International Journal of Chronic Obstructive Pulmonary Disease Dovepress
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ORIGINAL RESEARCH

# Exploring a Potential Causal Link Between Dietary Intake and Chronic Obstructive Pulmonary Disease: A Two-Sample Mendelian Randomization Study

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**Background:** Chronic Obstructive Pulmonary Disease (COPD), the most prevalent chronic respiratory condition, significantly impairs patients' quality of life. The pivotal element in disease management lies in prevention, underscoring the paramount importance of employing a scientific approach to investigate early prevention strategies for COPD.

**Methods:** This study delved into the causal link between 28 dietary intakes and COPD employing two-sample Mendelian randomization. We primarily utilized the Inverse Variance Weighted (IVW) method as the main outcome, complemented by Weighted Median (WM), MR-Egger method, along with several sensitivity analysis techniques, all accompanied by visual representations.

**Results:** We identified higher odds of COPD following exposure to green beans (OR=1.381, 95% CI=1.119–1.704, P=0.003) and pork intake (OR=2.657, 95% CI=1.203–5.868, P=0.016). In contrast, the odds of developing COPD were lower following exposure to dried fruit (OR=0.481, 95% CI=0.283–0.819, P=0.007), cereal (OR=0.560, 95% CI=0.356–0.880, P=0.012), and whole egg consumption (OR=0.700, 95% CI=0.504–0.972, P=0.033).

**Conclusion:** In light of our study's findings, we anticipate that strategically modifying dietary choices may offer an avenue for early COPD prevention in the future.

**Keywords:** Mendelian randomization, dietary intake, chronic obstructive pulmonary disease, causal relationship, early prevention

## Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease characterized by associated progressive and incompletely reversible airflow limitation.[1] The pathogenesis of COPD is based on an innate and adaptive inflammatory immune response to the inhalation of toxic particles and gases. COPD is the third leading cause of death worldwide due to its high morbidity and mortality, with global morbidity and deaths from COPD increasing by 86% and 30%, respectively, from 1990 to 2019. COPD places a huge burden on the global economy, with the global COPD impediment to macroeconomic development projected to be $4.3 trillion over 30 years starting in 2020.[2] Smoking, a major risk factor for COPD, poses a significant challenge as only about 20% of individuals can successfully quit due to tobacco dependence.[3] The results of the study show that exposure to biomass fumes significantly increases the

Received: 8 November 2023
Accepted: 14 January 2024
Published: 26 January 2024

risk of developing COPD, a condition closely associated with social determinants such as economic hardship and low education levels.[4,5] Hence, we acknowledge the possibility of examining prevention and interventions to investigate whether modifying daily dietary intake can reduce the likelihood of developing COPD.

The impact of diet, as an economic and easily accessible and controllable factor, on COPD is currently a research hotspot. Increasing evidence suggests that dietary factors may play a key role in the long-term incidence rate of COPD.[6] A prospective cohort study of Swedish men found that long-term heavy consumption of fruits and vegetables was independently and negatively associated with the incidence rate of COPD. Another large cohort study from seven countries showed an independent negative correlation between fruit and fish intake and COPD mortality rate.[7] On the contrary, studies have found that consuming a large amount of red meat or processed meat, saturated fat, and sweets increases the risk of COPD.[8] It is worth noting that most of the evidence on diet and COPD risk comes from observational studies. Due to possible differences in dietary habits among individuals, the results of observational studies may be biased due to reverse causality and confusion, and the causal relationship between diet and COPD cannot be clarified. Therefore, these findings need further clarification.

Genome-wide association Study (GWAS) is a research method employed to explore the genetic foundation and associations of traits, with SNPs (Single Nucleotide Polymorphisms) being genetic markers frequently utilized within GWAS to pinpoint genetic variants linked to specific traits or diseases.[9] Mendelian randomization is a statistical analysis method that allows for the evaluation of causality in relationships between observed modifiable exposures or risk factors and clinically significant outcomes.[10] MR addresses bias associations caused by confounding or reverse causal relationships by using SNPs as instrumental variables for testing exposure, such as dietary intake. At present, MR has been widely used to explore the relationship between diet and various diseases, including depression,[11] coronary heart, and asthma. Nevertheless, there is no evidence to investigate the causal relationship between dietary intake and COPD.

In this study, we conducted a comprehensive two-sample Mendelian randomization analysis to evaluate the potential causal relationship between 28 commonly consumed dietary factors and the risk of COPD. Our ultimate objective is to mitigate the risk of COPD development by making scientifically informed choices in dietary intake.

# Materials and Methods

## Study Design

This study employed a two-sample Mendelian randomization (MR) approach to investigate the causal link between different dietary exposures and COPD outcomes (Figure 1). SNPs, as prevalent genetic variations within the genome, offer insights into the association between genetic variants and disease, allowing for an understanding of how specific genetic changes influence disease risk.[12] To ensure the effectiveness of Two-Sample Mendelian Randomization (TSMR), three fundamental assumptions must be satisfied regarding the chosen instrumental variables (IVs). To establish the SNP as a reliable surrogate for dietary factors, it must exhibit a strong correlation with these 28 specific dietary components.

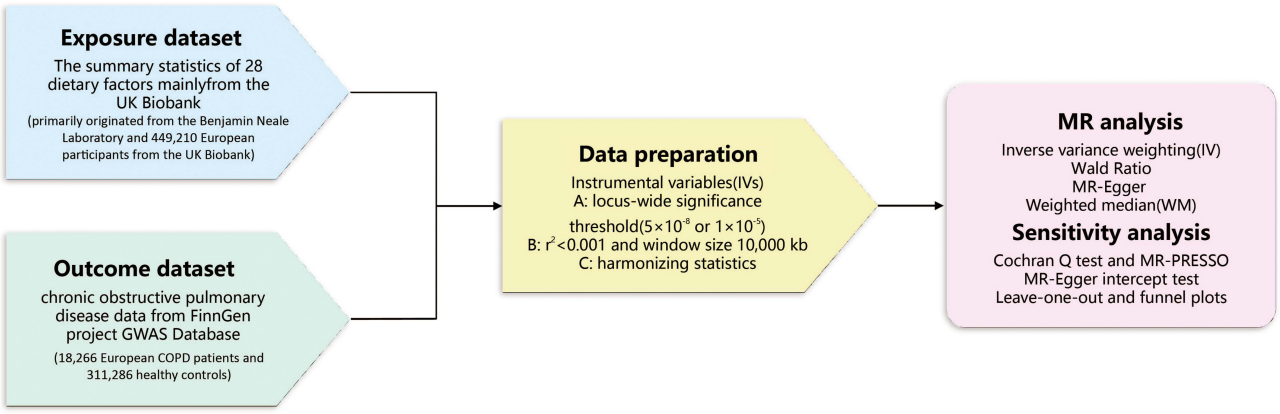


**Figure 1** The specific protocol for a two-sample Mendelian randomization analysis.

Ensure SNPs utilized are unrelated to any recognized or possible confounding factors, thus upholding the precision of causal deductions. Ultimately, the chosen SNPs solely exerted their impact on the outcomes through the intricate interplay between dietary elements and COPD.

## Source of Data

The GWAS data for the 28 dietary exposures were obtained from the IEU Open GWAS Project (https://gwas.mrcieu.ac.uk/), dedicated to facilitating global data sharing for genomic association studies, with a focus on exploring the interplay between genes and complex disease and health correlations. The 28 dietary factors are grouped into six main categories: meat intake (oily fish intake, bacon intake, processed meat intake, poultry intake, beef intake, pork intake, lamb/mutton intake, non-oily fish intake), vegetable intake (cooked vegetable intake, baked bean intake, fresh tomato intake, tinned tomato intake, salad/raw vegetable intake), fruit intake (Fresh fruit intake, Dried fruit intake), fluid intake (coffee intake, tea intake, water intake, red wine intake, average weekly beer plus cider intake), staple food intake (cereal intake, bread intake, whole-wheat intake, whole-wheat cereal intake), and other dietary habits (salt added to food, whole egg intake)(Table 1). The dietary data primarily originated from the Benjamin Neale Laboratory (http://www.nealelab.is/uk-biobank/). The primary analyses encompassed heritability and GWAS evaluations of individual food intake, employing linear mixed models to establish curated single Food Intake Quantitative Traits (FI-QTs) for the analysis. Additionally, Principal Component-derived Dietary Patterns (PC-DPs) were generated utilizing data from Food Frequency Questionnaires (FFQ). The study involved up to 449,210 European

**Table 1** Exposure and Outcome GWAS Summary Data Source

| GWAS ID | Exposure and Outcome | Number of SNPs | F-Statistic Mean | Sample Size |
|---|---|---|---|---|
| **ukb-b-10565** | **Tinned tomato intake** | 24 | 11.99 | 64949 |
| **ukb-b-2299** | **Green bean intake** | 28 | 16.45 | 64949 |
| **ukb-b-2375** | **Whole-wheat cereal intake** | 6 | 11.26 | 64949 |
| **ukb-b-4058** | **Baked bean intake** | 28 | 12.48 | 64949 |
| **ukb-b-4075** | **Whole egg intake** | 12 | 14.26 | 64949 |
| **ukb-b-730** | **Fresh tomato intake** | 19 | 46.90 | 64949 |
| **ukb-b-7753** | **Yogurt intake** | 13 | 21.00 | 64949 |
| **ukb-b-5174** | **Average weekly beer plus cider intake** | 15 | 19.94 | 327634 |
| **ukb-b-2862** | **Beef intake** | 11 | 26.11 | 461053 |
| **ukb-b-11348** | **Bread intake** | 27 | 38.54 | 452236 |
| **ukb-b-15926** | **Cereal intake** | 29 | 29.33 | 441640 |
| **ukb-b-1489** | **Cheese intake** | 57 | 40.13 | 451486 |
| **ukb-b-5237** | **Coffee intake** | 31 | 24.94 | 428860 |
| **ukb-b-8089** | **Cooked vegetable intake** | 14 | 20.37 | 448651 |
| **ukb-b-16576** | **Dried fruit intake** | 34 | 22.30 | 421764 |
| **ukb-b-3881** | **Fresh fruit intake** | 40 | 15.52 | 446462 |
| **ukb-b-14179** | **Lamb/mutton intake** | 28 | 17.72 | 460006 |
| **ukb-b-17627** | **Non-oily fish intake** | 11 | 28.15 | 460880 |
| **ukb-b-2209** | **Oily fish intake** | 49 | 38.93 | 460443 |
| **ukb-b-5640** | **Pork intake** | 13 | 17.96 | 460162 |
| **ukb-b-8006** | **Poultry intake** | 4 | 24.08 | 461900 |
| **ukb-b-6324** | **Processed meat intake** | 20 | 38.68 | 461981 |
| **ukb-b-1996** | **Salad / raw vegetable intake** | 18 | 14.61 | 435435 |
| **ukb-b-8121** | **Salt added to food** | 87 | 37.53 | 462630 |
| **ukb-b-6066** | **Tea intake** | 34 | 41.87 | 447485 |
| **ukb-b-14898** | **Water intake** | 33 | 26.17 | 427588 |
| **ukb-b-13556** | **Red wine intake** | 1 | 50.28 | 64949 |
| **ukb-b-4414** | **Bacon intake** | 3 | 19.42 | 64949 |
| **J10_COPD** | **COPD** | NA | NA | 18266 |

participants from the UK Biobank.[13] Detailed information is provided in the accompanying table. The latest GWAS summary data for COPD is sourced from the FinnGen Consortium (https://r9.finngen.fi/), accessed in August 2023, including 18,266 COPD cases and 311,286 healthy controls. The Consortium's focus on specific genotypes and phenotypes through genomic research and the exploration of genetic factors contributes to a deeper understanding of complex diseases, health, and biology.[14] COPD phenotypes, derived from health registries (endpoints), were established by amalgamating data sourced from one or more national health registries, primarily employing International Classification of Diseases (ICD) and Anatomical Chemical Therapeutic (ACT) classification codes.[14]

## Selection of Instrumental Variables

To ensure both robustness and an adequate number of instrumental variables (IVs), we carefully selected scientifically validated SNPs as IVs to assess the causal link between diet and COPD. We applied a strict threshold of $P < 5\times10^{-8}$ or $P < 1\times10^{-5}$ to ensure the inclusion of a sufficient number of SNPs while maintaining the statistical integrity of the results.[15] Applying $R^2 < 0.001$ and opting for a broader region size (10,000 kb) as the IVs selection criteria achieves a dual purpose: it minimizes the correlation between IVs and the target locus while mitigating potential confusion stemming from linkage disequilibrium (LD). To mitigate bias caused by weak instrumental variables, a crucial measure is to ensure that the F-statistic surpasses 10, thereby confirming the instrumental variable's (IV) validity and ensuring robust causal inference. Furthermore, the Phenoscanner tool was employed to remove genetic variants that might introduce confounding, ensuring that the chosen IVs remain free from covariance with the exposure variable during causal inference establishment.[16]

## Methodology of MR

The Inverse Variance Weighted (IVW method), comprehensively addressing each SNP's effects through weighted averaging of effect estimates from numerous genetic variants, served as the primary approach for estimating causal effects in this study. In contrast, the Wald Ratio method was employed as a supplementary tool to evaluate the impact of individual SNP (red wine intake). The weighted median and MR-Egger methods synergistically enhance analyses, each excelling in distinct conditions. The weighted median approach reduces extreme effect influence amid heterogeneity. MR-Egger, not demanding uniform effect directions for all IVs, suits skewed situations, curbing genetic variation's added impact on exposure-outcome links.[17]

## Statistical Analysis

To address potential horizontal pleiotropy, this study employed MR-Egger regression and MR-PRESSO tests to identify and exclude outliers. Additionally, a leave-one-out analysis was conducted to assess the impact of each SNP on the stability of the results. The presence of heterogeneity was examined using Cochran's Q test (with a significance level of $P<0.05$ indicating the presence of heterogeneity).

All analyses were performed using R Version 4.3.1, with the utilization of the R packages "TwoSampleMR" and "MRPRESSO" for these specific analyses.

# Result

Presented below is an overview of the causal connection between 28 dietary factors and COPD. The objective of this study is to offer a robust dietary approach for averting the onset of COPD, aligned with the findings obtained through Two-Sample Mendelian Randomization (TSMR) analysis. In this study, the selected instrumental variables (IVs) were carefully chosen to ensure that their F-statistics exceeded 10 (ranging from 10.07 to 161.26). Following the exclusion of SNPs associated with smoking and BMI, the ultimate count of utilized SNPs ranged between 1 and 68 (Supplementary Table 1).

Using the IVW (Inverse Variance Weighted) method as the primary analytical approach, this study successfully identified five distinct causal relationships with significance. Notably, the intake of green beans (OR=1.381, 95% CI=1.119–1.704, P=0.003) and Pork (OR=2.657, 95% CI=1.203–5.868, P=0.016) exhibited a significant association with higher odds of COPD. Conversely, the consumption of Dried fruit (OR=0.481, 95% CI=0.283–0.819, P=0.007), Cereal (OR=0.560, 95% CI=0.356–0.880, P=0.012), and Whole egg (OR=0.700, 95% CI=0.504–0.972, P=0.033) demonstrated lower odds against the development of COPD (Figures 2 and Figure 3). Furthermore, the utilization of

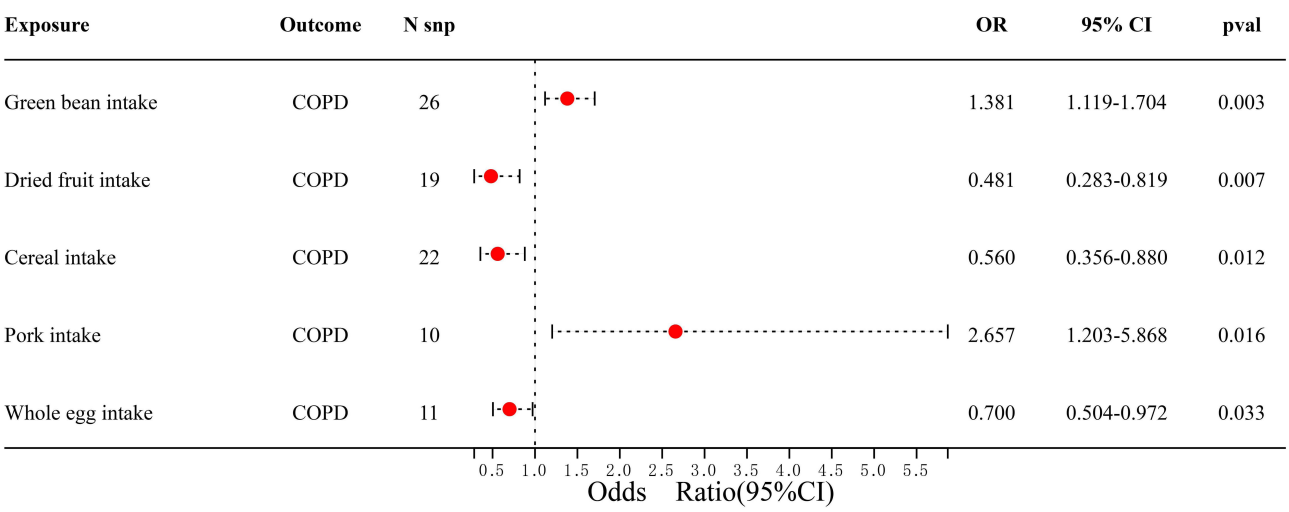


**Figure 2** The forest plot showed primary results of the causal associations between dietary intake and COPD.

the weighted median approach enhances the credibility of scientific evidence supporting the preventive effects of two dietary factors, namely Cereal intake and Whole egg intake, against the development of COPD.

In this investigation, the MR-PRESSO global test method was adeptly applied to identify and mitigate horizontal variability, effectively mitigating the potential for spurious significance stemming from numerous comparisons. Notably, among the five positive outcomes, no outlier influence was detected, underscoring the genetic variant loci's limited impact on multiple results. Furthermore, the MR-Egger intercept test, serving as a supplementary measure of horizontal multivariate soundness, yielded p-values exceeding 0.05, further fortifying the robustness of the causal inferences. The Cochran's Q statistic yielded p-values exceeding the predetermined significance threshold ($p>0.05$) for all analyses, signifying the absence of substantial heterogeneity among the genetic variant loci (Table 2). No conspicuous asymmetry is discernible in the funnel plot (Figure 4). Subsequently, a Leave-one-out analysis was applied, systematically excluding individual genetic variant loci, yet no singular SNP was observed to exert a significant influence on the overarching outcomes (Figure 5).

## Discussion

GWAS data were obtained from public databases, and a two-sample Mendelian randomization method was used to investigate the causal role of diet and COPD. We identified a significant causal relationship between five diets and COPD, with the consumption of dried fruits, grains, and whole eggs reducing the odds of COPD. On the contrary, green bean and pork intake were associated with an increased odds of developing COPD.

In our MR results, we observed lower COPD odds values only in the population with dried fruit intake, leading us to consider that dried fruit may offer certain advantages over fresh fruit. Some of the bioactive substances with antioxidant capacity (eg, phenolic compounds) and micronutrients (eg, vitamins, calcium, phosphorus, iron, and selenium) will be in higher concentrations, which can reduce tissue damage to prevent the development of COPD through anti-inflammatory and antioxidant effects.[18–20] It is now known that polyphenols possess potent anti-inflammatory properties, Studies have shown that polyphenols possess anti-inflammatory properties, as polyphenols contain the presence of hydroxyl groups, which are easily oxidized to generate O-quinones, which scavenge reactive oxygen species by combining free radicals with reactive oxygen species to play an antioxidant role.[21] Vitamin E, as a lipid antioxidant, has an antioxidant effect simultaneously. However, it also has the scavenging of reactive nitrogen in vivo, able to inhibit cyclooxygenase and 5-lipoxygenase catalyzed eicosanoids, thereby inhibiting pro-inflammatory signaling (eg, NF-κ B and STAT3/6) from playing a role in reducing the inflammatory response.[22] In addition, increased intake of micronutrients (calcium, phosphorus, iron, selenium, and vitamin C) from dried fruits has been associated with reduced odds of COPD according to case-control studies[23] and cross-sectional studies,[24] it was found that micronutrient intake is positively correlated with

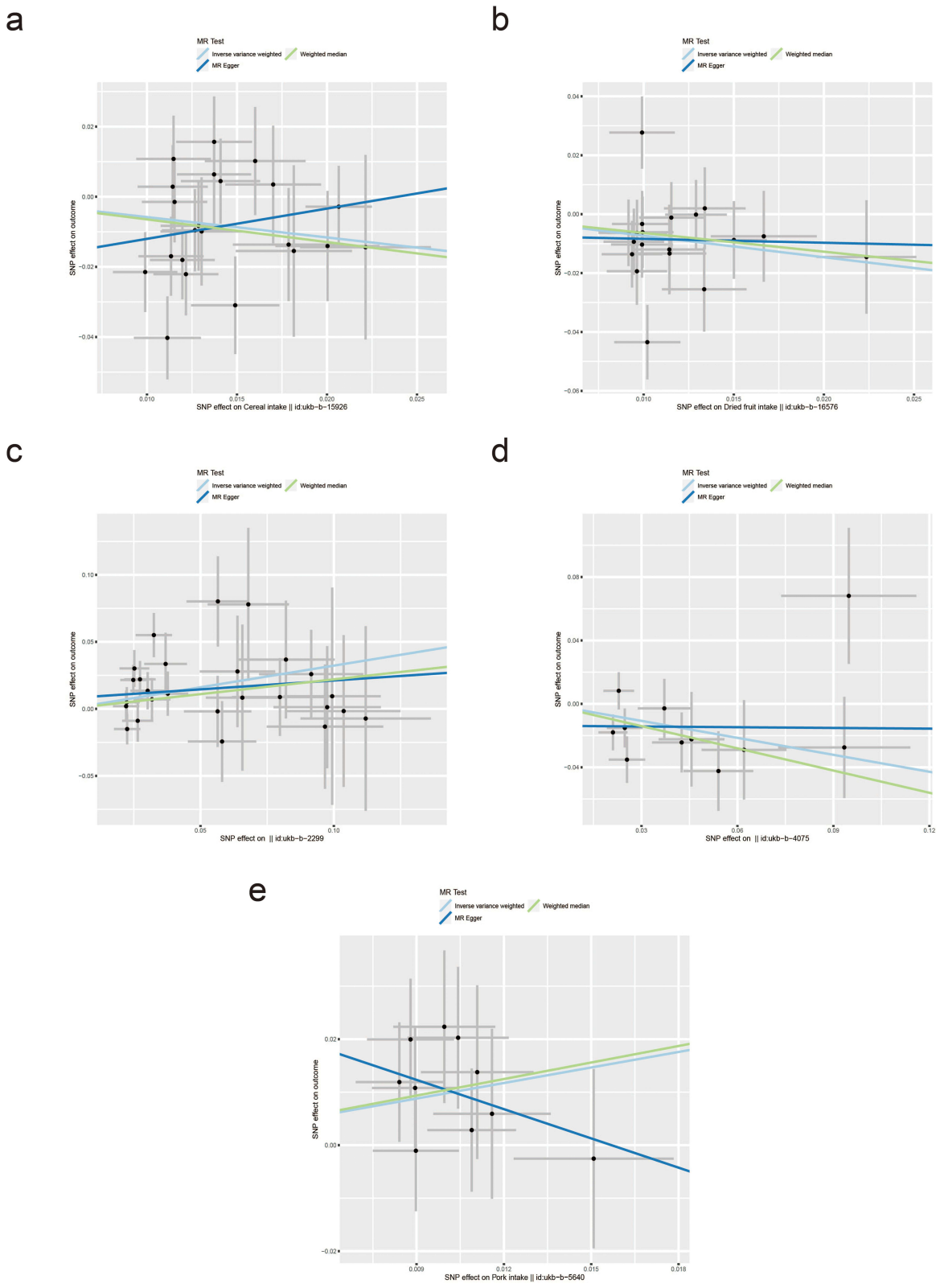


**Figure 3** Scatter plots for the causal association between dietary intake and COPD (**a**) Cereal intake, (**b**) Dried fruit intake, (**c**) Green bean intake, (**d**) Whole egg intake, (**e**) Pork intake.

**Table 2** Sensitivity Test for Positive Results

| Exposure | Heterogeneity | | MR-Egger Regression | | | MR-PRESSO |
|---|---|---|---|---|---|---|
| | MR Egger | IVW | Intercept | SE | P | P |
| **Green bean intake** | 0.297 | 0.301 | 0.008 | 0.008 | 0.358 | 0.33 |
| **Dried fruit intake** | 0.229 | 0.268 | −0.007 | 0.014 | 0.629 | 0.299 |
| **Cereal intake** | 0.218 | 0.168 | −0.021 | 0.014 | 0.168 | 0.164 |
| **Pork intake** | 0.896 | 0.849 | 0.029 | 0.025 | 0.288 | 0.841 |
| **Whole egg intake** | 0.222 | 0.204 | −0.014 | 0.013 | 0.311 | 0.22 |

indicators of lung function and that an increased intake of calcium reduces the odds of COPD. In conclusion, dried fruit intake has a potential preventive effect on COPD, and the mechanism of action of dried fruit on COPD needs to be further explored.

Cereals are high in dietary fiber, with antioxidant and anti-inflammatory properties that protect human health. It is, therefore, often used as one of the primary sources of fiber. Studies indicate that consuming dietary fiber can elevate adiponectin serum levels (cytokines with anti-inflammatory properties) while reducing cytokines and C-reactive protein (IL-6, TNF-α) levels.[25] In addition, the dietary fiber in cereals produces short-chain fatty acids (SCFAs) through the action of intestinal microorganisms, which play an anti-inflammatory and immune-regulating role in the lungs via the body circulation, and short-chain fatty acids (SCFAs) increase the number and function of TH17 effector cells, T regulatory cells (T regulatory), and helper T cells (T helper) by inhibiting Histone deacetylase (HDAC), to reduce inflammation and immune responses in the lungs and helper T-cell (T helper) numbers and functions to reduce lung inflammation and immune responses.[26] In addition, butyrate (a type of short-chain fatty acid) reduces inflammatory responses by inhibiting the nuclear factor-κB (NF-κB) signaling pathway while stimulating neutrophils to produce anti-inflammatory cells (IL-10).[27] Based on cross-sectional and longitudinal studies, it is known that increased dietary fiber intake improves lung function, reducing the odds of developing COPD.[28,29] Consequently, dietary fiber intake helps prevent the deterioration of lung function and reduces airflow limitation, thereby contributing to the prevention and protection of COPD.[30]

It is now known that whole egg intake is associated with lower odds of developing COPD and that whole eggs are not only rich in protein but also consist of various types of protein and contain substances with anti-inflammatory and immune-protective effects, including lysozyme and various biologically active compounds.[31] Some COPD patients usually exhibit symptoms such as malnutrition, frailty, and sarcopenia. It has been found that increased resting energy loss (REE) in COPD patients compared with normal subjects is one of the reasons for these phenomena.[32] The occurrence of frailty and sarcopenia is associated with the poor prognosis of COPD patients.[33] In addition, COPD patients with malnutrition, frailty, and sarcopenia are more susceptible to oxidative stress, which causes a significant increase in the levels of inflammatory factors (eg, IL-6, TNF-α) in the body, leading to the development of COPD and the improvement of the nutritional status and the reduction of muscle loss through the intake of a high-protein diet to improve the immune protection function.[34] In animal studies, protein supplementation in mice increased glutathione in the heart, which reduces oxidative stress and inflammation in the body.[35] Meanwhile, whole eggs contain high protein levels with immunoprotective properties, including immunoglobulin Y (IgY), which has a similar function to IgG in the human body and can play a protective role in human health.[36] Studies have shown that IgY in whole eggs can reduce intestinal inflammation in mice and regulate the immune response. In addition, lysozyme found within whole eggs has been shown to protect against COPD disease by reducing the local expression of pro-inflammatory factors such as TNF-α, IL-6, IL-8, and IL-17, while increasing the expression of anti-inflammatory species such as IL-4 and TGF-β.[37]

Pork has the highest fat content compared to other meats (eg, beef and sheep) and is a significant source of saturated fatty acids. Studies have known that excessive intake of saturated fatty acids can trigger respiratory inflammation, leading to impaired lung function,[38] resulting in increased odds of developing COPD. Furthermore, pork is a type of red meat, and a prospective study in Sweden showed that high consumption of processed red meat was associated with an increased risk of COPD. A meta-analysis found that weekly consumption of processed red meat (>75–785.5 g/week)

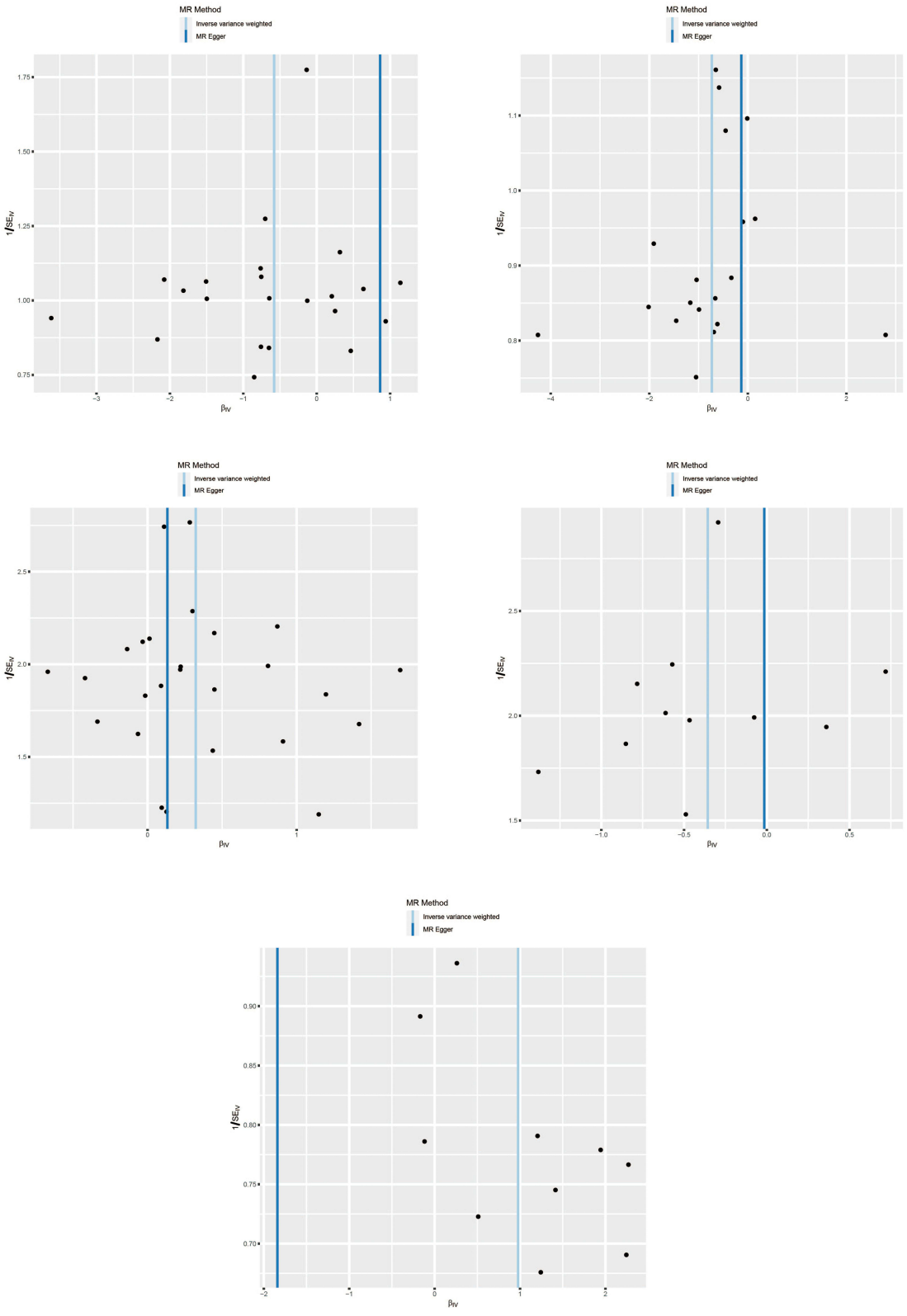


**Figure 4** Funnel plots for the causal association between dietary intake and COPD.

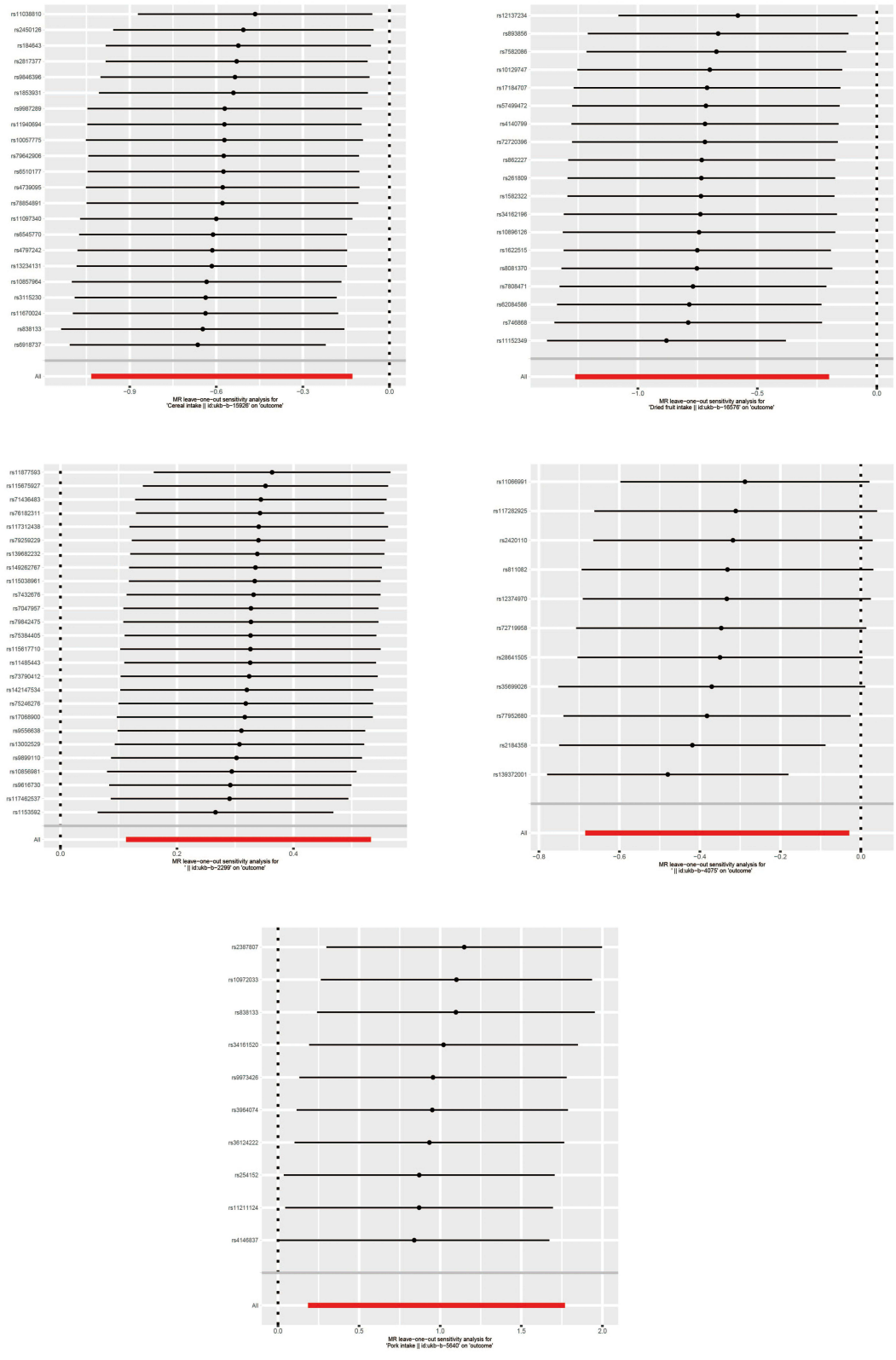


**Figure 5** Leave-one-out plots for the causal association between dietary intake and COPD.

increased the odds of COPD by 40%, and consumption of cured pork increased the risk of readmission in COPD patients.[39] Pork consumed in Europe and the United States is mainly processed and cured, which can contain nitrates, which act as pro-oxidants that can increase cellular oxidative stress and lead to organismal damage. Processed pork is now known to contain nitrite, which produces reactive nitrogen species (eg, peroxynitrite) that impair the antioxidant status of the lungs and promote inflammatory processes, leading to DNA damage, inhibition of mitochondrial respiration, and cellular dysfunction.[40] However, regarding the fact that green bean intake increases the odds of COPD, it has been found that green beans induce respiratory disorders and contribute to the development of the disease by stimulating the body's immune system to produce an inflammatory response.[41,42] Although there are no direct studies on the effect of green bean intake on the risk of COPD, the results of the above studies allow us to hypothesize that mung bean intake may trigger an immune-inflammatory response in the body, which can cause damage to the body and lead to the occurrence of COPD. However, the exact mechanism of occurrence needs to be further explored.

In this study, we employed MR analysis for the first time to investigate the causal link between diverse dietary intakes and COPD development. Stringent measures were taken to exclude COPD-associated SNPs from our analyses, minimizing potential confounding effects. Furthermore, our study boasted a sizable sample size for both exposures and outcomes, bolstering its reliability. However, we must recognize certain limitations. The genetic and dietary data used here were drawn exclusively from a European population, and the results may not be generalizable to other countries and populations. Necessitating exploration in different populations and countries in future research. Moreover, our study predominantly operates at a methodological level, emphasizing the need for extensive longitudinal cohort studies and long-term follow up controlled trials to comprehensively evaluate the potential of diet in disease prevention.

## Conclusion

This work describes the causal relationship between genetically predicted dietary intake and COPD. We found that increased intake of dried fruits, grains, and whole eggs decreased the odds of developing COPD, and increased intake of green beans and pork increased the odds of developing COPD. Therefore, we are contemplating the examination of whether supplementing scientific dietary intake choices, in addition to the existing management for COPD patients, could potentially reduce the odds of COPD progression.

## Data Sharing Statement

The study utilized publicly available datasets. These statistics can be accessed at IEU Open GWAS Project (https://gwas.mrcieu.ac.uk/) and FinnGen (https://www.finngen.fi/en).

## Ethical Approval

Participants in the FinnGen study gave informed consent for the biospecimen banking study, compliant with the Finnish Biospecimen Banking Act. The study protocol of FinnGen (No. HUS/990/2017) received approval from the Helsinki and Uusimaa Hospital District Coordinating Ethics Committee (HUS). The GWAS data on dietary exposure were obtained from the raw data aggregated by the IEU, originally sourced from the UK Biobank (UKBB). UK Biobank has approval from the North West Multi-centre Research Ethics Committee (MREC) as a Research Tissue Bank (RTB) approval. This approval means that researchers do not require separate ethical clearance and can operate under the RTB approval. The Institutional Review Board (IRB) of the First Hospital of Shanxi Medical University exempted this study from IRB review and participant informed consent requirements.

## Acknowledgment

We express our gratitude to the IEU Open GWAS Project for their invaluable efforts in collecting and archiving the GWAS summary statistics related to dietary intake. We also extend our appreciation to the FinnGen Consortium for generously providing us with the raw data about COPD.

## Funding

This work was financially supported by the Shanxi Provincial Nature Foundation of China (201901D111355) and NHC Key Laboratory of Pneumoconiosis in Shanxi (2020-PT320-005).

## Disclosure

The authors report no conflicts of interest in this work.

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