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Evaluating the Causal Relationship between Omega-3 Polyunsaturated Fatty Acids and Hypertension: Insights From a Two-Sample Mendelian Randomization Study

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KEYWORDS

Omega-3 Polyunsaturated Fatty Acids,
Hypertension,
Mendelian Randomization,
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ABSTRACT

To investigate the causal relationship between dietary intake of omega-3 polyunsaturated fatty acids (ω-3 PUFA) and hypertension using a two-sample Mendelian randomization (MR) approach. Data from a comprehensive genome-wide association study (GWAS) database was used to identify single-nucleotide polymorphisms (SNPs) associated with ω-3 PUFA levels as instrumental variables. Five MR methods were employed for causal inference: MR-Egger regression, weighted median, inverse-variance weighted (IVW), simple mode, and weighted mode. The analysis was complemented by pleiotropy tests using the MR-Egger intercept and the MR-PRESSO method, alongside a 'leave-one-out' sensitivity analysis. The analysis showed no significant causal effects of ω-3 PUFA on hypertension across all methods ($P > 0.05$). The pleiotropy tests and sensitivity analysis confirmed the robustness of these findings. This MR study found no evidence supporting a causal relationship between ω-3 PUFA intake and hypertension, indicating that additional factors may modulate this association.

INTRODUCTION

Hypertension represents a critical global health challenge, serving as the foremost contributor to cardiovascular diseases and premature mortality worldwide. Over the last four decades, the global adoption of antihypertensive medication has resulted in a marginal reduction or stabilization of average blood pressure levels. Nonetheless, the incidence of hypertension has markedly escalated in low and middle-income nations. As of 2010, an estimated 1.39 billion hypertension, or 31.1% of the adult populace, were afflicted with hypertension on a global scale. The prevalence is notably higher in low- and middle-income countries, where it reaches 31.5%, in contrast to 28.5% in high-income countries [1]. Hypertension is a intricate pathophysiological condition characterized by an imbalance in the constriction and dilation of blood vessels in the outer regions of the body [2]. Key mechanisms underlying hypertension include impaired vasodilation, characterized by reduced nitric oxide (NO) bioavailability and dysregulated vascular smooth muscle cell (VSMC) function, both of which are crucial in sustaining elevated vascular tension [3, 4]. This imbalance arises from a intricate interplay between genetic and environmental factors, including lifestyle and dietary habits. Consequently, all individuals with hypertension are advised to modify their lifestyle and dietary habits, serving as the initial step in their treatment. Dietary interventions target-

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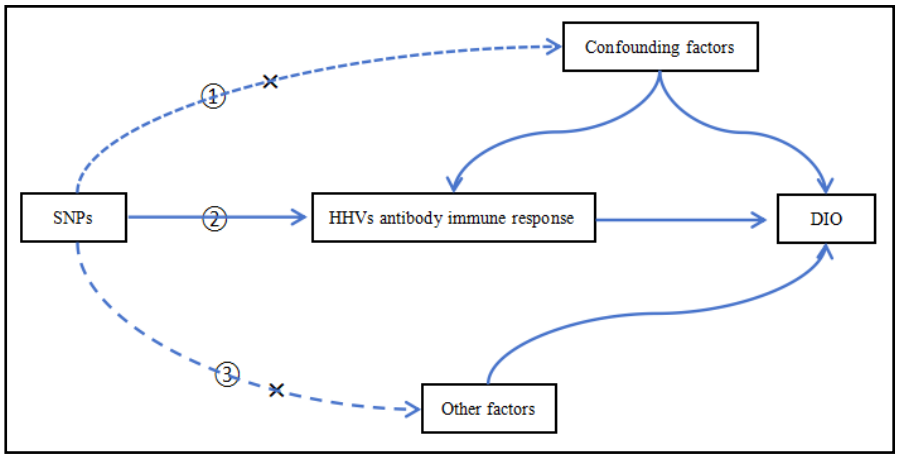

Figure 1 | Core Assumptions of Mendelian Randomization

1) Independence Assumption;

2) Association Assumption;

3) Exclusion Restriction Assumption

ing these pathways present a viable avenue for research into blood pressure management.

Omega-3 polyunsaturated fatty acids (ω-3 PUFA) possess properties such as reducing oxidative stress, mitigating inflammation, preventing blood clot formation, and safeguarding the inner lining of blood vessels [5].The intricate link between dietary consumption of ω-3 PUFA and hypertension has emerged as a focal point in cardiovascular research. Evidence indicates that eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may exert beneficial effects on hypertension [6]. Various studies have documented that a moderate intake of ω-3 PUFA is correlated with reduced blood pressure levels [7, 8], with mechanisms likely related to the enhancement of endothelial responses in both intact and impaired endothelia and antioxidative stress [9, 10]. Experimental investigations have elucidated the cellular mechanisms through which ω-3 PUFA may lower blood pressure, including modulation of ion channel activity in VSMCs, reduction of oxidative stress, and changes in membrane-associated protein functions [11].

However, clinical trials have not demonstrated a significant positive effect of ω-3 PUFA supplementation on cardiovascular outcomes, such as cardiovascular diseases, myocardial infarction, or stroke [12, 13]. Assertions that ω-3 PUFA intake reduces blood pressure may lack reliability, and the evidence supporting its role in the primary prevention of hypertension is tenuous [14-16]. Additionally, a research study conducted by Matsumoto C et al. utilized a randomized controlled trial design to demonstrate that there is no association between the intake of ω- 3 fatty acids and hypertension [17]. This discrepancy raises an interesting question.

Therefore motivating the current study's application of the Mendelian randomization (MR) technique to delve deeper into the ω-3 PUFA's impact on hypertension. MR employs single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) for deducing the causal connection between genetic variations linked to exposure factors and the risk of the outcome and it functions as a natural form of randomized controlled trial that effectively mitigates the influence of confounders and concerns related to the representativeness of randomized controlled trials [18-21]. By leveraging specific genetic variants as instrumental variables for ω-3 PUFAs levels, the MR approach addresses certain observational study limitations, offering a more dependable basis for causal deductions regarding ω-3 PUFA's influence on hypertension.

MATERIALS AND METHODS

Study Design

This investigation employed a two-sample MR approach, utilizing summary statistics from genome-wide association studies (GWAS) to examine the causal link between ω-3 PUFA and hypertension. Adherence to three fundamental MR assumptions—relevance, independence, and exclusivity—was essential (Fig. 1) [22]. The selection of single nucleotide polymorphisms (SNPs) was guided by a genome-wide significance threshold ($P < 5\times10^{-8}$) and strict linkage disequilibrium parameters ($r^2 < 0.001$, maximum distance of 10,000 kb) to ensure statistical independence and significant association [23].

Sources of Ω-3 PUFA and Hypertension Genetic Data

ω-3 PUFA genetic data were obtained from the largest GWAS dataset made available by the UK Biobank, which encompasses 114,999 samples and 12,321,875 SNPs (https://gwas.mrcieu.ac.uk/datasets/met-d-Omega_3/) (**Table 1**). Hypertension genetic data were sourced from IEU Open GWAS (https://gwas.mrcieu.ac.uk/), comprising 463,010 samples and 9,851,867 SNPs. These datasets, being publicly accessible and pertaining to secondary analysis, did not necessitate further ethical clearance. To mitigate potential biases linked to race, the genetic background of the study population was exclusively of European descent.

Statistical Methods

Statistical analyses were conducted using R software version 4.3.1, with the TwoSampleMR package facilitating the MR analysis. The study utilized five MR methods: MR Egger, weighted median estimator (WME), random-effects inverse-variance weighted (IVW), Simple mode, and Weighted mode. The MR-Egger regression intercept was assessed for pleiotropy, while the MR-PRESSO test was applied for outlier correction related to pleiotropy, and attention was given

Table 1 | Brief information of GWAS database study data in this study

Variable	GWAS ID	Sample Size (N)	Number of SNPs	Ethnicity	Sex	Year
ω-3 PUFA	met-d-Omega_3	114, 999	12, 321, 875	European Ancestry	Males and Females	2020
hypertension	ukb-b-12493	463, 010	9, 851, 867	European Ancestry	Males and Females	2018

Table 2 | Characteristics of the SNPs associated with ω-3 PUFA concentrations and their associations with hypertension

SNPs	Chr	EA	NEA	F-stat	ω-3 PUFA			hypertension		
					Beta	SE	p value	Beta	SE	p value
rs1132899	19	C	T	44	0.0270834	0.00410188	8.60E-11	0.00115362	0.000671853	0.0860003
rs1167998	1	A	C	282	0.0713574	0.00425038	3.60E-66	0.00036686	0.000696518	0.6
rs117143374	21	C	T	40	-0.0370966	0.005847	2.20E-10	-0.00210239	0.000957578	0.0280001
rs12226389	11	C	T	93	-0.050608	0.00524839	1.10E-22	0.00104152	0.000863266	0.23
rs13424225	2	T	G	29	0.0221268	0.00408591	2.20E-08	-0.000696972	0.000669414	0.3
rs139974673	15	C	T	85	0.117987	0.0128075	2.30E-21	0.00500421	0.00208901	0.017
rs143355652	11	T	C	57	-0.154138	0.0204073	9.40E-14	0.000963869	0.00331019	0.77
rs1672811	16	C	T	29	0.0251849	0.0046967	3.00E-08	-0.00129241	0.000769686	0.0929994
rs16940904	17	T	C	53	-0.0355285	0.0048772	3.90E-14	-0.000664788	0.000795764	0.4
rs182611493	19	G	A	115	-0.209571	0.0195777	1.10E-27	-0.00160707	0.00322505	0.62
rs2394976	6	T	G	70	-0.0461429	0.00550837	1.20E-15	-0.000101412	0.000902276	0.91
rs3018731	11	G	A	60	-0.0353357	0.00456603	2.00E-14	0.000616587	0.00075195	0.41
rs34663616	15	A	C	35	0.0356728	0.00602277	4.40E-10	-0.00270554	0.000987477	0.0061
rs35135293	2	T	C	26	-0.0208868	0.00408348	3.90E-08	-0.000601913	0.000668499	0.37
rs4000713	7	A	G	42	-0.0288196	0.00446039	1.00E-11	0.00137377	0.000729495	0.0599998
rs62466318	7	T	C	203	-0.0721329	0.00506371	1.20E-45	-0.0012811	0.000830078	0.12
rs6601924	10	C	T	39	0.0350603	0.00563873	8.50E-10	-0.000199607	0.000923159	0.83
rs6693447	1	G	T	31	0.0229488	0.00407772	4.80E-09	-0.000181075	0.000668009	0.79
rs6882345	5	A	G	47	0.0288844	0.00421159	1.90E-13	-0.000190667	0.000690374	0.780001
rs77960347	18	G	A	83	0.161749	0.0177574	7.20E-22	-0.00131191	0.00289403	0.649999
rs7970695	12	A	G	36	-0.0253039	0.00419603	1.20E-10	-0.00136808	0.000686738	0.0460002

to palindromic SNPs to avoid genotyping inaccuracies and subsequent pleiotropy misestimations. A "leave-one-out" sensitivity analysis was performed to evaluate the robustness of the findings, with the odds ratio (OR) and 95% confidence interval (95% CI) determining the causal relationship between ω-3 PUFA levels and hypertension, considering $P < 0.05$ as indicative of statistical significance.

RESULTS

Information on Instrumental Variable SNPs

Instrumental variables were rigorously selected based on predefined criteria. Following MR-PRESSO analysis, several SNPs were excluded due to pleiotropy concerns or palindromic nature. Additional SNPs associated with total cholesterol and body mass index were identified and removed after consulting the PhenoScanner v2 database (as of February 2024). Ultimately, 21 SNPs were deemed suitable as instrumental variables, each exhibiting an F-value greater than 10, thus negating potential weak instrument bias.

Two-Sample MR Analysis Results

The IVW analysis yielded an OR of 1.0038 (95% CI = 0.9923~1.0155, P = 0.5136), indicating no causal association between ω-3 PUFA and hypertension (**Table 3**). This conclusion was corroborated by other MR methods (MR Egger, WME, Simple mode, and Weighted mode), all of which showed P-values greater than 0.05, thereby affirming the re-

Table 3 | The OR values and 95% CIs of the 5 types of MR statistical methods

Statistical methods	SNPs	OR(95%CI)	p value
MR Egger	21	1.0114(0.9886~1.0347)	0.3417
WME	21	1.0050(0.9924~1.0178)	0.4405
IVW	21	1.0038(0.9923~1.0155)	0.5136
Simple mode	21	0.9971(0.9749~1.0197)	0.8001
Weighted mode	21	1.0039(0.9895~1.0186)	0.5997

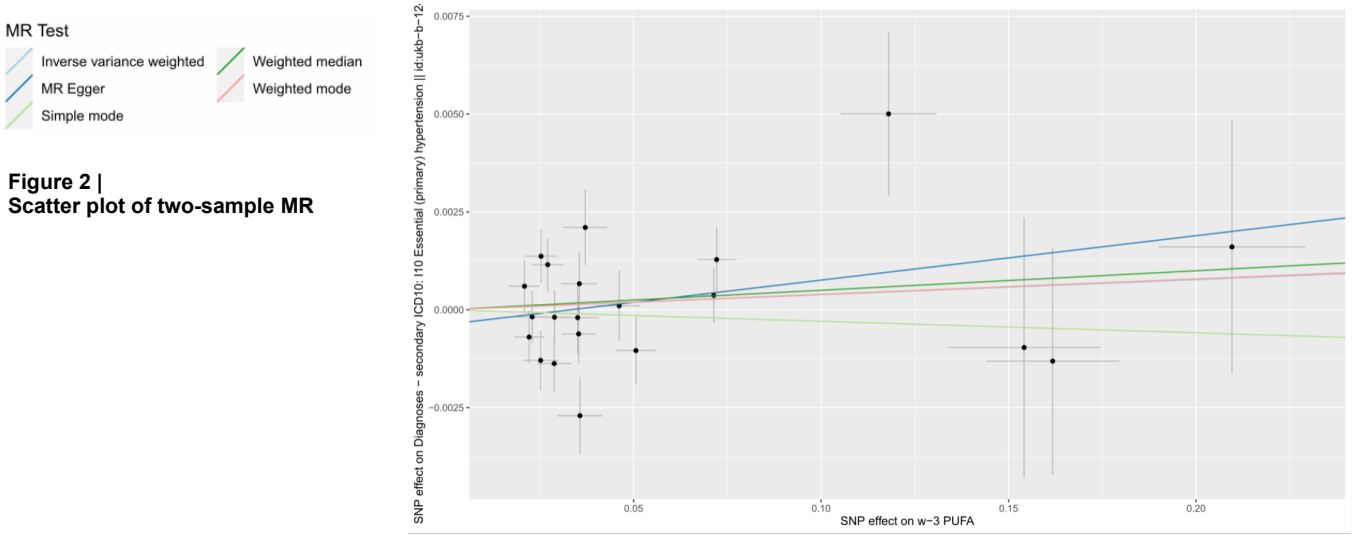

Figure 2 |
Scatter plot of two-sample MR

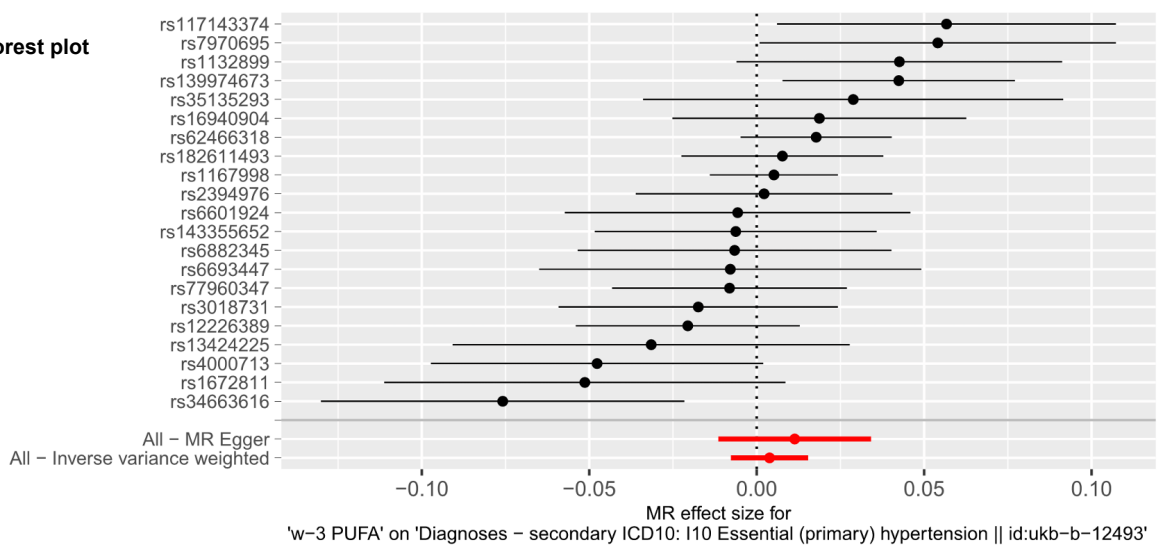

Figure 3 |
Two-sample MR forest plot

sults' stability. Scatter and forest plots further illustrated the lack of causal effect, as did the MR-Egger intercept test, which found no evidence of horizontal pleiotropy ($P > 0.05$) (**Figure 2** and **Figure 3**). Funnel plots also indicated the absence of study bias (**Figure 4**).

To further assess the robustness of the aforementioned results, an additional analysis was conducted on the included SNP loci using the MR-Egger intercept test. The P-value obtained was 0.4621, indicating no evidence of horizontal pleiotropy ($P > 0.05$). Similarly, the funnel plot did not reveal any bias in the study (**Figure 4**).

Sensitivity Analysis

The "leave-one-out" sensitivity analysis was conducted to ascertain the influence of individual SNP loci on the overall causal estimation (**Figure 5**). This analysis demonstrated that the exclusion of any single SNP and subsequent MR reanalysis did not significantly alter the causal effect observed, suggesting that the estimated causal relationship is not contingent upon any singular genetic variant. This enhances the credibility of the study's conclusions.

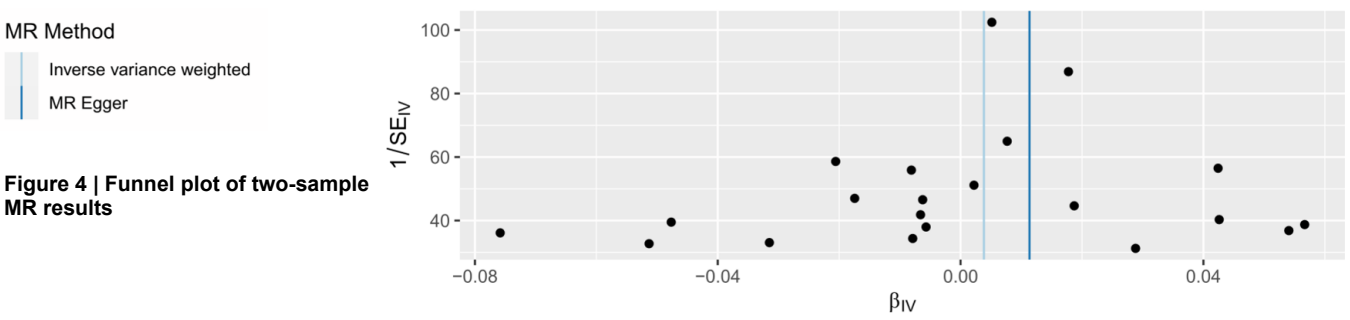

Figure 4 | Funnel plot of two-sample MR results

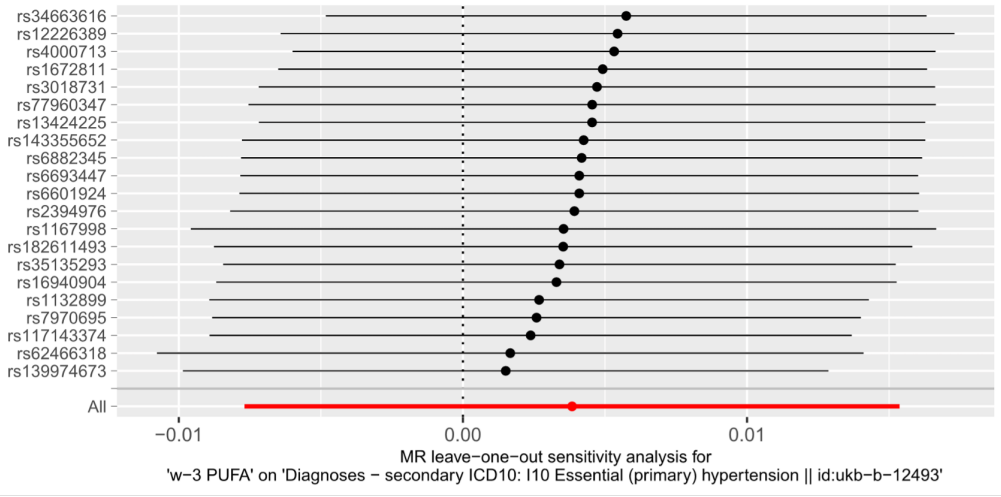

Figure 5 | Two-sample MR "leave-one-out" method

DISCUSSION

This investigation utilized a two-sample MR methodology to examine the causal dynamics between ω-3 PUFA and hypertension. The outcomes suggest an absence of a causal connection between ω-3 PUFA levels and hypertension, thereby contributing novel insights to the discourse on the role of ω-3 PUFA within hypertension research.

A multitude of research indicates that ω-3 PUFAs offer several benefits to the vasculature, although results from cardiovascular prevention interventions remain mixed.The advantages of ω-3 PUFA likely surpass merely reducing triglycerides, encompassing the prevention of vascular inflammation and thrombosis, as well as enhancing endothelial function [24-27]. Research conducted both in vitro and in vivo, involving animals and humans, indicates that ω-3 PUFA can reduce blood pressure by influencing endothelium-dependent and independent vascular reactions, mitigating arteriosclerosis, decelerating atherosclerosis progression, and enhancing arterial plaque stability, which in turn improves peripheral blood flow resistance [9, 28, 29]. Despite these interesting observations, the existing evidence on the benefits of ω-3 PUFA for hypertension has never been considered worthy of inclusion in hypertension guidelines [30, 31]. This could be attributed to the fact that this claim is substantiated by evidence from studies involving subgroups of patients with high blood pressure, although there is a scarcity of comprehensive studies on cardiovascular prevention specifically targeting individuals with high blood pressure using ω-3 PUFA. Moreover, the study have additionally explored the scrutiny of the consequences of ω-3 PUFA within the framework of primary prevention. In a notable trial involving 13,078 participants at a high risk for cardiovascular disease, characterized by high levels of lipids in the blood, low levels of HDL cholesterol, and high blood pressure, the supplementation of 4g/d of EPA-DHA or a placebo of corn oil alongside statin treatment did not exhibit any significant difference in cardiovascular outcomes after 42 months of monitoring [32]. In a separate randomized, placebo-controlled investigation encompassing a cohort of over 25,000 individuals, nearly half of whom were afflicted with hypertension, the effectiveness of vitamin D and ω-3 PUFA (1g/d) in deterring cardiovascular diseases and cancer was studied. The study yielded results indicating that ω-3 PUFA did not produce a noteworthy reduction in the occurrence of cardiovascular events during a follow-up period of 5.3 years [33]. Another investigation, centered on diabetic patients, of whom 77% also suffered from hypertension, was conducted over an average follow-up duration of 7.4 years. The individuals were assigned in a haphazard fashion to either receive a supplement containing 1g per day of ω-3 PUFA or to ingest olive oil. The resulting analysis demonstrated no significant variance in the frequency of cardiovascular events between the two groups [34].

The influence of ω-3 PUFA on hypertension could be modulated by a variety of elements, including genetic predispositions, additional risk determinants, and the metabolic processing of ω-3 PUFA. These aspects may collectively account for the observed variability in ω-3 PUFA's impact on hypertension. ω-3 PUFA is known to mediate effects through mechanisms such as vasodilation and contraction regulation,

modulation of renal sodium excretion, and interaction with omega-6 PUFA within metabolic pathways, reducing the synthesis of vasoconstrictive agents [35]. Such mechanisms are capable of enhancing vasodilatory responses and the compliance of vascular structures. Nevertheless, the magnitude of ω-3 PUFA's vascular effects may differ across diverse populations, influenced by genetic variations and environmental risk factors.

Conversely, numerous epidemiological and retrospective analyses have posited a correlation between ω-3 PUFA consumption and a diminished prevalence of cardiovascular conditions, though this association has not been uniformly corroborated by early intervention studies. Recent large-scale randomized controlled trials, especially those examining high-dose EPA formulations, have reevaluated ω-3 PUFA's preventive capacity regarding cardiovascular diseases [8]. Additionally, ω-3 PUFA are reported to attenuate angiotensin-converting enzyme activity, angiotensin II synthesis, expression of tumor growth factor-β, and to augment endothelial NO production, thereby activating the parasympathetic nervous system [36, 37]. Such biochemical actions potentially enhance vasodilatory function and arterial flexibility, yet their efficacy may exhibit interindividual variability, thereby affecting their overall influence on hypertension management.

Prior investigations, predominantly cross-sectional, retrospective, or prospective cohort studies, were constrained by their observational designs, rendering them susceptible to unmeasured confounding variables [38]. The present MR study mitigated this limitation by examining the genetic underpinnings of ω-3 PUFA levels and their association with hypertension risk, thereby excluding unmeasured confounders. Additionally, the absence of detected horizontal pleiotropy in this analysis supports the reliability of its conclusions. Nonetheless, the study's applicability is confined to European populations, and its generalizability to other demographic groups remains uncertain. Moreover, despite efforts to address and exclude outlier variants, the potential for unnoticed pleiotropic influences persists, as is common in MR studies [39].

In summary, findings derived from extensive GWAS data via MR analysis indicate a lack of causal linkage between ω-3 PUFA levels and hypertension. Nonetheless, establishing the causal relationship between ω-3 PUFA and hypertension holds significance for its diagnosis and the implementation of targeted, individualized prevention and treatment strategies.

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