Research article

Association of dietary intake with pneumothorax: A Mendelian randomization study

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ABSTRACT

Background: An association between dietary habits and lung disease has been demonstrated in previous studies. Employing Mendelian randomization, we aimed to explore how different dietary intakes relate to pneumothorax, shedding light on the interplay among gut flora, the lung-gut axis, and pneumothorax.

Methods: Employing both two-sample and multi-sample Mendelian randomization (MR) analyses, we investigated 24 dietary intake variables to establish a strong association with pneumothorax. Causal inferences were drawn using the inverse variance weighted (IVW) method. To fortify our findings, we employed a diverse array of methodologies, including Weighted Median Estimator (WME), Weighted Mode, Simple Mode, Mendelian Randomization Pleiotropy Residual Sum and Outlier (MR-PRESSO), MR-Egger regression, and LASSO.

Results: Our analysis identified genetic variants reliably predicting dietary intakes, meeting stringent criteria ($p < 5 \times 10^{-8}$) and demonstrating independence ($r^2 < 0.001$). Causal-effect estimates derived from the IVW model unveiled a statistically significant association, indicating a causal correlation between pneumothorax and three dietary intakes. Specifically, heightened consumption of fresh fruit (OR = 0.196, 95%CI: 0.063–0.606, p = 0.004) and dried fruit (OR = 0.323, 95%CI: 0.114–0.911, p = 0.032) correlated with reduced pneumothorax risk, while increased processed meat intake (OR = 2.705, 95%CI: 1.026–7.128, p = 0.044) showed a positive correlation.

Conclusion: In summary, our MR analysis yields robust evidence supporting a causal correlation between dietary elements and pneumothorax. This study significantly advances our comprehension of pneumothorax risk factors, protective agents, and the intricate mechanisms of the lung-gut axis.

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1. Introduction

Pneumothorax, commonly known as a collapsed lung, occurs when air infiltrates the pleural cavity, disrupting the normal lung-chest wall interaction and hindering lung expansion [1]. Subtypes include familial spontaneous pneumothorax, tension pneumothorax, and menstrual pneumothorax, the latter posing a severe risk by compressing blood vessels due to heightened pleural pressure. It can develop as a complication of medical procedures such as lung biopsies or central venous catheterization, or interventions requiring access to the chest cavity. Spontaneous pneumothorax, devoid of trauma or iatrogenic causes, arises from abnormal air communication among alveolar spaces [2,3]. It represents a prevalent lower respiratory pleural disorder necessitating thoracic surgical intervention, with hospitalization rates increasing from 9.1 to 14.1 per 100,000 annually over the past five decades [4]. Recurrence rates are notably high, with one study indicating a 35 % recurrence rate among American males [5]. Additionally, COVID-19 viral pneumonia in non-ventilated patients can lead to spontaneous pneumothorax [6,7]. Mechanisms typically involve structural lung parenchymal changes, such as fibrotic and cystic alterations, resulting in alveolar ruptures [8,9]. Significant risk factors include elevated body mass index (BMI), smoking, subpulmonary abnormalities, emphysema-like changes, inflammation, matrix metalloproteinases (MMPs), and familial causes [10,11]. Needle aspiration (NA) and intercostal chest drain (ICD) insertion with

Table 1
Detailed information on 24 dietary habits.

Dietary habits	GWAS ID	Sample size	Types of diet	ACE touchscreen question
Cereal intake	ukb-b-15926	4,41,640	Cereal	"How many bowls of cereal do you eat a WEEK?"
Bread intake	ukb-b-11348	4,52,236	Bread	"How many slices of bread do you eat each WEEK?" (For other types of bread: one bread roll = 2 slices; - one pitta bread = 2 slices)
Fresh fruit intake	ukb-b-3881	4,46,462	Fruit and vegetables	"About how many pieces of FRESH fruit would you eat per DAY? (Count one apple, one banana, 10 grapes etc as one piece; put '0' if you do not eat any)"
Dried fruit intake	ukb-b-16576	4,21,764	Fruit and vegetables	"About how many pieces of DRIED fruit would you eat per DAY? (Count one prune, one dried apricot, 10 raisins as one piece; put '0' if you do not eat any)"
Salad/raw vegetable intake	ukb-b-1996	4,35,435	Fruit and vegetables	"On average how many heaped tablespoons of SALAD or RAW vegetables would you eat per DAY? (Include lettuce, tomato in sandwiches; put '0' if you do not eat any)"
Cooked vegetable intake	ukb-b-8089	4,48,651	Fruit and vegetables	"On average how many heaped tablespoons of COOKED vegetables would you eat per DAY? (Do not include potatoes; put '0' if you do not eat any)"
Beef intake	ukb-b-2862	4,61,053	Meat and fish	"How often do you eat beef? (Do not count processed meats)"
lamb/mutton intake	ukb-b-14179	4,60,006	Meat and fish	"How often do you eat lamb/mutton? (Do not count processed meats)"
pork intake	ukb-b-5640	4,60,162	Meat and fish	"How often do you eat pork? (Do not count processed meats such as bacon or ham)"
Poultry intake	ukb-b-8006	4,61,900	Meat and fish	"How often do you eat chicken, turkey or other poultry? (Do not count processed meats)"
Processed meat intake	ukb-b-6324	4,61,981	Meat and fish	"How often do you eat processed meats (such as bacon, ham, sausages, meat pies, kebabs, burgers, chicken nuggets)?"
Oily fish intake	ukb-b-2209	4,60,443	Meat and fish	"How often do you eat oily fish? (e.g. sardines, salmon, mackerel, herring)"
Non-oily fish intake	ukb-b-17627	4,60,880	Meat and fish	"How often do you eat other types of fish? (e.g. cod, tinned tuna, haddock)"
Cheese intake	ukb-b-1489	4,51,486	Diary products	"How often do you eat cheese? (Include cheese in pizzas, quiches, cheese sauce etc)"
Coffee intake	ukb-b-5237	4,28,860	Drinks	"How many cups of coffee do you drink each DAY? (Include decaffeinated coffee)"
Tea intake	ukb-b-6066	4,47,485	Drinks	"How many cups of tea do you drink each DAY? (Include black and green tea)"
Water intake	ukb-b-14898	4,27,588	Drinks	"How many glasses of water do you drink each DAY? "
Hot drink temperature	ukb-b-14203	4,57,873	Drinks	"How do you like your hot drinks? (Such as coffee or tea)"
Alcohol usually taken with meals	ukb-b-16878	2,35,645	Drinks	"When you drink alcohol is it usually with meals?"
Average weekly red wine intake	ukb-b-5239	3,27,026	Drinks	"In an average WEEK, how many glasses of RED wine would you drink? (There are six glasses in an average bottle)"
Average weekly spirits intake	ukb-b-1707	3,26,565	Drinks	"In an average WEEK, how many measures of spirits or liqueurs would you drink? (there are 25 standard measures in a normal sized bottle; spirits include drinks such as whisky, gin, rum, vodka, brandy)"
Average weekly beer plus cider intake	ukb-b-5174	3,27,634	Drinks	"In an average WEEK, how many pints of beer or cider would you drink? (Include bitter, lager, stout, ale, Guinness)"
Average weekly champagne plus white wine intake	ukb-b-5716	3,26,801	Drinks	"In an average WEEK, how many glasses of WHITE wine or champagne would you drink? (There are six glasses in an average bottle)"
Salt added to food	ukb-b-8121	4,62,630	Salt	"Do you add salt to your food? (Do not include salt used in cooking)"

underwater seal connection are presently the primary therapeutic interventions for spontaneous pneumothorax. However, given its recurrent and potentially fatal nature, early preventive measures and identification of modifiable risk factors are crucial to reducing pneumothorax incidence.

In recent years, there has been a notable increase in interest concerning the influence of dietary habits on physical well-being, propelled by a burgeoning body of evidence linking diverse dietary elements to health outcomes [12,13]. Notably, an expanding corpus of research has begun to unveil connections between diet and pulmonary disorders [14–20]. Epidemiologic studies have underscored the positive correlation between the consumption of antioxidant-rich foods—such as vitamin C, vitamin E, beta-carotene, and flavonoids—and lung health [21]. Conversely, the ingestion of processed meats and akin products has been implicated in compromised pulmonary function and related ailments [22]. However, a significant caveat of these investigations is their vulnerability to confounding variables that may confound lifestyle influences, thereby casting doubt on their findings. Moreover, scant attention has been paid to investigating the impact of dietary patterns on pneumothorax.

Conventional observational studies are prone to biases stemming from myriad confounding variables, including factors like BMI and smoking, which could potentially influence pneumothorax outcomes. Therefore, we chose Mendelian randomization (MR) as a methodological recourse to explore the causal correlation between specific dietary profiles and pneumothorax incidence. MR, as a research method that simulates the causal inference of randomized controlled trials (RCTs) by using genetic variance as an instrumental variable (IV), thus mitigating a key limitation of RCTs—unmeasured confounding factors [23,24]. Pursuant to this objective, we have undertaken both two-sample MR and multi-sample MR analyses to explore 24 dietary parameters and delineate robust associations with pneumothorax. These findings aspire to yield enriched insights conducive to clinical decision-making on preventive interventions [25,26].

2. Materials and methods

2.1. Data source

Data pooled from the UK Biobanking Study on Dietary Intake Habits, facilitated by the IEU Open GWAS program, were obtained, comprising approximately 500,000 participants from Scotland, Wales, and England, aged 40–69 years between 2006 and 2010 [27]. Participants offered comprehensive data on biomedical samples, anthropometric measurements, lifestyle, and consent for health monitoring. Utilizing a touchscreen questionnaire, the study assessed the frequency of consumption of various food items and beverages over the preceding year. For instance, participants were asked about their daily intake of fresh fruits. Detailed information on 24 dietary habits is presented in Table 1. Pneumothorax data for European populations, encompassing 479,902 individuals (3798 cases of European descent and 476,104 European ancestry controls [28], were sourced from Sakaue et al. Both datasets stem from the Integrative Epidemiology Unit (IEU) study of European populations and are accessible for download via the IEU Open GWAS program (https://gwas.mrcieu.ac.uk/datasets/). Given their availability in public databases, no additional ethical approval is required, facilitating unrestricted access for researchers.

2.2. Selection of instrumental variables

In this study, MR served as the analytical framework for assessing the causal influence of dietary intake habits on pneumothorax
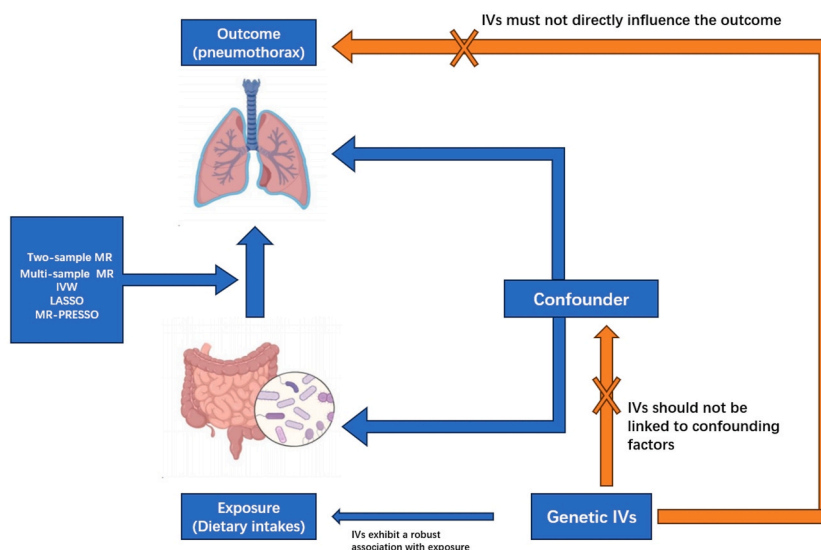

Fig. 1. Directed acyclic graph of Mendelian randomization (MR) framework showing hypothesis of dietary intake and pneumothorax.

(Fig. 1). To establish genetic variation as a robust IV, MR established three key assumptions crucial for valid IVs.

(1) IVs must demonstrate robust associations with each dietary intake habit.
(2) IVs should exhibit no correlation with confounding factors.
(3) IVs ought not to have a direct connection with the outcome, exerting an influence on dietary intake patterns solely through pneumothorax.

To bolster the solidity of the study's conclusions, stringent criteria were employed for selecting single nucleotide polymorphisms (SNPs) as IVs. A significance threshold of $p < 5 \times 10^{-8}$ was imposed to filter the IVs, followed by consolidation to identify pertinent genetic variants meeting the criteria of independence ($r^2 < 0.001$, within 10,000 kb) [29]. Assessment of the genetic instrument's strength entailed computation of the F-statistic and R^2, both calculated for each SNP individually and for the amalgamated SNPs. To rectify bias in effect estimation, SNPs with F-values below 10 were excluded, indicative of limited explanatory capacity concerning exposure [26,30].

The R^2 and F statistics were calculated using the following equation (31):

$$R^2 = 2 \times (1 - \mathrm{EAF}) \times \mathrm{EAF} \times \beta^2$$

$$F = \left(\frac{R^2}{1 - R^2} \right) \left(\frac{N - k - 1}{k} \right)$$

Excluded from the analysis were SNPs that conflicted with resultant SNPs to ensure alignment of effector alleles, while those exhibiting palindromic traits and intermediate allele frequencies were omitted.

2.3. MR analysis

In the univariate MR analysis, the inverse variance weighting (IVW) method was predominantly employed to examine the relationship between various dietary intake habits and pneumothorax. Auxiliary analyses utilized Simple Mode methods, Weighted Mode, Weighted Median Estimator (WME), and MR-Egger regression [32]. The IVW method is the most robust analytical technique in MR studies, maximizing statistical power. It estimates the pooled causal effect by aggregating Wald ratios from each SNP [33,34]. MR-Egger regression is utilized to evaluate pleiotropy, delivering a reliable causal effect estimate even with a varying proportion of invalid IVs. MR-Egger intercept tests further determine the average horizontal pleiotropic effect; a significant intercept term (P < 0.05) signifies the presence of overall directional pleiotropy [30]. Heterogeneity is examined through Cochran's Q-tests for IVW and Rücker's Q-tests for MR-Egger, with P-values less than 0.05 indicating substantial heterogeneity. WME combines multiple SNPs to yield a consistent causal estimate. A potential causal relationship between outcome and exposure was considered plausible if the IVW results yielded statistical significance and the estimates from the four MR analyses aligned directionally. Two-sample MR involves selecting two sets of samples, namely SNP-exposure variables and SNP-outcome variables. This approach may introduce heterogeneity due to fixed SNP loci and potential variations in populations and sequencing methods. To ascertain the reliability and robustness of results, sensitivity analysis was performed using Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) and leave-one-out analysis. Subsequently, credible evidence of causality was screened for, facilitating further multivariate MR analysis. The IVW method was primarily utilized for multivariate MR analysis, followed by LASSO for selection of feature SNPs and enhancement of stability. To ensure the stability of results, the MR-PRESSO test was employed to detect outliers and directional heterogeneity [35]. In this exploratory study, the FDR method was employed to adjust for multiple comparisons in multivariate MR [31]. Causality is deemed credible if the FDR result is below 0.05. Statistical analyses were executed using R 4.3.2, leveraging software packages "MRPRESSO," "MVMR," "TwoSampleMR," and "MendelianRandomization."

3. Results

In our univariate MR analysis, we explored the relationship between 24 dietary habits and pneumothorax incidence (Table 2). Our results unveiled three dietary factors significantly linked to pneumothorax. Specifically, increased consumption of dried fruit (OR = 0.323, 95 % CI: 0.114–0.911, p = 0.032) and fresh fruit (OR = 0.196, 95 % CI: 0.063–0.606, p = 0.004) correlated with reduced pneumothorax risk, while elevated intake of processed meat (OR = 2.705, 95 % CI: 1.026–7.128, p = 0.044) was positively associated with pneumothorax incidence. The strength of these causal associations was assessed using the appropriate methods [36], as depicted in Fig. 2.

Sensitivity analyses were performed on these variables. Although variability was noted in dried fruit intake, attributed to differences in analytical platforms, experimental procedures, or study cohorts, the MR Egger intercept test did not yield statistically significant results for any variable, suggesting the absence of horizontal pleiotropy among SNPs. Similarly, the MR-PRESSO method performed did not yield meaningful results in the presence of horizontal pleiotropy (Table 3). Rücker's Q-tests and Cochran's Q-tests, examining IVW and MR-Egger regression for fresh fruit and processed meat intake, indicated no significant SNP heterogeneity. Hence, the presence of such variability does not affect our findings' interpretation. Additionally, leave-one-out analysis, as illustrated in Fig. 3, underscored the robustness of causality scores for positive associations. Subsequent multivariate analyses focused on the three identified variables [37]. Initially, the LASSO technique for selection of feature SNPs. Subsequent multivariate MR analysis identified

Table 2
MR results of 24 dietary associations with pneumothorax.

Dietary habits	Method	N snps	OR	95%CI	Pval	Q_pval	Intercept	Intercept Pval
Cereal intake	MR Egger	38	3.318439	0.067–162.982	0.5498	0.1680812	−0.02359787	0.4080259
	Weighted median	38	0.760091	0.232-2.481	0.6495			
	Inverse variance weighted	38	0.655933	0.275-1.560	0.3404	0.1747284		
	Simple mode	38	1.319727	0.115-15.021	0.8243			
	weighted mode	38	1.023764	0.119-8.759	0.9830			
Bread intake	MR Egger	30	3.303585	0.048–224.105	0.5830	0.2165002	−0.01537347	0.6170826
	Weighted median	30	1.262495	0.361-4.416	0.7152			
	Inverse variance weighted	30	1.142800	0.459-2.841	0.7738	0.2450099		
	Simple mode	30	1.059053	0.081-13.739	0.9653			
	weighted mode	30	1.541732	0.150-15.795	0.7180			
Fresh fruit intake	MR Egger	53	0.061557	0.001–3.634	0.1862	0.05828288	0.01097197	0.5644321
	Weighted median	53	0.144430	0.030-0.675	0.0139			
	Inverse variance weighted	53	0.196197	0.063-0.606	0.0046	0.06532985		
	Simple mode	53	0.058150	0.003-1.122	0.0652			
	weighted mode	53	0.115368	0.010-1.219	0.0784			
Dried fruit intake	MR Egger	41	0.542629	0.004–68.626	0.8057	0.01537207	−0.006434315	0.8307278
	Weighted median	41	0.349486	0.100-1.212	0.0976			
	Inverse variance weighted	41	0.322999	0.114-0.911	0.0327	0.01964159		
	Inverse variance weighted (multiplicative random effects)	41	0.322999	0.114-0.911	0.0327			
	Simple mode	41	0.450032	0.035-5.643	0.5395			
	weighted mode	41	0.408405	0.034-4.860	0.4826			
Salad/raw vegetable intake	MR Egger	19	0.213616	8.270E-05-553.221	0.7051	0.4968794	0.001089926	0.9798256
	Weighted median	19	0.142352	1.396E-02-1.451	0.0998			
	Inverse variance weighted	19	0.236245	4.665E-02-1.196	0.0812	0.5658059		
	Simple mode	19	0.087867	1.427E-03-5.409	0.2624			
	weighted mode	19	0.062638	8.033E-04-4.883	0.2285			
Cooked vegetable intake	MR Egger	17	1.430659	0.001–1.668E+11	0.2671	0.8405	−0.1112119	0.2115002
	Weighted median	17	4.436074	0.060-3.253E+00	0.4239			
	Inverse variance weighted	17	2.947513	0.066-1.305E+00	0.1077	0.7864433		
	Simple mode	17	9.344050	0.025-3.433E+01	0.9710			
	weighted mode	17	9.010872	0.032-2.489E+01	0.9517			
Beef intake	MR Egger	14	19.590830	0.003–103102.416	0.5091	0.6733878	−0.02320667	0.671382
	Weighted median	14	1.589887	0.182-13.859	0.6747			
	Inverse variance weighted	14	3.024139	0.622-14.687	0.1699	0.7316746		
	Simple mode	14	1.544460	0.037–63.204	0.8220			
	weighted mode	14	1.131977	0.041-31.540	0.9428			
lamb/mutton intake	MR Egger	31	0.073753	0.001–9.489	0.3014	0.7755091	0.03739211	0.1730295
	Weighted median	31	0.737463	0.145-3.738	0.7130			
	Inverse variance weighted	31	2.126429	0.665-6.791	0.2028	0.7262933		
	Simple mode	31	0.618205	0.027-14.083	0.7650			
	weighted mode	31	0.732484	0.043-12.338	0.8304			
Pork intake	MR Egger	14	0.002551	5.312E-08-122.461	0.2989	0.5537563	0.06151909	0.2969053
	Weighted median	14	0.584271	6.223E-02-5.485	0.6381			
	Inverse variance weighted	14	0.952293	1.744E-01-5.197	0.9549	0.5357698		
	Simple mode	14	0.796149	1.268E-02-49.979	0.9156			
	weighted mode	14	0.903101	1.754E-02-46.497	0.9303			
Poultry intake	MR Egger	7	4.933494	3.486E-50-6.974E+82	0.6418	1.48E-05	−0.4383348	0.6247583
	Weighted median	7	7.234293	3.291E-03-1.590E+00	0.0957			
	Inverse variance weighted	7	1.341793	9.359E-04-1.923E+01	0.4278	1.93E-05		
	Inverse variance weighted	7	1.341793	9.359E-04-1.923E+01	0.4278			

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Table 2 (*continued*)

Dietary habits	Method	N snps	OR	95%CI	Pval	Q_pval	Intercept	Intercept Pval
	(multiplicative random effects)							
	Simple mode	7	4.932710	5.956E-04-4.085E+00	0.2301			
	weighted mode	7	4.932710	5.431E-04-4.471E+00	0.2387			
Processed meat intake	MR Egger	23	160.920048	1.127–22959.130	0.0577	0.8154153	−0.06174656	0.1146345
	Weighted median	23	1.531984	0.404-5.804	0.5302			
	Inverse variance weighted	23	2.705026	1.026-7.128	0.0441	0.7143567		
	Simple mode	23	1.143096	0.090-14.395	0.9185			
	weighted mode	23	1.245787	0.114-13.606	0.8586			
Oily fish intake	MR Egger	61	0.354627	0.024-5.208	0.4525	0.1912685	0.01125271	0.5715222
	Weighted median	61	0.982918	0.402-2.402	0.9698			
	Inverse variance weighted	61	0.756138	0.397-1.437	0.3937	0.2076652		
	Simple mode	61	2.775895	0.330-23.338	0.4861			
	weighted mode	61	1.857738	0.328-10.504	0.3863			
Non-oily fish intake	MR Egger	11	0.313817	8.269802E-5-1190.856	0.7890	0.4925091	0.0009376595	0.9856112
	Weighted median	11	0.369641	3.378E-02-4.044	0.4148			
	Inverse variance weighted	11	0.338706	6.298E-02-1.821	0.2071	0.5879227		
	Simple mode	11	0.044581	6.660E-04-2.983	0.1776			
	weighted mode	11	0.044581	5.551E-04-3.580	0.1946			
Cheese intake	MR Egger	61	0.483384	0.049-4.676	0.5325	0.4209281	0.01054313	0.5922317
	Weighted median	61	1.225969	0.531-2.826	0.6326			
	Inverse variance weighted	61	0.884573	0.506-1.543	0.6654	0.4464595		
	Simple mode	61	2.030689	0.278-14.807	0.4873			
	weighted mode	61	2.224651	0.355-13.917	0.3960			
Coffee intake	MR Egger	38	0.286161	0.058-1.389	0.1294	0.18173	0.02217637	0.09604401
	Weighted median	38	0.666855	0.207-2.144	0.4965			
	Inverse variance weighted	38	0.953462	0.433-2.098	0.9057	0.1244467		
	Simple mode	38	0.683869	0.088-5.282	0.7177			
	weighted mode	38	0.505676	0.177-1.441	0.2101			
Tea intake	MR Egger	39	0.230954	0.062-0.861	0.0355	0.4683488	0.02509753	0.05444888
	Weighted median	39	0.697938	0.279-1.745	0.4418			
	Inverse variance weighted	39	0.769006	0.425-1.389	0.3842	0.3418303		
	Simple mode	39	0.672554	0.126-3.569	0.6440			
	weighted mode	39	0.541751	0.187-1.566	0.2649			
Water intake	MR Egger	41	8.889239	0.921-85.757	0.0663	0.2842419	−0.03330434	0.05779815
	Weighted median	41	1.575521	0.472-5.253	0.4594			
	Inverse variance weighted	41	1.065311	0.473-2.394	0.8783	0.1853339		
	Simple mode	41	1.028732	0.109-9.648	0.9803			
	weighted mode	41	1.533885	0.307-7.640	0.6439			
Hot drink temperature	MR Egger	68	149.315080	3.037–7340.246	0.0141	0.4645974	−0.04096733	0.02488135
	Weighted median	68	2.358736	0.617-9.010	0.2095			
	Inverse variance weighted	68	1.768731	0.691-4.521	0.2337	0.3262407		
	Simple mode	68	5.726797	0.168–194.161	0.3351			
	weighted mode	68	7.986310	0.285-223.777	0.2260			
Alcohol usually taken with meals	MR Egger	33	39.740487	0.003–5.870E+05	0.4578	0.2418611	−0.03183831	0.4618374
	Weighted median	33	3.030310	0.496-1.849E+01	0.2296			
	Inverse variance weighted	33	1.072827	0.274-4.191E+00	0.9194	0.2577954		
	Simple mode	33	7.195133	0.278-1.860E+02	0.2431			
	weighted mode	33	5.679848	0.263-1.225E+02	0.2759			
Average weekly red wine intake	MR Egger	17	0.537352	0.053-5.439	0.6066	0.5609996	0.002384765	0.9032739
	Weighted median	17	0.567929	0.131-2.448	0.4479			
	Inverse variance weighted	17	0.612880	0.224-1.673	0.3394	0.6321321		
	Simple mode	17	0.628101	0.064-6.073	0.6932			
	weighted mode	17	0.565377	0.105-3.043	0.5161			

Table 2 (*continued*)

Dietary habits	Method	N snps	OR	95%CI	Pval	Q_pval	Intercept	Intercept Pval
Average weekly spirits intake	MR Egger	4	0.956166	7.779E-06–117513.989	0.9946	0.489468	0.03321562	0.743908
	Weighted median	4	4.852219	3.118E-01-75.505	0.2593			
	Inverse variance weighted	4	8.590833	8.374E-01-88.122	0.0701	0.6663833		
	Simple mode	4	3.585117	7.857E-02-163.574	0.5591			
	weighted mode	4	3.959830	1.264E-01-124.044	0.4906			
Average weekly beer plus cider intake	MR Egger	20	0.810267	0.031-20.667	0.9001	0.2018315	0.008397716	0.7095237
	Weighted median	20	0.745535	0.158-3.502	0.7098			
	Inverse variance weighted	20	1.444486	0.432-4.828	0.5503	0.2420222		
	Simple mode	20	3.437062	0.283-41.670	0.3443			
	weighted mode	20	0.755138	0.110-5.173	0.7779			
Average weekly champagne plus white wine intake	MR Egger	4	2.450715	6.197E-09-9.691E+48	0.2971	0.4971635	−0.5864053	0.2992282
	Weighted median	4	8.805628	4.270E-02-1.815E+01	0.9343			
	Inverse variance weighted	4	1.363901	9.867E-02-1.885E+01	0.8168	0.3438235		
	Simple mode	4	6.833596	7.603E-03-6.141E+01	0.8787			
	weighted mode	4	5.651165	5.533E-03-5.771E+01	0.8245			
Salt added to food	MR Egger	102	2.546277	0.521-12.443	0.2509	0.545022	−0.0152791	0.188638
	Weighted median	102	0.826023	0.411-1.657	0.5906			
	Inverse variance weighted	102	0.916093	0.569-1.473	0.7176	0.5235127		
	Simple mode	102	1.032913	0.233-4.577	0.9661			
	weighted mode	102	0.989588	0.281-3.478	0.9870			

one statistically significant causal link: processed meat intake's effect on pneumothorax (p = 0.016, FDR = 0.047) (Table 4). These results align with our univariate MR analysis, suggesting that processed meat consumption heightens pneumothorax risk, with no evidence of pleiotropy in the MR Egger intercept analysis (p = 0.056) (Fig. 4).

4. Discussion

4.1. Potential mechanisms

Our study delved into an extensive analysis of the latest genome-wide association study (GWAS) data, unveiling significant connections between pneumothorax and dietary habits regarding fresh fruit, dried fruit, and processed meat intake. Specifically, we unearthed an inverse relationship between fresh fruit and dried fruit consumption and the likelihood of pneumothorax, contrasting with a positive association found between processed meat consumption and pneumothorax risk. Studies suggest that the onset of pneumothorax is rooted in minute inflammatory irregularities and disruptions in the integrity of elastic tissues, notably mediated by matrix metalloproteinase [10]. Lungs, inhabiting a hyperoxic environment, become particularly susceptible to oxidative harm, as evidenced by experimental data indicating the potential of oxidants to incite lung ailments by catalyzing the release of pro-inflammatory agents like cytokines and chemokines [38]. The presence of antioxidants in fruits, including vitamin E, vitamin C, and an array of carotenoids (e.g., lutein, lycopene, β-carotene, and α-carotene), confers robust protection against oxidative stress [39]. The role of vitamins and their derivatives in maintaining pleural health is well-established [35–41]. In cases of pneumothorax, characterized by oxidative stress, vitamins are essential for neutralizing free radicals. They counteract the effects of inflammatory mediators, such as vascular endothelial growth factor (VEGF), which increase pleural permeability and impair the mesothelial barrier. For instance, vitamin C and its derivatives shield mesothelial cells from oxidative damage during inflammation and help sustain the mesothelial barrier [42]. The nuclear transcription factor NF-κB connects oxidative stress with the expression of genes related to systemic inflammation, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-8 (IL-8), and intercellular adhesion molecule-1 (ICAM-1 or CD54) [40–42]. TNF-α and interleukin-1 beta (IL-1β) have been found to reduce ascorbic acid uptake in human endothelial cells via the sodium-dependent vitamin C transporter (SVCT2) [43,44]. An animal study showed that retinoic acid, compared to simvastatin, significantly reduced inflammatory damage and promoted repair of lung tissue, indicating a vitamin A-dependent mechanism for mitigating oxidative damage and aiding lung regeneration [48]. Furthermore, vitamin B has been shown to suppress T lymphocyte function and proliferation, as well as inhibit the release of cytokines and chemokines [36]. Moreover, fruits stand as rich sources of soluble fiber, subject to partial fermentation by commensal gut bacteria, yielding short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate. These SCFAs exhibit anti-inflammatory properties through the activation of free fatty acid receptors (G protein-coupling receptors (GPRs) 41 and 43) and the inhibition of histone deacetylases (HDACs). Similarly, dried fruits, having undergone dehydration to preserve nutrient content, serve as valuable reservoirs of fiber and vitamins [45,46].
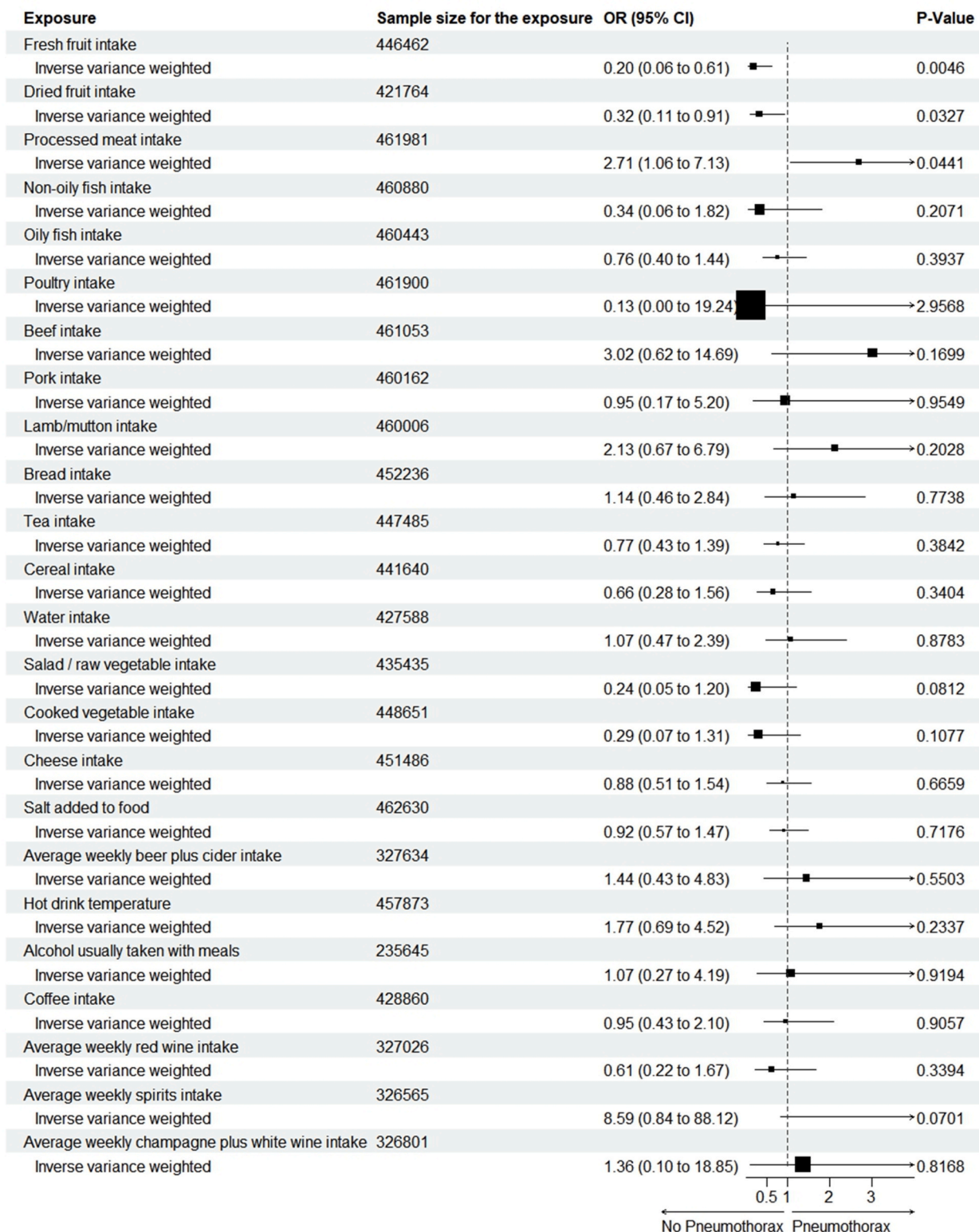
Exposure	Sample size for the exposure	OR (95% CI)	P-Value
Fresh fruit intake	446462		
Inverse variance weighted		0.20 (0.06 to 0.61)	0.0046
Dried fruit intake	421764		
Inverse variance weighted		0.32 (0.11 to 0.91)	0.0327
Processed meat intake	461981		
Inverse variance weighted		2.71 (1.06 to 7.13)	0.0441
Non-oily fish intake	460880		
Inverse variance weighted		0.34 (0.06 to 1.82)	0.2071
Oily fish intake	460443		
Inverse variance weighted		0.76 (0.40 to 1.44)	0.3937
Poultry intake	461900		
Inverse variance weighted		0.13 (0.00 to 19.24)	2.9568
Beef intake	461053		
Inverse variance weighted		3.02 (0.62 to 14.69)	0.1699
Pork intake	460162		
Inverse variance weighted		0.95 (0.17 to 5.20)	0.9549
Lamb/mutton intake	460006		
Inverse variance weighted		2.13 (0.67 to 6.79)	0.2028
Bread intake	452236		
Inverse variance weighted		1.14 (0.46 to 2.84)	0.7738
Tea intake	447485		
Inverse variance weighted		0.77 (0.43 to 1.39)	0.3842
Cereal intake	441640		
Inverse variance weighted		0.66 (0.28 to 1.56)	0.3404
Water intake	427588		
Inverse variance weighted		1.07 (0.47 to 2.39)	0.8783
Salad / raw vegetable intake	435435		
Inverse variance weighted		0.24 (0.05 to 1.20)	0.0812
Cooked vegetable intake	448651		
Inverse variance weighted		0.29 (0.07 to 1.31)	0.1077
Cheese intake	451486		
Inverse variance weighted		0.88 (0.51 to 1.54)	0.6659
Salt added to food	462630		
Inverse variance weighted		0.92 (0.57 to 1.47)	0.7176
Average weekly beer plus cider intake	327634		
Inverse variance weighted		1.44 (0.43 to 4.83)	0.5503
Hot drink temperature	457873		
Inverse variance weighted		1.77 (0.69 to 4.52)	0.2337
Alcohol usually taken with meals	235645		
Inverse variance weighted		1.07 (0.27 to 4.19)	0.9194
Coffee intake	428860		
Inverse variance weighted		0.95 (0.43 to 2.10)	0.9057
Average weekly red wine intake	327026		
Inverse variance weighted		0.61 (0.22 to 1.67)	0.3394
Average weekly spirits intake	326565		
Inverse variance weighted		8.59 (0.84 to 88.12)	0.0701
Average weekly champagne plus white wine intake	326801		
Inverse variance weighted		1.36 (0.10 to 18.85)	0.8168

0.5 1 2 3
No Pneumothorax   Pneumothorax

Fig. 2. Forest plot of two-sample Mendelian randomization (MR) estimates of the association between dietary intake and pneumothorax risk.

Table 3
MR-PRESSO results of 24 dietary associations with pneumothorax.

Dietary habits	Method	N snps	p	Global p
Fresh fruit intake	MR-PRESSO	53	0.009	0.078
Dried fruit intake	MR-PRESSO	41	0.113	0.061
Processed meat intake	MR-PRESSO	23	0.036	0.715
Non-oily fish intake	MR-PRESSO	11	0.199	0.599
Poultry intake	MR-PRESSO	7	0.432	<0.001
Beef intake	MR-PRESSO	14	0.232	0.855
Pork intake	MR-PRESSO	14	0.954	0.548
Bread intake	MR-PRESSO	30	0.656	0.107
Lamb/mutton intake	MR-PRESSO	31	0.199	0.757
Tea intake	MR-PRESSO	39	0.371	0.379
Cereal intake	MR-PRESSO	38	0.406	0.204
Water intake	MR-PRESSO	41	0.875	0.145
Salad/raw vegetable intake	MR-PRESSO	19	0.102	0.695
Cooked vegetable intake	MR-PRESSO	17	0.074	0.802
Coffee intake	MR-PRESSO	38	0.916	0.078
Oily fish intake	MR-PRESSO	61	0.363	0.293
Cheese intake	MR-PRESSO	61	0.979	0.430
Salt added to food	MR-PRESSO	102	0.682	0.551
Average weekly beer plus cider intake	MR-PRESSO	20	0.754	0.291
Hot drink temperature	MR-PRESSO	68	0.183	0.436
Alcohol usually taken with meals	MR-PRESSO	33	0.970	0.335
Average weekly red wine intake	MR-PRESSO	17	0.203	0.794
Average weekly spirits intake	MR-PRESSO	4	0.087	0.728
Average weekly champagne plus white wine intake	MR-PRESSO	4	0.832	0.385
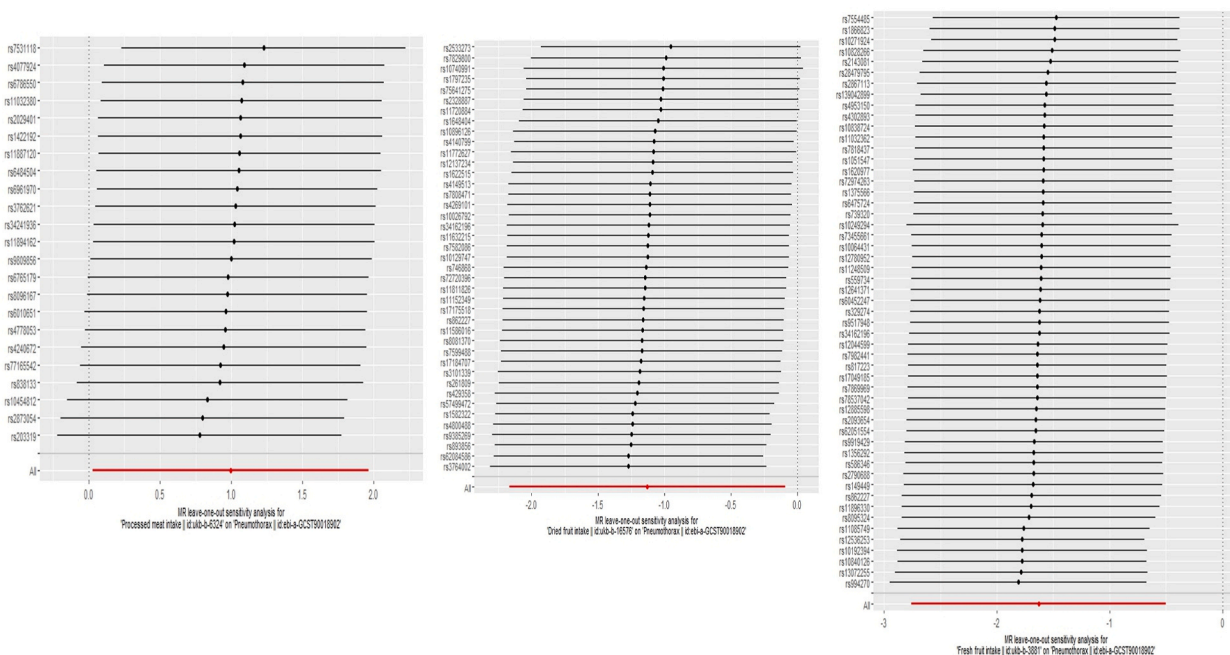
Fig. 3. Leave-one-out analysis of dietary intake and risk of pneumothorax.

Table 4
MVMR results of 3 dietary associations with pneumothorax.

Exposure	Sample size for the exposure	N-SNP	OR	95%Cl	P-Value	FDR
Fresh fruit intake	4,46,462	43	0.7021	0.2074-2.3764	0.5697	0.5697
Dried fruit intake	4,21,764	35	0.3846	0.0845-1.7506	0.2165	0.3248
Processed meat intake	4,61,981	19	4.3100	1.3156-14.1263	0.0158	0.0475

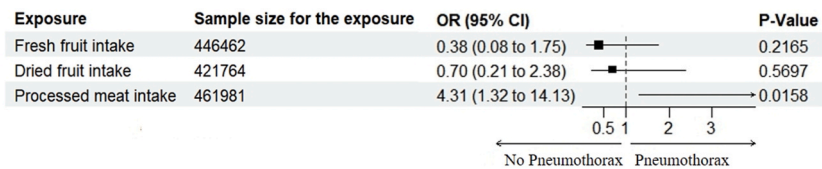| Exposure	Sample size for the exposure	OR (95% CI)	P-Value
Fresh fruit intake	446462	0.38 (0.08 to 1.75)	0.2165
Dried fruit intake	421764	0.70 (0.21 to 2.38)	0.5697
Processed meat intake	461981	4.31 (1.32 to 14.13)	0.0158

Fig. 4. Forest plots of multivariable Mendelian randomization (MR) in specific dietary intakes.

Dietary variations influence gut microbiota composition, thereby impacting nutrient metabolism [47,48]. Notably, murine models have revealed a correlation between alterations in gut microbiota and enhanced airway responsiveness [49]. Furthermore, our findings resonate with the idea that processed meat consumption contradicts the antioxidant and anti-inflammatory properties linked with fresh and dried fruit intake [50]. Processed meat products often contain trace amounts of nitrites (in dry salt or brine solutions), generating reactive nitrogen species that exacerbate inflammatory processes in airways and lung tissues [51]. Animal studies, including long-term exposure of rats to nitrite-rich water, have reported the development of emphysema [52]. Nitric oxide, primarily produced by inducible nitric oxide synthase (iNOS/NOS2), is the main source of reactive nitrogen involved in inflammation, leading to oxidative and nitrative lung damage [57]. Meat contains high levels of advanced glycation end products (AGEs), which increase further during cooking. Dietary AGEs (dAGEs) contribute to elevated oxidative stress and inflammation, activating nuclear factor (NF)-κB [53–55]. Diets high in processed meats are linked to increased biomarkers of chronic low-grade inflammation (61). Specifically, high meat intake correlates with higher serum levels of C-reactive protein, vascular endothelial growth factor, interleukin-6 (IL-6), and anti-alpha-1-antitrypsin (AAT) [56].

4.2. Strength and limitations

This study marks a pioneering application of MR analysis to investigate the causal relationship between dietary intake and pneumothorax. By strictly adhering to instrumental variable conditions in MR studies and making necessary model assumptions, we discerned no significant evidence of heterogeneity. Notably, this study offers several advantages over traditional observational research, chiefly due to its superior data sources and study design. First, MR analysis allows for the assessment of causal relationships with minimal confounder interference and reverse causation bias, thus circumventing inherent limitations of conventional observational methods. Second, our utilization of GWAS data from the most extensive and current studies bolsters the statistical robustness of causal inference. Finally, employing a stringent protocol for SNP screening and employing multiple complementary MR analysis techniques yielded highly meaningful results, thereby mitigating false positives and ensuring result accuracy.

However, our MR analysis faces limitations. First, the GWAS data, drawn from individuals of European descent, lack age and sex information, limiting generalizability and warranting broader population-based GWAS studies. Second, our study falls short of fully elucidating the mechanism underpinning the relationship between gastroesophageal reflux disease (GERD) and pneumothorax, necessitating further laboratory investigations. Third, assessment of dietary habits via touchscreen questionnaires introduces potential biases in analysis. Lastly, focusing solely on dietary intake habits as an exposure phenotype precludes exploration of the effects of specific nutrients on pneumothorax, given the complexity of food composition. Nonetheless, this study sheds light on a pivotal interaction between gut microbial homeostasis and lung health, known as the "lung-gut axis" [57,58]. Mounting evidence suggests the significant role of gut flora in maintaining metabolic stability and triggering lung disease pathogenesis [59]. Microbial fermentation of dietary fiber produces short-chain fatty acids like acetic acid, propionic acid, and butyric acid, potentially crucial in regulating airway inflammation. Therefore, the lung-gut axis emerges as a promising therapeutic target for lung disease. Dysbiosis of gut microbiota compromises gut barrier function, predisposing individuals to lung diseases. Modulating dietary intake to influence gut flora may mitigate associated lung diseases.

5. Conclusions

This study hypothesizes a link between dietary habits and pneumothorax risk. However, the effectiveness of dietary interventions for pneumothorax treatment must be confirmed through RCTs. Adolescents, who have the highest rates of pneumothorax, frequently face repeated hospitalizations and relapses (66). Our study attempted to reduce pneumothorax-related complications and alleviate the psychological stress on adolescents by improving their daily dietary habits.

Pneumothorax imposes a substantial global economic burden annually and profoundly affects patients' quality of life. Our findings offer insights to empower clinicians in enhancing health education for pneumothorax patients, emphasizing modifications in vitamins, dietary fiber, etc., and advocating dietary habit adjustments such as increased fruit intake and reduced processed meat consumption. Such dietary modifications hold promise in reducing pneumothorax risk for high-risk individuals, thereby enriching our understanding of pneumothorax risk factors, protective elements, and the role of the lung-gut axis.

Data availability statement

Genetic association data for the selected risk factors can be found in the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/)

CRediT authorship contribution statement

Qichen Liang: Writing – review & editing, Writing – original draft, Resources, Investigation, Data curation, Conceptualization. **Huimin Ma:** Writing – review & editing, Supervision, Software, Project administration. **Liming Zhang:** Writing – original draft, Methodology, Formal analysis. **Lu Ning:** Writing – review & editing, Funding acquisition, Formal analysis. **Yajun Zhao:** Writing – review & editing, Formal analysis, Data curation. **Yang Li:** Writing – review & editing, Validation, Formal analysis. **Baoyu He:** Writing – review & editing, Supervision, Methodology. **Aiping Yang:** Writing – review & editing, Supervision, Resources, Project administration. **Ziteng Zhang:** Writing – review & editing, Methodology, Funding acquisition.

Declaration of competing interest

The authors declare no conflict of interest.

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