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ORIGINAL RESEARCH

Causal Effect of Fatty Fish Consumption on Influenza: Evidence From Two-Sample Mendelian Randomization

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Background: Influenza continues to pose a significant public health threat, with substantial morbidity and mortality worldwide. While vaccines and antiviral treatments exist, the role of dietary factors, particularly fatty fish consumption, in modulating influenza susceptibility remains underexplored. Fatty fish, rich in omega-3 polyunsaturated fatty acids (PUFAs), is believed to influence immune responses, but its specific impact on influenza risk is not fully understood. This study aims to investigate the causal relationship between fatty fish consumption and influenza susceptibility using a two-sample Mendelian randomization (MR) approach.

Methods: Genetic instruments for fatty fish consumption were derived from publicly available genome-wide association studies (GWAS). Summary-level data on influenza susceptibility were sourced from the largest GWAS available. A two-sample MR analysis was conducted using inverse-variance weighted (IVW) and MR-Egger methods to assess the causal effect of fatty fish consumption on influenza risk.

Results: The analysis revealed a potential protective effect of higher fatty fish consumption on influenza susceptibility. Genetically predicted higher intake of fatty fish was associated with a reduced risk of influenza, suggesting that omega-3 PUFAs may help lower susceptibility to the virus. Sensitivity analyses confirmed the absence of horizontal pleiotropy, supporting the robustness of the results.

Conclusion: This study provides evidence for a potential causal relationship between increased fatty fish consumption and a decreased risk of influenza. These findings have implications for dietary recommendations and public health strategies aimed at reducing influenza burden. However, this study has some limitations, such as the potential influence of gene-environment interactions and the predominantly European-based study population, which may limit generalizability. Future research should aim to replicate these findings in diverse populations and further explore the biological mechanisms linking fatty fish intake with influenza susceptibility.

Keywords: fatty fish consumption, influenza, Mendelian randomization, omega-3 polyunsaturated fatty acids, causal inference, public health

Introduction

Influenza is an acute respiratory infection caused by the influenza virus, characterized by high transmissibility and seasonal patterns.[1] According to data from the World Health Organization (WHO), there are approximately 100 million to 500 million cases of influenza globally each year, with hundreds of thousands of deaths resulting from the disease. Influenza viruses are classified into four types: A, B, C, and D, with types A and B being the primary pathogens responsible for human influenza outbreaks.[2,3] The primary modes of transmission for influenza are through respiratory droplets and contact infection. Individuals at higher risk include children, the elderly, and those with underlying health conditions. Influenza not only poses a significant threat to individual health but also places a substantial burden on public health systems and the economy. Therefore, understanding the risk factors and preventive strategies for influenza is of critical importance.

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In recent years, an increasing number of studies have focused on the relationship between dietary factors and influenza. For example, cohort studies have found that higher intake of coffee, tea, oily fish, and fruits is independently associated with a reduced risk of pneumonia events.[4] Furthermore, some studies have reported a positive correlation between the consumption of large amounts of fruits, vegetables, oily fish, and whole grains and forced expiratory volume in one second (FEV1).[5] Oily fish, which is rich in omega-3 fatty acids, a polyunsaturated fat with anti-inflammatory properties, may have a positive impact on the immune system. However, despite these observations, there remains a significant gap in understanding the causal relationship between oily fish consumption and influenza prevention.

While previous studies have explored the associations between diet and immune function, few have specifically investigated the direct causal impact of dietary factors, such as oily fish intake, on the incidence of influenza. Additionally, existing research often relies on observational data, which may be prone to confounding factors. The novelty of this study lies in its use of a two-sample Mendelian randomization (MR) approach, a method that addresses these limitations by providing more reliable causal inferences.[6] This approach leverages genetic variants associated with oily fish consumption to establish a clearer cause-effect relationship, minimizing confounding and reverse causality biases common in traditional epidemiological studies. Thus, this study aims to explore the causal influence of oily fish intake on the risk of influenza, offering new insights into its potential role in influenza prevention.

By providing more robust evidence through Mendelian randomization, this study contributes to the existing literature by addressing the causality of dietary factors in the prevention of influenza, which has not been thoroughly examined. The findings could inform public health strategies and dietary recommendations for reducing the burden of influenza globally.

Materials and Methods

Study Design

As illustrated in Figure 1, this study employed a Mendelian randomization (MR) design to systematically investigate the association between fatty fish consumption and the risk of influenza. Given that this study is a secondary analysis of publicly available genome-wide association study (GWAS) data, no additional ethical approval or informed consent was

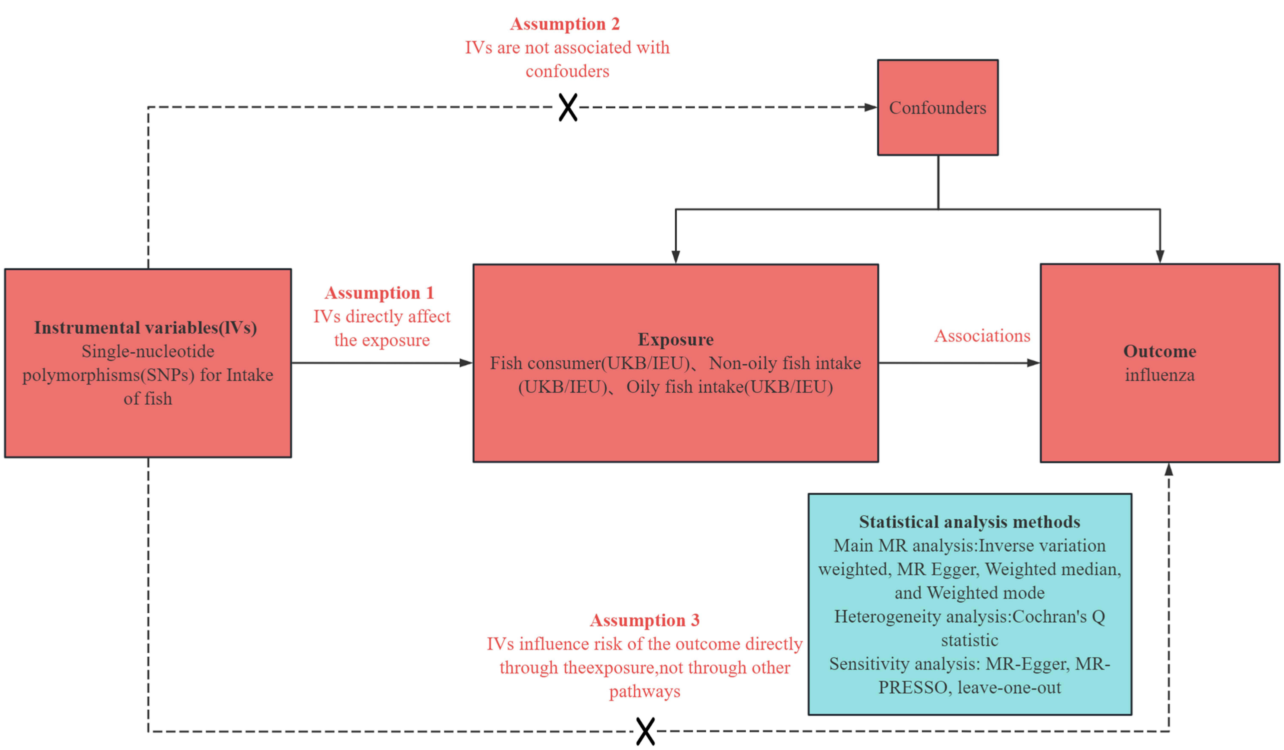

Figure 1 Mendelian Randomized Analysis Process of Intake of Oily Fish and influenza.

required. The MR approach utilizes genetic variants as instrumental variables to estimate the causal relationship between exposure (fatty fish consumption) and outcome (influenza risk), minimizing confounding and reverse causality issues that are commonly present in observational studies.

Data Sources

In this study, we employed a comprehensive Mendelian Randomization (MR) analysis to explore the causal relationship between oily fish consumption and influenza. The patients included in the study were diagnosed according to the International Classification of Diseases (ICD) criteria. The exposure variables under investigation were fish consumption, encompassing total fish intake, oily fish consumption, and non-oily fish consumption. The outcome variable was influenza. To further enhance the robustness of our findings, we incorporated exposure data from the IEU database,[7] the UK Biobank (UKB) database, and outcome data from the Finnish dataset. The disease group for the outcome variable consisted of 10,134 individuals, while the control group comprised 378,292 individuals. Detailed information on the ID numbers, sample sizes, SNP counts, and population characteristics for both the exposure and outcome variables is provided in Table 1.

Selection of Instrumental Variables

Mendelian Randomization (MR) analysis is based on three fundamental assumptions: (1) genetic variations must be strongly associated with the exposure; (2) genetic variations must be independent of confounders; and (3) genetic variations should not be influenced by the outcome.[8,9] The initial genome-wide significance threshold was set at 5×10^{-8} identify single nucleotide polymorphisms (SNPs) significantly associated with lipid metabolic traits.[10] To ensure the independence of these SNPs, we set a linkage disequilibrium (LD) threshold of r^2=0.001r^2 = 0.001r^2=0.001 and required a physical distance greater than 10,000 KB to ensure that no LD occurred between the selected SNPs.[11]

Additionally, we calculated the F-statistic for each instrumental variable (IV) to assess the potential for weak instrument bias. The F-statistic was calculated using the formula $F = Beta^2/Se^2$, where Beta represents the effect size of the allele, and Se is the standard error of Beta. Only IVs with an F-statistic greater than 10 were retained for further analysis, minimizing the risk of bias due to weak instruments.[12]

Finally, to further ensure the robustness of our analysis, all selected SNPs were checked using the Phenoscanner database (www.phenoscanner.medschl.cam.ac.uk) on November 2, 2024, to exclude any SNPs potentially associated with confounding phenotypes.[13] This step ultimately ensured the validity and reliability of our MR study.

Mendelian Randomization Analysis

In this study, we employed the inverse variance weighting (IVW) method as the primary approach to estimate causal effects. IVW is considered a robust tool for detecting causal relationships in two-sample Mendelian Randomization (MR) analysis. To ensure the robustness of our findings, we conducted supplementary analyses, including the use of MR-Egger regression, weighted median, and weighted mode methods.[14]

Additionally, we performed a series of sensitivity analyses to further validate the results. First, we applied Cochran's Q test to assess heterogeneity, which could impact causal estimates. A p-value greater than 0.05 indicates that

Table 1 Basic Information of Fish Intake and Influenza Data Set

Variable	GWAS ID	Feature	Sample Size	Number of SNPs	Population	Year
Exposure	ebi-fi38-GCST90096895	Fish consumer	308,008	5,745,854	European	2022
Exposure	ebi-fi38-GCST90096917	Non-oily fish intake	318,136	5,745,854	European	2022
Exposure	ebi-fi38-GCST90096918	Oily fish intake	297,881	5,745,854	European	2022
Exposure	ukb-r2-103140	Fish consumer	51,427	13,187,546	European	2018
Exposure	ukb-r2-1339	Non-oily fish intake	359,682	13,187,546	European	2018
Exposure	ukb-r2-1329	Oily fish intake	359,340	13,187,546	European	2018
Outcome	finngen_R11_J10_INFLUENZA	All influenza	388,426	378,292	European	2024

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heterogeneity has a negligible effect on the causal relationship, justifying the use of a fixed-effects model. In contrast, a p-value less than or equal to 0.05 suggests the adoption of a random-effects model to account for heterogeneity.[15]

To detect potential bias due to horizontal pleiotropy in the MR results, we conducted the MR-Egger intercept test. Furthermore, we used the MR-PRESSO outlier detection method to identify and correct for outliers in SNPs, thereby addressing any potential horizontal pleiotropy.[16] Residual sensitivity analyses were also performed to evaluate the robustness of the findings. All statistical analyses were conducted using R software (version 4.3.1), with the “TwoSampleMR” and “MRPRESSO” packages facilitating the MR analysis, and the “forest plot” package used for visualization. A p-value less than 0.05 was considered statistically significant.

Results

Instrumental Variables

In this study, we aimed to meet the three core assumptions of Mendelian Randomization. In the UK Biobank (UKB) database, we selected 12, 7, and 35 single nucleotide polymorphisms (SNPs) as instrumental variables for Fish consumer (UKB), Non-oily fish intake (UKB), and Oily fish intake (UKB), respectively. In the IEU database, we selected 22, 4, and 41 SNPs as instrumental variables for Fish consumer (IEU), Non-oily fish intake (IEU), and Oily fish intake (IEU), respectively. Detailed information on the instrumental variables can be found in Supplementary Material 1.

Two-Sample Mendelian Randomization Analysis

This study utilized four statistical methods (Inverse Variance Weighted, MR-Egger, Weighted Median, and Weighted Mode) to assess the causal relationship between fish intake and the incidence of influenza. As shown in Figure 2, the analysis results indicate that the odds ratios (ORs) for “Fish consumer”, “Non-oily fish intake”, and “Oily fish intake”

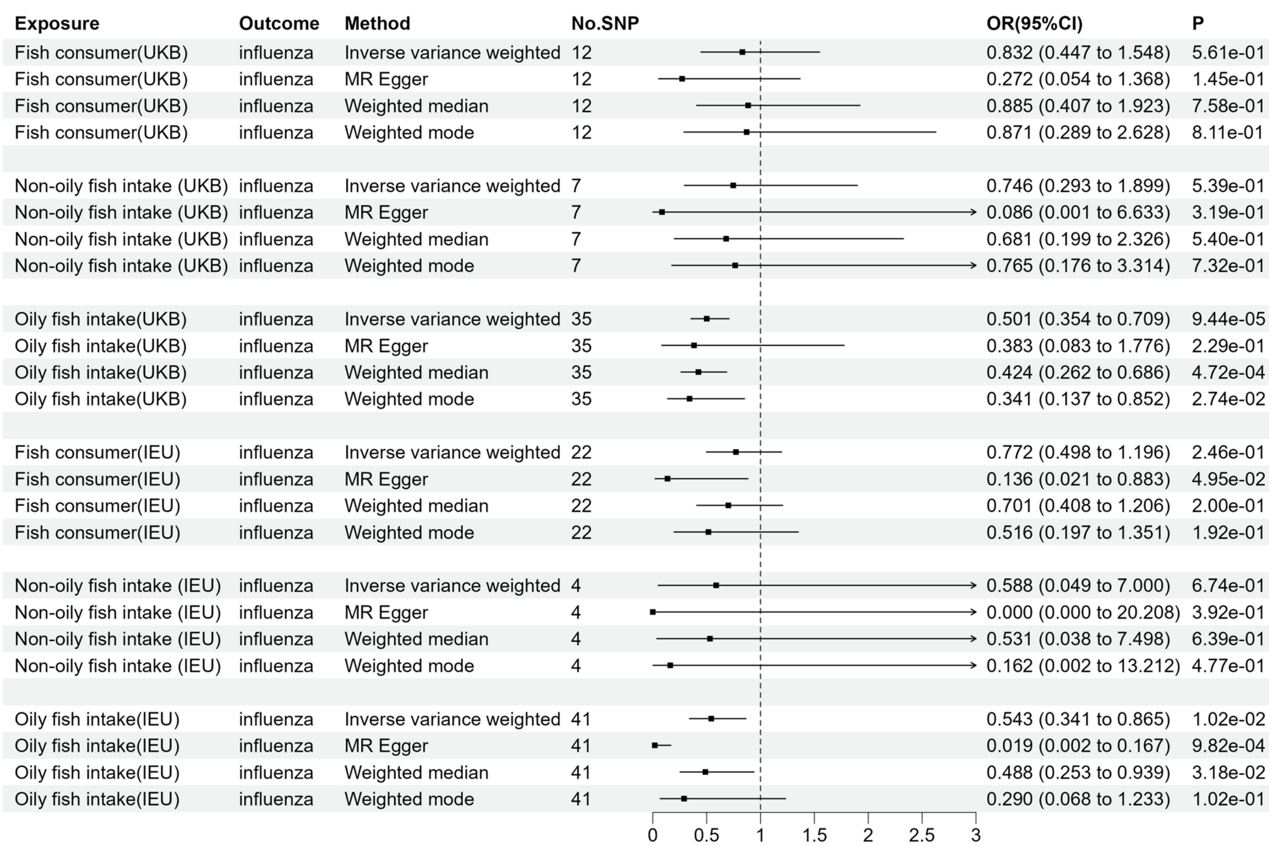

Figure 2 Forest chart of causal relationship between fish intake and influenza.

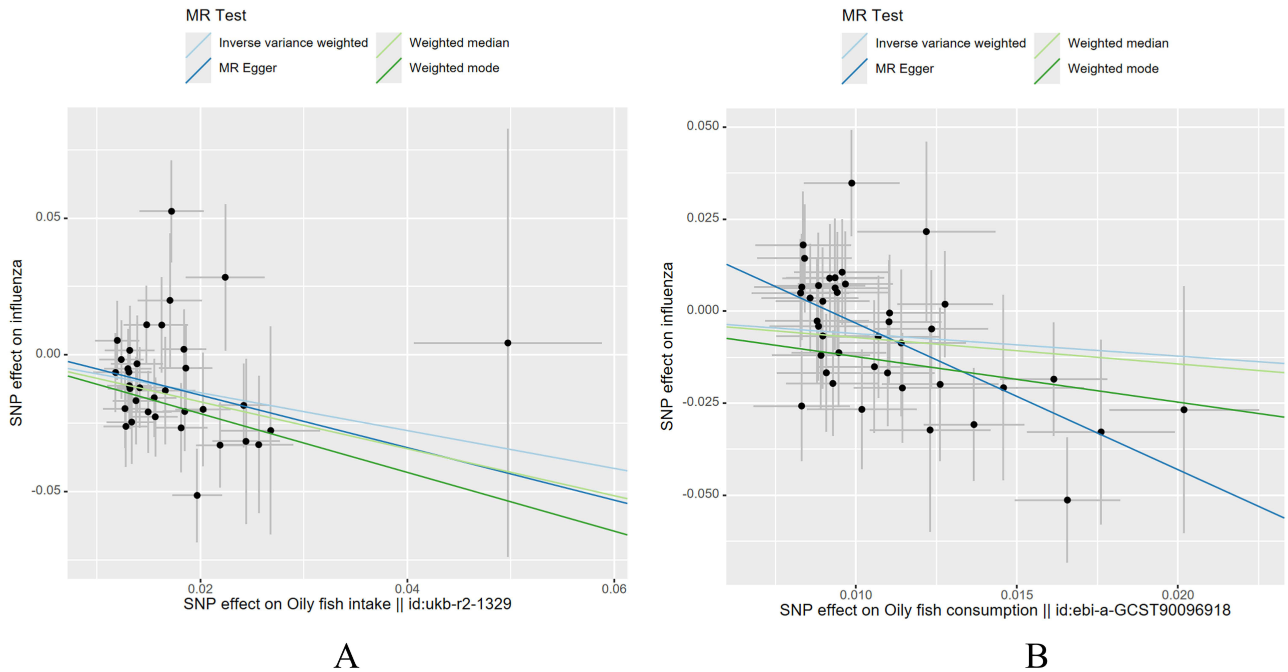

Figure 3 Scatter diagram of causal relationship between fish intake and influenza. (**A**) represents the scatter plot of oily fish intake and influenza occurrence in the UKB database; (**B**) represents the scatter plot of oily fish intake and influenza occurrence in the IEU database; The overall trend of the two is negatively correlated.

from both the UK Biobank (UKB) and the International Epidemiology Union (IEU) databases were all less than 1, suggesting a negative correlation between fish intake and the incidence of influenza.

Specifically, in the UKB database, the OR for "Oily fish intake" calculated using the Inverse Variance Weighted (IVW) method was 0.50 (95% confidence interval [CI]: 0.35–0.71, $p = 9.44 \times 10^{-5}$). In the IEU database, the same algorithm yielded an OR of 0.54 (95% CI: 0.34–0.86, p = 0.01). All four methods showed consistent directionality, indicating that "Oily fish intake" has a significant protective effect against influenza. In contrast, "Fish consumer" and "Non-oily fish intake" did not show statistical significance in either database ($p > 0.05$).

Furthermore, we plotted a scatter diagram with "Oily fish intake" on the x-axis and the incidence of influenza on the y-axis (Figure 3A and B). The results demonstrated a significant decreasing trend in influenza incidence with increasing "Oily fish intake".

Reliability Assessment

Pleiotropy Test: As shown in Table 2, in the MR analysis of "Oily fish intake" (UKB) and influenza, the MR-Egger intercept test yielded a significant result ($p < 0.05$), indicating the presence of horizontal pleiotropy in this analysis. However, in the MR analysis of "Oily fish intake" (IEU) and influenza, the MR-Egger intercept test showed no significant difference from zero ($p > 0.05$), suggesting the absence of horizontal pleiotropy in this analysis. The findings from both databases corroborate each other, thereby strengthening the reliability of our study conclusions.

Table 2 Reliability Assessment of the Causal Association Between Fish Intake and Influenza Incidence in Mendelian Randomization (MR) Analysis

Expose	Outcome	Cochran Q		MR Egger	
		MR Egger	IVW	Q	*P*
Oily fish intake(UKB)	Influenza	P=0.85	P=0.50	0.03	0.003
Oily fish intake(IEU)	Influenza	P=0.34	P=0.38	0.01	0.72

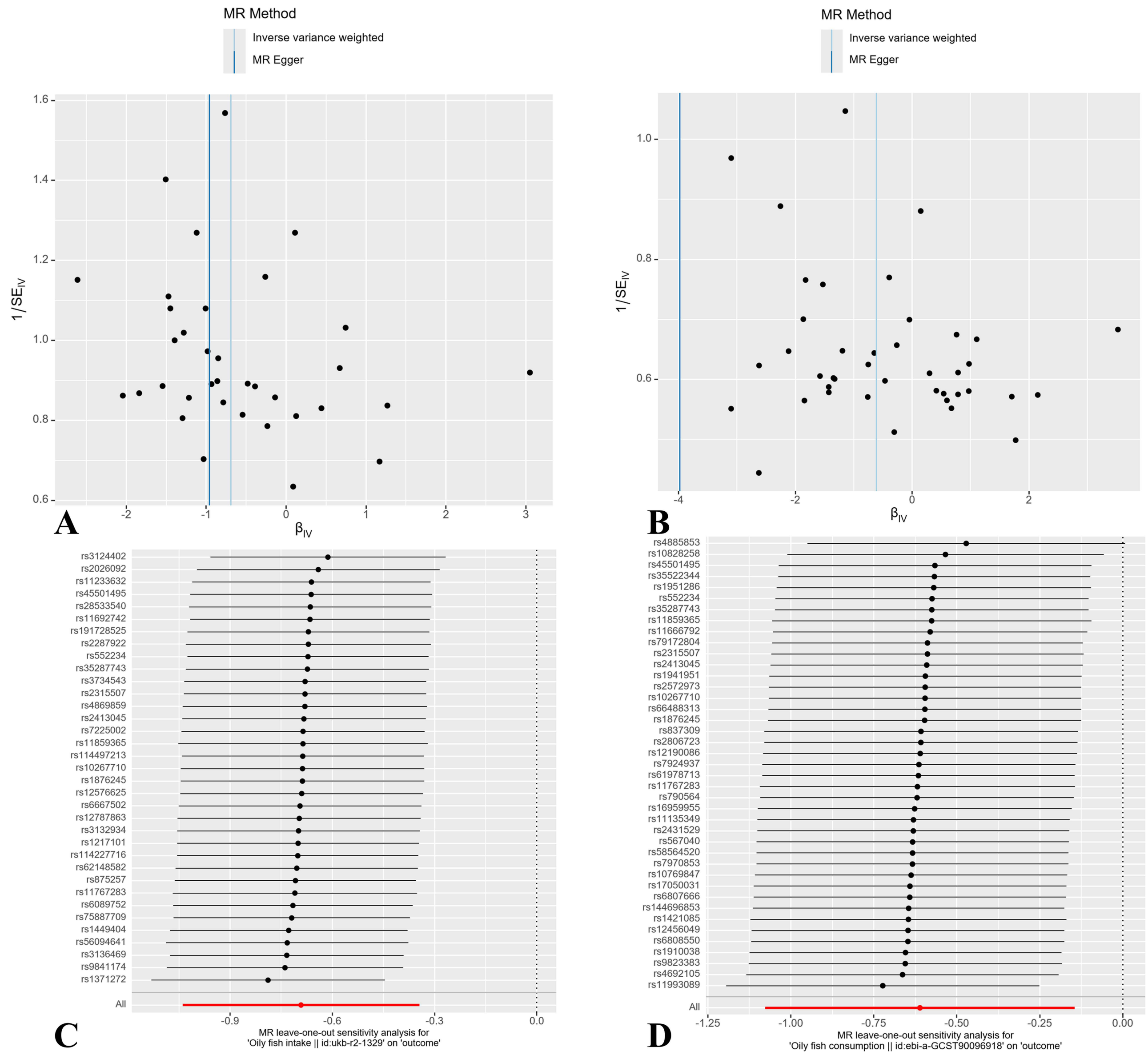

Figure 4 Funnel Plot and Leave-One-Out Sensitivity Analysis of the Causal Association Between Fish Intake and Influenza Incidence. (**A**) Funnel plot depicting the causal effect of "Oily fish intake" (UKB) on influenza. (**B**) Funnel plot depicting the causal effect of "Oily fish intake" (IEU) on influenza. (**C**) Leave-one-out sensitivity analysis for the causal effect of "Oily fish intake" (UKB) on influenza. (**D**) Leave-one-out sensitivity analysis for the causal effect of "Oily fish intake" (IEU) on influenza.

Heterogeneity Analysis: As shown in Table 2, the Cochran's Q test for the MR analysis of "Oily fish intake" (UKB) and influenza, as well as for "Oily fish intake" (IEU) and influenza, both yielded p-values greater than 0.05, indicating no significant heterogeneity in the MR analyses. Additionally, the funnel plots for each group of MR analyses showed that the scatter of causal effect estimates was symmetrically distributed, suggesting that there was no potential bias (Figure 4A and B).

Sensitivity Analysis: The leave-one-out test demonstrated that the results of the IVW analysis were consistent even after sequentially removing individual SNPs. Specifically, no SNPs had a large impact on the causal estimates for "Total concentration of branched-chain amino acids", "Leucine", and "Valine" in the analysis of the association with influenza. This further supports the stability of our results (Figure 4C and D).

Discussion

Dietary habits have a profound impact on an individual's nutritional status and immune metabolism. A balanced diet not only provides the energy required by the body but also ensures the intake of essential nutrients, thereby maintaining overall health and preventing diseases. Fish, as a key component of daily diets, holds significant nutritional value. The high-quality proteins found in fish are crucial for the development of immune cells, organs, tissues, and the immune system. On one hand, fish proteins contain all the essential amino acids required by the human body, particularly leucine and lysine, which are vital for the generation and function of immune cells.[17,18] On the other hand, fish is rich in trace elements such as zinc, selenium, and iodine, which serve as raw materials for many enzymes in the body, facilitating smoother biochemical metabolism and enhancing immune function.[19,20] In recent years, fish oils and fatty acids have garnered increasing attention due to their potential impact on immune responses.

Comparison with Existing Studies

This study explored the causal relationship between fish consumption and the occurrence of influenza using Mendelian randomization (MR) methods. The results indicated a significant negative correlation between oily fish intake and the incidence of influenza (ALL), suggesting that oily fish consumption may have a preventive effect on influenza. However, no significant association was found between total fish intake, non-oily fish intake, and influenza. This suggests that although fish consumption can enhance immunity and reduce the risk of influenza, oily fish intake is particularly effective in preventing influenza. Non-oily fish typically contain lower levels of omega-3 polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are likely key components in the protective effect of oily fish. Therefore, the lack of a significant effect of non-oily fish and total fish intake may be due to the relatively lower content of omega-3 fatty acids in non-oily fish, which could explain why it is less effective in preventing influenza. This contrast highlights the specific role of omega-3 fatty acids in influenza prevention and underscores the unique value of oily fish consumption.

Thanh-Huyen T. Vu et al[4] conducted a cohort study using the UK Biobank (UKB) database and found that increased consumption of coffee, tea, oily fish, and fruits was significantly associated with a reduced risk of future pneumonia events. This finding is generally consistent with our results, further supporting the potential role of oily fish in preventing respiratory infections.

Biological Mechanism Explanation

The occurrence of influenza is influenced by various factors, primarily including weakened immune function, as seen in vulnerable populations such as the elderly, children, pregnant women, and individuals with underlying diseases. The high infectivity and seasonal characteristics of the influenza virus make its prevention and control a major global public health challenge. Apart from immune status, dietary habits are also an important factor influencing susceptibility to influenza. Oily fish, as a nutritionally rich food, contains amino acids, ω-3 fatty acids, and trace elements, which are considered vital for improving immune function, regulating immune responses, and alleviating inflammatory reactions.[4,21] In this study, we explored the causal relationship between oily fish intake and the risk of influenza, and analyzed its potential biological mechanisms in conjunction with its nutritional components.

Firstly, oily fish are rich in high-quality proteins, particularly essential amino acids such as leucine, lysine, and tryptophan, which are crucial for the synthesis and function of immune cells.[22] Leucine not only promotes the proliferation and activation of immune cells but also enhances the immune system's ability to recognize and eliminate pathogens.[23] Additionally, the amino acid composition in oily fish provides essential raw materials for the immune system, supporting the body's defense against viral infections.[24] By enhancing immune cell function, the consumption of oily fish helps reduce the incidence of influenza.

Secondly, oily fish are particularly rich in omega-3 polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These omega-3 fatty acids are widely recognized for their anti-inflammatory properties and their ability to modulate immune responses, reducing the overactivation of inflammatory reactions. Research has shown that omega-3 fatty acids influence the fluidity of immune cell membranes and their signal transduction, reducing the production of inflammatory mediators such as prostaglandins and leukotrienes, thereby lowering inflammation.[25] In particular, omega-3 fatty acids have a significant positive regulatory effect on the function of regulatory T cells (Tregs), which may be one of the biological mechanisms underlying the protective effect of oily fish against influenza.[26]

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However, the species of fish can significantly affect the content and types of omega-3 fatty acids. For example, fatty fish like salmon and herring, which are high in fat content, tend to be rich in EPA and DHA, while other fish, such as cod, contain lower levels of omega-3 fatty acids. Therefore, different types of oily fish may vary in their protective effects, and this requires further exploration in future studies. Additionally, the bioavailability of omega-3 fatty acids can be influenced by various factors, such as the cooking methods of the fish and an individual's ability to absorb them. These factors may affect the actual efficacy of omega-3 fatty acids, and thus, when evaluating the protective effect of oily fish consumption on influenza, these variables should be considered.

Furthermore, oily fish is rich in various trace elements such as zinc, selenium, and iodine, which play a crucial role in immune system function. Zinc is a key element in immune cell proliferation and antiviral activity, enhancing the activity of T cells and macrophages, thus helping the body effectively combat viral infections.[27] Selenium has antioxidant properties, scavenging free radicals and reducing oxidative stress-induced cell damage, thereby boosting immune responses.[28] Iodine is essential for thyroid function and immune regulation.[29] These trace elements in oily fish play a vital role in maintaining immune health, further explaining the negative correlation between oily fish intake and the risk of influenza.

In addition to influenza, the immune-boosting properties of omega-3 fatty acids, trace elements, and amino acids found in oily fish are relevant for the prevention of other infectious diseases and chronic health conditions. For example, increased omega-3 fatty acid intake has been associated with reduced inflammation and enhanced immune responses, which may benefit individuals with autoimmune diseases, cardiovascular conditions, and even cancer. Omega-3s have also shown promise in reducing the risk of respiratory infections, improving lung health, and supporting overall cardiovascular health.[30]

In summary, oily fish, through their rich content of amino acids, omega-3 fatty acids, and trace elements, may significantly reduce the risk of influenza and other infectious diseases by modulating the immune system. It is recommended to increase the intake of oily fish, particularly during flu season, as an effective dietary intervention strategy to enhance individual immunity and prevent the onset of influenza. However, the broader implications of oily fish consumption extend to a wide range of health outcomes, including improved cardiovascular health, reduced inflammation, and a bolstered immune system that may help reduce susceptibility to various infections.

In the context of public health policies, promoting oily fish consumption could complement existing prevention strategies for not only influenza but also other chronic conditions, such as heart disease, autoimmune disorders, and respiratory infections. As part of broader health campaigns, incorporating oily fish recommendations into national dietary guidelines could encourage the population to adopt healthier eating habits, especially in high-risk groups such as the elderly and children. This dietary intervention could serve as a low-cost, widely accessible approach to improving public health and preventing a range of diseases.

However, in addition to dietary factors, environmental factors and lifestyle variables also play a significant role in the incidence of influenza and immune function. For example, air pollution, climate change, and densely populated environments can increase the risk of influenza transmission. Moreover, individual lifestyle factors such as physical activity, sleep quality, psychological stress, smoking, and alcohol consumption can influence immune system function. Therefore, while increasing oily fish consumption may contribute to influenza prevention, it is important to consider these environmental and lifestyle factors and integrate them into a comprehensive health intervention strategy to maximize the effectiveness of influenza and disease prevention.

Limitations of the Study

Although this study provides strong evidence supporting a negative correlation between oily fish intake and influenza risk, there are several limitations. First, Mendelian randomization (MR) analysis relies on the selection of genetic instrumental variables, which may be influenced by rare variants and gene-environment interactions. While we acknowledge that our analysis does not fully account for the complexities of gene-environment interactions, these interactions may have a significant impact on both oily fish intake and influenza risk. For example, environmental factors such as diet, lifestyle, and geographical differences could interact with genetic predispositions, potentially influencing both fish consumption patterns and susceptibility to influenza. This limitation may introduce bias and reduce the precision of our causal inference.

Specifically, using genetic markers as proxies for fish consumption may not accurately reflect actual dietary habits, as the relationship between genetic variation and dietary behavior is complex and influenced by various factors. While these genetic markers are associated with fish intake, they may not fully align with an individual's real-world dietary patterns. Therefore, using these genetic proxies to infer dietary habits in real-world scenarios may introduce some bias.

Second, the study population is predominantly of European descent, which may limit the generalizability of the results. Populations from different ethnicities and geographic regions may have distinct genetic backgrounds and dietary habits, which could affect the bioavailability and efficacy of omega-3 PUFAs. Lastly, despite analyzing data from multiple databases, MR analysis cannot completely eliminate all potential confounding factors, such as lifestyle, socio-economic status, and other unmeasured confounders. Therefore, the conclusions drawn from this study require further validation in future research, particularly considering the potential influence of gene-environment interactions.

Conclusion

This study provides significant evidence from Mendelian randomization analysis that oily fish intake is negatively correlated with influenza risk, suggesting a preventive effect of consuming oily fish. The amino acids, omega-3 fatty acids, and trace elements found in oily fish play a crucial role in modulating the immune system, reducing inflammatory responses, and enhancing immune cell function, which likely explain the observed reduction in influenza risk. Based on these findings, we recommend that public health organizations incorporate oily fish consumption into dietary guidelines, particularly during the flu season, as a strategy to enhance immunity and reduce influenza incidence, especially in high-risk groups such as the elderly and children. Targeted dietary interventions, such as promoting oily fish consumption in school meal programs and senior health initiatives, could further support these efforts. Public education campaigns should also emphasize the immune-boosting benefits of oily fish, while in areas with limited access to fresh fish, fish oil supplements may serve as an alternative. Additionally, further research is necessary to validate these findings in broader and more diverse populations and to explore the biological mechanisms underlying the relationship between oily fish intake and influenza risk, particularly in relation to specific nutrients and gene-environment interactions. These recommendations, combined with continued research, can help shape effective public health strategies to reduce influenza burden.

Abbreviations

GWAS, Genome-Wide Association Studies; PUFAs, Polyunsaturated Fatty Acids; MR, Mendelian Randomization; WHO, World Health Organization; ICD, International Classification of Diseases; UKB, UK Biobank; IEU, (Not explicitly defined in the document); IVW, Inverse-Variance Weighted; TIPRA, Tool for Influenza Pandemic Risk Assessment; ROS, Reactive Oxygen Species; HIF-1α, Hypoxia-inducible factor 1-alpha; Tregs, Regulatory T cells.

Data Sharing Statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics Approval

This research is based on publicly available abstract-level data obtained from comprehensive genome-wide association studies (GWAS). According to the national legislation guidelines, such as item 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China, this study is exempt from ethical approval.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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