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A Mendelian randomized study of circulating antioxidants in the diet and risk of cardiovascular disease

Ruonan Yang[1]✉, Mingyue Lv[2], Xiujuan Yang[1] & Siwei Zhai[1]✉

Cardiovascular diseases (CVD) are a major global mortality cause, heavily impacted by diet and oxidative stress. This study investigates the causal effects of five circulatory antioxidants on various cardiovascular diseases using Mendelian randomization (MR) to mitigate confounding biases.We conducted a two-sample Mendelian Randomization (MR) analysis utilizing summary-level genome-wide association study (GWAS) data from both the UK Biobank and FinnGen. Genetic instrumental variables for antioxidants, including vitamin A, beta-carotene, vitamin C, α-tocopherol, and lycopene, were identified based on rigorous criteria. The outcomes included arrhythmia, cardiomyopathy, heart failure, myocardial infarction, pericarditis, angina pectoris and coronary atherosclerosis.Higher genetically determined levels of α-tocopherol were associated with an increased risk of myocardial infarction (OR 5.10, 95% CI 2.92–8.91, P < 0.001) and cardiac arrhythmias (OR 1.94, 95% CI 1.34–2.83, P = 0.001). Retinol was linked to heightened risks of cardiomyopathy (OR 6.38, 95% CI 1.23–33.20, P = 0.028) and heart failure (OR 2.26, 95% CI 1.01–5.07, P = 0.047). A meta-analysis corroborated the pathogenic effects of α-carotene on arrhythmias (OR, 2.00; 95% CI, 1.39–2.86; P < 0.001) and myocardial infarction (OR, 4.81; 95% CI, 2.84–8.15; P < 0.001), α-tocopherol on angina pectoris (OR: 4.33; 95% CI: 2.07–9.09; *P* < 0.001) and coronary atherosclerosis (OR: 5.34; 95% CI: 2.81–10.12; *P* < 0.001).Our study indicates that elevated levels of specific antioxidants, particularly α-tocopherol and retinol, may increase the risk of certain cardiovascular diseases. Further research is necessary to clarify the impact of these antioxidants on cardiovascular health and to explore potential gene-environment interactions.

Keywords Cardiovascular diseases, Antioxidants, Mendelian randomization

Abbreviations

CVD	Cardiovascular diseases
ROS	Reactive oxygen species
MR	Mendelian randomization

Cardiovascular diseases (CVD) represent a major global cause of mortality, especially in low and middle-income countries[1]. In 2017, research indicated that CVD was responsible for over 17 million deaths, almost double the number of cancer-related fatalities. This figure reflects an almost 50% increase from 1990. Notably, there are significant disparities in CVD mortality rates across different countries and regions. In 2017, East Asia accounted for 4.58 million CVD deaths, which constituted 25.8% of global CVD fatalities. Furthermore, incidence rates are higher among males than females[2]. Dietary habits, hypertension, obesity, and physical inactivity are among the primary risk factors for cardiovascular diseases[3].

Cardiovascular diseases are closely linked to oxidative stress. ,which arises when the production of reactive oxygen species (ROS) exceeds the cellular antioxidant system's ability to neutralize them. This imbalance leads to cellular and molecular abnormalities, ultimately resulting in cardiac dysfunction[4]. Additionally, oxidative stress is implicated in the occurrence of arrhythmias. Reactive oxygen species can induce local electrical activity and re-entry, alter cardiac ion currents, promote myocardial fibrosis, and impair gap junction function. These changes reduce coupling between myocardial cells and facilitate re-entry, ultimately leading to the development of arrhythmias[5]. Oxidative stress is a key factor in the development of atherosclerosis, vascular inflammation,

[1]Department of Medical Quality Control, Chengdu Seventh People's Hospital, Chengdu, Sichuan, China. [2]The Sixth Affiliated Hospital of Shenzhen University, Shenzhen, Guangdong, China. ✉email: 348629508@qq.com; 1149902136@qq.com

and endothelial dysfunction in vascular pathology [6]. It contributes to the cardiovascular disease by affecting various elements of the heart and vasculature.

Antioxidants alleviate oxidative stress by reducing reactive oxygen species (ROS) or enhancing effectiveness of the antioxidant defense system. Research indicates that vitamin C, due to its antioxidant properties, may provide protective benefits against cardiovascular diseases[7], particularly by mitigating oxidative and nitrosative stress as well as inflammation induced by doxorubicin, thereby improving cardiac structure and function[8]. Furthermore, a dose–response meta-analysis[9] ,it suggests that as the intake and circulating concentrations of vitamin C increase, the risk of mortality from cardiovascular disease decreases. Additionally, α-tocopherol may have a protective effect against cardiovascular diseases[10]. However, some studies have not found vitamin E to exhibit a preventive effect on cardiovascular diseases[11], and Gilbert et al.[12] reported that beta-carotene and vitamin A, which are common antioxidants, neither reduced the risk of cardiovascular disease nor prevented potential adverse effects.

Current research on the effects of circulatory antioxidants on cardiovascular diseases presents contradictory and inconsistent results. Nevertheless, most existing studies are observational and prone to various confounding factors, leading to unclear causal relationships. This study employs Mendelian randomization(MR), a genetic approach, to evaluate the causal effects of five circulatory antioxidants—vitamin A, beta-carotene, vitamin C, α-tocopherol, and lycopene—on cardiovascular diseases. This methodology mitigates the influence of confounding variables, thereby clarifying causal relationships. This research aims to establish a foundational understanding of the causal effects of antioxidants on the cardiovascular system, with the goal of inform the development of more effective cardiovascular disease .

Materials and methods

Study design overview

This study employs a two-sample Mendelian randomization analysis of summary-level genome-wide association data to investigate potential causal links between dietary antioxidants (α- and γ-tocopherols, ascorbic acid, retinol, β-carotene, and lycopene) and five cardiovascular diseases: (arrhythmia, cardiomyopathy, heart failure, myocardial infarction, pericarditis, angina pectoris and coronary atherosclerosis). We analyze absolute levels of dietary antioxidants in the bloodstream and the relative concentrations of circulating antioxidant metabolites in plasma or serum, representing two distinct phenotypes.

Genetic instruments selection

We adopted a rigorous approach to identifying genetic instrumental variables for antioxidants, adhering to a strict significance threshold of $P < 5 \times 10^{-8}$. Single nucleotide polymorphisms(SNPs) exhibiting linkage disequilibrium ($r^2 = 0.001$) within a clumping distance of 10,000 kb were subsequently excluded. From genome-wide association study(GWAS) data, we identified genetic instrumental variables for circulating antioxidants, including three independent SNPs linked to α-tocopherol[13]. Specifically, three distinct SNPs linked to α-tocopherol were discovered in the most recent GWAS conducted with 4,014 participants of European descent. For ascorbate[14], ten unique SNPs were identified from a recent GWAS involving up to 52,018 European individuals, following the aforementioned criteria. In relation to retinol[15], two particular SNPs associated with this antioxidant were identified in a GWAS that involved 5,006 Caucasian participants from two distinct cohort studies. Two to β-carotene[16], Two distinct SNPs associated with β-carotene were identified in a GWAS that included 2,344 participants from the Nurses' Health Study. And five to lycopene[17], Five distinct SNPs associated with lycopene were discovered in a GWAS that examined 441 older Amish adults participating in the Heredity and Phenotype Intervention Heart Study.

For circulating antioxidant metabolites' genetic instrumental variables, we derived α-tocopherol, thirteen SNPs were found to correlate with α-tocopherol among 5,822 individuals. For β-tocopherol, a thorough analysis revealed eleven single nucleotide polymorphisms (SNPs) linked to β-tocopherol in a cohort of 7,276 participants. Regarding ascorbate[18], the study identified 14 SNPs associated with ascorbate from a dataset of 2,063 participants and uncovered 18 SNPs linked to urate based on data from 7,819 individuals. Additionally, for retinol[19] genetic instrumental variables were derived from two recent large-scale GWAS data, sets, leading to the identification of 26 independent SNPs, in a subgroup of 1,960 individuals of European descent. In total, we identified 11, 13, 14, and 26 independent SNPs respectively as instrumental variables. We employed F statistics to ensure the strength of these instrumental variables, maintaining $F > 10$ to prevent weakness.

Sources of GWAS data

Data for five cardiovascular diseases were sourced from the UK Biobank and FinnGen studies. The UK Biobank, a cohort study involving the general population, enrolled more than 500,000 participants aged 40 to 69 from 2006 to 2010. This study utilized second-round analysis data from the UK Biobank, obtained through the Pan-UK Biobank project (https://pan.ukbb.broadinstitute.org/, accessed on 17 March 2022). The phone_codes for cardiac arrhythmias, cardiomyopathy, heart failure, myocardial infarction, pericarditis, angina pectoris and coronary atherosclerosis in the UK Biobank are 20002–1077, 425, I50, I70, 411.2, I20, and 411.4, respectively. The FinnGen research project (R7 release in 2022)[20] enhanced the study by integrating genotype data from Finnish biobanks with digital health records from Finnish health registries. SNPs that were absent in the outcome genome-wide association studies(GWAS)and lacked suitable proxy SNPs were excluded. The total number of individuals in the R7 FinnGen database is 309,154, comprising 173,746 females and 135,408 males. The phone_codes for cardiac arrhythmias, cardiomyopathy, heart failure, myocardial infarction, pericarditis, angina pectoris and coronary atherosclerosis in FinnGen are CARDIAC_ARRHYTM, FG_CARDMYO, I9_HEARTFAIL, I9_MI, I9_PERICARD, I9_ANGINA and I9_CORATHER respectively.

Statistic analysis

We employed various methods for Mendelian Randomization (MR) analysis. The MR-Egger intercept test was utilized to identify potential multivariable confounding, however, no significant results were found due to rigorous instrumental variable screening. Heterogeneity was assessed using the I^2 statistic and Cochran's Q test. In most instances, we applied the fixed-effect inverse variance weighting (IVW) model, resorting to the random-effect IVW model when heterogeneity was present. To ensure the robustness of our findings, we conducted sensitivity analyses using four complementary MR methods—MR-Egger, simple mode, weighted mode, and weighted median—to aid in the interpretation and validation of causal inference. Additionally,We employed the MR-PRESSO method to identify horizontal pleiotropy, with the results are presented in Table S1 and Table S2. In our main analysis, a Bonferroni-corrected threshold of $P < 0.007$ ($\alpha = 0.05/7$ outcomes) was established to denote strong evidence of association, while *P*-values ranging from 0.01 to 0.05 were considered suggestive evidence of association. A meta-analysis was subsequently conducted on the outcomes of the MR analysis. Statistical analyses were performed using R software (v4.3.2). The MR analysis and meta-analysis were conducted using the R-based 'TwoSampleMR'and 'meta' packages, respectively.

Result

Absolute circulating antioxidants and cardiovascular diseases

Our analysis indicates that genetically elevated absolute retinol levels may be associated with an increased risk of cardiomyopathy (OR: 6.38; 95% CI: 1.23–33.20; $P = 0.028$, Fig. 1.b) heart failure (OR: 2.26; 95% CI: 1.01–5.07; $P = 0.047$, Fig. 1.c) We also found that elevated genetic levels of absolute retinol may be associated with an increased risk of angina pectoris (OR: 1.34; 95% CI: 0.82–2.21; $P = 0.244$, Fig. 1.f) and coronary atherosclerosis (OR: 1.32; 95% CI: 0.81–2.15; $P = 0.257$, Fig. 1.g) .within the UK Biobank cohort. Following Bonferroni correction, the FinnGen study revealed that genetically elevated absolute α-tocopherol levels significantly correlate with a heightened risk of myocardial infarction (OR: 5.10; 95% CI: 2.92–8.91, $P < 0.001$, Fig. 1.b)、 cardiac arrhythmias (OR: 1.94, 95% CI 1.34–2.83; $P = 0.001$, Fig. 1.a), angina pectoris(OR:5.42; 95% CI: 2.23–13.17; $P < 0.001$, Fig. 1.f), and coronary atherosclerosis(OR: 6.13; 95% CI: 2.83–12.98; $P < 0.001$, Fig. 1.g). A meta-analysis of the UK Biobank and FinnGen studies demonstrated that absolute α-carotene significantly contributes to the risk of cardiac arrhythmias (OR; 2.00; 95% CI; 1.39–2.86; $P < 0.001$, Fig. 1.a) and myocardial infarction (OR; 4.81; 95% CI; 2.84–8.15; $P < 0.001$, Fig. 1.d). Additionally, our meta-analysis identified a suggestive pathogenic effect of retinol on cardiomyopathy (OR, 3.49; 95% CI, 1.25–9.77; $P = 0.017$, Fig. 1.b), α-tocopherol is significantly associated with angina pectoris (OR: 4.33; 95% CI: 2.07–9.09; $P < 0.001$, Fig. 1.f) and coronary atherosclerosis (OR: 5.34; 95% CI: 2.81–10.12; $P < 0.001$, Fig. 1.g). We did not find any significant effects of other circulating antioxidants on cardiovascular diseases (Fig. 1.e, f, g). The leave-one-out single nucleotide polymorphism (SNP) analysis yielded stable results. The outcomes of the pleiotropy test and heterogeneity test are presented in Table S1. Due to an insufficient number of SNPs for retinol and β-carotene, pleiotropy testing could not be conducted.

Circulating antioxidant metabolites and cardiovascular diseases

Our analysis of the UK Biobank data reveals significant evidence that genetically elevated ascorbate metabolite levels correlate with an increased risk of cardiomyopathy (OR, 1.31; 95% CI, 1.09–1.57; $P = 0.004$, Fig. 2.b). Moreover, In the FinnGen study, γ-tocopherol was significantly associated with an increased risk of angina pectoris(OR: 1.29; 95% CI: 1.09–1.52; $P = 0.003$,Fig. 2.f), However no significant association was found in the UK Biobank or in the meta-analysis. We did not find any significant effects of other circulating antioxidant metabolites on cardiovascular diseases (Fig. 2.a, c, d, e, g). Additionally, the leave-one-out SNP analysis yielded stable results. The outcomes of the pleiotropy test and the heterogeneity test are presented in Table S2.

Discussion

This study employed the UK Biobank and FinnGen databases to explore the genetic links between antioxidant metabolites and cardiovascular diseases. Our findings indicate that elevated genetically influenced retinol levels correlate with an incresed risk of cardiomyopathy and heart failure. The FinnGen study revealed that genetically elevated absolute α-tocopherol levels, after Bonferroni correction, are significantly associated with a higher risk of myocardial infarction, cardiac arrhythmias, angina pectoris and coronary atherosclerosis. A meta-analysis of UK Biobank and FinnGen data demonstrated that absolute α-carotene definitively contributes to the pathogenesis of cardiac arrhythmias and myocardial infarction. And α-tocopherol is significantly associated with angina pectoris and coronary atherosclerosis. α-Tocopherol, as an antioxidant, plays a significant role in inhibiting atherosclerosis. Traber & Stevens' research[21] indicates that α-tocopherol reduces the risk of cardiovascular diseases through multiple mechanisms, such as antioxidation and anti-inflammatory effects.Specifically, α-tocopherol can scavenge free radicals, inhibit LDL oxidation, and modulate inflammatory responses, thereby slowing the progression of atherosclerosis. This supports our study. Moreover, In the FinnGen study, γ-tocopherol was significantly associated with an increased risk of angina pectoris. Pankaj Mathur's research indicates that γ-tocopherol may exacerbate the risk of atherosclerosis and angina pectoris[22]. Specifically, under high concentrations or specific pathological conditions, γ-tocopherol may promote oxidative stress or interfere with lipid metabolism, thereby adversely affecting cardiovascular health· This finding is consistent with our research. Additionally, our meta-analysis suggested a potential pathogenic effect of retinol on cardiomyopathy. Our analysis provided significant evidence linking genetically elevated ascorbate levels to an increased risk of cardiomyopathy in the UK Biobank. No causal link between antioxidant metabolites and cardiovascular diseases was identified in the FinnGen database. Our study results are consistent with some existing literature, while also revealing notable differences. Previous research indicates that antioxidants such as α-tocopherol and ascorbate may confer cardiovascular benefits by mitigating oxidative stress damage[23,24]. For instance, Gilbert et

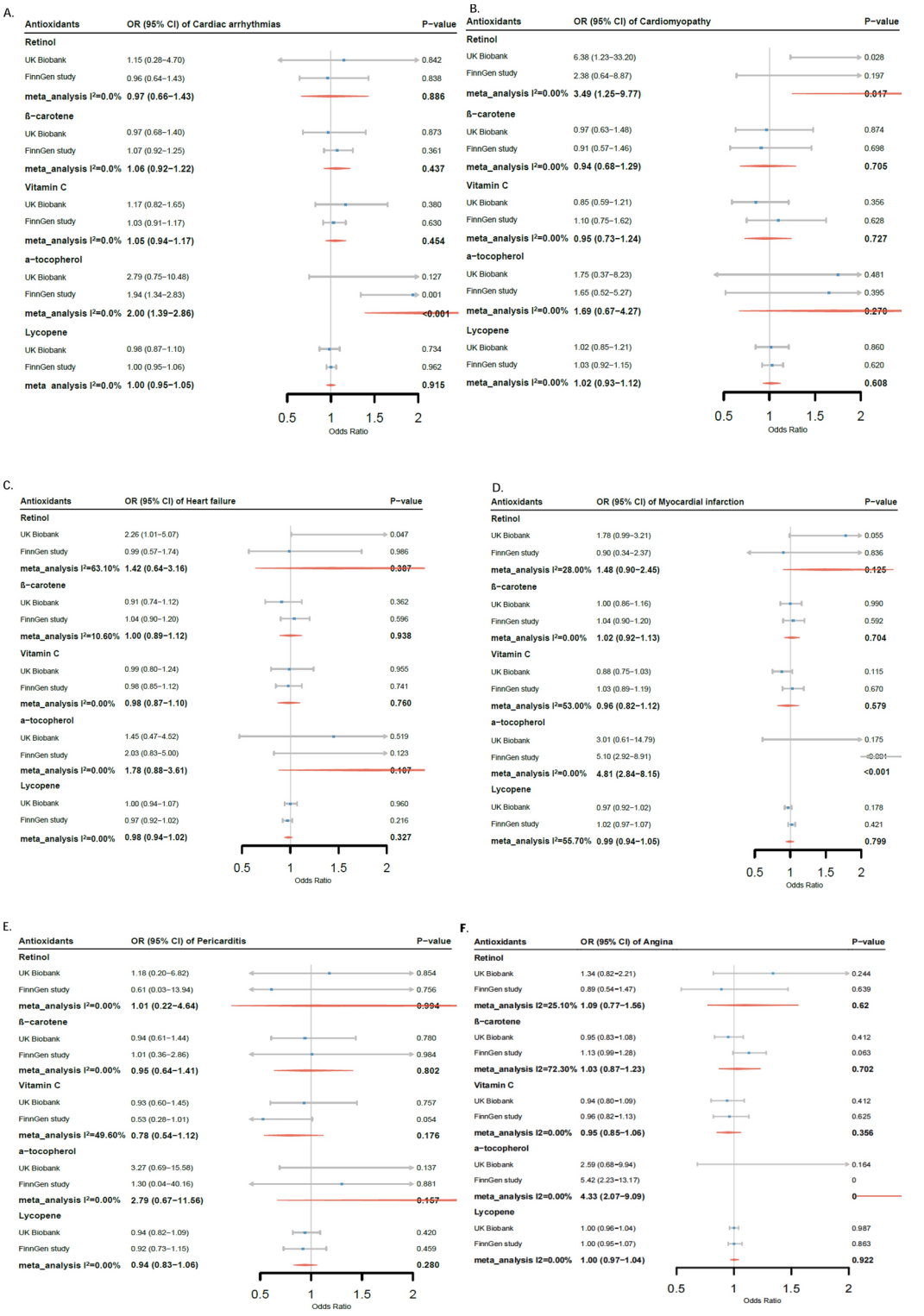

Fig. 1. MR results about the influence of antioxidants on cardiovascular diseases. (**a**). Influence on cardiac arrhythmias; (**b**).Influence on cardiomyopathy; (**c**).Influence on heart failure; (**d**).Influence on myocardial infarction; (**e**).Influence on pericarditis. The OR value is greater than 1, with a 95% confidence interval that does not include 1, indicates that the factor promotes the occurrence of the outcome. Conversely the OR value less than 1 accompanied by a 95% confidence interval that does not include 1, suggests that the factor inhibits the occurrence of the outcome. When the 95% confidence interval of the OR value includes 1, it is interpreted as the factor having no statistically significant effect on the occurrence of the outcome.

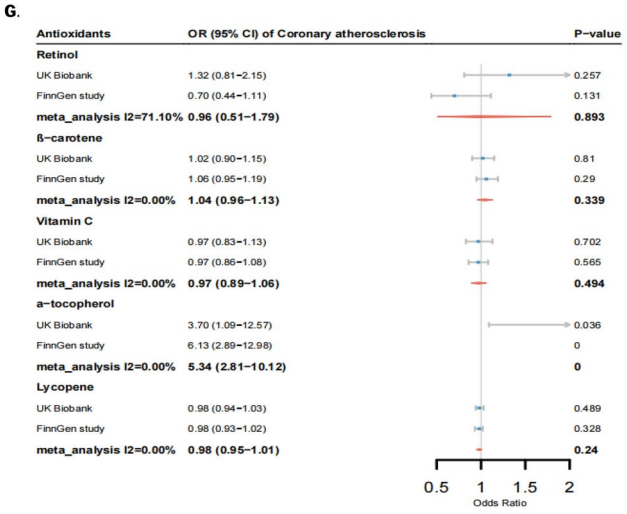

Figure 1. (continued)

al.[12] found that α-tocopherol can reduce all-cause mortality and coronary artery disease mortality. Additionally, α-tocopherol may prevent atherosclerotic plaque formation by enhancing oxidative resistance[10]. Similarly, some studies suggest that high doses of ascorbate supplements may increase the risk of all-cause mortality, including heart failure and hemorrhagic stroke[3], supporting our findings.

Notably, our meta-analysis confirmed the pathogenic effects of α-carotene on arrhythmias and myocardial infarction. This finding appears to contradict previous research indicating that α-carotene intake is associated with a reduced risk of cardiovascular diseases. For instance, a long-term follow-up study found that α-carotene intake was significantly associated with a lower mortality rate from coronary heart disease[25]. Furthermore, other studies have shown that the intake of α-carotene and β-carotene is negatively correlated with cardiovascular disease mortality[26]. Given that cardiovascular diseases are typically characterized by increased oxidative stress in the vasculature, heart, kidneys, and brain, α-carotene, as an antioxidant, may have potential therapeutic effects.

The conflicting findings regarding α-carotene highlight the complexity of interpreting the relationship between antioxidants and cardiovascular diseases. This discrepancy may arise from differences in study designs, populations, and methods of assessing antioxidant levels. Additionally, the role of α-carotene in cardiovascular health may be influenced by various factors, including genetic predisposition, dietary habits, and interactions with other nutrients[27]. Conversely, MR studies leverage genetic variants as instrumental variables to infer causality, thereby minimizing residual confounding but they may overlook post-translational modifications, metabolic pathways, or compensatory biological mechanisms that influence antioxidant function in vivo. Furthermore, genetic predisposition, dietary interactions, and nutrient co-dependencies may modify the impact of α-carotene on cardiovascular health. For example, certain genetic polymorphisms in carotenoid metabolism pathways, such as those affecting β-carotene 15,15'-monooxygenase 1 (BCMO1), could modulate α-carotene conversion into retinoids, thereby altering its physiological effects[28].

A critical factor requiring further scrutiny is the role of vitamin A, an essential micronutrient with both antioxidant and pro-oxidant properties. While retinol and its derivatives are vital for cellular function, excessive levels have been implicated in oxidative stress, endothelial dysfunction, and the progression of atherosclerosis. Our findings align with previous studies indicating that high-dose vitamin A supplementation may increase CVD risk, potentially due to its pro-oxidative effects under certain conditions[29]. Furthermore, β-carotene, a precursor to vitamin A, has been shown to exhibit both protective and deleterious cardiovascular effects depending on its concentration, metabolic state, and interaction with other antioxidants[30]. The oxidative balance within the cardiovascular system is a finely regulated process, and an excessive intake of antioxidants may disrupt redox homeostasis, inadvertently promoting oxidative damage rather than preventing it.

Given these complexities, future research should aim to elucidate the precise mechanisms underlying the divergent effects of α-carotene and other antioxidants on cardiovascular outcomes. Large-scale randomized controlled trials and advanced genomic studies that incorporate gene-environment interactions could provide deeper insights into these relationships. Additionally, personalized nutritional strategies based on genetic profiles and metabolic phenotyping may help optimize antioxidant intake for cardiovascular health. Our study underscores the necessity of cautious interpretation when considering antioxidant supplementation for CVD prevention, emphasizing the need for a nuanced approach rather than a universal recommendation.

The role of retinol in cardiovascular health is multifaceted. Retinol is involved in numerous biological processes, including the progression of atherosclerosis. High doses of vitamin A supplements have been associated with an increased risk of cardiovascular disease. This association may arise from the pro-oxidant effects of β-carotene, a precursor to vitamin A, which can potentially contribute to damage within the cardiovascular system[31,32]. These findings align with our study's results,indicating that retinol may have both antioxidant and pro-oxidant properties, rendering it a controversial supplement in the context of cardiovascular health.

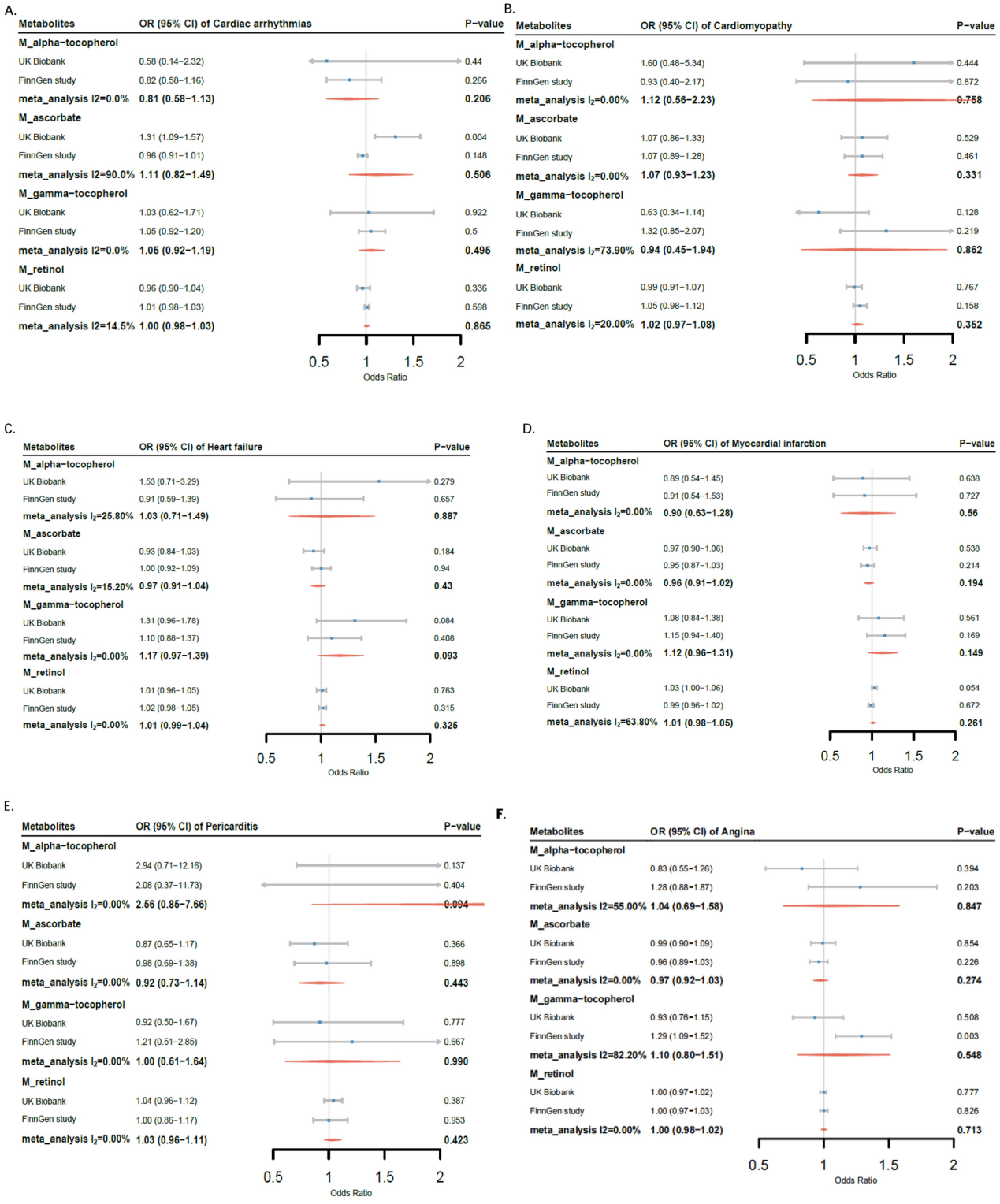

Fig. 2. MR results about the influence of antioxidants on cardiovascular diseases. (**a**). Influence on cardiac arrhythmias; (**b**).Influence on cardiomyopathy; (**c**).Influence on heart failure; (**d**).Influence on myocardial infarction; (**e**).Influence on pericarditis.The OR value is greater than 1, with a 95% confidence interval that does not include 1, indicates that the factor promotes the occurrence of the outcome. Conversely, the OR value less than 1, accompanied by a 95% confidence interval that does not include 1,suggests that the factor inhibits the occurrence of the outcome. When the 95% confidence interval of the OR value includes 1, it is interpreted as the factor having no statistically significant effect on the occurrence of the outcome.

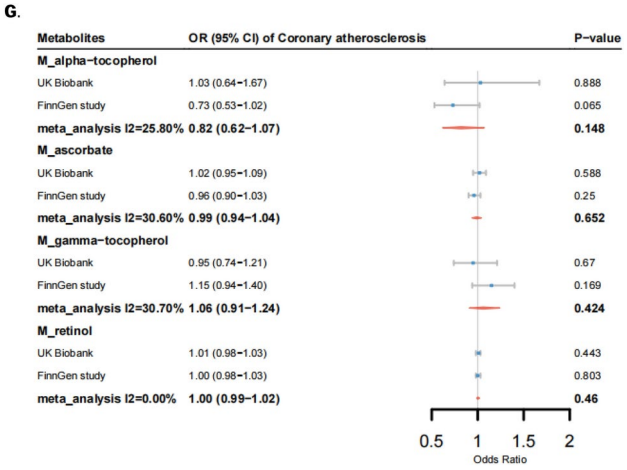

Figure 2. (continued)

Our analysis of the UK Biobank data identified a significant link between high levels of ascorbate metabolite and an increased cardiomyopathy. This finding is supported by existing literature, which suggests that excessive accumulation of ascorbate metabolites in the body can lead to damage of myocardial cells through oxidative stress pathways, thereby elevating the risk of developing cardiomyopathy[7]. However, this conclusion is not universally applicable, as certain studies have not found a significant association between ascorbate and cardiovascular diseases[33]. Our findings further reinforce the potential role of ascorbate metabolism in the development of cardiomyopathy.

Several factors may account for the discrepancies observed in study results. Key considerations include sample size and statistical power; variations in these factors and population characteristics between the UK Biobank and FinnGen can lead to different statistical outcomes. Furthermore, genetic backgrounds and environmental factors—such as dietary habits, lifestyle choices, and baseline health status—vary across populations and can significantly influence the effects of antioxidants on cardiovascular health. Gene-environment interactions may also play a pivotal role, as specific genetic variants may exert differing effects on cardiovascular health depending on the environmental context. Our study employed genetic tools to investigate genetically determined metabolite levels, rather than levels derived from exogenous supplements. This methodology minimizes confounding factors, although it may not fully capture the actual effects of supplement use. Despite utilizing extensive genetic data and rigorous statistical analyses, our study is not without limitations. Firstly, as an observational study, it cannot entirely eliminate the possibility of reverse causality and residual confounding, even with the application of genetic tools. This means that while we have made efforts to minimize the impact of confounding variables, there remains a potential for unmeasured factors to influence the observed associations. Secondly, our reliance on data from the UK Biobank and FinnGen studies limits the generalizability of our findings. These datasets primarily consist of individuals of European descent, which may not be representative of other ethnic populations. Thirdly, the genetic instruments utilized in our study may not fully capture the complexity of antioxidant metabolism. Although we employed rigorous criteria to select genetic instrumental variables, the potential for pleiotropy—where a genetic variant affects multiple traits—cannot be entirely ruled out. This could introduce bias into our estimates of causal effects. Additionally, the identified genetic variants may not be specific to dietary sources of antioxidants, potentially confounding the interpretation of our results. Fourthly, our study focused on the absolute levels of circulating antioxidants and their metabolites. However, the bioavailability and biological activity of these compounds can vary significantly based on factors such as diet, lifestyle, and overall health status. This variability may not be fully accounted for in our analyses. Lastly,the instrumental variables(IVs) used in this study were obtained from previous research[34]. Since complete GWAS data were not available, we could not conduct other analyses based on GWAS data . Furthermore, suitable exposure-related information could not be obtained from open-source population databases such as NHANES and CHARLS, precluding the possibility of observational studies. Due to the limited number of instrumental variables for retinol, β-carotene, and α-tocopherol, the MR-PRESSO analysis could not be performed.

Future research should investigate the causal relationship between antioxidant metabolites and cardiovascular diseases, particularly with respect to variations across diverse populations. We advocate for conducting similar genetic studies in larger and more heterogeneous populations to validate our findings. Forthermore, examining gene-environment interactions and their implications for antioxidants and cardiovascular diseases may uncover underlying mechanisms. Such insights could facilitate the development of targeted interventions for cardiovascular diseases, ultimately enhancing clinical prevention and treatment outcomes.

Data availability

The datasets generated and/or analysed during the current study are available in the [Pan-UKBB, FinnGen] repository, [https://pan.ukbb.broadinstitute.org/; https://www.finngen.fi/en] We did not purchase the population data from UK Biobank.

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Author contributions

Conceptualization: Ruonan Yang, Siwei Zhai; Data curation: Xiujuan Yang, Mingyue Lv; Formal analysis: Ruonan Yang; Methodology: Ruonan Yang; Software: Siwei Zhai; Supervision: Siwei Zhai, Ruonan Yang; Writing-original: Ruonan Yang; Writing-review & editing: Siwei Zhai, Mingyue Lv.

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
Ethical approval for the UK Biobank and FinnGen studies was obtained from the respective institutional review boards. All participants provided informed consent for the use of their data in research studies.

Additional information
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Correspondence and requests for materials should be addressed to R.Y. or S.Z.

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