Original Article

Exploring the protective role of maternal lung cancer history on allergic rhinitis

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Background: The causal relationship between family history of lung cancer and allergic rhinitis remains unclear. This study aimed to explore the association between family history of lung cancer and allergic rhinitis, along with potential mediating mechanisms, using Mendelian randomization. Methods: A bidirectional two-sample Mendelian randomization analysis was conducted to assess the causal relationship between family history of lung cancer (including parental, paternal, maternal, and sibling histories) and allergic rhinitis, using genetic variants associated with family history of lung cancer as instrumental variables. Additionally, mediation Mendelian randomization analysis was performed to investigate the role of specific metabolites in mediating this relationship. Results: The analysis revealed a significant causal relationship between parental history of lung cancer and allergic rhinitis, with maternal lung cancer history showing a strong protective effect against allergic rhinitis (OR = 0.28, $p<0.05$). Mediation analysis further indicated that metabolites such as 1-linoleoyl-GPE (18:2) and *N*-palmitoyl-sphingosine exhibited negative mediating effects in the association between maternal lung cancer and allergic rhinitis. Lower levels of these metabolites enhanced the protective effect of maternal lung cancer history on allergic rhinitis. Conclusion: This study demonstrates a significant causal relationship between maternal lung cancer history and allergic rhinitis, with specific metabolites potentially playing a mediating role. Changes in the levels of 1-linoleoyl-GPE (18:2) and *N*-palmitoyl-sphingosine are associated with the protective effect of maternal lung cancer history on allergic rhinitis, suggesting that metabolites may be crucial in regulating this relationship. These findings provide new insights into the relationship between family history of lung cancer and immune-related diseases, offering potential directions for future clinical prevention and treatment strategies.

***Key Words*: Mendelian randomization, family history of lung cancer, allergic rhinitis, metabolite mediation, immune regulation**

Allergic rhinitis (AR) is a widespread chronic condition characterized by inflammation of the nasal mucosa, primarily triggered by allergens such as pollen, dust mites, and pet dander. This disease affects approximately 10–30% of the global population, significantly impairing patients' quality of life.[1,2] Symptoms include nasal congestion, sneezing, and itchy eyes, often leading to fatigue and sleep disturbances, which in turn affect work and learning efficiency. Economically, allergic rhinitis increases healthcare expenditures and leads to productivity loss, particularly in regions with high allergen exposure. Additionally, it is frequently comorbid with other conditions such as asthma and sinusitis, further exacerbating its overall societal burden.[3,4] Despite its prevalence, the diagnosis and treatment of allergic rhinitis remain inadequate, underscoring the urgent need to enhance public health measures to address this challenge.

Lung cancer is one of the leading causes of cancer-related deaths worldwide,[5] with approximately 1.8 million deaths annually attributed to the disease.[6] The high mortality rate of lung cancer is largely due to the absence of noticeable symptoms in its early stages, often leading to diagnosis at an advanced stage, which significantly complicates treatment. Although recent advancements in immunotherapy and targeted therapies have yielded some progress in lung cancer treatment,[7] the issue of drug resistance to targeted therapies remains a significant challenge.[8] Consequently, the long-term survival rate for most lung cancer patients remains low, especially in cases where the cancer has metastasized to other organs. Beyond the severe impact on the physical health of the patient, lung cancer also imposes a substantial burden on families and society, including increased economic costs, reduced quality of life, and heightened psychological stress.

The development of lung cancer is influenced by a variety of environmental and genetic factors, among which a family history of lung cancer has been widely recognized as a significant risk factor. Genetic susceptibility may increase an individual's risk of lung cancer through certain gene mutations or polymorphisms. For instance, mutations in genes such as TP53, EGFR, and KRAS are commonly observed in lung cancer patients,[9–11] and these mutations are particularly prevalent in cases with a family history of the disease. Moreover, a family history of lung cancer has been associated with an increased risk of other types of cancer. Research suggests that individuals with a family history of lung cancer not only have a higher risk of developing lung cancer but may also be more susceptible to other malignancies, such as breast cancer, colorectal cancer, and prostate cancer.[12] Lung cancer is also correlated with non-cancerous diseases like chronic obstructive pulmonary disease (COPD)[13,14] and cardiovascular disease,[15] which may share common pathogenic mechanisms with lung cancer, such as prolonged smoking and chronic inflammation.

In studies examining the relationship between lung cancer and allergic rhinitis, the existing literature predominantly reports a negative correlation between the two conditions.[16] This inverse relationship may stem from distinct differences in immune responses and inflammatory pathways involved in each disease. For example, some epidemiological studies indicate that lung cancer patients are less likely to present with allergic conditions,[17] potentially due to the reduced activity of certain immune cells in these individuals. However, intriguingly, certain observational studies have found a positive correlation between a family

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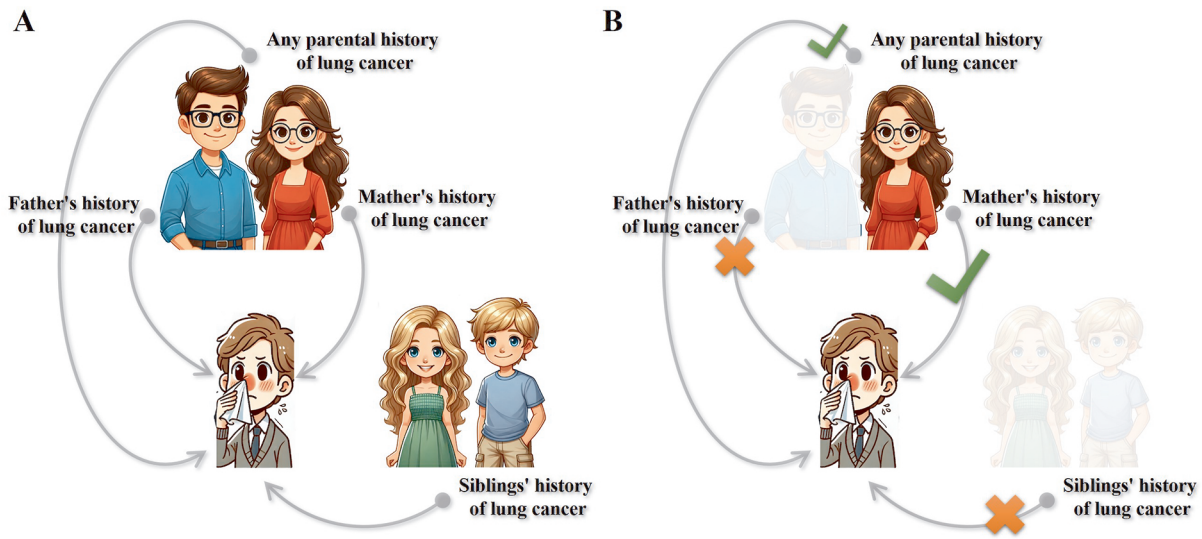

Fig. 1. Schematic diagram of the study on the impact of family history of lung cancer on allergic rhinitis. (A) represents the study design, including any parental history of lung cancer, and individual histories from the father, mother, and siblings. (B) illustrates the study outcomes, indicating significant findings (check marks) and non-significant findings (cross marks) in terms of the influence of lung cancer history from fathers, mothers, and siblings on allergic rhinitis. See color figure in the on-line version.

history of lung cancer and allergic rhinitis, suggesting that individuals with such a family history may have an increased predisposition to developing allergic rhinitis.[18] This seemingly paradoxical phenomenon could result from the interplay of multiple factors, including genetic predisposition, environmental exposures, and lifestyle influences. The complexity of this association becomes even more pronounced when considering that familial lung cancer may be tied to underlying genetic susceptibilities.

These findings prompt us to further investigate the potential causal relationship between a family history of lung cancer and allergic rhinitis. Using the Mendelian randomization (MR) approach, this study aims to eliminate confounding factors and assess whether this association has a genetic causal basis. Moreover, exploring the metabolic mechanisms involved in this causal framework will help elucidate the intrinsic link between a family history of lung cancer and allergic rhinitis, enabling a deeper understanding of the interactions between these two diseases and the underlying biological mechanisms. This research not only contributes to a better comprehension of the relationship between the two conditions but also offers new insights that may inform the development of prevention and treatment strategies.

Methods

Bidirectional MR. MR is a tool commonly used in epidemiological research to effectively assess the causal relationship between exposure factors and disease or health outcomes.[19] This study aims to evaluate the causal relationship between a family history of lung cancer and allergic rhinitis, encompassing parental lung cancer history, individual histories of lung cancer in the father or mother, and sibling lung cancer history. We employed a bidirectional two-sample MR approach. First, using parental lung cancer history, paternal lung cancer history, maternal lung cancer history, and sibling lung cancer history as exposure factors, we applied genetic variants associated with these exposures as instrumental variables to assess their causal relationship with allergic rhinitis. Subsequently, in a reverse analysis, we treated allergic rhinitis as the exposure factor to evaluate its impact on family lung cancer history (including parents and siblings), aiming to clarify the bidirectional causal relationship between the two conditions (Fig. 1A).

This bidirectional design allows us to simultaneously assess the causal effect of family lung cancer history on allergic rhinitis and whether allergic rhinitis might, in turn, influence family lung cancer history. This rigorous analytical framework helps to eliminate confounding bias, thereby enhancing the reliability of the results.

Metabolite-mediated MR. To further explore the potential metabolic mechanisms underlying the relationship between a family history of lung cancer and allergic rhinitis, this study employed a two-step MR approach to identify potential metabolites and assess their mediating role.[20] In the first step, we used genetic variants (single nucleotide polymorphisms; SNPs) associated with a family history of lung cancer as instrumental variables to screen for metabolites significantly correlated with parental and sibling lung cancer history. Through analyzing different familial lung cancer histories, we preliminarily identified metabolites that may be influenced by a family history of lung cancer.

In the second step of the analysis, based on the metabolites identified in the previous step, we used SNPs associated with these metabolites, but independent of family history of lung cancer, as new instrumental variables to further assess their impact on allergic rhinitis. By analyzing the relationship between metabolite-related genetic variants and the risk of allergic rhinitis, we inferred whether these metabolites mediate the association between family history of lung cancer and allergic rhinitis. The two-step MR approach provides an effective method to identify potential metabolic mediation pathways, thereby offering further insight into whether the protective effect of family history of lung cancer on allergic rhinitis is mediated through metabolites.

In the analysis, the inverse variance weighted (IVW) method[21] was primarily used as the main estimation approach, as it provides the most efficient estimates in the absence of pleiotropy. To enhance the robustness and reliability of the results, we also employed a variety of sensitivity analysis methods, including MR Egger,[22] the weighted median,[23] to address potential biases and issues related to weak instruments. Each of these methods operates under different assumptions, allowing us to validate the causal effects from multiple perspectives. To ensure the validity of the instrumental variables and to

Table 1. Causal effects of family history of lung cancer on allergic rhinitis estimated using MR-IVW, MR-weighted median, and MR-Egger

Exposure	Sample size	Outcome	MR-IVW		MR-Egger		MR-Egger intercept	Intercept *p* value
			OR (95% CI)	*p*	OR (95%CI)	*p*		
Any parental history of lung cancer (Firth correction)	407,521	Allergic rhinitis	0.96 (0.93–1.00)	**0.044**	0.94 (0.86–1.04)	0.231	0.001	0.669
Any parental history of lung cancer (SPA correction)	407,521	Allergic rhinitis	0.96 (0.93–1.00)	**0.045**	0.94 (0.86–1.04)	0.235	0.001	0.677
Father's history of lung cancer	401,624	Allergic rhinitis	0.92 (0.61–1.38)	0.692	1.04 (0.38–2.85)	0.94	–0.0006	0.798
Father's history of lung cancer	292,053	Allergic rhinitis	0.78 (0.50–1.21)	0.26	0.81 (0.29–2.28)	0.686	–0.0002	0.935
Mather's history of lung cancer	423,258	Allergic rhinitis	**0.28** (0.14–0.54)	**<0.001**	**0.13** (0.02–0.84)	**0.034**	0.0023	0.389
Sibling's history of lung cancer	361,586	Allergic rhinitis	0.4 (0.11–1.38)	0.147	1.38 (0.01–184.67)	0.897	–0.0026	0.607

rule out potential horizontal pleiotropy, pleiotropy testing was conducted. Specifically, we assessed the pleiotropy of the instrumental variables through the MR Egger intercept test, further confirming the robustness of the analysis.

Family history of lung cancer data sets. All data used in this study were obtained from the Integrative Epidemiology Unit (IEU) Open GWAS database[24] (https://gwas.mrcieu.ac.uk/). This study utilized multidimensional family lung cancer history datasets, encompassing various types of familial lung cancer histories, to assess their causal relationship with allergic rhinitis. Specifically, two independent datasets on parental lung cancer history (ebi-a-GCST90013922; ebi-a-GCST90013972),[25] two datasets on paternal lung cancer history (ukb-b-14521; ukb-a-205), one dataset on maternal lung cancer history (ukb-b-20176), and one dataset on sibling lung cancer history (ukb-b-15826) were used. These datasets, which capture lung cancer history from different family members, provide a diverse set of exposure variables, enabling a more comprehensive exploration of the causal relationship between family lung cancer history and allergic rhinitis.

Allergic rhinitis data set. To ensure the reliability of the exposure variables and the robustness of the analysis results, we prioritized the largest available genome-wide association study (GWAS) dataset as the exposure variable for allergic rhinitis. Other large-scale GWAS datasets were considered under the following conditions: 1) an insufficient number of instrumental variables; 2) racial discrepancies or incomplete data; 3) failure of the dataset to pass the horizontal pleiotropy test. Based on these screening criteria, the allergic rhinitis dataset (ebi-a-GCST90013920) that met the requirements was selected, ensuring the accuracy and representativeness of the study results.

Results

Causal relationship between parental history of lung cancer and allergic rhinitis. This study used datasets on parental history of lung cancer as the exposure factor to explore the causal relationship between a parental history of lung cancer (either one or both parents) and allergic rhinitis in offspring. To enhance the robustness of the results, two datasets were analyzed, each adjusted using Firth correction and Saddlepoint approximation correction.[26] Bidirectional MR analysis was employed to investigate the two-way causal relationship between parental lung cancer history and allergic rhinitis. The results indicated that all included parental lung cancer history datasets exhibited a significant negative correlation with allergic rhinitis ($p<0.05$), suggesting that a parental history of lung cancer may offer a protective effect by reducing the risk of allergic rhinitis in offspring (Table 1). In contrast, reverse analysis showed no statistically significant effect of allergic rhinitis on parental lung cancer history, indicating a unidirectional causal relationship—parental lung cancer history influences allergic rhinitis, but allergic rhinitis does not affect the risk of lung cancer in parents. Further odds ratio (OR) analysis revealed a weak protective effect of parental lung cancer history on allergic rhinitis, suggesting that having a parent with lung cancer may lower the likelihood of developing allergic rhinitis or reduce the severity of the condition. All analyses ruled out the influence of horizontal pleiotropy, thereby strengthening the reliability of the results (Fig. 2).

Independent effects of paternal or maternal lung cancer on allergic rhinitis. This study conducted a stratified analysis of parental lung cancer history to examine the independent effects of paternal or maternal lung cancer on allergic rhinitis. First, the maternal lung cancer history dataset was used as the exposure factor, with allergic rhinitis as the outcome, in a two-sample MR analysis. The results showed a significant negative causal relationship between maternal lung cancer history and allergic rhinitis ($p<0.05$), indicating that the risk of allergic rhinitis is significantly reduced in offspring when the mother has a history of lung cancer. Reverse analysis revealed no statistically significant effect of allergic rhinitis on maternal lung cancer history, confirming that maternal lung cancer history is a unidirectional causal factor for allergic rhinitis. Further OR analysis indicated a strong protective effect of maternal lung cancer history on allergic rhinitis (OR = 0.28), demonstrating a strong negative correlation. This suggests that individuals with a maternal history of lung cancer have a substantially lower risk of developing allergic rhinitis, and the severity of the condition may also be mitigated. These findings highlight the significant role of maternal lung cancer history in reducing the risk of allergic rhinitis in offspring (Fig. 3).

Next, the study further analyzed the impact of paternal lung cancer history on allergic rhinitis, using the paternal lung cancer history dataset as the exposure factor and assessing the causal relationship through two-sample MR analysis. The results indicated no significant causal relationship between paternal lung cancer history and allergic rhinitis, suggesting that the influence of paternal lung cancer history on allergic rhinitis is minimal or not significant.

Additionally, the study examined the relationship between sibling lung cancer history and allergic rhinitis. The results similarly showed no significant causal relationship between sibling lung cancer history and allergic rhinitis, further indicating that the protective effect of lung cancer history on allergic rhinitis is predominantly concentrated in the maternal group.

The above results suggest that, after stratifying the population, the protective effect against allergic rhinitis is specifically concentrated on the maternal side, exhibiting a strong protective effect, indicating that maternal factors may play a crucial role in regulating the occurrence of allergic rhinitis (Fig. 1B). This may reflect the influence of maternal lung cancer history on the offspring's immune response through pathways such as genetics, immune regulation, or mitochondrial function, enhancing tolerance to allergic diseases. Moreover, this strong protective effect suggests that maternal genetic factors may play a key role in immune regulation and inflammatory responses. Further research

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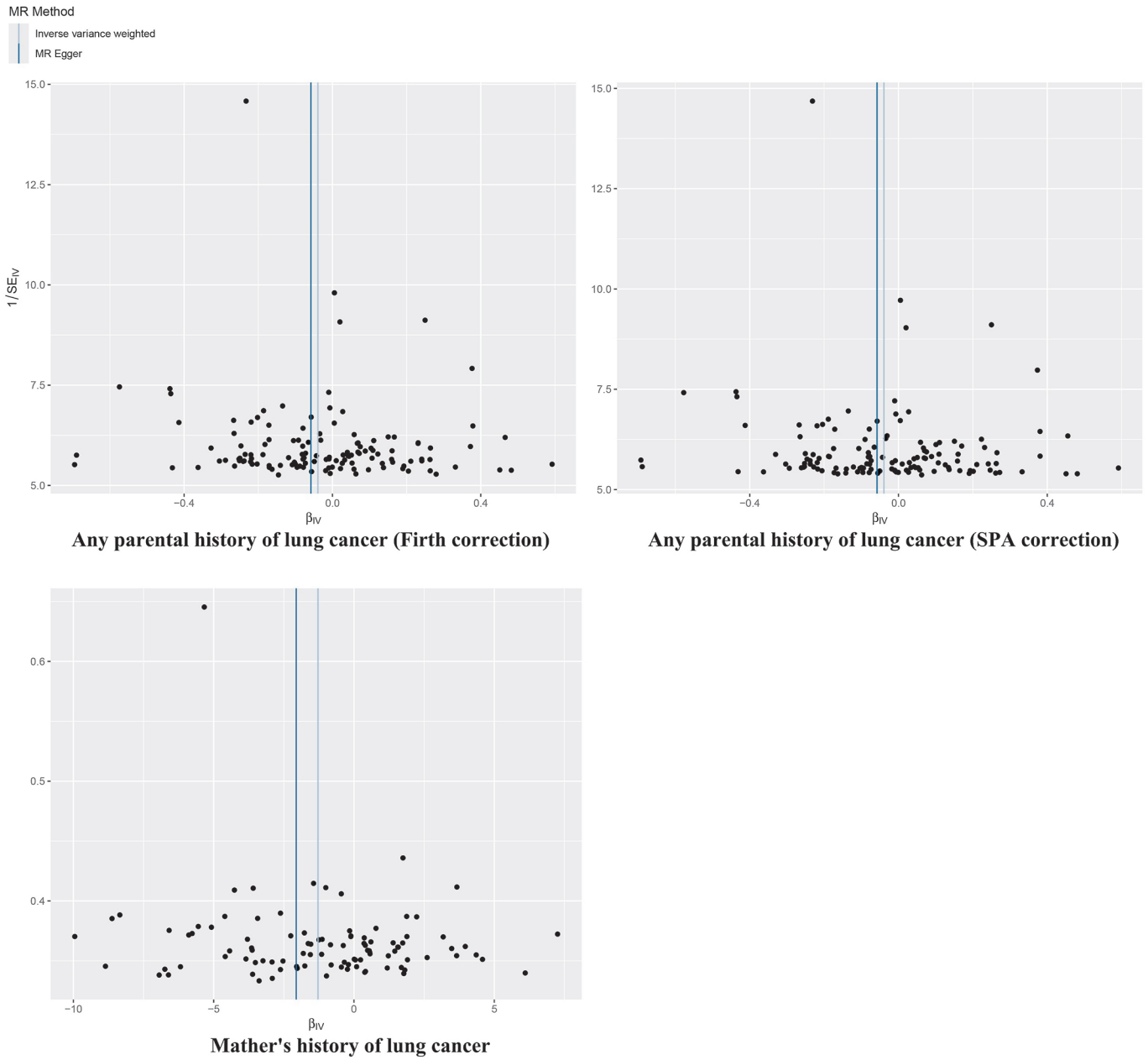

Fig. 2. Funnel plot from MR analysis of the family history of lung cancer on allergic rhinitis.

into the biological mechanisms linking maternal lung cancer and allergic rhinitis could help uncover potential immune regulatory pathways.

Exploring the metabolic mechanisms between maternal lung cancer and allergic rhinitis. Based on the metabolite data from Chen *et al.*[27] and previous related studies, we screened 212 potential mediator metabolites and constructed a candidate metabolite library to further explore the metabolic mechanisms between maternal lung cancer and allergic rhinitis. First, MR analysis was conducted to assess the association between all metabolites in the library and allergic rhinitis. The results showed that 91 metabolites were significantly associated with allergic rhinitis. OR analysis and horizontal pleiotropy analysis revealed that 67 of these 91 metabolites demonstrated consistency across multiple analytical methods, suggesting that these metabolites may be closely related to the underlying mechanisms of allergic rhinitis.

Next, we used MR to further evaluate the relationship between maternal lung cancer history and these allergic rhinitis-related metabolites. The analysis indicated that maternal lung cancer history significantly affected the levels of 1-linoleoyl-GPE (18:2), the ratio of leucine to *N*-palmitoyl-sphingosine (d18:1 to 16:0), and the ratio of glucose to *N*-palmitoyl-sphingosine (d18:1 to 16:0). These changes in metabolite levels suggest that these metabolites may serve as mediators, forming a potential causal chain between maternal lung cancer and allergic rhinitis (Fig. 4).

To verify whether these metabolites mediate the relationship between maternal lung cancer and allergic rhinitis, the study employed the MR mediation method to further assess the mediating effects of the three metabolites. The results showed that 1-linoleoyl-GPE (18:2), the ratio of leucine to *N*-palmitoyl-sphingosine (d18:1 to 16:0), and the ratio of glucose to *N*-palmitoyl-sphingosine (d18:1 to 16:0) exhibited consistent mediating effects across different statistical tests, with results

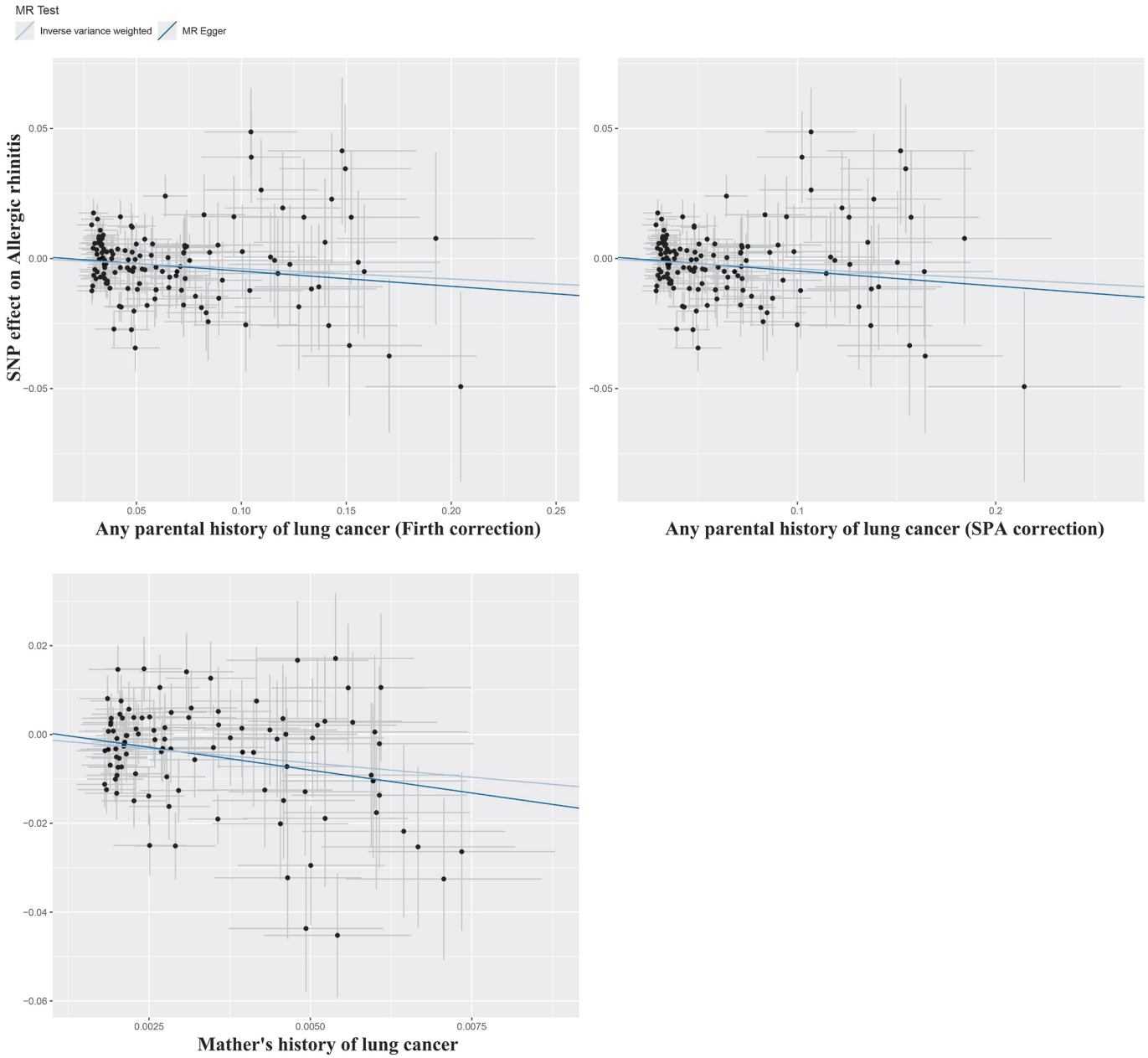

Fig. 3. Scatterplot of MR analysis on the causal effects of family history of lung cancer on allergic rhinitis risk. This graph illustrates the relationship between the impacts of SNPs on any parental history of lung cancer, Mather's history of lung cancer, and their effects on allergic rhinitis risk. Each point represents an SNP, with the various lines indicating causal effect estimates derived from different MR methods.

demonstrating high robustness. Additionally, the mediating effects of these three metabolites accounted for −4.90%, −5.49%, and −4.13% of the total effect, respectively, all negative values. This indicates that these metabolites have a negative mediating role in the protective effect of maternal lung cancer on allergic rhinitis, meaning that they play a key role in inhibiting the protective effect of maternal lung cancer on allergic rhinitis. When the levels of these three metabolites decrease, the protective effect of maternal lung cancer history on allergic rhinitis becomes more pronounced. These three metabolites play critical roles in cellular function. 1-linoleoyl-GPE (18:2) and *N*-palmitoyl-sphingosine are key lipid metabolites that play distinct roles in maintaining mitochondrial membrane stability and regulating apoptosis, respectively (Table 2).

Discussion

This study aimed to explore the causal relationship between a family history of lung cancer, particularly parental and sibling lung cancer history, and allergic rhinitis. By employing MR analysis, we were able to evaluate the effect of a family history of lung cancer on allergic rhinitis while accounting for potential confounding factors. The results indicated that a parental history of lung cancer, especially maternal history, has a protective effect against allergic rhinitis in offspring, while no similar effect was observed for paternal or sibling lung cancer history. This finding not only highlights the key role of maternal genetic factors in regulating allergic diseases but also suggests a potential link between maternal lung cancer history and immune system function.

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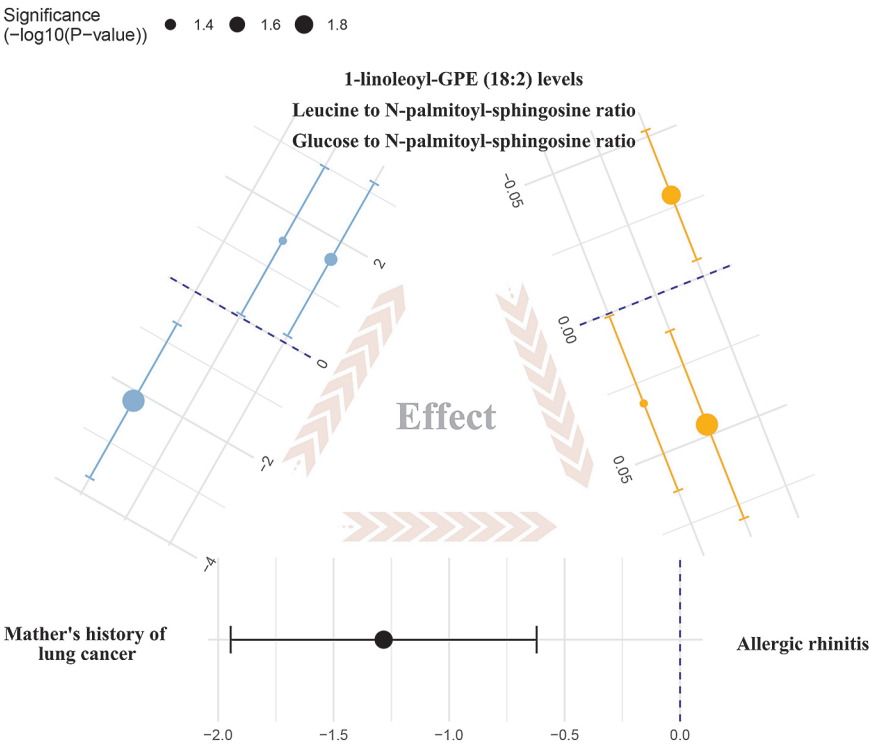

Fig. 4. Mediating effects between maternal lung cancer history and allergic rhinitis. The diagram presents three primary pathways: the effect of maternal lung cancer history on metabolite levels [1-linoleoyl-GPE (18:2), leucine to *N*-palmitoyl-sphingosine ratio, glucose to *N*-palmitoyl-sphingosine ratio], the influence of these metabolites on allergic rhinitis, and the direct impact of maternal lung cancer history on allergic rhinitis.

Table 2. Mediation effects of the metabolite between Mather's history of lung cancer and allergic rhinitis

Exposure	Metabolite	Outcome	Mediated effect	Mediated proportion
Mather's history of lung cancer	1-linoleoyl-GPE (18:2) levels	Allergic rhinitis	0.06	–4.90%
Mather's history of lung cancer	Leucine to *N*-palmitoyl-sphingosine (d18:1 to 16:0) ratio	Allergic rhinitis	0.07	–5.49%
Mather's history of lung cancer	Glucose to *N*-palmitoyl-sphingosine (d18:1 to 16:0) ratio	Allergic rhinitis	0.05	–4.13%

First, the relationship between parental lung cancer history and allergic rhinitis was validated through bidirectional MR analysis. Using both Firth correction and Saddlepoint approximation correction, the results showed that a parental history of lung cancer has a significant negative effect on allergic rhinitis, suggesting that having a parent with lung cancer may reduce the risk of allergic rhinitis in offspring. Further OR analysis demonstrated the statistical significance of the protective effect of parental lung cancer history. However, reverse analysis—assessing the impact of allergic rhinitis on parental lung cancer history—did not reach statistical significance, indicating that the causal relationship is unidirectional. The lack of significant effects for paternal and sibling lung cancer history suggests that the protective effect is primarily associated with maternal history. The significant protective effect of maternal lung cancer history points to the potential involvement of maternal genetic or immune regulatory mechanisms in the development of allergic rhinitis. In contrast, the absence of similar associations for paternal or sibling lung cancer history underscores the unique importance of maternal factors in this process.

In further exploration of the underlying mechanisms, we assessed the relationship between maternal lung cancer history and specific metabolite levels. Through MR mediation analysis, we discovered that maternal lung cancer significantly influenced the levels of 1-linoleoyl-GPE (18:2), the ratio of leucine to *N*-palmitoyl-sphingosine (d18:1 to 16:0), and the ratio of glucose to *N*-palmitoyl-sphingosine (d18:1 to 16:0). The mediating effects of these metabolites in the relationship between maternal lung cancer history and allergic rhinitis further reveal how maternal lung cancer may regulate the offspring's immune system via metabolic pathways. Mediation analysis showed that these three metabolites exerted a negative effect on the protective role of maternal lung cancer history—indicating that lower metabolite levels strengthen the protective effect of maternal lung cancer history on allergic rhinitis.

Notably, these metabolites are closely related to mitochondrial function. Both 1-linoleoyl-GPE (18:2) and *N*-palmitoyl-sphingosine, as lipid metabolites, play crucial roles in maintaining mitochondrial membrane stability and function.[28] 1-linoleoyl-GPE (18:2) is a glycerophospholipid primarily involved in regulating the fluidity of the mitochondrial inner membrane. A reduction in its levels may weaken mitochondrial energy supply, leading to shifts in cellular metabolism, such as an increased reliance on glycolysis to meet energy demands. *N*-palmitoyl-sphingosine, on the other hand, regulates mitochondrial membrane permeability, influencing the process of apoptosis.[29,30] Lower levels of *N*-palmitoyl-sphingosine may reduce apoptosis, allowing lung cancer cells to evade normal apoptotic mechanisms and thereby promote cancer progression.[31]

The association between maternal lung cancer and metabolites

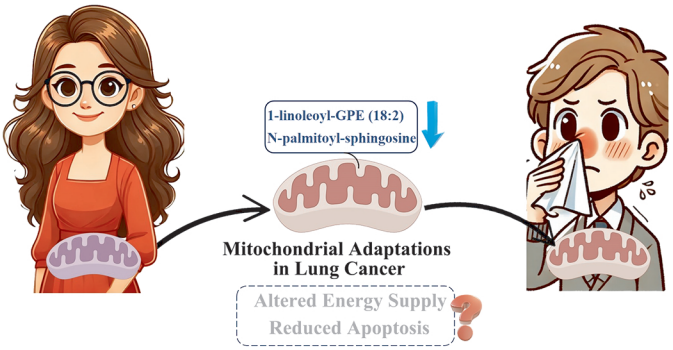

Fig. 5. Speculative mechanisms of mitochondrial dysfunction in maternal lung cancer affecting offspring allergic rhinitis. This diagram hypothesizes the potential transgenerational transmission of mitochondrial alterations associated with lung cancer in mothers and their impact on the incidence of allergic rhinitis in offspring. For instance, reductions in levels of 1-linoleoyl-GPE (18:2) and *N*-palmitoyl-sphingosine may lead to changes in energy production and apoptosis, integral aspects of mitochondrial function altered in cancer pathology, which could be inherited through mtDNA. Such inherited alterations could modulate the immune response and metabolic state of the descendants, thereby highlighting the complex interactions between hereditary mitochondrial damage due to maternal lung cancer and increased susceptibility to allergic symptoms in progeny. Some elements of the figure were created by Figdraw.

suggests potential mitochondrial dysfunction caused by lung cancer. Since mitochondrial function is inherited through mtDNA, the mitochondrial damage resulting from maternal lung cancer may influence the immune response and metabolic state of offspring via this genetic mechanism, thereby exerting a protective effect against allergic rhinitis (Fig. 5). Mitochondrial dysfunction induced by maternal lung cancer may affect allergic rhinitis through two pathways. First, the reduction in 1-linoleoyl-GPE (18:2) levels may weaken mitochondrial energy supply, forcing cells to rely on alternative metabolic pathways, such as glycolysis, to meet energy demands. This process may be linked to the rapid proliferation of cancer cells and could also suppress immune cell function in offspring, reducing the incidence of allergic rhinitis. Second, the decrease in *N*-palmitoyl-sphingosine levels may inhibit apoptosis, thereby increasing the risk of tumor development. However, apoptosis also plays a critical role in epithelial barrier damage and repair. When epithelial cells encounter harmful factors such as microbial infections, air pollution, or allergens, apoptosis occurs, leading to barrier disruption.[32] Damage to the epithelial barrier and its weakened function is a key factor in the development of rhinitis.[33] In individuals with maternal genetic traits, enhanced anti-apoptotic effects may increase the risk of tumorigenesis but protect epithelial barrier function from apoptosis-induced damage, thus reducing the incidence of allergic rhinitis. Whether the balance between anti-apoptotic mechanisms and the relationship between tumor genetics and AR can be leveraged to inform prevention and treatment of allergic diseases requires further research. Therefore, the enhancement of anti-apoptotic function associated with maternal lung cancer history may contribute to a reduced risk of allergic rhinitis in offspring.

However, this study also has certain limitations. First, although the MR method effectively controlled for potential confounding factors, some unmeasured environmental factors may still influence the interpretation of the results. Additionally, while the mediating effect of metabolites was statistically validated, the precise biological mechanisms underlying this effect require further experimental investigation.

In conclusion, this study revealed a significant protective effect of maternal lung cancer history on allergic rhinitis, potentially mediated through mitochondrial inheritance and the regulation of metabolite levels. Maternal lung cancer, by influencing key metabolites such as 1-linoleoyl-GPE (18:2) and *N*-palmitoyl-sphingosine, alters the immune response capabilities of offspring, thereby reducing the risk of allergic diseases. These findings provide new insights into the complex relationship between lung cancer and immune-related diseases, particularly highlighting the critical role of maternal genetic factors in regulating immune responses.

Author Contributions

Y-YH and J-YZ conceptualized and designed the study; S-SW, J-YZ, and Y-YH acquired and vali-dated the data; Y-YH and J-YZ curated the datasets; S-SW, J-YZ, and Y-YH drafted and revised the manuscript. All authors have read and approved the final version of the manuscript.

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Data Availability Statement

Data are available in a public, open-access repository.
Data URLs: https://gwas.mrcieu.ac.uk;
https://www.ebi.ac.uk/gwas/down-loads/summary-statistics

Conflict of Interest

No potential conflicts of interest were disclosed.

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