Review

CARDIAC RESEARCH

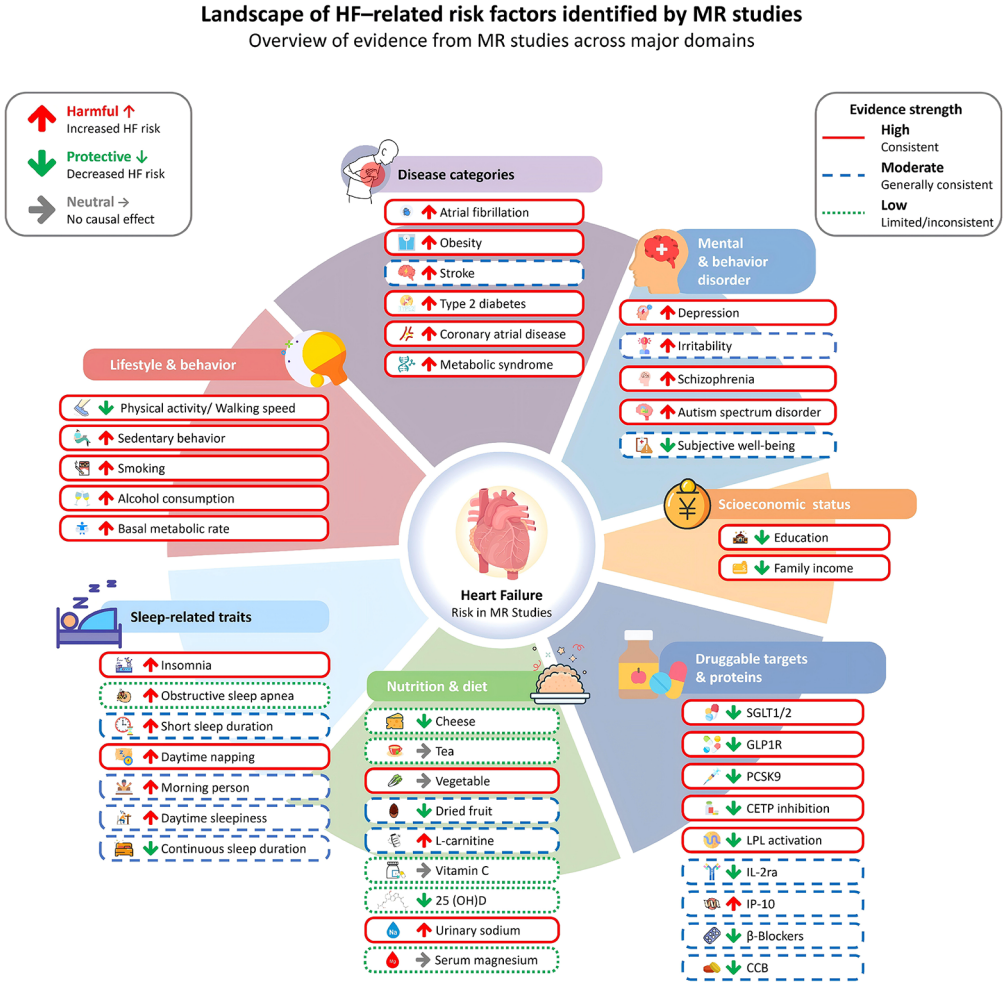
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Risk factors of heart failure

New insights from Mendelian randomization

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Graphical abstract



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Abstract: Heart failure (HF) causes a heavy disease burden globally. Identifying etiological risk factors is essential for informing disease prevention and developing new treatment strategies. This review synthesizes insights from published Mendelian randomization (MR) studies on risk factors associated with HF. MR analyses support potential causal associations between various risk factors and HF, including lifestyle habits (e.g., physical activity, smoking, and sleep patterns), cardiometabolic factors (e.g., obesity, hypertension, type 2 diabetes, and dyslipidemia), nutritional exposures (e.g., 25-hydroxyvitamin D, sodium intake, and diet), emerging biomarkers (e.g., fibroblast growth factor 23), gut microbiota, and potential druggable targets. These studies uncover molecular processes that may contribute to HF pathogenesis and provide leads for therapeutic intervention. However, findings are not always consistent across studies, and discrepancies may arise from differences in study design, genetic instruments, population characteristics, and analytical methods. Key assumptions, including the absence of horizontal pleiotropy and the validity of instrumental variables, may not always be fully satisfied, since the interpretation of MR results requires caution. Future MR studies integrating multiomics data, advanced methodologies, and diverse populations will be essential to refine causal inference and enhance translational relevance. Overall, MR provides valuable insights into the potential causal determinants of HF and may contribute to improved prevention strategies and identification of therapeutic targets, although further validation and integration with clinical evidence are required.

Keywords: causal inference, genetic epidemiology, heart failure, Mendelian randomization, risk factors, therapeutic targets

Nonstandard Abbreviations and Acronyms

HF	heart failure
MR	Mendelian randomization

HIGHLIGHTS

- This review synthesizes evidence from Mendelian randomization (MR) studies to clarify causal risk factors for heart failure (HF), overcoming confounding and reverse causation inherent to observational research.
- MR findings confirm that several modifiable lifestyle factors causally influence HF risk. Higher physical activity—particularly faster walking pace—is strongly protective, while sedentary behavior (TV screen time), smoking across multiple phenotypes, and adverse sleep traits (insomnia, short sleep duration, daytime napping, sleepiness) increase HF risk. Genetic predisposition to smoking cessation reduces HF risk, reinforcing prevention strategies.
- In nutrition and diet, MR does not support routine supplementation of most vitamins or minerals (A, B, C, E, calcium, magnesium) for HF prevention. However, higher 25-hydroxyvitamin D levels show a protective association, and elevated urinary sodium causally increases HF risk. Specific dietary components display causal effects: cheese and dried fruit intake are protective, whereas higher L-carnitine levels (linked to red meat intake) increase HF risk.
- MR evidence robustly links cardiometabolic diseases—atrial fibrillation, coronary artery disease, ischemic stroke, obesity, hypertension, and type 2 diabetes—to HF. Among lipid traits, ApoB emerges as a key causal factor, with effects largely mediated by coronary disease. Most conventional inflammatory markers are not causal, though select proteins (e.g., Galectin-3, MIF) show potential roles.
- Emerging MR studies implicate gut microbiota and metabolites as novel contributors to HF risk, suggesting future preventive and therapeutic avenues. Additionally, MR-proteomics identifies multiple druggable targets, supporting HF risk reduction via SGLT2 inhibitors, GLP-1 receptor agonists, and lipid-modifying pathways (PCSK9, CETP, LPL).
- Overall, this review highlights MR as a powerful tool to prioritize causal risk factors, inform prevention, and guide drug development in HF, while underscoring the need for larger, diverse genome-wide association study and refined MR methodologies.

1. Introduction

Heart failure (HF) is a heterogeneous disease characterized by the heart's inability to adequately pump blood to meet the body's metabolic demands and is represented by symptoms of dyspnea, ankle swelling, and fatigue.[1] This condition has become a major public health concern affecting approximately 60 million individuals worldwide. Its incidence is increasing, with around 3.2 cases per 1,000 person-years in Europe. Additionally, it leads to significant morbidity (affecting 1%–3% of the general adult population) and high mortality rates (with a 5-year mortality rate of 50%–75%).[2] Despite advancements in therapeutic approaches for HF, clinical outcomes continue to exhibit limited improvement, and the prognosis remains poor.[3] Understanding the etiological factors that contribute to HF has been a subject of extensive research to identify modifiable risk factors for prevention, as well as potential therapeutic targets for intervention.

Current major guidelines have identified several risk factors for HF, including obesity, hypertension, and diabetes mellitus.[1] While some recommendations are based on robust evidence from randomized controlled trials (RCTs), a substantial portion of the evidence comes from observational studies. This reliance on observational evidence is due to the resource-intensive, time-consuming, and sometimes unethical nature of RCTs for certain risk factors, such as smoking. However, observational studies have their limitations, as our comprehension of the intricate factors contributing to HF development is hindered by residual confounding and reverse causation. Consequently, the relationships between previously identified factors in observational studies and the risk of HF remain uncertain and require further validation.

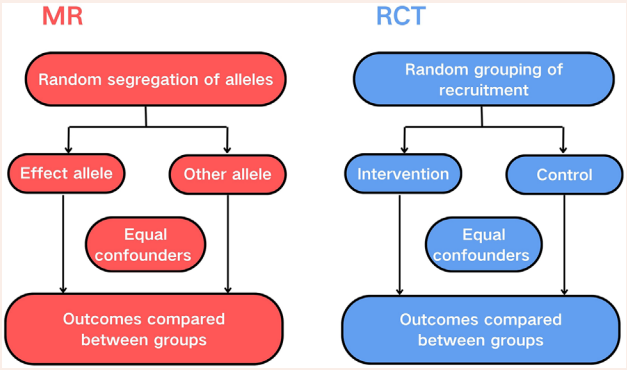


Figure 1. Comparison of the designs of MR and RCT studies. MR and RCT reduce the influence of confounding factors through natural genetic randomization and random allocation of participants, respectively. MR, Mendelian randomization; RCT, randomized controlled trial.

Recent advances in genetic epidemiology, particularly Mendelian randomization (MR) studies, have provided a paradigm shift in our understanding of causal relationships between various risk factors and the development of HF.[4,5] MR is an epidemiological technique that utilizes genetic variations as instrumental variables to investigate how exposure (e.g., metabolic risk factors) influences outcome (e.g., diseases).[6] Owing to the inherent stability of genetic variants and their compliance with Mendel's principles of inheritance, estimates derived from MR are presumed to demonstrate reduced susceptibility to the effects of reverse causation and confounding factors.[7] Mendel's law of random independent assortment of alleles contributes to numerous shared characteristics between MR and RCTs (Fig. 1).[8] If the primary assumptions, namely the relevance assumption, independence assumption, and exclusion restriction assumption (Fig. 2), are satisfied, the associations inferred from MR can be interpreted as causal effects.[6] Thus, MR has opened avenues for exploring causal relationships in HF, shedding new light on the collective findings from existing studies.

The primary goal of this comprehensive review is to compile and summarize insights acquired from published MR studies focusing on risk factors associated with incident HF. By consolidating the existing panorama of MR studies in HF research, this review aims to deepen the understanding of the pathophysiological mechanisms driving HF and identify potential avenues for future research and clinical intervention. In Supplementary Table 1, Supplemental Digital Content, https://links.lww.com/CARES/A21, we summarize and update the associations of a wide range of exposures with HF from MR studies. In addition to summarizing published MR evidence, this review aims to interpret apparent inconsistencies across studies and discuss their implications for prevention, risk stratification, and translational target discovery.

2. Literature search and study selection

This work is a narrative review informed by a structured literature search. The search was performed in the PubMed database from inception to May 2025. The search strategy combined terms related to MR and HF as follows: ("Mendelian Randomization Analysis"[MeSH Terms] OR "Mendelian Randomization"[Title/Abstract]) AND ("heart failure"[MeSH Terms] OR "heart failure"[Title/Abstract] OR "cardiac failure"[Title/Abstract] OR "congestive heart failure"[Title/Abstract] OR "myocardial failure"[Title/Abstract] OR "left-sided heart failure"[Title/Abstract] OR "right-sided heart failure"[Title/Abstract]). We included original MR studies that evaluated potential causal associations between any exposure and HF outcomes in human populations. Studies were excluded if they were reviews, editorials, methodological papers without primary MR analyses, or did not report HF as an outcome. Reference lists of relevant articles were also screened to identify additional eligible studies. Two reviewers independently screened titles/abstracts and full texts, with disagreements resolved by discussion. Given the narrative nature of this review, no formal meta-analysis was conducted, as the included studies were highly heterogeneous in terms of exposures, outcome definitions, and MR study designs. However, findings

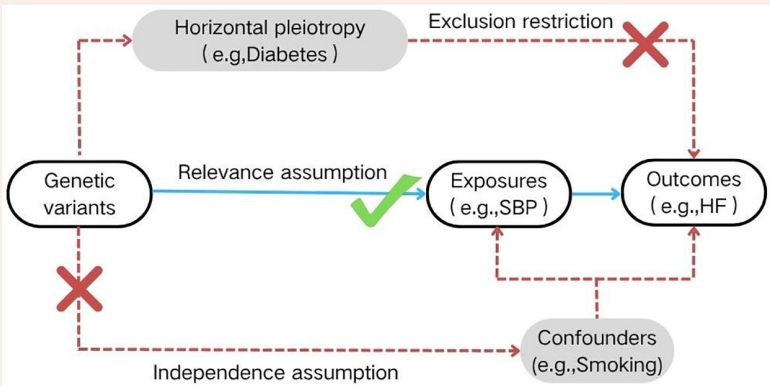


Figure 2. The core assumptions of Mendelian randomization. HF= heart failure, SBP = systolic blood pressure.

were qualitatively synthesized, and the level of evidence was assessed based on consistency across MR, observational, and randomized studies.

3. Causal risk factors for HF identified by MR studies

3.1. Lifestyle and socioeconomic factors

3.1.1. Activity behaviors and energy expenditure. A previous meta-analysis of observational studies consistently demonstrated that physical activity (PA) has a protective effect against HF.[9] However, relatively few RCTs specifically focus on the primary prevention of HF through PA. MR studies provide complementary causal evidence, further supporting the beneficial effects of PA on HF prevention.

Regarding sedentary behavior and HF risk, current MR studies indicate that genetically predicted television (TV) screen time, a proxy for sedentary behavior, is associated with increased HF risk (odds ratio [OR]: 1.23 per SD higher TV screen time, 95% confidence interval [CI]: 1.09–1.38).[10,11] However, no significant associations were found for computer use or driving.[10,11] For PA, the protective effect of self-reported walking speed on HF mentioned in the European Society of Cardiology (ESC) position paper[3] was confirmed by MR. The risk of HF decreases by 69% for each level increment in self-reported walking speed (OR: 0.31, 95% CI: 0.23–0.41).[12]

Regarding energy expenditure, evidence from traditional epidemiological studies on the role of basal metabolic rate (BMR) in the primary prevention of HF remains limited. However, MR studies provide evidence that genetically predicted higher BMR is associated with an increased risk of HF (OR range: 1.35–1.53).[13,14] One potential explanation is that an elevated basal metabolic state may be associated with increased oxygen consumption and mitochondrial oxidative burden, thereby promoting reactive oxygen species generation and metabolic stress, processes implicated in myocardial injury and HF pathophysiology.[15] However, these mechanistic links remain speculative and require further experimental validation.

3.1.2. Nutrition and diet

3.1.2.1. Vitamins and electrolytes. Observational studies and RCTs have examined the association of vitamins with HF. Vitamin C showed a protective effect[16,17] while vitamin B[18,19] and vitamin D[20] were not associated with HF prevention, and the role of vitamin E was controversial.[17,21] However, MR analysis did not reveal an association between absolute levels of vitamins A, B9, B12,[22] C,[22–24] or circulating metabolites of vitamins A, B, C, E and the risk of HF.[22] Notably, MR findings on vitamin D and HF risk appear to vary depending on the specific biomarker or exposure definition used. The causal relationship between absolute vitamin D level and HF was not significant.[22] However, when using 25-hydroxyvitamin D (25(OH)D) as the exposure, a negative causal relationship (OR range: 0.81–0.84) with HF was observed.[25,26] Circulating 25(OH)D, the standard indicator of vitamin D status, primarily reflects endogenous metabolism and bioavailability, whereas total vitamin D exposure may capture broader determinants, including dietary intake and lifestyle-related factors. The genetic instruments underlying these exposures differ substantially, with variants associated with 25(OH)D largely involved in vitamin D metabolism and transport pathways. Such differences may partly account for the observed heterogeneity in MR estimates, particularly given that variants for total vitamin D exposure are more likely to capture pleiotropic pathways beyond vitamin D metabolism.

Regarding electrolytes, the association between sodium intake levels and high risk of developing HF has been established in traditional studies,[27] but little research has been done on other electrolytes. MR studies confirmed that per-log-SD, elevated urinary sodium levels increased the risk of HF (OR: 1.77, 95% CI: 1.19–2.62),[28] but did not support a causal role for serum calcium[29] or serum magnesium in HF.[29,30] In general, when considered within a triangulation framework, integrating MR evidence with existing observational and randomized studies, the potential benefits of vitamins, calcium, or magnesium supplementation for the primary prevention of HF may be limited.

3.1.2.2. Diet. HF guidelines state that healthy dietary patterns, such as the Mediterranean diet, a predominantly plant-based diet, are inversely associated with the incidence of HF.[31] However, not all studies found a clear link. For instance, in a multicenter RCT involving Spanish adults (N = 7,403), the Mediterranean diet was not found to reduce the incidence of HF.[32] MR studies provided further insights into specific eating habits, demonstrating that higher intake of cheese (OR: 0.62 per SD, 95% CI: 0.49–0.79)[33] and dried fruit (OR: 0.60 per SD, 95% CI: 0.42–0.85)[34] was genetically associated with a decreased risk of HF. In contrast, no significant association was found with vegetable intake, possibly due to weak instrument bias, as single nucleotide polymorphisms (SNPs) only explained 0.8% and 2.4% of the variance in cooked and raw vegetable intake, respectively.[35] Regarding meat intake, MR studies revealed that genetically predicted L-carnitine levels were associated with an increased risk of HF (OR = 1.05 per SD increase in L-carnitine, 95% CI: 1.01–1.09),[36] suggesting that limiting foods high in L-carnitine, such as red meat, might help prevent HF.

Evidence for other dietary factors remains inconclusive. Current MR studies have not reached a consensus on whether tea consumption protects against HF.[37–39] As for coffee, no significant association was found with HF risk.[40,41] This lack of association could be partly explained by weak instrument bias (0.48% variance in coffee consumption was explained by the SNPs in both studies).[41] In addition to potential weak instrument bias, another explanation for the inconsistent MR findings on

tea and coffee is that these beverages represent complex exposures rather than single nutritional entities, with cardiovascular effects potentially varying according to preparation methods, subtype composition, caffeine content, and polyphenol profiles. Genetic instruments for beverage intake are more likely to reflect habitual consumption behavior rather than the biologically active components most relevant to HF pathophysiology. In addition, any true effects may be modest or nonlinear, which may further reduce consistency across MR studies using different exposure definitions and genetic instruments. Thus, the current evidence may reflect both limited instrument strength and substantial exposure heterogeneity.

3.1.2.3. Early-life nutritional and developmental indicators. Observational studies have reported an association between low birth weight, a common complication of pregnancy, and an increased risk of cardiometabolic disease in later life.[42] Nutritional deprivation during fetal growth is an important cause of low birth weight.[43,44] Although MR analysis did not find a direct relationship between genetically predicted low birth weight and HF, it did suggest an association with adverse cardiac remodeling.[45] Specifically, genetically determined lower birth weight was associated with parameters indicative of poor heart function, such as smaller chamber volumes, lower stroke volumes, and greater contractility.[45] This implies that adverse remodeling changes are inherently subclinical.

3.1.3. Smoking. MR studies further confirm the adverse effect of smoking on HF risk. Smoking is regarded as a modifiable risk factor for HF.[46,47] However, given that the majority of the available data originates from observational studies, potential biases due to residual confounders and reverse causality cannot be entirely ruled out.[48] MR studies reveal that different smoking phenotypes, including smoking initiation (current or former smoker) (OR range: 1.28–1.53),[41,48] current smoking (OR: 1.32, 95% CI: 1.23–1.42)/smoking status ($\beta = 0.52$, $P = 1.53 \times 10^{-6}$),[49,50] frequency of smoking (i.e., number of cigarettes smoked daily) (OR range: 1.26–1.37 per SD increase),[41,51,52] ever smokers (OR: 1.28, 95% CI: 1.22–1.36), and higher composite lifetime smoking index (a composite of smoking initiation, heaviness, duration, and cessation) (OR range: 1.49–2.58 per SD increase),[51,53] are all associated with a high risk of HF. Genetically predicted smoking cessation is associated with a reduced risk of HF (OR: 0.80, 95% CI: 0.66–0.97) compared with current smokers, indicating that individuals with a genetic predisposition to quit smoking are at a lower risk of developing HF. This underscores the importance of smoking cessation in HF prevention strategies.[41]

3.1.4. Alcohol consumption. While heavy alcohol consumption has been considered a risk factor for HF in previous HF guidelines,[1,3,47] earlier MR studies have not found significant evidence to support a causal relationship between alcohol consumption and HF.[41,49,54,55] However, a recent large-scale MR study, leveraging a greater number of genetic instruments than earlier analyses, reported that genetically predicted higher alcohol consumption was associated with an increased risk of HF (OR: 1.17, 95% CI: 1.06–1.29 per SD drinks per week) and, more prominently, nonischemic heart failure with reduced ejection fraction (HFrEF) (OR: 1.87, 95% CI: 1.37–2.55 per SD drinks per week), supporting a potential causal role of alcohol intake in HF pathogenesis.[52]

3.1.5. Sleep-related traits. By exploring the association of different sleep phenotypes with HF, MR and observational studies provide additional evidence supporting the potential reduction of HF risk through sleep interventions, although the evidence lacks consistency. Obstructive sleep apnea (OSA) has been identified as a risk factor for HF in traditional studies.[56,57] In MR research, a study using the FinnGen consortium for exposure and the Heart Failure Molecular Epidemiology for Therapeutic Targets Consortium (HERMES) for outcomes, which included five SNPs, found that a per-log increase of genetically predicted OSA was associated with a 26% higher risk of HF (OR: 1.26, 95% CI: 1.08–1.47).[58] However, when using the same database, that is, the HERMES consortium for outcome but with exposure variables provided by larger-sample-size meta-GWAS (genome-wide association study) data, no causal relationship between OSA and HF was found.[59,60] The inconsistency likely arises from differences in instrumental variables and underlying phenotype definitions. Genetic proxies based on clinical diagnosis versus self-reported symptoms capture distinct constructs, and residual confounding from body mass index (BMI)-related pathways, along with the use of binary rather than continuous traits, may further affect estimates. Since continuous variables provide more detailed information, in the future, establishing a GWAS for a continuous trait, such as the apnea hypoventilation index (the number of apnea and hypopnea events per hour), might offer deeper insights.

Regarding other risk factors, genetically predicted insomnia (OR range: 1.10–1.24)[5,61] and daytime napping (OR range: 1.1–1.8)[5,62,63] were both associated with an increased risk of HF. The causal effect of daytime napping remained significant after adjusting for OSA and obesity,[62] with BMI, triglycerides (TG), and high-density lipoprotein (HDL) possibly mediating the causal pathway.[61] MR studies provide further evidence supporting previous cohort studies.[64–66] These sleep characteristics could be considered potential risk factors in HF prevention guidelines. Daytime sleepiness (OR: 1.82, 95% CI: 1.15–2.87, $P = 0.01$) and being a morning person (i.e., preferring to go to bed and wake up earlier) (OR: 1.06, 95% CI: 1.01–1.11, $P = 0.01$) appear to be potential risk factors for HF.[5] For morning people, this counterintuitive finding may be explained by increased arterial wave reflection; elevated blood pressure (BP) and heart rate in the early morning may contribute to higher left ventricular

afterload and myocardial oxygen demand.[5] In terms of sleep duration, short sleep duration (< 7 h per day vs. 7–8 h per day) was related to increasing HF risk (OR about 1.14).[5,46,67] Conversely, each 1-h increase in continuous sleep duration had a protective effect on HF (OR range: 0.73–0.77).[46,68] While longer sleep duration (> 9 h per day vs. 7–8 h per day) showed a trend toward benefit, none of the findings were statistically significant.[5,41,68,69]

3.1.6. Socioeconomic status. Socioeconomic status has also emerged as a potential determinant of HF in MR studies. Genetically predicted higher educational attainment has been consistently associated with a lower risk of HF (OR range: 0.51–0.99), with BMI and smoking identified as mediators in this relationship.[70–72] In addition, higher household income has been associated with lower genetic susceptibility to HF (OR: 0.83, 95% CI: 0.71–0.96).[73] Together, these findings support a potential role for socioeconomic conditions in shaping HF risk.

In summary, MR findings on lifestyle and socioeconomic factors provide a basis for a stratified prevention framework for HF. MR findings suggest a potential interplay between genetic susceptibility and modifiable risk factors, indicating that individuals with a higher genetic predisposition to adverse exposures may derive greater benefits from targeted interventions. Integrating genetic risk with behavioral and socioeconomic profiles may help identify high-risk subgroups and inform more stratified or personalized prevention strategies for HF.

3.2. Environmental and sex-specific life-course factors

3.2.1. Air pollution. MR studies provide evidence supporting causal effects of air pollutants on HF. A large-scale prospective cohort indicates a dose–response relationship between exposure to air pollutants and an increased risk of HF events.[67] At the genetic level, elevated particulate matter 10 (PM10) concentrations were associated with a higher risk of HF (OR: 2.02, 95% CI: 1.08–3.75) when using a more lenient significance threshold ($P < 5 \times 10^{-7}$).[74] MR studies found no association between PM2.5 and HF, but higher concentrations of PM2.5 were linked to elevated TG and reduced HDL-C levels.[74]

However, it is worth noting that using air pollution as an exposure in MR studies is controversial. Since SNPs cannot affect air pollution levels, the exclusion restriction assumption is not likely to be satisfied. Some researchers assumed that genetic makeup can biologically influence individuals' residential choices or social status, thereby affecting exposures, such as air pollution. However, this raises the concern that any genetic associations with air pollutants may simply reflect underlying confounding factors.[75] Therefore, despite conclusions being consistent with the position paper,[3] establishing air pollution as the exposure in MR studies might be inappropriate.

3.2.2. Reproductive and sex-specific life-course factors. Reproductive-related factors examined in MR studies of HF remain limited. Earlier age at first sexual intercourse and earlier age at first birth have been associated with an increased risk of HF,[76,77] potentially reflecting broader life-course and socioeconomic pathways. However, current MR evidence in this domain remains sparse. Future studies are warranted to investigate female-specific pregnancy-related conditions—such as preeclampsia, gestational hypertension, and gestational diabetes—and their potential causal roles in HF, which may provide more direct insights into pathophysiological mechanisms.

4. Disease categories

4.1. Cardiometabolic disorders

MR studies support causal roles of multiple cardiovascular metabolic diseases (CMD)—including atrial fibrillation (AF),[78–80] coronary artery disease (CAD),[52,81,82] ischemic stroke,[83] cardioembolic stroke,[83] obesity,[52,84–88] and type 2 diabetes[89–92]—in HF. Notably, AF, systolic BP (SBP),[52] and BMI[52,93] are significantly associated with overall HF, as well as its nonischemic subtypes, including nonischemic HFrEF and nonischemic heart failure with preserved ejection fraction (HFpEF). In contrast, CAD does not show a causal association in these nonischemic HF subtypes,[52] suggesting that its genetic contribution to HF is primarily mediated through ischemic mechanisms.

4.2. Lipid metabolism and related traits

Regarding lipid metabolism, studies indicate that while HDL-C may not be a causal risk factor,[93,94] TG,[93,94] low-density lipoprotein cholesterol (LDL-C), and ApoB show a positive causal effect,[94,95] while ApoAI[94] has shown protective effects on HF. Among these lipids, ApoB has been identified as the most likely causal factor for HF.[96] Notably, emerging evidence suggests heterogeneity across HF subtypes: lipid-related traits, particularly LDL-C and total cholesterol, demonstrate causal associations primarily with HFrEF, whereas no significant causal effects have been observed for HFpEF.[93] This subtype-specific pattern suggests that lipid-related risk may be more closely linked to atherosclerosis-driven myocardial injury and remodeling, which are more central to HFrEF. Consistent with this, multivariable MR (MVMR) analyses indicate that the effects of lipid-related traits (e.g., LDL-C, triglycerides, and ApoB) are largely mediated through CAD.[94,95] In contrast, type 2 diabetes shows both mediated and direct effects, with its association remaining significant after adjustment for adiposity and BP.[92,93] These findings underscore the crucial role of managing cardiometabolic disorders to prevent HF.

4.3. Inflammatory pathways and biomarkers

MR studies have also investigated the relationship between chronic inflammation[97] as well as several

inflammatory biomarkers and HF, but largely ruled out a causal relationship. These include C-reactive protein,[98,99] interleukin-1, interleukin-6 pathways,[100] tumor necrosis factor, interleukin-2, interleukin-16, interleukin-17, interleukin-18, and toll-like receptor 4,[101] as well as suppression of tumorigenicity 2 and galectin-3.[102]

4.4. Mental and behavioral disorders

Genetically predicted mental disorders, including depression,[103,104] irritability,[105] schizophrenia,[106] and autism spectrum disorder[107] have also been associated with an increased risk of HF, while subjective well-being appears to have a protective effect.[107]

4.5. Other comorbid conditions

Other conditions such as atopic dermatitis,[108,109] systemic lupus erythematosus,[110] hip osteoarthritis,[111] multisite chronic pain,[112] chronic obstructive pulmonary disease,[52] anemia,[113] and gastroesophageal reflux disease[114] have also been considered as risk factors for HF. For patients suffering from these diseases, it is important to be aware of the potential HF risk.

5. Therapeutic target discovery

5.1. Gut microbiome

Recent MR studies have revealed causal relationships indicating either protective or risk associations between specific gut microbiomes and HF. As the role of gut microbiota and their metabolites in cardiovascular disease becomes clearer,[115] gut microbiota have emerged as a promising target for HF prevention and treatment. One study suggested that six microbial taxa, represented by *Bacteroides dorei*, may act as either causal risk or protective factors for HF, with ApoB mediating 10.1% of the effect.[96] Another study examined *Candida*, *Campylobacter*, *Shigella*, and *Yersinia*, which have been linked to increased risk of HF in observational studies.[116] However, MR analysis did not find any causal association, although these bacteria may contribute to myocarditis and chronic kidney disease, which could lead to HF.[117] Another MR study analyzing the entire gut microbiome and specific groups also did not find a causal association, with horizontal pleiotropy limiting the reliability of its conclusions.[118] However, in terms of microbial metabolites, several metabolites, represented by betaine, phenylalanine, and tryptophan, are associated with HF and its risk factors (i.e., BP) in both protective and detrimental ways, but the exact mechanisms remain unclear and require further validation.[117]

The use of MR in gut microbiome research offers a new perspective for HF prevention and treatment, suggesting that targeted interventions involving specific gut microbiota in high-risk populations might be a novel strategy for HF prevention. Potential therapeutic approaches may include small molecule antibiotics, prebiotics, engineered bacteria (symbiotic and probiotic), and biologically active metabolites.[96,119] However, gut microbiota are primarily influenced by diet, environmental factors, lifestyle, and antibiotic use, making it biologically implausible that specific genetic variants exert direct and exclusive effects on individual microbial taxa. Moreover, the use of gut microbiota as exposures is highly susceptible to horizontal pleiotropy, which substantially limits the reliability of causal inferences.[120]

5.2. Druggable targets and proteins

Current MR studies have identified drug targets and revealed causal associations between certain circulating proteins and HF, providing valuable leads for drug development. Several pathways discussed in preceding sections, particularly those related to glycometabolic dysfunction, lipid metabolism, inflammation, and adiposity, are revisited here as potential therapeutic targets rather than solely as risk factors.

5.3. Genomic target discovery

Cross-platform genomic integration has aided in identifying genetic loci and causal risk proteins, translating into possible clinical insights. A multiancestry GWAS meta-analysis with 1,665,481 participants identified 47 risk loci and nine causally related circulating proteins, along with four proteins related to HF-associated traits.[121] Another study based on the HERMES consortium identified 12 independent variants at 11 genomic loci associated with HF risk that not only impact left ventricular structure and function but also modulate risk factors such as CAD, AF, and BMI. These variants play a role in cardiac development, protein homeostasis, and cellular senescence.[122] Additionally, a meta-GWAS study revealed 39 HF risk variants, including 18 previously unreported. Seven novel genes were identified through GWAS and MR-proteomics, with their encoded proteins serving as potential targets for HF prevention.[123] Another GWAS study found a positive correlation between endogenous testosterone and HF in men, indicating that regulating endogenous testosterone levels may help prevent HF.[124]

5.4. Protein-based target discovery

Proteomics analysis in large populations has provided insights into the molecular processes underlying HF risk. One study extracted circulating protein data from a GWAS meta-analysis of 14 European ancestry cohorts, identifying eight causally related proteins, seven of which were druggable and five considered potential therapeutic targets for HF.[4] Another study identified 91 genetic variants and 304 circulating proteins causally related to ventricular traits, the measurements of biventricular structure and function, with nine proteins affecting at least three cardiac magnetic resonance traits and associated with HF outcomes. The study uniquely measured, relevant to HFpEF, identifying seven proteins impacting peak filling rates and HF or dilated cardiomyopathy

risk, with five being druggable.[125] Additionally, another study identified 19 proteins causally associated with HF, enriched in ligand-receptor and glycosylation molecules, with seven proteins highlighted as potential HF therapy targets through drug-target analysis.[126]

Beyond these proteome-wide findings, specific candidate proteins have also been investigated individually to clarify their context-dependent effects. FGF-23, a key regulator of phosphate and vitamin D metabolism, is one such example.[27] Although most MR studies have not supported a causal association between genetically predicted FGF-23 and overall HF,[28–30] positive associations have been observed for HFpEF and among individuals with genetic susceptibility to low estimated glomerular filtration rate (eGFR),[30] suggesting that the effects of FGF-23 may be phenotype-specific and more relevant in cardiorenal contexts. At the same time, the apparently protective signal from proteome-wide MR should not be considered directly equivalent to MR analyses of circulating FGF-23 concentrations, as these approaches may capture different biological constructs.[4] Taken together, these discordant findings likely reflect a combination of biological heterogeneity, effect modification by kidney function, and methodological differences in exposure definitions and instrument selection. No causal relationship has been found between serum albumin levels and HF, indicating that serum albumin is unlikely to be a causal factor in HF development.[127]

5.5. Integrative quantitative trait locus (QTL)-based approaches for target discovery

To refine and prioritize candidate targets identified from genomic and proteomic analyses, QTL-informed frameworks provide an additional layer of evidence. QTL-informed analyses have further refined the interpretation of inflammatory signaling in HF. Cis-protein quantitative trait loci (cis-pQTL) and cis-expression quantitative trait loci (cis-eQTL) analyses demonstrated a protective effect of interleukin-2 receptor alpha (IL-2ra) and an exacerbating effect of both interferon gamma-induced protein 10 (IP-10) and interleukin-6 on HF.[128] Cis-protein quantitative trait loci and cis-expression quantitative trait loci analyses suggest a potentially protective effect of IL-2ra, whereas interferon gamma–IP-10 and interleukin-6 have been associated with increased HF risk.[128] Positive causal correlations were observed between HF and galectin-3[4] and macrophage migration inhibitory factor,[126,128] with the latter being mediated by BP and CAD.[126] These findings are particularly informative, as they refine and strengthen biomarker-based associations by providing genetically anchored evidence, thereby helping to prioritize specific molecular regulators with potential therapeutic relevance.

5.6. Antihyperglycemic targets

MR provides supplementary evidence supporting the clinical use of corresponding drugs for HF treatment. For antihyperglycemic drugs, an MR study using the sodium/glucose co-transporter-1 (SGLT1) haplotype as an instrument found that a reduction of glucose level in a 2-h oral glucose tolerance test was associated with lower HF incidence.[129] The anti-HF effect of sodium/glucose co-transporter-2 (SGLT2) was also confirmed by MR, with chemokine C-X-C motif ligand 10 (CXCL10) mediating 17.85% of the total effect.[130] Additionally, genetically predicted glucagon-like peptide-1 receptor (GLP1R) agonism was linked to a reduced risk of HF and higher left ventricular ejection fraction, with this effect not attributable to chronic IHD.[131]

5.7. Lipid-modifying targets

Regarding lipid-modifying targets, a univariable MR study identified three targets whose inhibition or activation is associated with a lower risk of HF: inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) and cholesteryl ester transfer protein (CETP), and activation of lipoprotein lipase. In contrast, this association was not observed for 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the target gene of statins. Summary-data-based MR (SMR) further revealed that these targets were linked to multiple lipid markers, with CAD mediating the observed causal effects between lipid modification and HF risk. The aforementioned lipid-modifying drugs may serve as potential targets for HF prevention, especially in patients with CAD or at high risk of CAD.[94] Additionally, lower CETP concentrations were causally linked to lower BP and glucose levels, while lower PCSK9 concentrations were associated with increased carotid intima-media thickness, systolic BP, urea nitrogen, hemoglobin A1c (HbA1c), higher estimated glomerular filtration rate, C-reactive protein, pulse rate, and blood cell counts.[132]

5.8. Antihypertensive drug targets

For antihypertensive drugs, genetically predicted use of beta-blockers and calcium channel blockers, rather than angiotensin-converting enzyme inhibitors[133,134] or thiazide diuretics,[133] was associated with a lower risk of HF. This apparent divergence from current clinical practice should be interpreted with caution rather than as a direct contradiction. Drug-target MR primarily estimates the effect of lifelong genetically proxied perturbations of antihypertensive pathways on incident HF, whereas guideline recommendations for angiotensin-converting enzyme inhibitors and beta-blockers are largely based on treatment effects in established HFrEF or selected high-risk states. Accordingly, a null MR estimate for ACE inhibition does not necessarily imply a lack of therapeutic benefit. In addition to limited numbers of SNPs, available ACE-related instruments may incompletely capture the full pharmacological effects of angiotensin-converting enzyme inhibitors, including tissue Renin–Angiotensin–Aldosterone System (RAAS) modulation and reverse remodeling following ventricular injury. Moreover,

because HF outcomes in MR studies are often heterogeneous, phenotype-specific effects may be diluted in analyses of overall HF. By contrast, the protective signal for beta-blockers and calcium channel blockers may partly reflect long-term BP reduction rather than a uniform class-wide benefit in manifest HF.

6. Discussion

By integrating evidence from MR, RCTs, and observational studies, our study provides a triangulated framework to interpret the causal relevance of risk factors for HF and their alignment with current prevention guidelines. Overall, the findings can be structured into three distinct layers based on the consistency of evidence across study designs, thereby enhancing their clinical interpretability (Supplementary Table 1, Supplemental Digital Content, https://links.lww.com/CARES/A21).

First, a group of well-established risk factors demonstrated highly concordant evidence across MR, RCTs, and observational studies, strongly reinforcing current guideline recommendations. Lifestyle-related factors such as PA, sedentary behavior, and smoking showed consistent directional effects, with MR estimates supporting protective effects of PA and harmful effects of prolonged sedentary exposure and tobacco use. Similarly, cardiometabolic conditions—including obesity, type 2 diabetes, and metabolic syndrome—were robustly associated with increased HF risk across all evidence sources, with particularly strong and consistent effect sizes observed for BMI, including across HF subtypes. In addition, cardiovascular diseases such as AF and CAD exhibit stable causal effects, supporting the concept of a cardiovascular continuum emphasized in both European Society of Cardiology and American Heart Association/American College of Cardiology (AHA/ACC) guidelines. Collectively, these findings constitute a "high-confidence causal layer" in which agreement across methodologies provides strong support for current preventive strategies.

Second, our analysis identifies several emerging risk factors that are not yet fully incorporated into existing guidelines but are supported by MR and, in some cases, observational evidence. Notably, sleep-related traits—including insomnia, short sleep duration, daytime napping, and daytime sleepiness—showed consistent harmful associations with HF risk, suggesting that sleep health may represent an underrecognized but potentially modifiable target for HF prevention. In addition, psychosocial factors, such as depression and severe mental disorders, demonstrate causal effects, reinforcing the importance of integrating mental health into cardiovascular risk assessment. Dietary-related findings further refine current nutritional recommendations, with evidence supporting harmful effects of higher sodium exposure and potential protective effects of specific food components, such as dried fruit, while also identifying potentially adverse metabolites, such as L-carnitine. Furthermore, novel biomarkers, such as FGF-23, show subtype-specific associations, particularly in HFpEF or populations with impaired renal function, indicating potential pathways for precision prevention. These factors form an "emerging evidence layer" representing promising targets for future guideline updates.

Third, several findings challenge or refine existing assumptions derived primarily from observational studies. For example, circulating vitamin levels, particularly vitamin D and vitamin C, show largely neutral associations in MR analyses despite prior observational evidence suggesting protective effects, consistent with the lack of benefit observed in most RCTs. Other dietary exposures, such as tea and coffee consumption, also show predominantly null effects in MR frameworks. These discrepancies highlight the potential influence of residual confounding and reverse causation in traditional epidemiological studies and define an "inconsistent evidence layer" where caution is warranted before translating associations into clinical recommendations.

Beyond individual exposures, several risk factors discussed in this review, including obesity, type 2 diabetes, metabolic syndrome, dyslipidemia, physical inactivity or sedentary behavior, smoking, OSA, and air pollution, are likely to converge on a limited set of shared pathophysiological pathways contributing to HF development.[3] A central axis may involve comorbidity-driven systemic inflammation and coronary microvascular endothelial activation, which may reduce nitric oxide bioavailability, impair cyclic GMP (cGMP)–protein kinase G (PKG), and promote cardiomyocyte stiffness, hypertrophy, and diastolic dysfunction.[135–138] In parallel, obesity- and diabetes-related metabolic overload may contribute to myocardial injury through altered substrate handling, lipotoxic ceramide accumulation, mitochondrial dysfunction, and apoptosis, thereby compromising myocardial energetics and promoting maladaptive remodeling.[139–141] Sedentary behavior may further amplify these abnormalities by reducing vascular shear stress and impairing endothelial function.[142] In addition, smoking and fine particulate air pollution may exacerbate mitochondrial oxidative stress, endothelial dysfunction, and profibrotic signaling, thereby providing a plausible mechanistic link between environmental exposures and myocardial remodeling.[143–145] Finally, adipose–cardiac crosstalk may represent an important integrative mechanism linking obesity and sleep-disordered breathing to myocardial fibrosis, as visceral adipose tissue–derived profibrotic mediators and intermittent hypoxia–induced adipose senescent remodeling have both been implicated in adverse myocardial structural changes.[146,147] Collectively, these findings suggest that diverse cardiometabolic, behavioral, and environmental exposures may not act through isolated pathways but rather through interconnected inflammatory, microvascular, metabolic, oxidative, and fibrotic mechanisms that ultimately increase susceptibility to HF.

However, the validity of causal inference in MR is inherently contingent upon the plausibility of the core instrumental variable assumptions, which should be

critically appraised in the context of specific exposures. For instance, the use of air pollution as an exposure is conceptually problematic, as genetic variants are unlikely to influence environmental pollutant levels, thereby casting doubt on the relevance assumption. Likewise, emerging exposures such as the gut microbiota present substantial challenges, given that microbial composition is predominantly shaped by diet, lifestyle, environmental factors, and medication use, making it biologically implausible for host genetic variants to exert specific and isolated effects on individual taxa. Collectively, these considerations underscore the need for more stringent sensitivity analyses and triangulation strategies in future MR studies, as well as a more cautious appraisal of whether certain exposures are conceptually and biologically amenable to MR frameworks.

In conclusion, MR has emerged as an important tool for clarifying the causal architecture of HF. Beyond strengthening etiological inference, its broader value lies in providing a genetically informed framework for evaluating the causal relevance of risk factors and bridging the gap between epidemiological associations and actionable insight. By enabling more robust causal inference, MR offers a foundation for improving the interpretability and translational potential of risk factor research (Fig. 3). Nevertheless, these implications require cautious interpretation and further validation before translation into clinical practice or public health policy.

7. Future perspectives

Despite the growing body of MR evidence related to HF, several key directions should be prioritized to enhance its translational and methodological impact. First, future MR studies should focus on HF subtypes, particularly HFrEF and HFpEF, given their substantial differences in pathophysiology, risk factor profiles, and therapeutic responses. With the expansion of subtype-specific GWAS resources, more refined and well-powered analyses are becoming feasible. Nevertheless, to date, most MR analyses have treated HF as a homogeneous outcome, with only a limited number of recent studies distinguishing between subtypes. Among these, subtype-specific analyses have primarily focused on disease-related exposures, such as CAD, while evidence on modifiable lifestyle factors remains scarce. Future studies should prioritize HF-specific evidence rather than relying on broader cardiovascular outcomes, thereby enabling a stronger focus on HF subtypes and improving the specificity and clinical relevance of causal inference.

Second is the incomplete MR evaluation of several clinically relevant HF risk factors. In particular, some

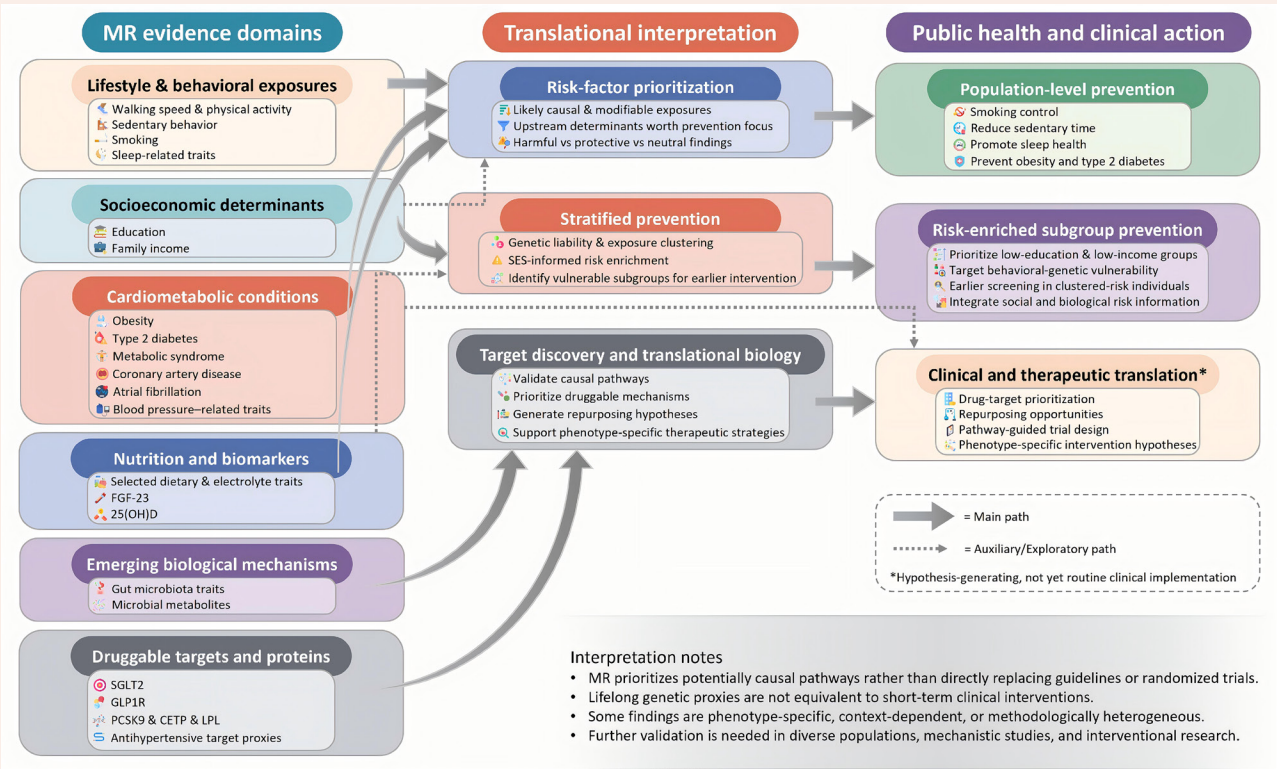


Figure 3. Translational framework from MR findings to public health and clinical action in HF. CETP = cholesteryl ester transfer protein, FGF-23 = fibroblast growth factor 23, GLP1R = glucagon-like peptide-1 receptor, HF = heart failure, LPL = lipoprotein lipase, MR = Mendelian randomization, PCSK9 = proprotein convertase subtilisin/kexin type 9, SES = socioeconomic status, SGLT2 = sodium/glucose co-transporter-2.

exposures highlighted in traditional guidelines or observational literature, such as influenza-related susceptibility or severity, cocaine use, pregnancy-related complications (e.g., preeclampsia), and iatrogenic factors (e.g., cardiotoxic therapies), have not yet been evaluated using MR in relation to HF.[1,3] These factors may therefore represent important priorities for future genetic epidemiology studies. In addition, greater attention should be paid to reverse causation and potential feedback loops, as HF itself may influence various circulating biomarkers (e.g., natriuretic peptides and renal function indicators). The application of reverse MR analyses may help disentangle the directionality of these associations and clarify whether observed relationships reflect causal effects or downstream consequences of HF.

Third, the majority of MR studies have focused on individuals of European ancestry, which limits generalizability. Inclusion of multiethnic cohorts will improve the external validity of findings and may reveal population-specific genetic architectures and risk profiles.

Fourth, integration of large-scale biobank resources with multiomics data represents a promising avenue. The combination of genomics with transcriptomics, proteomics, metabolomics, and microbiomics can provide a more comprehensive understanding of the biological pathways underlying HF. In particular, proteome-wide and metabolome-wide MR analyses may help identify intermediate phenotypes and refine causal pathways, thereby bridging the gap between genetic associations and clinical mechanisms.

Fifth, advances in MR methodology should be more widely adopted in HF research. Approaches such as cis-MR, which leverage genetic variants in or near drug-target genes, can improve the specificity of causal inference for therapeutic targets. MR-Phenome-Wide Association Studies enable systematic evaluation of potential on-target and off-target effects across a wide range of phenotypes, facilitating drug safety assessment. In addition, multivariable MR, nonlinear MR, and time-varying MR analyses can help disentangle direct versus mediated effects, assess dose–response relationships, and better approximate real-world exposure patterns.

Finally, greater emphasis should be placed on translational applications. MR findings can inform drug-target validation, repurposing of existing therapies, and prioritization of clinical trials. Strengthening the integration between MR evidence, RCTs, and clinical guidelines will be crucial for translating genetic insights into effective prevention and treatment strategies for HF.

8. Conclusion

By integrating MR with evidence from RCTs and observational studies, a clearer causal hierarchy of modifiable risk factors for HF can be established, reinforcing established determinants while distinguishing likely causal effects from confounded associations. This triangulated framework provides a more coherent pathway from genetic evidence to public health action—strengthening current guideline targets, highlighting emerging domains such as sleep and psychosocial health as potential priorities for prevention, and identifying candidate therapeutic targets. Nevertheless, key challenges remain, including the validity of MR assumptions for complex exposures, limited ancestry diversity, and the lack of subtype-specific evidence. Addressing these gaps, alongside the adoption of more advanced methodologies and deeper integration with multiomics and clinical research, will be essential for translating causal insights into effective and precise HF prevention strategies.

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AI statement

The authors used artificial intelligence (AI) tools to assist with language editing and improvement of manuscript readability. Apart from this, AI tools were not involved in any other aspect of the preparation of this review. All scientific content, interpretations, and conclusions were reviewed and approved by the authors, who take full responsibility for the final manuscript.

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