunch and dinner, leading individuals to choose high-sugar or high-carbohydrate foods that rapidly increase blood glucose [42,43]. Moreover, breakfast skipping can elevate stress hormone levels, such as cortisol, which in turn boost blood sugar as part of the body's response to physical and psychological stress[59]. Elevated blood glucose levels contribute to oxidative stress, causing free radicals to damage cardiac cells and promote inflammation, which impairs cardiac function[60]. Hyperglycemia also affects endothelial function, reducing vascular dilation capacity and worsening hemodynamics, thereby increasing cardiac workload and contributing to heart failure progression[61]. Additionally, chronic high blood sugar can cause metabolic disturbances like excessive fatty acid oxidation, leading to the accumulation of harmful metabolites such as advanced glycation end-products (AGEs), which further damage cardiac tissue[62]. Hyperglycemia also activates inflammatory pathways such as the NF-κB pathway, exacerbating cardiac inflammation and tissue damage[63]. Breakfast skipping is associated with poor glycemic control in healthy individuals[64] and significantly raises the risk of developing type 2 diabetes[10]. There is a significant correlation between type 2 diabetes patients and an increased risk of HF, even when blood glucose levels are controlled within the normal range during the prediabetic phase[11]. Therefore, breakfast skipping can disrupt the body's natural regulation of blood sugar levels, thereby exacerbating the risk of HF.

GlycA is a composite biomarker closely associated with both acute and chronic systemic inflammation and is considered an important indicator of cardiac metabolic risk[65]. It quantifies systemic inflammation through the measurement of various acute-phase proteins[66]. Elevated GlycA levels indicate heightened inflammation within the body, which is central to the pathogenesis of HF[67]. Inflammation plays a critical role in the development of HF by promoting cardiac remodeling and functional impairment, thereby increasing the risk of HF[68]. As we have previously discussed, breakfast skipping can lead to elevated blood glucose levels, which intensify the inflammatory response by activating the NF-κB pathway, subsequently elevating GlycA levels[57,63]. Additionally, breakfast skipping prolongs the overnight fasting period and increases adrenergic activity, further enhancing the inflammatory response[69]. Moreover, breakfast skipping can elevate stress hormone levels and encourage the consumption of foods high in sugar and fat during subsequent meals, thereby intensifying inflammatory responses[42,43,59]. These factors collectively influence GlycA levels. Numerous studies have highlighted the close relationship between levels of GlycA and CVD events[70–72], with a significant prospective study further confirming the correlation between GlycA levels and the incidence of HF[73]. Furthermore, research has discovered a link between the habit of breakfast skipping and chronic inflammation, suggesting that breakfast skipping could potentially have a negative impact on inflammation levels by increasing GlycA levels[45]. This has been corroborated by a cross-sectional study, which demonstrated that individuals who only ate breakfast five days a week exhibited higher levels of GlycA compared to those who ate breakfast six days a week[74]. Therefore, these findings underscore the potential value of improving dietary habits, particularly ensuring daily breakfast consumption, as a strategy to lower GlycA levels and reduce the risk of heart disease.

Although our study identified relatively modest mediated proportions of HF risk through glucose and GlycA at 6.17% and 5.68%, respectively, the clinical significance of these findings underscores the pivotal role of metabolic pathways in HF pathogenesis. The pathophysiology of HF is complex and multifaceted[75], and even these modest proportions have significant implications for risk assessment and preventive strategies across a broad population base. Across a broad population, these modest reductions in risk could yield significant public health gains. Compared with major risk factors such as hypertension and smoking, the effects of glucose and GlycA are less pronounced but provide additional explanatory power in the overall risk composition. This highlights the critical role of targeted metabolic regulation through dietary adjustments (such as maintaining a regular breakfast routine), lifestyle interventions, and pharmacological strategies to effectively manage blood glucose and reduce inflammation[76,77]. Specifically, glycemic control is not merely associated with direct prevention of heart failure but is also integral to enhancing the prognosis of those afflicted. Research has demonstrated that stringent blood glucose management in patients with diabetes markedly decreases the risk of developing HF[78]. Furthermore, as we have previously discussed, GlycA is an inflammatory biomarker linked to HF[73], suggesting that reducing its levels could attenuate inflammatory processes and potentially decrease the risk of HF. Moreover, the utility of monitoring glucose and GlycA levels in the early diagnosis of HF merits additional investigation, as these metabolites could potentially act as biomarkers for early risk assessment[79]. Early detection and intervention are critical in enhancing the prognosis of HF.

Perspective in the future and limitations

We were the first to use MR to explore the causal relationship between breakfast skipping and HF, as well as the mediating role of blood metabolites. Our study leveraged robust statistical methods to ensure the reliability of our findings on the causal effects of breakfast skipping on HF. We carefully selected genetic instruments based on R^2 values, F-statistics, and power estimates, which demonstrated their strong ability to avoid weak instrument bias and confirmed their effectiveness in our analyses. To address potential biases, we utilized MR-Egger Regression and the MR-PRESSO test to rigorously control for pleiotropy and other biases, confirming the accuracy of our causal estimates. Furthermore, our use of a MVMR approach effectively controlled for both measured and unmeasured confounders, reinforcing the strength of our findings that breakfast skipping significantly increases the risk of HF. These methodological approaches underscore the rigor and dependability of our study.

This discovery opens new avenues for the treatment and prevention of HF. Our findings provide a foundation for clinical interventions, clinical doctors may use this information to recommend dietary modifications for HF patients, particularly in terms of breakfast consumption. It is recommended that HF patients increase

their intake of DHA-rich foods, consume low glycemic index foods such as whole grains and legumes, and follow an anti-inflammatory Mediterranean diet to control blood sugar and reduce inflammation[80–82]. Beyond standard medication treatments, the research supports integrating dietary management into the routine care of HF patients. Furthermore, by identifying the metabolic changes in these three metabolites, this study provides a scientific foundation for early intervention strategies for HF patients[79]. From a public health perspective, our research underscores the significance of breakfast, promoting awareness of healthy dietary habits that can help decrease the incidence of HF. Additionally, building on our research, future investigations could explore the multifaceted impact of dietary habits on HF. Research directions should include examining the influence of meal timing and frequency, and evaluating various dietary patterns such as high-protein, low-carbohydrate, and vegan diets. It is also critical to assess the interactions between diet and pharmacotherapy, specifically how dietary practices affect the pharmacodynamics and side effects in HF management. Additionally, longitudinal studies assessing the long-term impacts of dietary interventions are essential. Further research should also consider demographic variability in dietary effects across different ages, genders, races, and socioeconomic statuses, as well as the implications of dietary habits on HF in patients with comorbid chronic conditions such as hypertension, obesity, and diabetes. These investigative pathways are crucial for enhancing our comprehension of the dietary influences on HF and will provide robust evidence for formulating more efficacious clinical and public health strategies to ameliorate patient health outcomes.

This study has several limitations. First, the MR approach relies on strong genetic IVs, whose effects may vary across different populations. Our study primarily involves European subjects, potentially limiting the applicability of our findings to other populations. To overcome this limitation, future research should aim to incorporate a more diverse, multi-ethnic cohort. This expansion is crucial not only for validating our current findings across different demographics but also for identifying potential population-specific effects. Such insights could lead to more precise and effective dietary recommendations tailored to specific groups. Second, the nature of GWAS data restricts our ability to grade the severity of HF and compare the causal impacts among patients with varying degrees of the condition. Furthermore, despite employing multiple MR methods to mitigate pleiotropy, fully eliminating its influence remains challenging. The basic assumption of MR is that genetic instruments should only affect outcomes through specified pathways[16], yet unmeasured confounders and environmental factors such as lifestyle, dietary habits, and socioeconomic status may interact with genetic predispositions, affecting the expression of phenotypes. Despite employing MVMR models and sensitivity analysis methods like MR-Egger regression to detect directional pleiotropy and assess the robustness of MR assumptions, these methods are limited and cannot fully eliminate the impact of all unmeasured confounders. Future research should consider employing stratified analyses or models incorporating interaction terms to explore the influence of environmental factors on genetic effects. Additionally, integrating environment-wide association studies (EWAS) could identify environmental variables that interact with genetic factors, offering a more comprehensive view of disease etiology[83]. Finally, Although the associations with glucose and GlycA may have biological relevance, we must acknowledge that they did not reach the stringent threshold set by Bonferroni correction. However, strict application of the Bonferroni correction, while minimizing the risk of Type I errors, may lead us to overlook potential biologically relevant pathways. Given the exploratory nature of our study, we also included these suggestively significant mediators to capture a broader spectrum of potential biological mechanisms. MR, by its hypothesis-driven nature, enables the detection of causally relevant associations that have biological underpinnings, independent of the stringent adjustments for multiple comparisons. Thus, our exploratory work prioritizes identifying biologically significant associations that merit further investigation in larger datasets, despite not achieving strict statistical significance after rigorous correction. This approach aligns with the exploratory and hypothesis-testing objectives of our study, highlighting potential pathways and targets for further detailed investigation and validation in larger cohorts.

Conclusion

As far as we are aware, this study stands as the inaugural comprehensive assessment of the causal connections among breakfast skipping, blood metabolites, and HF. Our MR analysis uncovers a potential causal pathway linking the act of breakfast skipping to HF, mediated through specific changes in blood metabolites, including the ratio of DHA to total fatty acids, glucose levels, and GlycA. These findings shed light on the genetic underpinnings of the relationship between breakfast habits, blood metabolite profiles, and HF, offering valuable insights for future research in both the mechanisms and clinical management of this condition.

Data availability

The article includes annotations indicating the sources of all original data. For access to these sources, please reach out to the original authors. To obtain the findings of this study, contact the corresponding author directly.

Received: 3 April 2024; Accepted: 9 August 2024
Published online: 15 August 2024

References

1. Martin, S. S. *et al.* 2024 Heart disease and stroke statistics: A report of US and global data from the American heart association. *Circulation* **149**, e347–e913. https://doi.org/10.1161/cir.0000000000001209 (2024).
2. Baman, J. R. & Ahmad, F. S. Heart failure. *Jama* **324**, 1015. https://doi.org/10.1001/jama.2020.13310 (2020).
3. Bonnet, J. P., Cardel, M. I., Cellini, J., Hu, F. B. & Guasch-Ferré, M. Breakfast skipping, body composition, and cardiometabolic risk: A systematic review and meta-analysis of randomized trials. *Obesity (Silver Spring)* **28**, 1098–1109. https://doi.org/10.1002/oby.22791 (2020).

4. Santos, H. O., Genario, R., Macedo, R. C. O., Pareek, M. & Tinsley, G. M. Association of breakfast skipping with cardiovascular outcomes and cardiometabolic risk factors: An updated review of clinical evidence. *Crit. Rev. Food Sci. Nutr.* **62**, 466–474. https://doi.org/10.1080/10408398.2020.1819768 (2022).
5. Gibney, M. J. *et al.* Breakfast in human nutrition: The international breakfast research initiative. *Nutrients* https://doi.org/10.3390/nu10050559 (2018).
6. Pengpid, S. & Peltzer, K. Prevalence and associated factors of skipping breakfast among university students from 28 countries: A cross-sectional study. *Int. J. Adolesc. Med. Health* **34**, 97–103. https://doi.org/10.1515/ijamh-2019-0256 (2020).
7. Chen, H. *et al.* Association between skipping breakfast and risk of cardiovascular disease and all cause mortality: A meta-analysis. *Clin. Nutr.* **39**, 2982–2988. https://doi.org/10.1016/j.clnu.2020.02.004 (2020).
8. Kaneko, H. *et al.* Possible association between eating behaviors and cardiovascular disease in the general population: Analysis of a nationwide epidemiological database. *Atherosclerosis* **320**, 79–85. https://doi.org/10.1016/j.atherosclerosis.2021.01.022 (2021).
9. Djoussé, L. & Gaziano, J. M. Breakfast cereals and risk of heart failure in the physicians' health study I. *Arch. Intern. Med.* **167**, 2080–2085. https://doi.org/10.1001/archinte.167.19.2080 (2007).
10. Ballon, A., Neuenschwander, M. & Schlesinger, S. Breakfast skipping is associated with increased risk of type 2 diabetes among adults: A systematic review and meta-analysis of prospective cohort studies. *J. Nutr.* **149**, 106–113. https://doi.org/10.1093/jn/nxy194 (2019).
11. Aune, D. *et al.* Diabetes mellitus, blood glucose and the risk of heart failure: A systematic review and meta-analysis of prospective studies. *Nutr. Metab. Cardiovasc. Dis.* **28**, 1081–1091. https://doi.org/10.1016/j.numecd.2018.07.005 (2018).
12. Schubert, J. *et al.* Low-density lipoprotein cholesterol reduction and statin intensity in myocardial infarction patients and major adverse outcomes: A Swedish nationwide cohort study. *Eur. Heart J.* **42**, 243–252. https://doi.org/10.1093/eurheartj/ehaa1011 (2021).
13. Swanson, S. A., Tiemeier, H., Ikram, M. A. & Hernán, M. A. Nature as a Trialist?: Deconstructing the analogy between mendelian randomization and randomized trials. *Epidemiology* **28**, 653–659. https://doi.org/10.1097/ede.0000000000000699 (2017).
14. Burgess, S. & Thompson, S. G. *Mendelian Randomization: Methods for Using Genetic Variants in Causal Estimation* (CRC Press, Boca Raton, 2015).
15. Emdin, C. A., Khera, A. V. & Kathiresan, S. Mendelian randomization. *Jama* **318**, 1925–1926. https://doi.org/10.1001/jama.2017.17219 (2017).
16. Burgess, S., Small, D. S. & Thompson, S. G. A review of instrumental variable estimators for Mendelian randomization. *Stat. Methods Med. Res.* **26**, 2333–2355. https://doi.org/10.1177/0962280215597579 (2017).
17. Corbin, L. J. *et al.* Formalising recall by genotype as an efficient approach to detailed phenotyping and causal inference. *Nat. Commun.* **9**, 711. https://doi.org/10.1038/s41467-018-03109-y (2018).
18. Schafer, J. L. Multiple imputation: A primer. *Stat. Methods Med. Res.* **8**, 3–15. https://doi.org/10.1177/096228029900800102 (1999).
19. Seaman, S. R. & White, I. R. Review of inverse probability weighting for dealing with missing data. *Stat. Methods Med. Res.* **22**, 278–295. https://doi.org/10.1177/0962280210395740 (2013).
20. Dashti, H. S. *et al.* Genome-wide association study of breakfast skipping links clock regulation with food timing. *Am. J. Clin. Nutr.* **110**, 473–484. https://doi.org/10.1093/ajcn/nqz076 (2019).
21. Julkunen, H. *et al.* Atlas of plasma NMR biomarkers for health and disease in 118,461 individuals from the UK Biobank. *Nat. Commun.* **14**, 604. https://doi.org/10.1038/s41467-023-36231-7 (2023).
22. Shah, S. *et al.* Genome-wide association and Mendelian randomisation analysis provide insights into the pathogenesis of heart failure. *Nat. Commun.* **11**, 163. https://doi.org/10.1038/s41467-019-13690-5 (2020).
23. Fang, P. *et al.* Exploring causal correlations between inflammatory cytokines and ankylosing spondylitis: A bidirectional mendelian-randomization study. *Front. Immunol.* **14**, 1285106. https://doi.org/10.3389/fimmu.2023.1285106 (2023).
24. Meijers, W. C. & de Boer, R. A. Common risk factors for heart failure and cancer. *Cardiovasc. Res.* **115**, 844–853. https://doi.org/10.1093/cvr/cvz035 (2019).
25. Larsson, S. C., Wallin, A. & Wolk, A. Alcohol consumption and risk of heart failure: Meta-analysis of 13 prospective studies. *Clin. Nutr.* **37**, 1247–1251. https://doi.org/10.1016/j.clnu.2017.05.007 (2018).
26. Aune, D. *et al.* Body mass index, abdominal fatness, and heart failure incidence and mortality: A systematic review and dose-response meta-analysis of prospective studies. *Circulation* **133**, 639–649. https://doi.org/10.1161/circulationaha.115.016801 (2016).
27. Pierce, B. L., Ahsan, H. & Vanderweele, T. J. Power and instrument strength requirements for Mendelian randomization studies using multiple genetic variants. *Int. J. Epidemiol.* **40**, 740–752. https://doi.org/10.1093/ije/dyq151 (2011).
28. Varbo, A. *et al.* Remnant cholesterol, low-density lipoprotein cholesterol, and blood pressure as mediators from obesity to ischemic heart disease. *Circ. Res.* **116**, 665–673. https://doi.org/10.1161/circresaha.116.304846 (2015).
29. Lee, C. H., Cook, S., Lee, J. S. & Han, B. Comparison of two meta-analysis methods: Inverse-variance-weighted average and weighted sum of Z-scores. *Genom. Inf.* **14**, 173–180. https://doi.org/10.5808/gi.2016.14.4.173 (2016).
30. Bowden, J., Davey Smith, G., Haycock, P. C. & Burgess, S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet. Epidemiol.* **40**, 304–314. https://doi.org/10.1002/gepi.21965 (2016).
31. Burgess, S. & Thompson, S. G. Interpreting findings from Mendelian randomization using the MR-Egger method. *Eur. J. Epidemiol.* **32**, 377–389. https://doi.org/10.1007/s10654-017-0255-x (2017).
32. Zou, X. L. *et al.* Childhood obesity and risk of stroke: A mendelian randomisation analysis. *Front. Genet.* **12**, 727475. https://doi.org/10.3389/fgene.2021.727475 (2021).
33. Brion, M. J., Shakhbazov, K. & Visscher, P. M. Calculating statistical power in Mendelian randomization studies. *Int. J. Epidemiol.* **42**, 1497–1501. https://doi.org/10.1093/ije/dyt179 (2013).
34. Noble, W. S. How does multiple testing correction work?. *Nat. Biotechnol.* **27**, 1135–1137. https://doi.org/10.1038/nbt1209-1135 (2009).
35. Takagi, H., Hari, Y., Nakashima, K., Kuno, T. & Ando, T. Meta-analysis of relation of skipping breakfast with heart disease. *Am. J. Cardiol.* **124**, 978–986. https://doi.org/10.1016/j.amjcard.2019.06.016 (2019).
36. Li, Z. H., Xu, L., Dai, R., Li, L. J. & Wang, H. J. Effects of regular breakfast habits on metabolic and cardiovascular diseases: A protocol for systematic review and meta-analysis. *Medicine (Baltimore)* **100**, e27629. https://doi.org/10.1097/md.0000000000027629 (2021).
37. Rong, S. *et al.* Association of skipping breakfast with cardiovascular and all-cause mortality. *J. Am. Coll. Cardiol.* **73**, 2025–2032. https://doi.org/10.1016/j.jacc.2019.01.065 (2019).
38. Li, Z., Li, H., Xu, Q. & Long, Y. Skipping breakfast is associated with hypertension in adults: A meta-analysis. *Int. J. Hypertens.* **2022**, 7245223. https://doi.org/10.1155/2022/7245223 (2022).
39. Wicherski, J., Schlesinger, S. & Fischer, F. Association between breakfast skipping and body weight-a systematic review and meta-analysis of observational longitudinal studies. *Nutrients* **13**, 1–272. https://doi.org/10.3390/nu13010272 (2021).
40. Sharma, K., Shah, K., Brahmbhatt, P. & Kandre, Y. Skipping breakfast and the risk of coronary artery disease. *Qjm* **111**, 715–719. https://doi.org/10.1093/qjmed/hcy162 (2018).
41. Richard, C. & Calder, P. C. Docosahexaenoic acid. *Adv. Nutr.* **7**, 1139–1141. https://doi.org/10.3945/an.116.012963 (2016).
42. Gwin, J. A. & Leidy, H. J. Breakfast consumption augments appetite, eating behavior, and exploratory markers of sleep quality compared with skipping breakfast in healthy young adults. *Curr. Dev. Nutr.* **2**, nyz074. https://doi.org/10.1093/cdn/nzy074 (2018).

43. Clayton, D. J. & James, L. J. The effect of breakfast on appetite regulation, energy balance and exercise performance. *Proc. Nutr. Soc.* **75**, 319–327. https://doi.org/10.1017/s0029665115004243 (2016).
44. Keski-Rahkonen, A., Kaprio, J., Rissanen, A., Virkkunen, M. & Rose, R. J. Breakfast skipping and health-compromising behaviors in adolescents and adults. *Eur. J. Clin. Nutr.* **57**, 842–853. https://doi.org/10.1038/sj.ejcn.1601618 (2003).
45. Zhu, S. *et al.* Habitually skipping breakfast is associated with chronic inflammation: A cross-sectional study. *Public Health Nutr.* **24**, 2936–2943. https://doi.org/10.1017/s1368980020001214 (2021).
46. Rimm, E. B. *et al.* Seafood long-chain n-3 polyunsaturated fatty acids and cardiovascular disease: A science advisory from the American heart association. *Circulation* **138**, e35–e47. https://doi.org/10.1161/cir.0000000000000574 (2018).
47. McLennan, P. L. Myocardial membrane fatty acids and the antiarrhythmic actions of dietary fish oil in animal models. *Lipids* **36**(Suppl), S111-114. https://doi.org/10.1007/s11745-001-0692-x (2001).
48. Li, G. R. *et al.* Omega-3 polyunsaturated fatty acids inhibit transient outward and ultra-rapid delayed rectifier K+currents and Na+current in human atrial myocytes. *Cardiovasc. Res.* **81**, 286–293. https://doi.org/10.1093/cvr/cvn322 (2009).
49. Li, K., Huang, T., Zheng, J., Wu, K. & Li, D. Effect of marine-derived n-3 polyunsaturated fatty acids on C-reactive protein, interleukin 6 and tumor necrosis factor α: A meta-analysis. *PLoS One* **9**, e88103. https://doi.org/10.1371/journal.pone.0088103 (2014).
50. Liu, R. *et al.* Omega-3 polyunsaturated fatty acids prevent obesity by improving tricarboxylic acid cycle homeostasis. *J. Nutr. Biochem.* **88**, 108503. https://doi.org/10.1016/j.jnutbio.2020.108503 (2021).
51. Harris, W. S. & Bulchandani, D. Why do omega-3 fatty acids lower serum triglycerides?. *Curr. Opin. Lipidol.* **17**, 387–393. https://doi.org/10.1097/01.mol.0000236363.63840.16 (2006).
52. Siscovick, D. S. *et al.* Omega-3 polyunsaturated fatty acid (fish oil) supplementation and the prevention of clinical cardiovascular disease: A science advisory from the American heart association. *Circulation* **135**, e867–e884. https://doi.org/10.1161/cir.0000000000000482 (2017).
53. Sakamoto, A., Saotome, M., Iguchi, K. & Maekawa, Y. Marine-derived omega-3 polyunsaturated fatty acids and heart failure: Current understanding for basic to clinical relevance. *Int. J. Mol. Sci.* **20**, 4025. https://doi.org/10.3390/ijms20164025 (2019).
54. Oikonomou, E. *et al.* Effects of omega-3 polyunsaturated fatty acids on fibrosis, endothelial function and myocardial performance, in ischemic heart failure patients. *Clin. Nutr.* **38**, 1188–1197. https://doi.org/10.1016/j.clnu.2018.04.017 (2019).
55. Chrysohoou, C. *et al.* Short term omega-3 polyunsaturated fatty acid supplementation induces favorable changes in right ventricle function and diastolic filling pressure in patients with chronic heart failure; a randomized clinical trial. *Vascul. Pharmacol.* **79**, 43–50. https://doi.org/10.1016/j.vph.2016.01.005 (2016).
56. Nomali, M. *et al.* Omega-3 supplementation and outcomes of heart failure: A systematic review of clinical trials. *Medicine (Baltimore)* **103**, e36804. https://doi.org/10.1097/md.0000000000036804 (2024).
57. Jakubowicz, D. *et al.* Influences of breakfast on clock gene expression and postprandial glycemia in healthy individuals and individuals with diabetes: A randomized clinical trial. *Diabetes Care* **40**, 1573–1579. https://doi.org/10.2337/dc16-2753 (2017).
58. Deshmukh-Taskar, P., Nicklas, T. A., Radcliffe, J. D., O'Neil, C. E. & Liu, Y. The relationship of breakfast skipping and type of breakfast consumed with overweight/obesity, abdominal obesity, other cardiometabolic risk factors and the metabolic syndrome in young adults. The national health and nutrition examination survey (NHANES): 1999-2006. *Public Health Nutr.* **16**, 2073–2082. https://doi.org/10.1017/s1368980012004296 (2013).
59. Witbracht, M., Keim, N. L., Forester, S., Widaman, A. & Laugero, K. Female breakfast skippers display a disrupted cortisol rhythm and elevated blood pressure. *Physiol. Behav.* **140**, 215–221. https://doi.org/10.1016/j.physbeh.2014.12.044 (2015).
60. Haidara, M. A., Yassin, H. Z., Rateb, M., Ammar, H. & Zorkani, M. A. Role of oxidative stress in development of cardiovascular complications in diabetes mellitus. *Curr. Vasc. Pharmacol.* **4**, 215–227. https://doi.org/10.2174/157016106777698469 (2006).
61. Gamrat, A., Surdacki, M. A., Chyrchel, B. & Surdacki, A. Endothelial dysfunction: A contributor to adverse cardiovascular remodeling and heart failure development in type 2 diabetes beyond accelerated atherogenesis. *J. Clin. Med.* **9**, 2090. https://doi.org/10.3390/jcm9072090 (2020).
62. Giacco, F. & Brownlee, M. Oxidative stress and diabetic complications. *Circ. Res.* **107**, 1058–1070. https://doi.org/10.1161/circresaha.110.223545 (2010).
63. Frati, G. *et al.* An overview of the inflammatory signalling mechanisms in the myocardium underlying the development of diabetic cardiomyopathy. *Cardiovasc. Res.* **113**, 378–388. https://doi.org/10.1093/cvr/cvx011 (2017).
64. Li, Y. *et al.* Relationship between skipping breakfast and impaired fasting glucose along with cardiovascular and pre-diabetes condition risk factors in apparently healthy subjects. *Endocrinol. Stud.* **1**, e17–e17 (2011).
65. Ballout, R. A. & Remaley, A. T. GlycA: A new biomarker for systemic inflammation and cardiovascular disease (CVD) risk assessment. *J. Lab. Precis. Med.* **5**, 17. https://doi.org/10.21037/jlpm.2020.03.03 (2020).
66. Connelly, M. A., Otvos, J. D., Shalaurova, I., Playford, M. P. & Mehta, N. N. GlycA, a novel biomarker of systemic inflammation and cardiovascular disease risk. *J. Transl. Med.* **15**, 219. https://doi.org/10.1186/s12967-017-1321-6 (2017).
67. Shirazi, L. F., Bissett, J., Romeo, F. & Mehta, J. L. Role of inflammation in heart failure. *Curr. Atheroscler. Rep.* **19**, 27. https://doi.org/10.1007/s11883-017-0660-3 (2017).
68. Halade, G. V. & Lee, D. H. Inflammation and resolution signaling in cardiac repair and heart failure. *EBioMedicine* **79**, 103992. https://doi.org/10.1016/j.ebiom.2022.103992 (2022).
69. Nas, A. *et al.* Impact of breakfast skipping compared with dinner skipping on regulation of energy balance and metabolic risk. *Am. J. Clin. Nutr.* **105**, 1351–1361. https://doi.org/10.3945/ajcn.116.151332 (2017).
70. Akinkuolie, A. O., Buring, J. E., Ridker, P. M. & Mora, S. A novel protein glycan biomarker and future cardiovascular disease events. *J. Am. Heart Assoc.* **3**, e001221. https://doi.org/10.1161/jaha.114.001221 (2014).
71. Fizelova, M. *et al.* Differential associations of inflammatory markers with insulin sensitivity and secretion: The prospective METSIM study. *J. Clin. Endocrinol. Metab.* **102**, 3600–3609. https://doi.org/10.1210/jc.2017-01057 (2017).
72. Duprez, D. A. *et al.* Comparison of the predictive value of GlycA and other biomarkers of inflammation for total death, incident cardiovascular events, noncardiovascular and noncancer inflammatory-related events, and total cancer events. *Clin. Chem.* **62**, 1020–1031. https://doi.org/10.1373/clinchem.2016.255828 (2016).
73. Jauhiainen, R. *et al.* Novel biomarkers associated with incident heart failure in 10 106 Finnish men. *ESC Heart Fail.* **8**, 605–614. https://doi.org/10.1002/ehf2.13132 (2021).
74. Guinter, M. A., Campbell, P. T., Patel, A. V. & McCullough, M. L. Irregularity in breakfast consumption and daily meal timing patterns in association with body weight status and inflammation. *Br. J. Nutr.* **122**, 1192–1200. https://doi.org/10.1017/s0007114519002125 (2019).
75. Snipelisky, D., Chaudhry, S. P. & Stewart, G. C. The many faces of heart failure. *Card. Electrophysiol. Clin.* **11**, 11–20. https://doi.org/10.1016/j.ccep.2018.11.001 (2019).
76. Forouhi, N. G., Misra, A., Mohan, V., Taylor, R. & Yancy, W. Dietary and nutritional approaches for prevention and management of type 2 diabetes. *Bmj* **361**, k2234. https://doi.org/10.1136/bmj.k2234 (2018).
77. Wronka, M., Krzemińska, J., Młynarska, E., Rysz, J. & Franczyk, B. The influence of lifestyle and treatment on oxidative stress and inflammation in diabetes. *Int. J. Mol. Sci.* **23**, 15743. https://doi.org/10.3390/ijms232415743 (2022).
78. Leung, M., Wong, V. W., Hudson, M. & Leung, D. Y. Impact of improved glycemic control on cardiac function in type 2 diabetes mellitus. *Circ. Cardiovasc. Imaging* **9**, e003643. https://doi.org/10.1161/circimaging.115.003643 (2016).
79. Chiesa, S. T. *et al.* Glycoprotein acetyls: A novel inflammatory biomarker of early cardiovascular risk in the young. *J. Am. Heart Assoc.* **11**, e024380. https://doi.org/10.1161/jaha.121.024380 (2022).

80. Nestel, P. J. & Mori, T. A. Dietary patterns, dietary nutrients and cardiovascular disease. *Rev. Cardiovasc. Med.* **23**, 17. https://doi.org/10.31083/j.rcm2301017 (2022).
81. Martínez-González, M. A., Gea, A. & Ruiz-Canela, M. The mediterranean diet and cardiovascular health. *Circ. Res.* **124**, 779–798. https://doi.org/10.1161/circresaha.118.313348 (2019).
82. Liu, J. & Cai, D. Causal relationship of cereal intake and type with cardiovascular disease: A Mendelian randomization study. *Front. Nutr.* **10**, 1320120. https://doi.org/10.3389/fnut.2023.1320120 (2023).
83. Zheng, Y. *et al.* Design and methodology challenges of environment-wide association studies: A systematic review. *Environ. Res.* **183**, 109275. https://doi.org/10.1016/j.envres.2020.109275 (2020).

Acknowledgements
We extend our sincere thanks to all individuals and researchers who have contributed to this MR study.

Author contributions
All authors contributed to the study's design. Data management, software operation, and analysis were primarily undertaken by L.L. and Y.L.G. The initial manuscript draft was prepared by L.L., Y.L.G., Z.Y.Z., while B.L. critically reviewed, edited, and facilitated funding for the project. All authors have examined and consented to the manuscript's final draft.

Funding
The research received funding from the Shanxi Province medical science and technology innovation talent strong medical plan (No: 2021RC01) and the key Medical Research Projects of Shanxi Province (No: 2021XM09).

Competing interests
The authors declare no competing interests.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-69874-7.

Correspondence and requests for materials should be addressed to B.L.