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Original article

Red and processed meat intake and risk of cardiovascular disease: A two-sample Mendelian randomization study

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SUMMARY

Background & aims: Previous observational studies have yielded inconsistent findings regarding associations between red/processed meat intake and the risk of cardiovascular disease (CVD). Some studies have suggested positive relationships, while others have demonstrated no significant associations. However, causal effects remain uncertain. This 2023 Mendelianrandomization (MR) study investigated the causal relationship between red and processed meat (porkmeat, mutton meat, beef meat)intake and CVD risk by analyzing summary data from the UK Biobank (exposure), CARDIoGRAMplusC4D (coronary artery disease [CAD]), MEGASTROKE (stroke), Nielsen et al. (atrial fibrillation [AF]), HERMES (heart failure [HF]), and FinnGen (cardiovascular outcomes) public databases.

Methods: Genome-wide association studies (GWAS) of red meat (pork, beef, and mutton) and processed meat were sourced from the United Kingdom (UK) Biobank. GWAS data on CVD for this study were obtained from the Gene and FinnGen consortia. The primary method employed for the two-sample MR analysis was inverse variance weighting (IVW). Sensitivity analysis was performed to assess the reliability and consistency of the results.

Results: Genetically predicted red and processed meat consumption did not demonstrate a causal association with any CVD outcomes when employing the IVW method. For processed meat intake, the odds ratios (ORs) (95% confidence intervals CIs) in large consortia were as follows: 0.88 (0.56−1.39) for CAD, 0.91 (0.65−1.27) for AF, 0.84 (0.58−1.21) for HF, and 1.00 (0.75−1.05) for stroke. In FinnGen, the ORs were as follows: 1.15 (0.83−1.59) for CAD, 1.25 (0.75−2.07) for AF, 1.09 (0.73−1.64) for HF, and 1.27 (0.85−1.91) for stroke. For beef intake, the ORs (95% CIs) in large consortia were as follows: 0.70 (0.28−1.73) for CAD, 0.85 (0.49−1.49) for AF, 0.80 (0.35−1.83) for HF, and 1.29 (0.85−1.95) for stroke. In FinnGen, the ORs were as follows: 2.01 (0.75−5.39) for CAD, 1.83 (0.60−5.56) for AF, 0.80 (0.30−2.13) for HF, and 1.30 (0.62−2.73) for stroke. For pork intake, the ORs (95% CIs) in large consortia were as follows: 1.25 (0.37−4.22) for CAD, 1.26 (0.73−2.15) for AF, 1.71 (0.86−3.39) for HF, and 1.15 (0.63−2.11) for stroke. In FinnGen, the ORs were as follows: 1.12 (0.43−2.88) for CAD, 0.39 (0.08−1.83) for AF, 0.62 (0.20−1.88) for HF, and 0.60 (0.21−1.65) for stroke. For mutton intake, the ORs (95% CIs) in large consortia were as follows: 0.84 (0.48−1.44) for CAD, 0.84 (0.56−1.26) for AF, 1.04 (0.65−1.67) for HF, and 1.06 (0.77−1.45) for stroke. In FinnGen, the ORs were as follows: 1.20 (0.65−2.21) for CAD, 0.92 (0.44−1.92) for AF, 0.74 (0.34−1.58) for HF, and 0.75 (0.45−1.24) for stroke. The results remained robust and consistent in both the meta-analysis and supplementary MR analysis.

Abbreviations: CVD, cardiovascular disease; CAD, coronary artery disease; AF, atrial fibrillation; HF, heart failure; GWAS, genome-wide association studies; UK, United Kingdom; IVs, Instrumental variables; IVW, inverse variance weighted model; WME, weighted-median estimator; MR, Mendelian randomization; SNPs, single-nucleotide polymorphisms; WM, weighted model-based method; EA, effect allele; OA, other allele.

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Conclusions: This MR study demonstrated no significant causal relationships between red/processed meat intake and the risk of the four CVD outcomes examined. Further investigation is warranted to confirm these findings.

1. Introduction

Cardiovascular disease (CVD) is a major global health challenge, contributing significantly to mortality and morbidity [1]. In 2020, CVD accounted for approximately 32% of all deaths, resulting in an estimated 19 million fatalities [2]. Patients with CVD often experience a reduced quality of life due to associated disabilities and comorbidities [3]. Hence, comprehensive research is urgently needed to identify and unravel modifiable risk factors related to CVD. One factor that has received considerable attention is diet, specifically the consumption of red and processed meats [4].

Diet significantly influences cardiovascular health and varies regionally. Nordic diets prioritize vegetables, fruits, whole grains, legumes, and lean meats, while certain Western patterns include more processed foods, red meat, sugary drinks, and refined grains, with lower intake of fruits and vegetables. The Mediterranean diet shares macronutrient similarities with Western diets, but the types of fats consumed differ. Although the impact of red and processed meat intake on cardiovascular outcomes has been studied, inherent limitations hinder definitive causal conclusions. Traditional epidemiological study designs cannot fully account for confounding factors and reverse causation [5].

Previous studies have proposed potential mechanisms linking red meat consumption to the pathogenesis of CVD. The high content of saturated fats, cholesterol, and haem iron in red meats, such as beef, pork, and mutton, has been hypothesized to contribute to cardiovascular risk [6]. Similarly, processed meats containing preservatives, sodium, and nitrates have been associated with increased CVD risk [7]. Further studies elucidating nuanced differences between processed and unprocessed meats would enable more targeted recommendations for optimal dietary choices.

However, significant uncertainties remain regarding the causal effects of red and processed meat intake on CVD outcomes. Previous observational findings have been mixed, with some studies suggesting positive associations [8–10], while others found no significant relationships [11,12]. Establishing robust evidence of causal effects requires the limitations of traditional observational designs to be overcome.

Mendelian randomization (MR) analysis is a robust approach for assessing causal relationships in epidemiological research. MR employs genetic variations as instrumental variables (IVs) to assess the causal effects of exposure on outcome [5]. This method assumes that genetic variants linked to a specific exposure exclusively affect results by affecting the exposure itself, free from interference from confounding variables [13]. By leveraging genetic variations as IVs, MR analysis provides valuable insights into causal relationships that may be obscured by the constraints of conventional observational studies. In this study conducted in June 2023, we aimed to overcome the limitations of previous observational investigations by employing an MR analysis to accurately assess the potential causal relationship between red and processed meat consumption and CVD. By utilizing genetic variations as instrumental variables, we can better elucidate the impact of these dietary factors on CVD risk, thereby informing public health recommendations and interventions.

2. Materials and methods

2.1. Study design

The MR design approach utilises association studies of 'exposure' and 'outcome' from accessible public datasets containing extensive large-sample genome-wide association studies (GWAS). This approach aims to examine whether exposure causes the development of the disease. Genetic variation is considered an IV in the MR design. Leveraging genetic variations, MR methods address the limitations of observational studies, enabling more robust causal inferences. The design of the present study was based on three key assumptions:

(1) Genetic variation is strongly associated with the exposure.
(2) Genetic variation is independent of other confounding factors.
(3) Genetic variation is associated with the outcome solely through the surveyed exposure [14].

We utilized publicly available GWAS summary statistics for the analysis. The respective studies were approved by their respective Institutional Review Boards, and no additional ethical approval was required for the current study. To investigate the causal relationship between red and processed meats and CVD, we employed a two-sample MR approach [15,16], as depicted in Fig. 1.

2.2. Data sources

Dietary exposures (processed meat, pork, beef, and mutton) were obtained from the UK Biobank cohort comprising 461,981, 460,162, 461,053, and 460,006 individuals of European ancestry, respectively. Single-nucleotide polymorphisms (SNPs) associated with processed meat, pork, beef, and mutton intake were identified using genome-wide significance thresholds ($p < 5 \times 10^{-8}$). Linkage disequilibrium among single exposed SNPs was estimated using the PLINK(whole−genome association analysis toolset) clustering method based on the 1000 Genomes European reference panel. Independent SNPs without linkage disequilibrium (R2>0.001 within a 10,000 kb window) were used as IVs (Supplementary Table 1). The F statistic and proportion of variance explained were calculated to assess the potential bias caused by weak instruments.

Summary-level data for the four CVD outcomes were acquired from extensive genetic consortia and the FinnGen consortium. Table 1 provides a comprehensive description of the data sources.

2.3. Selection and Exclusion Criteria

Selection Criteria: For exposure to meat intake, participants were included in the UK Biobank cohort if they satisfactorily completed a food frequency questionnaire, providing essential data on processed meat and red meat consumption.

Concerning cardiovascular disease outcomes, clinical diagnoses of coronary artery disease, atrial fibrillation, heart failure, or stroke

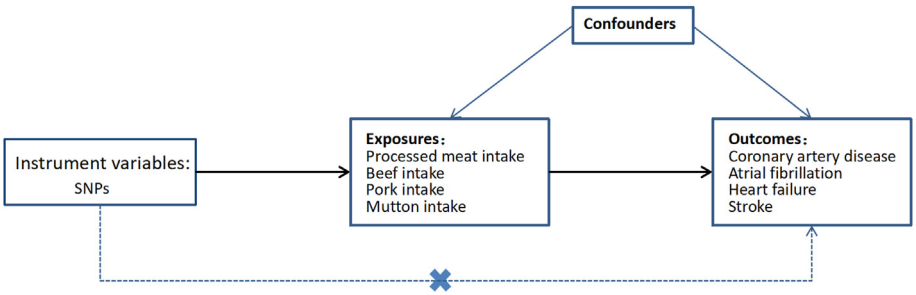

Fig. 1. Mendelian randomization model of meat intake and CVD.

Table 1
Details regarding the data sources for CVD outcomes included in this MR investigation.

Cardiovascular disease	Data source	Cases	Controls	Population	Access link
CAD	CARDIoGRAMplusC4D [17]	60,801	123,504	Mixed	http://www.cardiogramplusc4d.org/
	FinnGen consortium	25,707	234,698	European	https://www.finngen.fi/en, phenocode:I9_CHD
AF	Nielsen et al. [18]	60,620	970,216	European	http://csg.sph.umich.edu/willer/public/afib2018
	FinnGen consortium	28,670	135,821	European	https://www.finngen.fi/en, phenocode:I9_AF
HF	HERMES [19]	47,309	930,014	European	https://cvd.hugeamp.org/dinspector.html?dataset=GWAS_HERMES_eu
	FinnGen consortium	30,098	229,612	European	https://www.finngen.fi/en, phenocode:I9_HEARTFAIL_ALLCAUSE
Stroke	MEGASTROKE consortium [20]	40,585	406,111	European	https://www.megastroke.org/
	FinnGen consortium	14,171	133,027	European	https://www.finngen.fi/en, phenocode:I9_STROKE

CVD, cardiovascular disease; MR, Mendelian randomization; CAD, coronary artery disease; AF, atrial fibrillation; HF, heart failure; CARDIoGRAMplusC4D, Coronary Artery Disease Genome-wide Replication and Meta-analysis (CARDIoGRAM) plus Coronary Artery Disease (C4D) Genetics; HERMES, Heart Failure Molecular Epidemiology for Therapeutic Targets.

were established using the International Classification of Diseases, 9th and 10th revisions.

Exclusion Criteria: Participants were excluded from the analysis of meat intake exposure data if they failed to complete the food frequency questionnaire or if their data on processed meat or red meat consumption frequency were missing or incomplete.

Regarding cardiovascular disease outcomes, participants were excluded if they lacked available genome-wide genotyping data or did not possess a confirmed diagnosis for any of the cardiovascular endpoints of interest.

2.4. Statistical analysis

To evaluate the causal effect of meat intake on CVD, we performed a primary analysis using a random-effects inverse variance weighted model (IVW) [21]. Furthermore, the incorporation of three additional MR techniques (MR-Egger, weighted median, and weighted mode methods) in conjunction with IVW facilitated a more thorough evaluation of the causal association between exposure and outcome. The results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). A Bonferroni-corrected *P*-value <0.003 (corrected for four exposures and four outcomes) was considered a significance threshold, and a normal significance level (*P*-value <0.05) was considered suggestive.

2.5. Sensitivity analysis

To assess the robustness and potential bias of our results, we performed sensitivity analyses using the Cochran Q statistic, MR-PRESSO test, funnel plots, MR-Egger intercepts, and leave-one-out analysis [22–24]. MR analyses were conducted using R software (version 4.0.2) and the Two-Sample MR package [25].

3. Results

The association between processed and red meat intake (including beef, pork, and mutton) and the risk of CVD was examined using various MR methods. The results of the primary MR analysis, as detailed in Supplementary Table 2, showed no significant causal relationship between processed and red meat intake and the risk of CVD outcomes.

3.1. Causal relationship between processed meat and CVD

No causal association was observed between processed meat consumption and CVD outcomes in both the GWAS of large genetic consortia (coronary artery disease [CAD]: OR = 0.88, 95% CI, 0.56–1.39, $P = 0.59$; atrial fibrillation [AF]: OR = 0.91, 95% CI, 0.65–1.27, $P = 0.60$; heart failure [HF]: OR = 0.84, 95% CI, 0.58–1.21, $P = 0.36$; stroke: OR = 1.00, 95% CI, 0.75–1.05, $P = 0.98$) and the FinnGen consortium (CAD: OR = 1.15, 95% CI, 0.83–1.59, $P = 0.68$; AF: OR = 1.25, 95% CI, 0.75–2.07, $P = 0.38$; HF: OR = 1.09, 95% CI, 0.73–1.64, $P = 0.65$; stroke: OR = 1.27, 95% CI, 0.845–1.91, $P = 0.24$). Meta-analysis results combining MR estimates from different data sources also revealed no causal inference between processed meat consumption and CVD (*P*-values for all CVD outcomes were >0.05) (Fig. 2).

3.2. Causal relationship between beef intake and CVD

The MR analyses did not reveal significant causal associations between beef intake and CAD, AF, HF, or stroke in the GWAS of large genetic consortia (CAD: OR = 0.70, 95% CI, 0.28–1.73, $P = 0.44$; AF: OR = 0.85, 95% CI, 0.49–1.49, $P = 0.58$; HF: OR = 0.80, 95% CI, 0.35–1.83, $P = 0.60$; stroke: OR = 1.29, 95% CI, 0.85–1.95, $P = 0.22$) or the FinnGen consortium (CAD: OR = 2.01, 95% CI, 0.75–5.39, $P = 0.16$; AF: OR = 1.83, 95% CI, 0.60–5.56, $P = 0.27$; HF: OR = 0.80, 95% CI, 0.30–2.13, $P = 0.66$; stroke: OR = 1.30, 95% CI, 0.62–2.73, $P = 0.47$). The results of a meta-analysis combining MR estimates

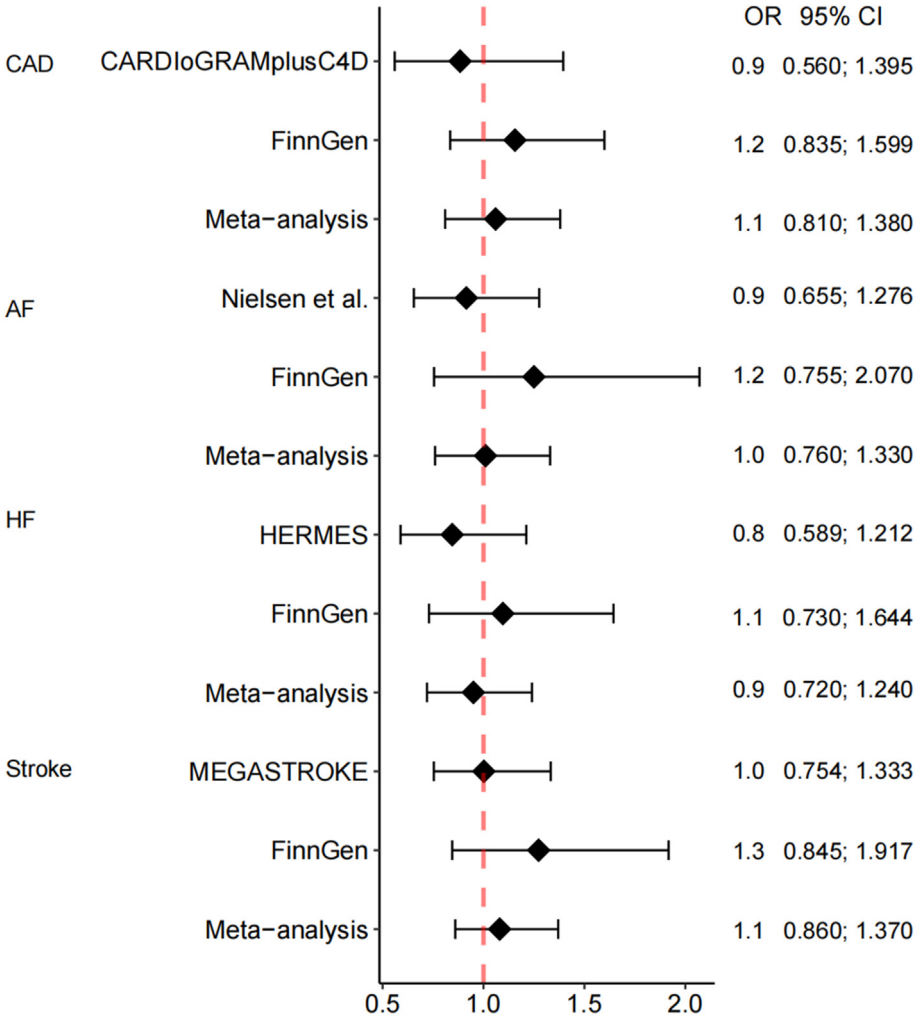

Fig. 2. Associations of genetically predicted processed meat intake with CVD in large genetic consortia and FinnGen and in meta-analysis.

from different data sources suggested P values > 0.05 for all CVD outcomes (Fig. 3).

3.3. Causal relationship between pork intake and CVD

The results for pork intake and CVD outcomes were also nonsignificant in both the GWAS of large genetic consortia (CAD: OR = 1.25, 95% CI, 0.37–4.22, P = 0.71; AF: OR = 1.26, 95% CI, 0.73–2.15, P = 0.39; HF: OR = 1.71, 95% CI, 0.86–3.39, P = 0.12; stroke: OR = 1.15, 95% CI, 0.63–2.11, P = 0.63) and FinnGen consortium (CAD: OR = 1.12, 95% CI, 0.43–2.88, P = 0.80; AF: OR = 0.39, 95% CI, 0.08–1.83, P = 0.23; HF: OR = 0.62, 95% CI, 0.20–1.88, P = 0.40; stroke: OR = 0.60, 95% CI, 0.21–1.65, P = 0.32). None of the meta-analyses that combined MR estimates from different data sources were statistically significant (P > 0.05) (Fig. 4).

3.4. Causal relationship between mutton intake and CVD

Likewise, the analysis of mutton intake did not reveal any significant associations with CAD, AF, HF, or stroke in the GWAS of large genetic consortia (CAD: OR = 0.84, 95% CI, 0.48–1.44, P = 0.53; AF:OR = 0.84, 95% CI, 0.56–1.26, P = 0.41; HF: OR = 1.04, 95% CI, 0.65–1.67, P = 0.85; stroke: OR = 1.06, 95% CI, 0.77–1.45, P = 0.70) or the FinnGen consortium (CAD:OR = 1.20, 95% CI, 0.65–2.21, P = 0.55; AF: OR = 0.92, 95% CI, 0.44–1.92, P = 0.83; HF: OR = 0.74, 95% CI, 0.34–1.58, P = 0.44; stroke: OR = 0.75, 95% CI, 0.45–1.24, P = 0.26). The MR estimates from the different data sources combined in the meta-analyses were all statistically nonsignificant (P > 0.05) (Fig. 5).

3.5. Sensitivity analysis

The results revealed pleiotropy between processed meat consumption and heart failure in the HERMES dataset and FinnGen consortium. Additionally, within the FinnGen consortium, pleiotropy was observed between processed meat consumption and AF, as well as between mutton consumption and stroke. However, no evidence of horizontal pleiotropy was found for any of the remaining outcomes (Supplementary Table 3). After identifying outliers using MR-PRESSO, the MR analysis was repeated after their exclusion. Based on the available evidence (Supplementary Table 4), no causal relationships were found between processed meat intake and HF, processed meat intake and AF, or mutton intake and stroke.

4. Discussion

This study aimed to investigate the causal relationship between red and processed meat intake and CVD risk using MR analysis. Our MR analysis, utilizing extensive genetic consortium data and the

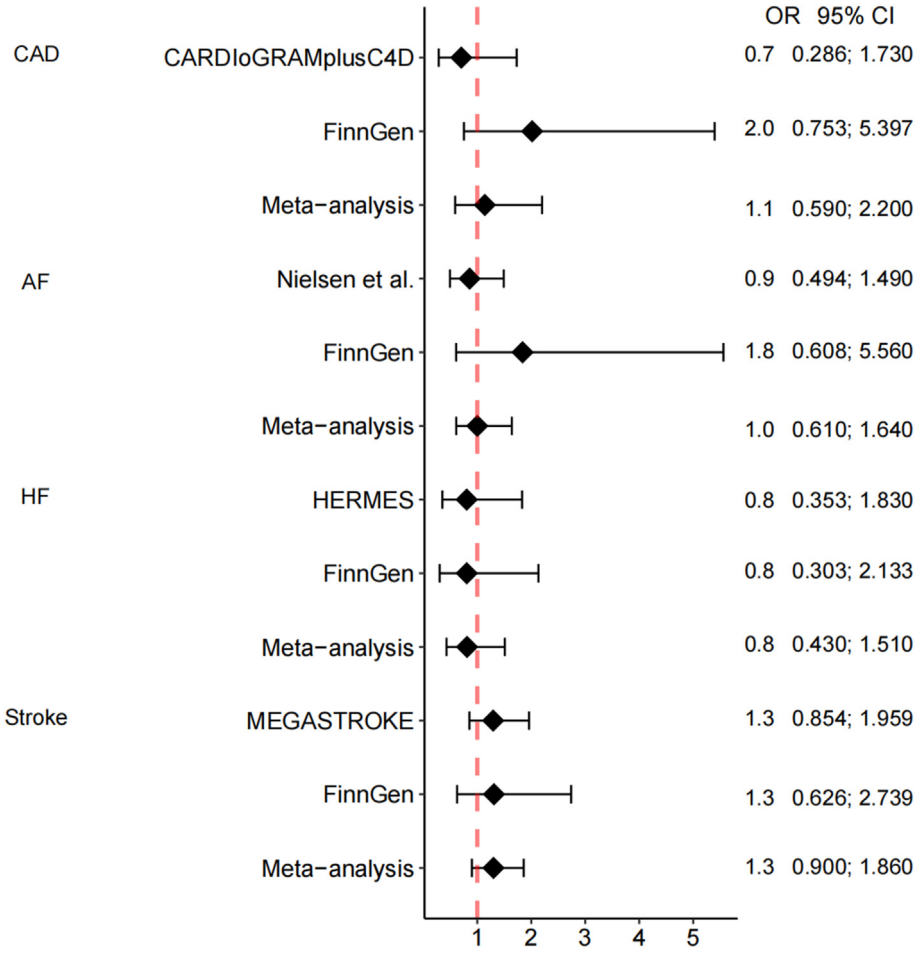

Fig. 3. Associations of genetically predicted Beef intake with CVD in large genetic consortia and FinnGen and in meta-analysis.

FinnGen consortium, revealed no significant association between genetically predicted processed and non-processed red meat intake and the four investigated CVD outcomes (CAD, AF, HF, and stroke). This result differs from those of previous observational studies [26–30].

Over the past decade, several cross-sectional and prospective studies have investigated the relationship between red and processed meat consumption and CVD. The conclusions drawn from the available data are inconsistent. In a US population-based study involving 29,682 participants, Zhong et al. found that a higher intake of processed meat, unprocessed red meat, or poultry (but not fish) was significantly associated with a slightly increased risk of CVD events [8]. In a large multinational prospective study involving 134,297 participants, Iqbal et al. found no significant associations between the intake of unprocessed red meat and poultry and mortality or major CVD. However, the intake of processed meat was positively correlated with an increased risk of death and major CVD [31]. A meta-analysis of twenty-one prospective cohort studies revealed that the consumption of both unprocessed red and processed meat was associated with the incidence of stroke. However, no positive association was observed with cardiovascular mortality [32].

This MR study found no significant effect of red and processed meat consumption on CVD risk, which is in line with the findings of previous observational studies [11,12] and meta-analyses [33,34]. The lack of causality in this MR study suggests that the observed effects of red and processed meat intake on CVD in multiple observational studies may be limited by confounding factors and reverse causation rather than by identifying a single causal correlation [35].

Several factors influence the intricate relationship between meat consumption, blood lipid profiles, and obesity. Previous research has yielded conflicting findings: while some studies suggest no adverse effects of moderate red meat intake [36,37], others link long-term red meat consumption to elevated blood lipid levels [38,39]. Similarly, increased white meat and poultry consumption can increase the overall risk of obesity [40], while processed meat intake is associated with central obesity [41]. However, some studies found no significant correlation between red meat consumption and overweight or obesity [42]. In addition, children and adolescents who abstain from meat may be at a greater risk of becoming overweight or obese [43]. Our study, which centers on the genetic mediation of meat consumption in cardiovascular disease (CVD), does not explicitly investigate direct connections with lipid levels and obesity. We acknowledge the potential mediating role of lipid profiles and obesity in the broader context of CVD risk factors. Further research is indispensable to disentangle these complexities, considering diverse factors and populations in studying these associations.

To assess these complex interactions, considering regional dietary habits that vary across different areas is essential. Understanding these differences in dietary patterns will provide a more comprehensive understanding of how dietary habits interact with meat consumption. For example, Northern European diets

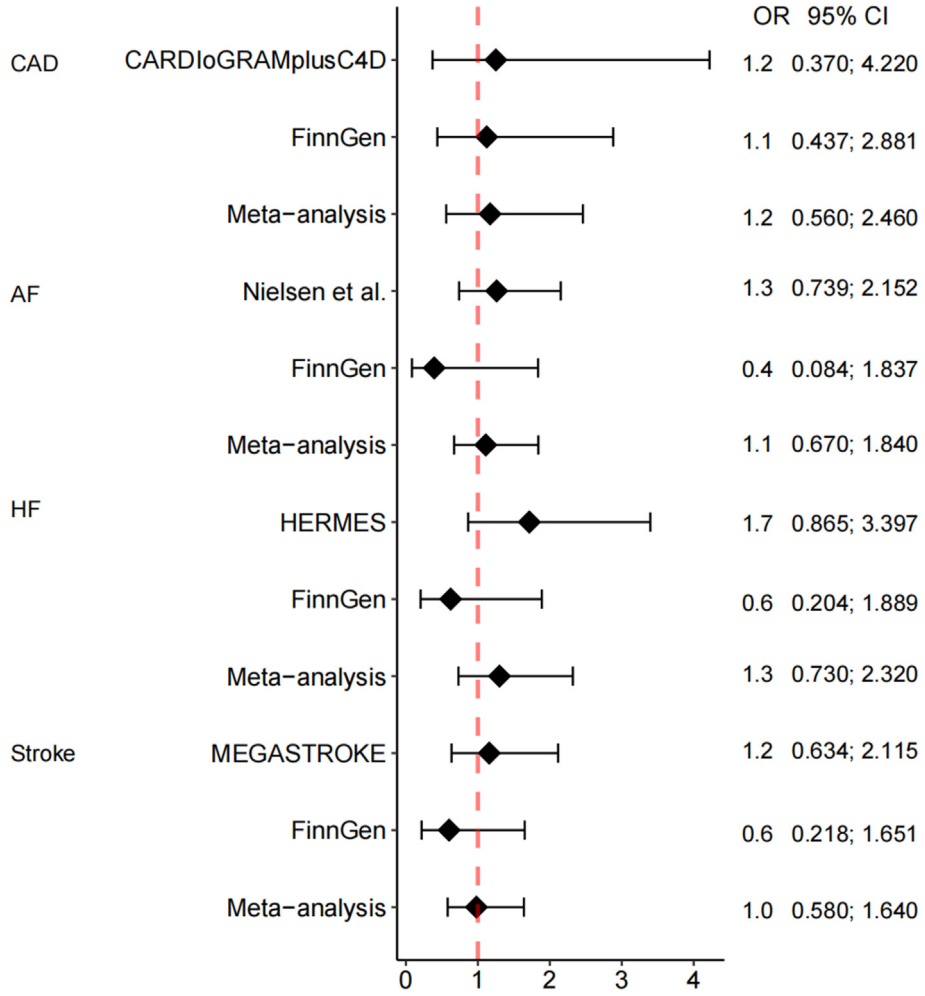

Fig. 4. Associations of genetically predicted Pork intake with CVD in large genetic consortia and FinnGen and in meta-analysis.

prioritize vegetables, fruits, whole grains, legumes, and lean meats and restrict sweet and sugary beverages. In contrast, certain Western dietary patterns include more processed foods, red meat, sugary drinks, and refined grains, with lower fruit, vegetable, and whole-grain intake [44]. Although the Mediterranean diet shares some macronutrient similarities with Western diets, the types of fats consumed differ. The Japanese diet is rich in fish, seafood, rice, vegetables, and fermented foods [45].

Epidemiological studies are affected by confounding factors, such as differences in lifestyle, cooking methods, alternative dietary choices, environmental contexts, and baseline health and socio-economic disparities [46,47]. Hence, MR methods are valuable for mitigating these confounding effects.

Meat intake warrants further investigation. The recommended daily intakes are 0–4 g of processed meat and 18–27 g of red meat [48]. These suggestions reflect a balanced dietary approach that aims to limit the excessive consumption of red and processed meats to mitigate potential health risks. No clear causal link was found between red and processed meat intake and CVD risk in this study. However, numerous observational studies have identified a positive association between high red, particularly processed, meat intake and increased cardiovascular morbidity. Several mechanisms may underlie this potential relationship: 1) saturated fats in red meat can increase cholesterol levels and promote atherosclerosis [49], 2) iron in red meat may cause oxidative stress and damage vessels [50], and 3) preservatives in processed meat can trigger vascular inflammation [51]. Therefore, moderate red meat consumption is advisable. However, optimal intake levels should be tailored to individual diets and health profiles.

4.1. Strength and limitations

The present study has several strengths that support the validity of its conclusions regarding the causal effects of meat intake on the risk of CVD. The use of a two-sample MR design allows the leveraging of genetic variants as IVs to emulate randomised controlled trials to make robust causal inferences while minimising confounding. To our knowledge, this is the first MR study to assess the causal role of meat consumption in cardiovascular pathogenesis in European populations. Furthermore, combining summary data from multiple large-scale genetic consortia and the FinnGen cohort through meta-analysis of MR estimates enhanced statistical power and precision, resulting in more reliable causal conclusions. Finally, the exposure and outcome cohorts were sourced from non-overlapping European populations in independent genetic datasets and the UK Biobank, precluding false-positive findings due to participant overlap. In summary, the MR design, large-scale genetic data sources, and analytical strategies enhanced the methodological rigor and causal specificity of this study's findings regarding the cardiovascular effects of meat intake.

Nevertheless, our study has certain limitations. First, the participants in our study were drawn from GWAS databases of European ancestry; therefore, the generalisability of our findings to other populations with different genetic backgrounds and dietary

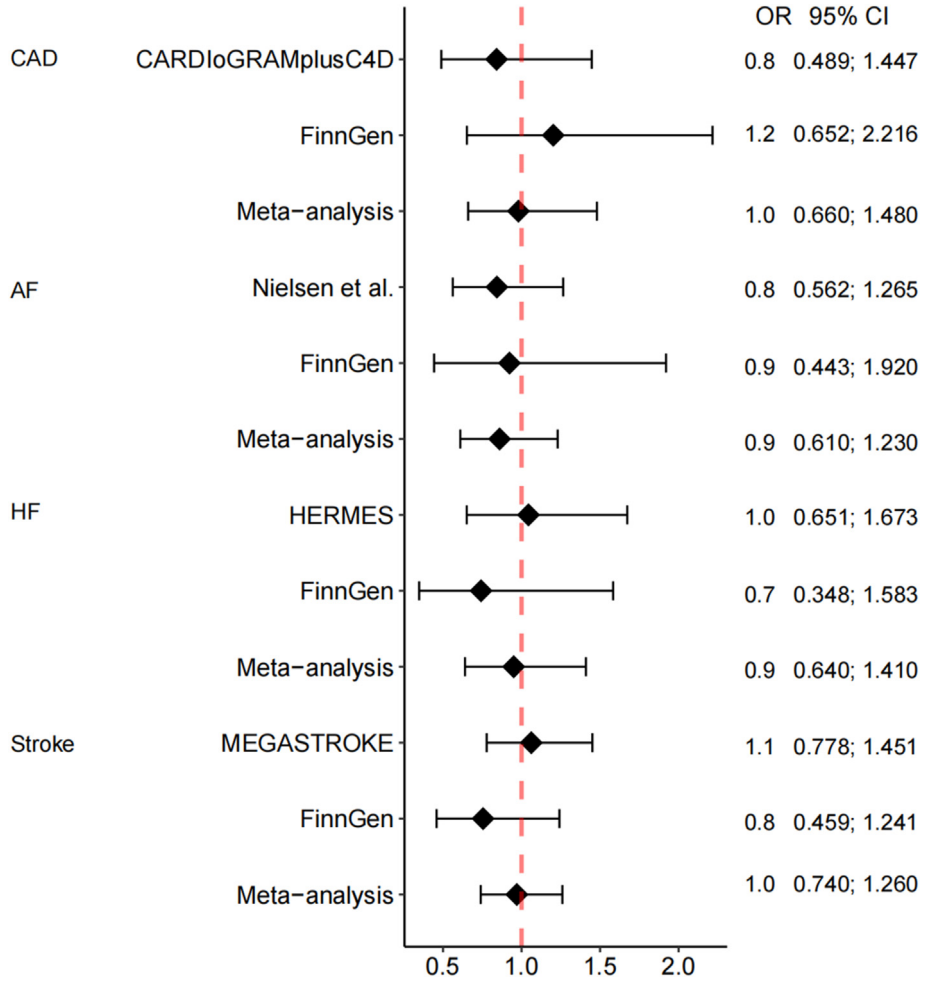

Fig. 5. Associations of genetically predicted Mutton intake with CVD in large genetic consortia and FinnGen and in meta-analysis.

patterns may be limited. Second, as in all MR studies, horizontal pleiotropy is a common problem that cannot be avoided; therefore, the possibility of bias cannot be ruled out.

5. Conclusion

In conclusion, our MR analysis, utilising large-scale GWAS data, did not find a significant causal association between genetically predicted consumption of red and processed meat, including pork meat, mutton meat, and beef meat, and the risk of coronary artery disease, atrial fibrillation, heart failure, or stroke. These findings suggest that the consumption of red and processed meat may not be a major contributor to the development of these cardiovascular disease outcomes.

6. Recommendation

Our study emphasizes the necessity for further research in exploring genetic intricacies, conducting longitudinal studies, and broadening the diversity of study populations. This will contribute to a more comprehensive understanding of the complex relationship between red meat consumption and health outcomes.

At the individual level, given the existing evidence recommending limits for processed meat intake (0–4 g daily) and red meat intake (18–27 g daily), we stress the significance of embracing a balanced dietary approach. Essential to this is personalized dietary guidance, considering individual dietary patterns, cardiometabolic conditions, and preferences. Furthermore, we encourage individuals to include regular health check-ups in their routine, acknowledging the diversity in health profiles and dietary needs across the population.

Author contributions

Bing Hu and **Xin He**, in their roles as first authors, conducted the data analysis and drafted the manuscript. **Jie Sun** and **Yanxiang Sun** conceived the study. Theory development and computations were undertaken by **Yongyi Hu** and **Hao Sun**. **Fei Li** provided recommendations for validating the analytical methods and revising the manuscript. **Feng Li** guided the experimental design and contributed to the final version of the manuscript. All the authors collectively discussed the results and contributed to the final manuscript.

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Conflicts of interest

None declared.

Data statement

The data utilized in this study were sourced from publicly available databases and consortia. Table 1 provides a detailed overview of the data sources, including relevant references.

Acknowledgments

We express our appreciation to the UK Biobank, CARDIoGRAMplusC4D, Nielsen et al., the HERMES consortium, and FinnGen for generously providing summary-level data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2024.02.014.

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