The Role of 418 Gut Microbiota in Small Cell Lung Cancer Progression: A Mendelian Randomisation Study

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ABSTRACT

Objective: To investigate the causal influence of gut microbiota on small cell lung cancer (SCLC) progression using Mendelian randomisation (MR), providing insights into the gut-lung axis in lung cancer pathology.

Study Design: Analytical study.

Place and Duration of the Study: Department of Radiotherapy, Binhai County People's Hospital, Yancheng, Jiangsu, China, and Department of Paediatrics, General Hospital of Ningxia Medical University, Yinchuan, Ningxia, China, from January to May 2024.

Methodology: The study used 18,340 single nucleotide polymorphisms (SNPs) as instrumental variables to analyse 418 gut microbiota varieties. The inverse variance weighted (IVW) and MR Egger's methods were applied to explore causal relationships. Sensitivity analyses, including leave-one-out tests and Cochrane's Q tests, ensured robust results. A uni-directional Mendelian randomisation (MR) analysis was conducted using summary statistics from genome-wide association studies (GWAS) provided by the MiBio-Gen and Finn-Gen consortia.

Results: MR identified several bacterial taxonomic groups significantly associated with SCLC risk. Protective factors included *Bacteroidetes* (p = 0.0154*), Eubacterium ruminantium* group (p = 0.0241), *Barnesiella* (p = 0.0015), *Clostridia* (p = 0.0242), *Christensenellaceae* (p = 0.0314), *Ruminococcaceae* UCG-003 (p = 0.0381), and an unknown genus in the *Ruminococcaceae* family (p = 0.0458). Conversely, the risk factors linked to increased SCLC risk included *Firmicutes* (p = 0.0456), *Pasteurellaceae* (p = 0.0177), *Eubacterium oxidoreducens* group (p = 0.0188), *Pasteurellales* (p = 0.0177), and *Alcaligenaceae* (p = 0.0423).

Conclusion: The study suggests a protective role of specific gut microbiota against SCLC and identifies others that may increase the risk. The absence of heterogeneity and pleiotropy supports the causal associations, underscoring the significance of the gut-lung axis in SCLC and the utility of MR in cancer epidemiology.

Key Words: *Small cell lung cancer, Gut microbiota, Mendelian randomisation, Causal inference, Cancer epidemiology*.

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INTRODUCTION

Lung cancer continues to be one of the deadliest cancers worldwide, characterised by alarmingly high incidence and mortality rates. According to global cancer statistics, each year sees over 20,000 new diagnoses of lung cancer.[1] Notably, approximately half of these cases are reported in Asia. Since 2011, lung cancer remains the primary cause of cancer mortality in China. Lung cancer encompasses various types, including non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with each having unique biological characteristics and clinical courses.[2] When comparing SCLC to NSCLC, SCLC tends to metastasise early, which complicates the treatment and results in lower survival rates compared to NSCLC, which often has more localised progression.

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Recent advancements in molecular profiling of lung cancer have further highlighted the differences in genetic mutations and tumour microenvironment between the two types. For example, while EGFR mutations and ALK rearrangements are common in NSCLC, they are rarely found in SCLC, which typically exhibits alterations in *TP53* and *RB1* genes, contributing to its unique therapeutic challenges.[3] Lung cancer encompasses various types, including SCLC stands out due to its aggressive nature and poor prognosis. In addition to smoking, other risk factors such as exposure to asbestos, radiation, and environmental pollutants, also play critical roles in the development of SCLC.[4,5]

Recent research increasingly supports the notion that microbiota is crucial in cancer onset, progression, and response to chemotherapy. Preclinical and clinical studies have shown connections between microbiota and lung cancer.[6] The gut and lungs share the same embryological origins and engage in physical interactions, as ingested microbes can enter both the gastrointestinal and respiratory tracts.[7] This extensive dialogue has spurred interest in the gut-lung axis (GLA), a concept that has become increasingly relevant in the disease research.[8] However, compared to other diseases such as Crohn's disease

or colitis, the impact of microbiota on the lungs is less understood.

A study examining female non-smokers with lung cancer found significant correlations between gut microbiota and tumour characteristics such as TNM staging and primary tumour size. Specifically, the abundance of *Fusobacteria* was positively correlated with the tumour size, while *Clostridia* and *Bacteroidetes* showed inverse relationships.[9] Research has shown variations in the gut microbiome between lung cancer patients and healthy people, with variations in *Firmicutes* and *Proteobacteria* concentrations.[10] The variability of gut microbiota across individuals suggests that the same bacterial groups may show inconsistent patterns among different lung cancer cases. It is crucial to note that these findings are from clinical samples, and the observed effects might be due to the influence of bacterial metabolites or molecules on the immune system, such as the activation of t-cells by a certain bacteria to inhibit tumour growth.[11] Considering these findings and the difficulty of controlling for confounding factors such as age, environment, diet, and lifestyle in observational studies, it is crucial to explore new methodologies to determine a causal link between the gut microbiota and SCLC. This is where Mendelian randomisation (MR) becomes essential. MR uses genetic variants as tools to identify causal links between exposures and disease outcomes. Because genetic sequences are inherited and not influenced by the common confounding factors, MR is particularly well-suited for identifying true causal links. This approach is widely employed to investigate the causal links between gut microbiota and various diseases, including gynaecological disorders, autoimmune diseases, and metabolic diseases. This study was conducted as a uni-directional MR analysis using GWAS summary statistics from the MiBio-Gen and Finn-Gen consortia and aimed to evaluate the causal link between gut microbiota and SCLC. This approach promises to provide a valuable layer of insight into the complex interactions between microbiota and lung cancer, potentially leading to novel prevention and treatment methods.

METHODOLOGY

This study was conducted at the Department of Radiotherapy, Binhai County People's Hospital, Yancheng, Jiangsu, China, and the Department of Paediatrics, General Hospital of Ningxia Medical University, Yinchuan, Ningxia, China. Using the GWAS (https://www.ebi.ac.uk/gwas/) summary statistics, this study conducted an MR analysis to explore the causal link between gut microbiota (exposure) and SCLC (outcome). The MR design hinges on three key assumptions: The genetic variants must be reliably associated with the exposure, they should not correlate with confounding factors influencing the exposure-outcome relationship, and they must impact the outcome only through the exposure (Figure 1).

A two-sample analysis of MR was conducted to assess the potential causal relationship between the gut microbiome and the development of SCLC.

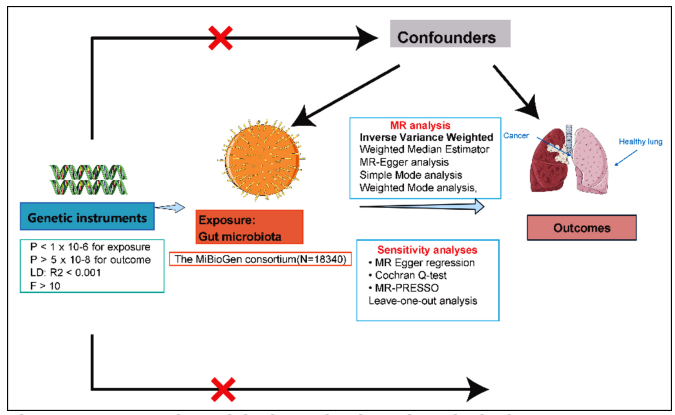

Figure 1: An overview of the hypothesis and study design.

The GWAS summary data on 418 gut microbiota types were sourced from the MiBio-Gen consortium and the Dutch microbiome project. The micro bio-gen consortium conducted a detailed examination and curation of genome-wide genotypes linked to 16S faecal microbiome data, gathered from an extensive European population base of 18,340 individuals. In parallel, the Dutch microbiome project conducted a comprehensive genome-wide association study, examining 207 taxa and 205 pathways. This research offered an in-depth insight into the microbial composition and functionality within a significant cohort of 7,738 participants.

Statistical data for SCLC were sourced from the Finn-Gen consortium's GWAS, which included 218,792 European adults, comprising 179 cases and 218,613 controls. All GWAS data used in this study are available from the IEU Open GWAS Project. Consistent with practices in contemporary MR studies, initially, set a genome-wide significance threshold for SNP selection was set at $p < 5 \times 10^{-8}$. Due to the limited number of SNPs at this level, a relaxed threshold of $p < 5 \times 10^{-6}$ to identify potential instrumental variables (IVs) for each exposure was used. IVs independence *via* linkage disequilibrium clumping with a 10 MB window and $R2 < 0.001$ were ensured, using the European ancestry data from the 1,000 Genomes Project. The F statistic, a measure used in hypothesis testing, was applied to evaluate IVs strength, with values over 10 indicating robust IVs and supporting the reliability of research causal inferences. F statistic signals a more potent genetic instrument. The robustness of the research analysis was further ensured by limiting it to results that included a minimum of three shared SNPs. In this research, the primary method used to determine the associations between gut microbiota and SCLC was the IVW approach. This technique aggregates the individual associations of variants with both the exposure and the outcome to estimate an overarching causal effect. This method assumes all genetic variants are valid instruments, influencing the outcome solely through their effect on the exposure, without horisontal pleiotropy. While IVW is widely used, it is essential to perform sensitivity analyses and use alternative methods such as MR-Egger regression and the weighted-median approach to ensure result stability and check for assumption violations. In this study, results were deemed significant if the IVW method showed a notable association ($p < 0.05$), supported by consistent directional effects in MR-Egger regression and weighted-median analyses.

To further assess the robustness of these findings, sensitivity analyses included the leave-one-out approach and the Q-test for heterogeneity, applied to both the MR-Egger and IVW methods. Additionally, the Egger intercept technique was used to examine potential directional horizontal pleiotropy. The leave-one-out analysis assesses the influence and stability of individual data points by sequentially removing each genetic instrument and recalculating causal estimates. The Q-test detects heterogeneity in causal estimates from different genetic instruments, especially within IVW and MR-Egger frameworks. The MR-Egger method, incorporating an intercept in the regression model, addresses biases from directional horizontal pleiotropy, where genetic variants may systematically affect the outcome. All statistical analyses were conducted using R (version 4.2.2) and the Two Sample MR package (version 0.5.7).

RESULTS

All of the selected SNPs had f-statistics greater than 10, indicating no weak instrument bias. IVW analysis results for 12 bacterial taxonomic groups showed significance (Figure 2), among which *Bacteroidetes* was associated with a causal risk ratio of 0.24 (95% CI: 0.08-0.76), genus *Eubacterium*, *ruminantium* group was associated with a causal risk ratio of 0.41 (95% CI: 0.19-0.89), genus *Barnesiella* was associated with a causal risk ratio of 0.14 (95% CI: 0.04-0.47), *Clostridia* was associated with a causal risk ratio of 0.36 (95% CI: 0.15-0.87), family *Christensenellaceae* was associated with a causal risk ratio of 0.09 (95% CI: 0.00-0.81), genus *Ruminococcaceae UCG-003* was associated with a causal risk ratio of 0.31 (95% CI: 0.10-0.94), and an unknown genus within the *Ruminococcaceae* family was associated with a causal risk ratio of 0.22 (95% CI: 0.05-0.97) as protective factors against SCLC.

Conversely, *Firmicutes* was associated with a causal risk ratio of 1.61 (95% CI: 1.01-2.56), family *Pasteurellaceae* was associated with a causal risk ratio of 2.99 (95% CI: 1.21-7.39), genus *Eubacterium oxidoreducens* group was associated with a causal risk ratio of 3.91 (95% CI: 1.25-12.21), order *Pasteurellales* was associated with a causal risk ratio of 2.99 (95% CI: 1.21-7.39), and family *Alcaligenaceae* was associated with a causal risk ratio of 3.51 (95% CI: 1.04-11.78), which may potentially contribute to the development of SCLC.

(A) A forest plot visualising the odds ratios (OR) with 95% confidence intervals (CI) for the association of various gut microbiota with SCLC risk, using the IVW method (B). A scatter-plot of the same associations, comparing different MR methods and indicating heterogeneity and method-specific effects with 95% CI. Each point represents a different gut microbiota genus or higher taxonomic classification, with corresponding p-values, highlighting the diversity of effects on SCLC risk.

To reinforce the proposed causal link between the gut microbiome and SCLC, sensitivity analyses were conducted. Heterogeneity was evaluated using leave-one-out analyses and Q-tests within the MR Egger and IVW frameworks. The sensitivity analysis results, presented in Table I, indicated no evidence of heterogeneity among the genera as Cochrane's Q test values were all above 0.05. Moreover, the discrepancies between the MR-Egger method intercepts and zero were not statistically significant, confirming the absence of horizontal pleiotropy in the findings.

Table I: Sensitivity analysis of gut microbiota on SCLC.

Bacterial taxa	MR-Egger		IVW		Horizontal pleiotropy	
	Q	p-value	Q	p-value	Egger_intercept	p-value
Alcaligenaceae	7.19	0.617	7.22	0.704	0.034	0.863
Christensenellaceae	0.99	0.319	0.99	0.609	-0.020	0.975
Pasteurellaceae	5.42	0.604	6.04	0.642	0.090	0.471
genus.Barnesiella	7.76	0.458	7.89	0.545	0.069	0.722
genus.Eubacterium oxidoreducens group	0.06	0.969	0.33	0.953	0.121	0.655
genus.Eubacterium Ruminantium group	7.07	0.529	7.11	0.625	-0.031	0.830
genus. RuminococcaceaeUCG-003	6.68	0.571	7.50	0.585	0.127	0.393
genus.unknowngenus	13.38	0.063	13.66	0.091	-0.158	0.713
order.Pasteurellales	5.45	0.604	6.04	0.643	0.090	0.471
k__Bacteria.p__Bacteroidetes.c	3.14	0.208	3.48	0.324	0.148	0.690
k__Bacteria.p__Firmicutes.c__Clostridia.o	6.31	0.389	6.45	0.489	0.072	0.733
k__Bacteria.p__Firmicutes.c__Bacilli.o	2.35	0.672	2.74	0.739	-0.208	0.563

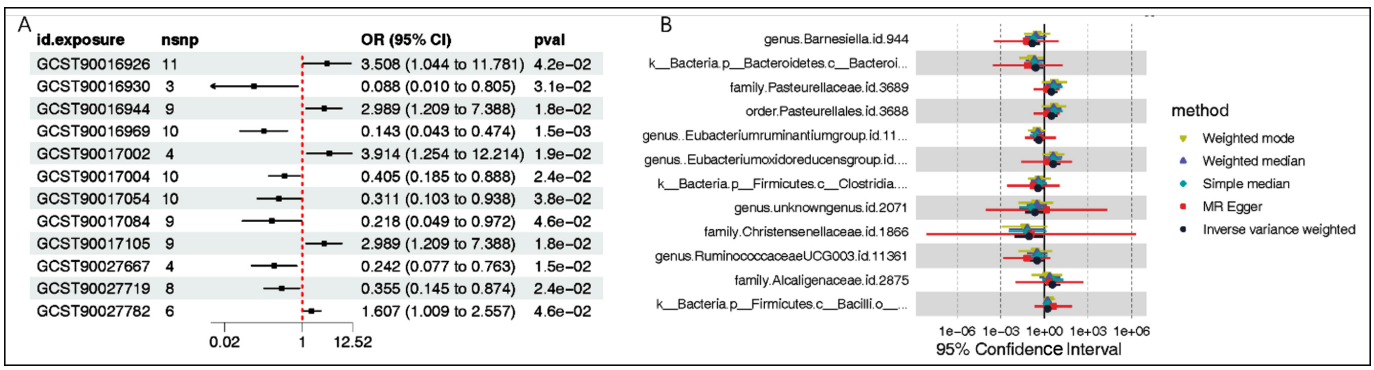

Figure 2: IVW Forest flot for gut microbiome impact on SCLC.

DISCUSSION

In this study, MR was employed to analyse numerous microbial groups in the gut, identifying several that microbial taxa are associated with SCLC. The present results indicated that the genus *Barnesiella* and an unspecified class within the *Phylum Bacteroidetes*, as well as the *Eubacterium Ruminantium* group, the genus *Subdoligranulum*, and the *Christensenellaceae* family from the *Phylum Firmicutes*, may provide protective effects against SCLC. Additionally, the undefined genus *Ruminococcaceae UCG-003* and an unknown genus within the *Ruminococcaceae* family also showed protective potential. These microbial groups might exert their protective effects by modulating the immune responses or affecting metabolic pathways involved in tumour growth. Conversely, an unspecified class within the *Phylum Firmicutes*, as well as the *Pasteurellaceae* and *Alcaligenaceae* families and the *Pasteurellales* order from the *Phylum Proteobacteria*, along with the *Eubacterium oxidoreducens* group, displayed the potential to promote the onset of SCLC. The promotive actions of these groups may be related to their roles in host inflammatory responses and immune regulation.

These findings suggest that changes in gut microbiota composition may influence the lung cancer risk. Future research should investigate how these microbial groups affect lung cancer development and explore their potential as targets for preventing or treating SCLC. The human gut microbiota is dominated by four major phyla: Which include *Actinobacteria, Bacteroidetes, Firmicutes*, and *Proteobacteria*.[12] Research shows that *Barnesiella (Bacteroidetes)* and *Desulfovibrio Piger (Proteobacteria)* are linked to various immunoregulatory cells.[13,14] These bacteria may play a role in creating an intestinal environment that is less prone to inflammation. Significant differences have been observed between the gut microbiomes of lung cancer patients and healthy individuals, with prior research suggesting that modifications in the gut microbiome are closely related to lung cancer. Treatments using antibiotics or probiotics, particularly in combination with immunotherapy or mutation prevention, may prove beneficial in lung cancer management. However, while much of the existing research focuses on non-small cell lung cancer (NSCLC), studies on SCLC, which also has a high incidence, are relatively scarce. Through a large-scale systematic analysis of 418 taxonomic groups in the gut microbiome, this study has identified specific bacterial groups that may have beneficial or harmful impacts on patients with SCLC. This investigation enhances the understanding of SCLC pathogenesis and could help in developing new therapeutic strategies.

The *Barnesiella* genus, a member of the *Bacteroidetes phylum*, has been associated with improved gut health.[15] It is known to selectively proliferate under certain conditions, such as the presence of specific oligosaccharides. This selective proliferation can lead to a more balanced gut microbiota, which is crucial for maintaining the overall gut health.[13] *Barnesiella* is known to produce short-chain fatty acids (SCFAs), including butyrate.[15]

The *Eubacterium ruminantium* group and the *Subdoligranulum* genus, both from the *Firmicutes phylum*, are known to play significant roles in the fermentation of dietary fibres.[16] This fermentation process leads to the production of SCFA, including acetate, propionate, and butyrate. These SCFAs are key metabolites in the gut that play a significant role in maintaining gut barrier integrity and modulating immune responses.[17]

The *Christensenellaceae* family, also from the *Firmicutes phylum*, is associated with a healthy gut microbiome.[18] It has been associated with lower body weight, establishing the strongest and most consistent link between gut microbial ecology and BMI in relation to metabolic disease.[18] The inverse relationship between *Christensenellaceae* abundance in the gut and BMI may indirectly affect cancer risk, given that obesity is a known risk factor for various cancers.[18] Therefore, the *Christensenellaceae* family might play a protective role against SCLC through its effects on body weight and metabolic health. Therefore, the *Eubacterium ruminantium* group, the *Subdoligranulum* genus, and the *Christensenellaceae* family, all play significant roles in maintaining gut health and modulating immune responses, which could potentially influence the risk of SCLC.

The *Ruminococcaceae* family, including the undefined genus *Ruminococcaceae UCG-003* and other unknown genera, play a crucial role in the gut microbiota. They are known for their ability to degrade complex carbohydrates.[19] This degradation process is particularly important as it leads to the production of SCFAs, including acetate, propionate, and butyrate. In the context of SCLC, the metabolic activities of these bacteria might have a protective potential. While the exact mechanisms are still under investigation, it is plausible that the SCFAs produced by these bacteria could influence the immune response, potentially creating an environment that is less conducive to the growth and spread of cancer cells.[20] However, more research is needed to fully understand the complex interactions between these bacteria, their metabolic activities, and their potential role in protecting against SCLC.

An unspecified class within the *Firmicutes phylum*, along with the *Pasteurellaceae* and *Alcaligenaceae* families and the *Pasteurellales* order from the *Proteobacteria phylum*, have been associated with inflammatory conditions.[21] The bacteria in these groups can trigger an immune response, leading to chronic inflammation. Over time, this inflammation can cause DNA damage and lead to the development of cancer cells.[22] However, the exact mechanisms by which these bacteria contribute to inflammation and cancer development are still being investigated. On the other hand, the *Eubacterium*

oxidoreducens group, despite being a producer of SCFAs, has been linked to the production of potentially harmful metabolites, such as hydrogen sulfide. Hydrogen sulfide, while necessary for certain physiological processes, can be harmful in high concentrations.[23] It can cause oxidative stress, which can lead to the DNA damage and potentially contribute to the development of cancer. Interestingly, *Eubacterium oxidoreducens* is known to degrade certain compounds, leading to the production of SCFAs. While SCFAs have been associated with beneficial effects on gut health, the production of hydrogen sulfide might counteract these benefits and contribute to the promotion of SCLC.

In this study, the innovative application of MR to link specific gut microbiota to SCLC risk offers new insights into the microbial contributions to cancer development, highlighting potential preventive and therapeutic targets. However, a limitation of this research is the reliance on genetic proxies, which may not capture the full complexity of host-microbiome interactions, necessitating further experimental validation. Future research should aim to elucidate the exact mechanisms through which these microbes influence the SCLC risk, which could involve in-depth metagenomic and metabolomic analyses. Furthermore, interventional studies could be conducted to investigate whether modulating the abundance of these microbial groups, through dietary interventions or probiotic supplementation, could influence SCLC risk or progression. This could pave the way for the development of novel preventive and therapeutic strategies against SCLC.

CONCLUSION

This study identifies gut microbial groups influencing SCLC risk, with certain taxa associated with a protective effect, while others are linked to an increased risk. Protective microbes may reduce inflammation or modulate cancer-related metabolic pathways, whereas risk-associated microbes could enhance inflammation or alter immune regulation. These findings emphasise the role of gut microbiota in SCLC, suggesting potential for microbial interventions in cancer prevention and therapy.

ETHICAL APPROVAL:
Ethical approval for these datasets was granted by the relevant Institutional Review Board (IRB), negating the requirement for additional ethical consent.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
RG: Concept and design of work, data analysis, and interpretation of data.
HL: Drafting of the work and critical revision for the important intellectual content.
Both authors approved the final version of the manuscript to be published.

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