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Causal Associations between Skin Microbiota and Lung Cancer: A Mendelian Randomization Study

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ABSTRACT

Purpose: In recent years, microbiome research has made significant progress in under-standing the relationship between human microbiota and pulmonary diseases. The lung and gut microbiota have received extensive attention in lung cancer research. Multiple studies have shown that dysregulation of the lung and gut microbiota is closely related to the occurrence and progression of lung cancer. The skin is the largest organ of the human body, as the first line of defense, it undertakes multiple functions such as de-fending against external pathogens and regulating body temperature and feeling. A complex and diverse microbial community also exists on the skin surface; however, the role of the skin microbiota in cancer has not been fully investigated. In particular, there is almost no research on the causal relationship between skin microbiota and lung can-cer.

Methods: In this Two-sample Mendelian randomization (MR) analysis study, we com-piled genome-wide association studies (GWAS) data on 150 different immune cell traits from 597 individuals of European ancestry. Additionally, Data on lung cancer were ob-tained from the FinnGen GWAS database to delve deeper into the potential causal rela-tionship between skin microbiome characteristics and lung cancer. In our MR Analysis, the inverse variance weighting (IVW) method is the main method, supplemented by MR-Egger regression, weighted median (WM), Simple Mode, and weighted mode. In addition, the MR-Egger intercept test, Cochran Q test, MR-PRESSO, and remain-one analysis were used to identify heterogeneity and pleiotropy, to ensure the reliability and stability of the research results.

Results: In studying the relationship between lung cancer and skin microbiota, we found that there are different interactions between lung cancer and specific types of skin microbiota. In the forward Mendelian randomization analysis, we included skin micro-biota as the exposure factor and each subtype of lung cancer (including Non-small cell lung cancer, Squamous cell carcinoma, Adenocarcinoma, and Small cell lung cancer) as the outcome factor. A total of 11 microbiota were found to be significantly associated with non-small cell lung cancer (NSCLC), of which 6 were protective and 5 were asso-ciated with increased risk of NSCLC. These micro biota are classified into 5 genera, 2 families, and 2 orders. For lung squamous cell carcinoma (LUSC), 5 related micro flora were identified, of which 3 showed protective effects and 2 were regarded as risk fac-tors. These microflora included 4 Genus and 1 Class. In the lung adenocarcinoma (LUAD) study, 13 significantly related microbial groups were found, of which 3 have protective effects and 10 are related to increased risk. These microbial groups are classi-fied into 7 genera, 2 Order, and 2 families. In the study of small cell lung cancer (SCLC), 6 microbiota were found to be significantly associated with the disease, of which 1 had a protective effect and 5 were considered to increase the risk. These mi-crobiota are classified into 5 genera and 1 family. In this study, we also used the reverse Mendelian randomized analysis method to explore the effects of various subtypes of lung cancer (including NSCLC, LUSC, LUAD, and SCLC) on the skin microbiota. The results showed no statistically significant causal relationship was found on the path from lung cancer to skin microbiota.

Conclusions: Our study confirms a potential causal relationship between skin microbi-ota and lung cancer, suggesting that these microbiota play a role in the progression of lung cancer. This discovery provides a new perspective on how skin microbiota affects lung cancer and lays a foundation for developing targeted diagnostic and treatment strategies for lung cancer in the future.

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Introduction

Lung cancer is one of the malignant tumors with high morbidity and mortality in the world, and nearly one million people lose their lives due to lung cancer every year [1]. Lung cancer is divided into SCLC (accounting for about 15% of cases) and NSCLC (accounting for about 85% of cases); the main histological subtypes of NSCLC include LUSC and LUAD [2]. In economically

developed countries and regions, the incidence of lung cancer has been controlled, but in developing countries or economically under-developed regions, the incidence rate of lung cancer is still on the rise [3 - 5]. This dif-ference is closely related to a variety of factors, including the implementation of tobacco control measures, the allocation of medical resources, the popularity of public health awareness, and the level of environmental pollution and occupational exposure [6,7]. In addition, studies in recent years have continuously revealed that there is a close rela-tionship between the occurrence and development of lung cancer and genetic mutations [8,9]. Therefore, developing effective prevention strategies and clarifying the potential causal relationship between risk factors and lung cancer is crucial for the prevention and treatment of lung cancer. In this process, genome-wide association studies (GWAS) can play an important role and potential. By comprehensively scanning the entire genome, GWAS can identify genetic variants associated with lung cancer risk, thereby revealing potential genetic susceptibility factors. These findings not only deepen our understand-ing of the pathogenesis of lung cancer but also provide an important scientific basis for developing personalized prevention and treatment strategies.

As the first line of defense in immune defense, the skin not only blocks the invasion of pathogens through physical and chemical barriers but also maintains overall health through immune function and self-repair mechanism, preventing potential diseases and infections [10]. Skin microbiota refers to various microbial communities that inhabit human skin, including bacteria, fungi, and viruses, and play an important role in main-taining skin and human health [11]. The imbalance of skin microbiota and ecological imbalance may not only lead to skin diseases but also have an impact on overall health [10-13].

In recent years, studies have found that there is a significant correlation between the lung and intestinal microbiota and the occurrence, development, and prognosis of lung cancer, which highlights the important role of the microbiota in lung diseases, especially lung cancer [14-18]. The imbalance of lung and intestinal microbiota may promote the occurrence and development of lung cancer by triggering metabolic changes, suppress-ing the immune system, and releasing inflammatory factors [15]. However, although the skin is another major microbial community gathering place and the relationship between its microbiota and skin diseases and systemic diseases has been studied, the relationship between the skin microbiota and lung cancer remains underexplored [12,19-23]. Given the important findings of lung and gut microbiota in lung cancer research, this raises concerns about the potential relevance of skin microbiota and lung cancer. Specifically, whether there is a correlation between the skin microbiota and lung cancer similar to that between the gut microbiota and lung cancer needs further research to verify.

MR is a powerful tool for exploring causal relationships between complex traits and genetic variation. It uses the data of genetic variation found in GWAS and uses these variations as instrumental variables (IV) to help researchers infer the causal relationship between environmental factors or biomarkers (i.e. exposure) and diseases or other health outcomes (i.e. outcomes). According to Mendelian inheritance law, these instru-mental variables can effectively reduce the influence of confounding factors due to the random allocation of alleles, thus providing higher research reliability. Compared with one-way MR, bidirectional MR can not only evaluate the causal effect of exposure on the outcome but also reveal the potential causal relationship of the outcome to the ex-posure, so that we can have a more comprehensive understanding of the causal rela-tionship. This study used a two-sample bidirectional Mendelian randomization (MR) analysis method to systematically evaluate the causal relationship between skin flora and lung cancer. Through this method, we can more accurately understand wheth-er skin flora causes lung cancer and explore possible biological mechanisms to provide a scientific basis for future disease prevention and treatment.

Materials and Methods

Research Design

We used a two-sample bidirectional Mendelian randomization (MR) analysis to explore the causal relationship between skin microbiota and lung cancer risk. First, we use skin microbiota phenotypes as exposure variables to analyze which skin microbiota pheno-types may have a potential causal relationship with lung cancer risk. Subsequently, we take lung cancer as an exposure variable to explore the potential reverse causal rela-tionship between lung cancer and skin flora phenotype. Our MR study is based on the following three main assumptions: (1) Correlation hypothesis: The selected genetic var-iation (as an instrumental variable) is significantly associated with the risk factors dis-cussed in the study; (2) Independence hypothesis: genetic variation is not associated with other confounding factors that may affect the results; (3) The exclusionary limita-tion hypothesis: The genetic variation selected as an instrumental variable affects the outcome only through the risk factor of interest, and not through other pathways that are not directly related.

Data Sources of Skin Microbiome and Lung Cancer

The summary statistics for 150 genome-wide association study (GWAS) traits related to skin bacteria are sourced from the GWAS database. The GWAS summary statistics are sourced from the identifiers GCST90133164 to GCST90133313 (https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90133001-GCST90134000/).Lucas Moitinho-Silva et al. conducted a genomic association study (GWAS) on 1656 skin samples from two German cohorts, KORA FF4 (324 subjects) and Pop-Gen (273 subjects) [24]. These skin samples covered Three different skin microenvi-ronments: dry, moist, and sebaceous.

Through analysis, they identified 23 sites that were significant at the genome-wide level and contained 30 potential key genes. A total of 79 bacterial characteristics were ana-lyzed, including 3 phyla, 4 classes, 7 orders, 7 families, 15 genera, and 43 ASVs. Data information. Appendix File 1: Table S2).

FinnGen database is an important research platform, that integrates large-scale health data from Finland's health registry and genetic data from Finland's biological library (https://www.finngen.fi/en). In this study, we obtained NSCLC (5,315 cases and 308,878 controls), LUAD (1,590 cases and 312,603 controls), and LUSC (1,510 cases and 312,683 controls) from the FinnGen database. GWAS of SCLC (717 cases and 313,476 controls). The detailed information on the data is shown in Table 1.

	Exposure and outcome	Case/controls or sample sizes	Year	Consortium	Phenotypic code	Ancestry
1	skin microbiota	1656	2022	References[24]	GCST90133164-GCST90133313	European
2	NSCLC	5,315/308,878	2022	FinnGen	C3_LUNG_NONSMALL_EXALLC	European
3	LUAD	1,590/312,603	2022	FinnGen	C3_NSCLC_ADENO_EXALLC	European
4	LUSC	1,510/312,683	2022	FinnGen	C3_NSCLC_SQUAM_EXALLC	European
5	SCLC	717/313,476	2022	FinnGen	C3_SCLC_EXALLC	European

Table 1: Data Sources

Selection of Instrumental Variables (IV)

Choosing appropriate instrumental variables is key to ensuring the validity of MR anal-ysis. The selected instrumental variables must strictly satisfy the three main assumptions mentioned above: correlation assumption, independence assumption, and exclusion re-striction assumption. In addition, we follow the guiding principles in the STROBE-MR Statement to ensure the normativity and reliability of the research (Appendix File 1: Ta-ble S1) [25]. Firstly, we used P<5e-06 as the significance threshold for screening in-strumental variables. This method is widely used in Mendelian randomization (MR) studies, especially when the number of genome-wide significant single nucleotide polymorphisms (SNPs) available for analysis is limited [26]. Through this threshold screening, more genetic variants can be captured, providing richer information for caus-al inference. Although including more SNPS may introduce some weak-effect instrumental variables, overall, this strategy enhances the statistical power of the analysis and the explanatory power of the results. Secondly, we evaluated these SNPs for genetic linkage imbalance using data provided by the European 1000 Genomes Project as a reference panel, with a threshold of r2 < 0.001 and a window size of 10,000 kb. Finally, we use the PhenoScannerV2 database (http://www.phenoscanner.medschl.cam.ac.uk/) for potential confounding factors related to identifying and eliminating SNPs, such as smoking and alcohol intake [27].

In this study, we used two-sample bidirectional MR analysis and combined with multi-ple statistical methods to explore the relationship between skin flora and different sub-types of lung cancer (including NSCLC, LUSC, LUAD, and SCLC) causal relation-ship between. The study mainly applied the inverse variance weighting (IVW) method to accurately estimate the overall causal effect, which improves the accuracy and ro-bustness of the results by weighting the average of the effect estimates of each instru-mental variable [28]. To verify the validity of the causal relationship under different conditions, we also conducted supplementary analyses using methods such as MR-Egger regression, weighted median (WM), simple mode, and weighted mode. Re-sults were expressed by odds ratio (OR) and 95% confidence interval (CI), and a P-value <0.05 was considered statistically significant [29]. To comprehensively evaluate the reliability of the research results, we conducted a number of sensitivity analyses. MR-Egger intercept test and MR-PRESSO global test analysis were used to detect po-tential horizontal pleiotropy or outliers (P value <0.05 indicates the presence of horizontal pleiotropy). After identifying the outliers, the MR-PRESSO outlier test excludes them from the analysis and re-performs the MR Analysis to correct for the horizontal pleiotropy caused by these outliers. Cochran's Q test was used to assess the heterogeneity of selected SNPs, and the heterogeneity was determined by calculating the variation of SNP effect estimates.

We also applied "Leave-one-out analysis" to evaluate the impact of each SNP by re-moving and reanalyzing SNPs one by one, which helps to verify whether the results are significantly affected by a single SNP and exclude possible outliers interference with the results [30]. In addition, we utilize visualization tools such as forest plots, scatter plots, funnel plots, and leave-one-out analysis plots to visually present the analysis results. (Appendix File 2-5). For the reverse causal relationship between skin microbiota and different subtypes of lung cancer (NSCLC, LUSC, LUAD, SCLC), we used the same method to perform reverse MR analysis.

All analyses were performed using R software (version 4.3.2, www.r-project.org/) and the TwoSampleMR software package (version 0.5.8).

Results

Our forward MR analysis results demonstrate that 11 distinct skin microbiota pheno-types are significantly associated with NSCLC. These microbiota can be categorized into the following groups: 5 genera (Genus): Staphylococcus Genus (including ASV122 [Staphylococcus (unc.)] and ASV002 [Staphylococcus (unc.)]), Corynebacte-rium Genus(including ASV004 [Corynebacterium (unc.)] and ASV015 [Corynebacterium (unc.)]), Paracoccus Genus(including Genus: Paracoccus), P. acnes Ge-nus(including ASV001 [P. acnes]), and Desulfovibrio Genus (including ASV009 [D. nitroreducens]).2 families: Moraxellaceae (including ASV031 [Moraxellaceae (unc.)]) and Clostridiales (noted as Family: Clostridiales twice); and one order: Actinomycetales (including Order: Actinomycetales). Among these microbiota, six are considered to have protective effects, including Staphylococcus (ASV122), Corynebacterium (ASV004 and ASV015), Moraxellaceae (ASV031), Desulfovibrio (ASV009), and Ac-tinomycetales (Order: Actinomycetales). The remaining five microbiota are considered risk factors, including Staphylococcus (ASV002), P. acnes (ASV001), Paracoccus (Genus: Paracoccus), and Clostridiales (Family: Clostridiales). Five skin microbiota phenotypes are significantly associated with LUSC. These microbiota are categorized as follows:Genus: Acinetobacter (Genus: Acinetobacter), Bacteroides (Genus: Bacteroides), Staphylococcus (including ASV076 [Staphylococcus (unc.)]), Propionibacte-rium acnes (including ASV001 [P. acnes]). Class: Gammaproteobacteria (Class: Gam-maproteobacteria).

Among these, Acinetobacter, Gammaproteobacteria, and Staphylococcus (ASV076) are identified as protective factors, while Bacteroides and Propionibacterium acnes (ASV001) are considered risk factors. In the study of LUAD, 13 skin microbiota phe-notypes show significant associations with the disease. These microbiota are catego-rized as follows:Genus: Corynebacterium (including ASV015 [Corynebacterium (unc.)] and ASV004 [Corynebacterium (unc.)]), Anaerococcus (including ASV007 [Anaero-coccus (unc.)]), Acinetobacter (Genus: Acinetobacter), Haemophilus (Genus: Hae-mophilus), Veillonella (including ASV070 [Veillonella (unc.)]), Staphylococcus (including ASV006 [S. hominis] and Genus: Staphylococcus), Bacteroides (Genus: Bac-teroides). At the Order level, the relevant categories are Actinomycetales (Order: Acti-nomycetales) and Burkholderiales (Order: Burkholderiales). At the Family level, the involved categories are Moraxellaceae (Family: Moraxellaceae) and Clostridiales (Fam-ily: Clostridiales). Among these, Corynebacterium (including ASV015 [Corynebacte-rium (unc.)] and ASV004 [Corynebacterium (unc.)]) and Actinomycetales (Order: Ac-tinomycetales) are considered to have protective effects. The following microbial phe-notypes are considered

risk factors associated with an increased risk of lung adenocarcinoma (LUAD): Veillonella (including ASV070 [Veillonella (unc.)]), Anaerococcus (ASV007 [Anaerococcus (unc.)]), Acinetobacter (Genus: Acinetobacter), Haemophilus (Genus: Haemophilus), Staphylococcus (including ASV006 [S. hominis] and Genus: Staphylococcus), Bacteroides (Genus: Bacteroides), Burkholderiales (Order: Burkhold-eriales), Moraxellaceae (Family: Moraxellaceae), and Clostridiales (Family: Clostridiales).In the study of small cell lung cancer (SCLC), six skin microbiota phenotypes were found to be significantly associated with the disease. These microbiota can be categorized as follows:Genus: Veillonella (including ASV070 [Veillonella (unc.)])Micrococcus (including ASV021 [Micrococcus (unc.)]) Haemophilus (Genus: Haemophilus) Staphylococcus (including ASV011 [Staphylococcus (unc.)]) Coryne-bacterium (including ASV015 [Corynebacterium (unc.)]) Family: Flavobacteriaceae (Family: Flavobacteriaceae) Among these, Veillonella is identified as having a protec-tive effect against small cell lung cancer, while the other five microbiota Micrococcus, Haemophilus, Staphylococcus, Corynebacterium, and Flavobacteriaceae are associated with an increased risk of the disease. (Figure 1-5, Table 2). To ensure that the associa-tion between skin microbiota and the risk of lung cancer subtypes is not affected by po-tential biases, heterogeneity, or individual data points, we conducted a comprehensive sensitivity analysis. Cochran's Q test, MR-Egger intercept test, and MR-PRESSO anal-ysis found no evidence of directional pleiotropy ($P > 0.05$) and detected no significant heterogeneity. Leave-one-out analysis further validated the causal relationships ob-served in the study, ruling out potential bias or outlier effects, thus enhancing the relia-bility and consistency of the findings. (Appendix File 2-5). In the reverse MR analysis, where lung cancer subtypes were treated as the exposure and skin microbiota as the outcome, no significant results were detected.

Trait	Serial number	ID	Skin_Site(Paracoccus)	Exposure (feature)	Effect	IVW		
						OR	CI	P_Value
NSCLC	1	GCST90133215	Forehead (sebaceous skin)	ASV122[Staphylococcus (unc.)]	Protection	0.939	0.909-0.991	0.009
	2	GCST90133208		ASV004 [Corynebacterium (unc.)]		0.963	0.933-0.993	0.018
	3	GCST90133222	Dorsal forearm (dry skin)	Order: Actinomycetales		0.961	0.93-0.994	0.019
	4	GCST90133235		ASV031[Moraxellaceae (unc.)]		0.972	0.951-0.994	0.014
	5	GCST90133303	Antecubital fossa (moist skin)	ASV009[D. nitroreducens]		0.966	0.933-0.999	0.043
	6	GCST90133181		ASV015[Corynebacterium (unc.)]		0.966	0.933-0.999	0.043
	7	GCST90133238	Dorsal forearm (dry skin)	Genus: Paracoccus	Risk	1.028	1.003-1.054	0.025
	8	GCST90133221		ASV001[P. acnes]		1.056	1.009-1.105	0.018
	9	GCST90133249		ASV002 [Staphylococcus (unc.)]		1.062	1.008-1.119	0.024
	10	GCST90133302	Incertae (moist skin)	Family: Clostridiales		1.034	1.006-1.062	0.018
	11	GCST90133225	Incertae (dry skin)	Family: Clostridiales		1.04	1.002-1.08	0.037
LUSC	1	GCST90133165	Antecubital fossa (moist skin)	Genus: Acinetobacter	Protection	0.925	0.856-0.999	0.046
	2	GCST90133198	Forehead (sebaceous skin)	Class: Gammaproteobacteria		0.925	0.872-0.982	0.01
	3	GCST90133275	Dorsal forearm (dry skin)	ASV076[Staphylococcus (unc.)]		0.925	0.875-0.979	0.007
	4	GCST90133291	Antecubital fossa (moist skin)	Genus: Bacteroides	Risk	1.076	1.001-1.156	0.046
	5	GCST90133221	Dorsal forearm (dry skin)	ASV001[P. acnes]		1.116	1.019-1.222	0.018
LUAD	1	GCST90133181	antecubital fossa (moist skin)	ASV015[Corynebacterium (unc.)]	Protection	0.929	0.876-0.986	0.043
	2	GCST90133222	dorsal forearm (dry skin)	order: actinomycetales		0.905	0.856-0.957	0.000
	3	GCST90133208	forehead (sebaceous skin)	ASV004 [Corynebacterium (unc.)]		0.92	0.867-0.976	0.006
	4	GCST90133209	forehead (sebaceous skin)	ASV007[Anaerococcus (unc.)]	Risk	1.061	1.008-1.117	0.024
	5	GCST90133237	dorsal forearm (dry skin)	genus: acinetobacter		1.085	1.017-1.157	0.014
	6	GCST90133219		genus: haemophilus		1.044	1.006-1.085	0.024
	7	GCST90133207		order: burkholderiales		1.067	1.011-1.126	0.018
	8	GCST90133274		ASV070 [Veillonella (unc.)]		1.058	1.007-1.111	0.026
	9	GCST90133176	antecubital fossa (moist skin)	ASV006 [S. hominis]		1.057	1.003-1.113	0.037
	10	GCST90133284		phylum: bacteroidetes		1.119	1.014-1.236	0.026
	11	GCST90133293		genus: staphylococcus		1.064	1-1.131	0.049
	12	GCST90133304		family: moraxellaceae		1.106	1.008-1.213	0.033
	13	GCST90133302	incertae (moist skin)	family: clostridiales		1.053	1.004-1.104	0.033
SCLC	1	GCST90133274	Cubital fossa (moist skin)	ASV070 [Veillonella (unc.)]	Protection	0.907	0.825-0.998	0.045
	2	GCST90133183	Cubital fossa (moist skin)	ASV021 [Micrococcus (unc.)]	Risk	1.085	1.009-1.166	0.028
	3	GCST90133219	Dorsal forearm (dry skin)	Genus: Haemophilus		1.067	1.014-1.123	0.012
	4	GCST90133256		ASV011[Staphylococcus (unc.)]		1.075	1.008-1.147	0.027
	5	GCST90133310		Family: Flavobacteriaceae		1.102	1.001-1.212	0.047
	6	GCST90133257		ASV015[Corynebacterium (unc.)]		1.109	1.026-1.198	0.009

Table 2: Factors of Harmful and Protective Effects of Skin Microbiota on Different Subtypes of Lung Cancer

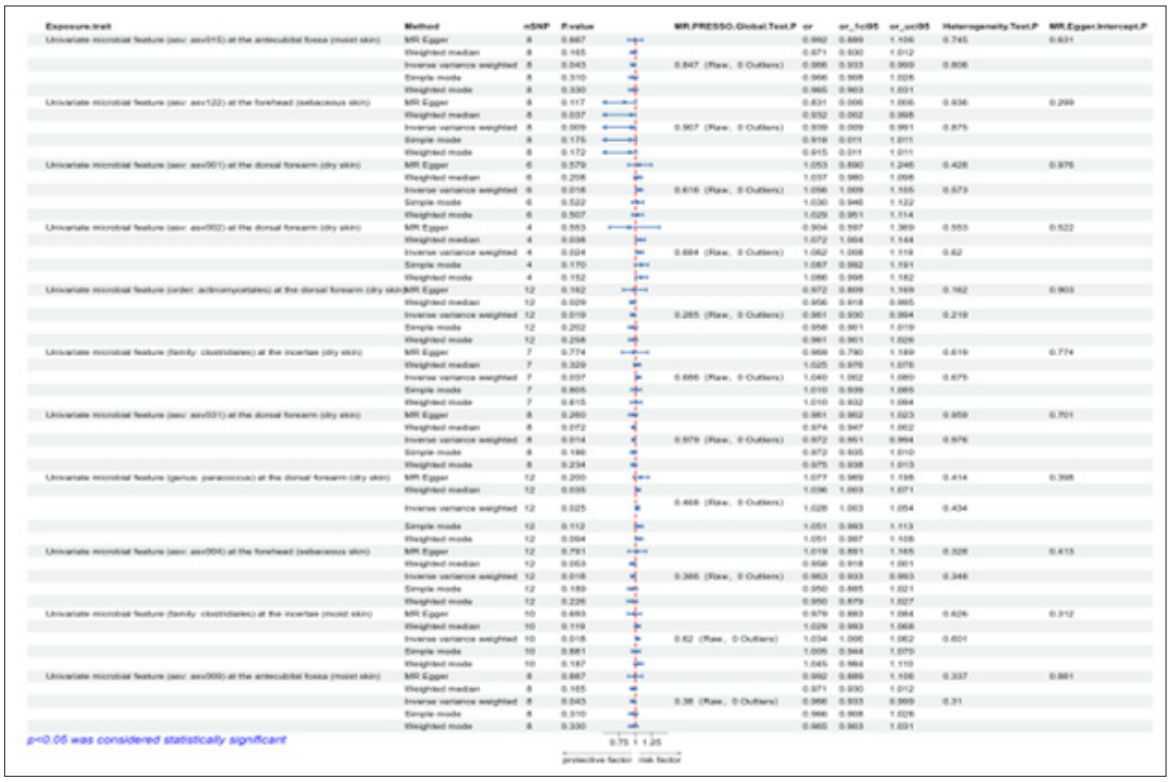

Figure 1: Forest Plot Illustrating the Causal Effects of Skin Microbiota on Non-Small Cell Lung Cancer

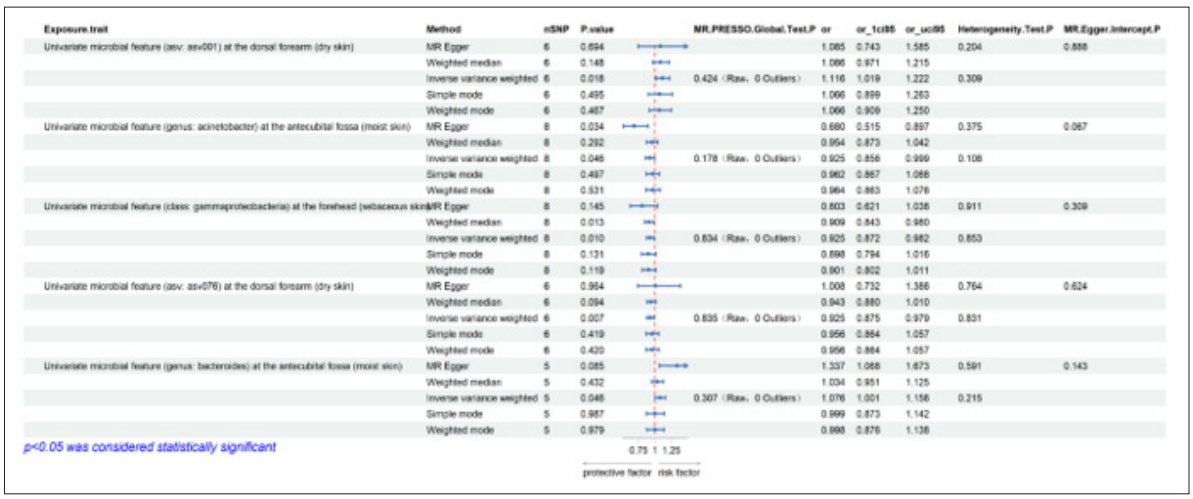

Figure 2: Forest Plot Illustrating the Causal Effects of Skin Microbiota on Lung Squa-mous Cell Carcinoma

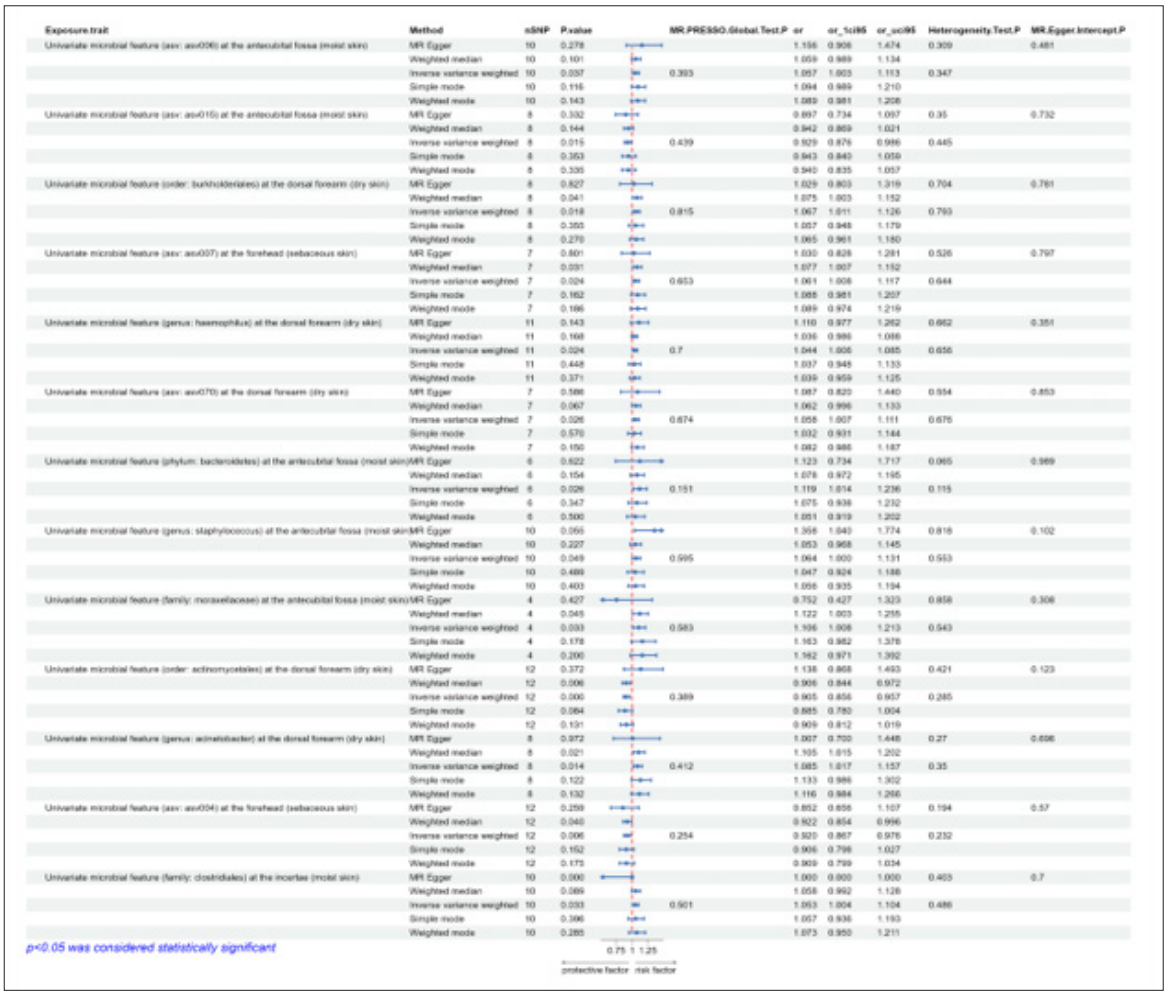

Figure 3: Forest Plot Illustrating the Causal Effects of Skin Microbiota on Lung Ade-nocarcinoma

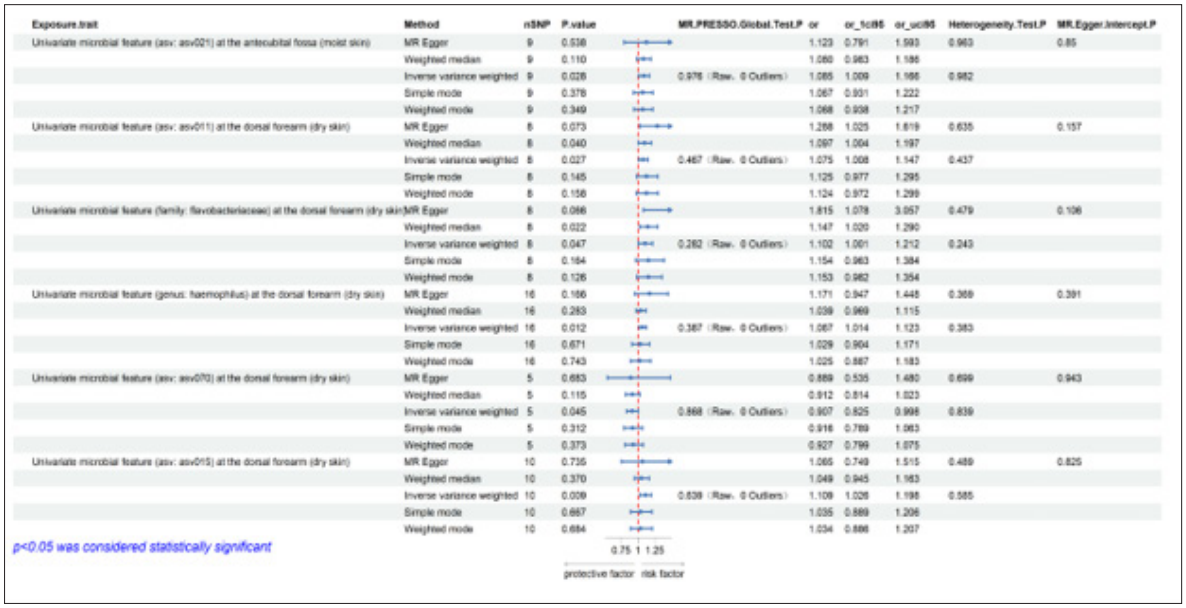

Figure 4: Forest Plot Illustrating the Causal Effects of Skin Microbiota on Small Cell Lung Cancer

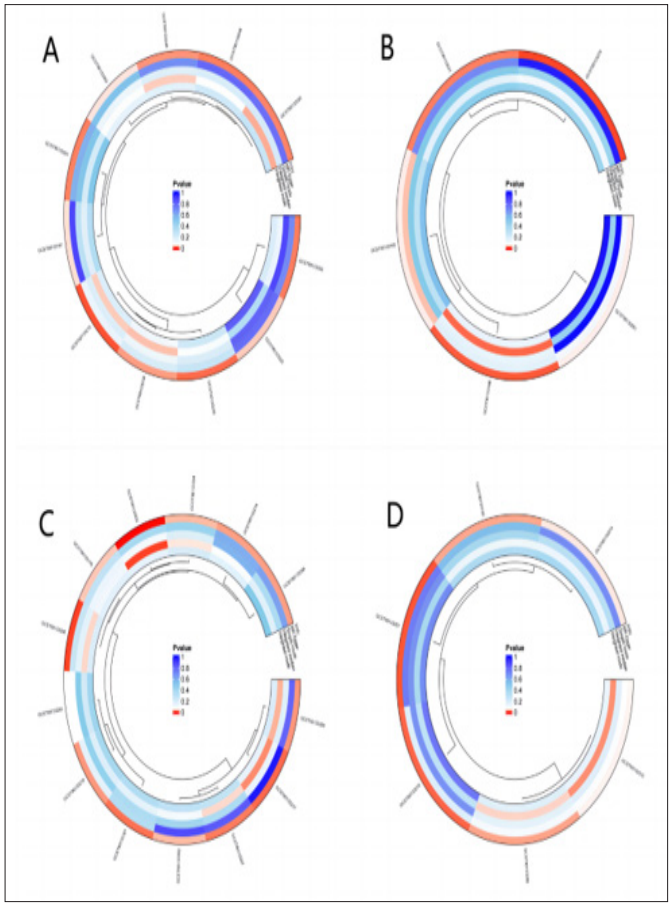

Figure 5: Circle Heatmap of MR Analysis Results Showing the Association between

Skin Microbiota and Lung Cancer Subtypes
A. Skin Microbiota and Non-Small Cell Lung Cancer
B. Skin Microbiota and Squamous Cell Lung Cancer
C. Skin Microbiota and Adenocarcinoma
D. Skin Microbiota and Small Cell Lung Cancer Risk

The outer circle of the heatmap displays the IDs of skin microbiota phenotypes with positive results, while the inner circle uses different colors to represent p-values from various sensitivity analyses.

Discuss

Based on the latest lung cancer summary statistics from large-scale genome-wide asso-ciation study (GWAS) databases, specifically the FinnGen database, we conducted bi-directional two-sample Mendelian randomization (MR) analysis to investigate the potential causal relationships between skin microbiota and various subtypes of lung cancer, including NSCLC, LUSC, LUAD, and SCLC. The results of the study indicate that different skin microbiota characteristics have varying impacts on the different subtypes of lung cancer. In NSCLC, the microbiota Staphylococcus ASV122, Corynebacterium ASV004 and ASV015, Moraxellaceae ASV031, Desulfovibrio ASV009, and Actinomycetales demonstrate significant protective effects. In contrast, Staphylococcus ASV002, Propionibacterium acnes ASV001, Paracoccus, and Clostridiales are strongly associated with an increased risk of NSCLC. For LUSC, Acinetobacter, Gammaproteobacteria, and Staphylococcus ASV076 show protective effects, whereas Bacteroides and Propionibacterium acnes ASV001 are identified as potential risk factors. In LUAD, Corynebacterium and Actinomycetales exhibit protective effects, while Veillonella, An-aerococcus, Acinetobacter, Haemophilus, Staphylococcus, Bacteroides, Burkholderiales, Moraxellaceae, and Clostridiales are associated with an increased risk of LUAD. For SCLC, Veillonella exhibits a protective effect, whereas Micrococcus, Haemophilus, Staphylococcus, Corynebacterium, and Flavobacteriaceae are closely associated with an increased risk of SCLC. Detailed genetic analysis reveals the complex roles of skin mi-crobiota in different lung cancer subtypes, and it fills the gap in existing studies.

In our MR analysis, skin microbiota exhibit complex and diverse roles across different lung cancer subtypes (NSCLC, LUSC, LUAD, SCLC). For example, Staphylococcus exhibits protective effects in NSCLC (ASV122), LUSC (ASV076), and LUAD (ASV006), but is identified as a risk factor in SCLC (ASV011). Similarly, Corynebac-terium shows protective effects in both NSCLC (ASV004 and ASV015) and LUAD (ASV004 and ASV015), yet presents as a risk factor in SCLC (ASV015). The differing roles of these microbiota across various lung cancer types likely reflect their multifunc-tionality in distinct biological contexts, suggesting that the impact of microbiota on can-cer may be highly dependent on the host's microenvironment.P. acnes (Propionibacte-rium acnes) is identified as a risk factor in NSCLC (ASV001) and LUSC (ASV001). Bacteroides is considered a risk factor in both LUSC and LUAD. Clostridiales is asso-ciated with increased risk in NSCLC and LUAD. Acinetobacter shows a protective ef-fect in LUSC but is a risk factor in LUAD. Veillonella is a risk factor in LUAD (ASV070) and exhibits a protective effect in SCLC (ASV070). This dual role indicates that its impact may vary across different microenvironments. Additionally, Micrococcus and Flavobacteriaceae are only observed in SCLC, suggesting that SCLC may have unique microbial characteristics. Taken together, these findings not only reveal similari-ties and differences between the skin microbiome in different lung cancer subtypes but also highlight the potential impact of microbial subtypes or specific phenotypes on lung cancer initiation and development, further reminding us to focus on subtle taxonomic differences when studying the microbiota.

Historically, due to limitations in early research and technology, it was widely believed that the lungs were sterile. However, with advancements in molecular biology and the progress of high-throughput sequencing technologies, researchers have discovered that the lungs actually host a complex microbial community [31,32]. As this traditional view has gradually shifted, an increasing number of studies have begun to focus on the relationship between the microbiome and lung cancer, particularly research investigating the impact of pulmonary microbiota and gut microbiota on lung cancer. Huang et al. found that there are differences in the microbial profiles of patients with different types of lung cancer, which may be closely related to the cancer's pathological type and meta-static status [33]. In patients with lung adenocarcinoma, the abundance of Thermus is higher, while Ralstonia is less abundant. Conversely, in patients with LUSC, the abun-dance of Acidovorax, Klebsiella, Rhodoferax, and Anaerococcus is significantly higher. Additionally, in non-metastatic lung adenocarcinoma patients, the abundance of Firmic-utes and Streptococcus is significantly higher compared to metastatic patients. Con-versely, in lung squamous cell carcinoma patients, the abundance of Veillonella and Rothia is higher in metastatic cases. The team led by S.H. Lee et al. used PCR amplification and pyrosequencing techniques to discover significant differences in the microbi-al communities in bronchoalveolar lavage fluid between lung cancer patients and those with benign

tumors [34]. Specifically, lung cancer patients have higher abundances of Firmicutes, Veillonella, and Megasphaera in their microbiota. They also proposed that Veillonella and Megasphaera could serve as potential biomarkers for lung cancer. Addi-tionally, Jin et al. analyzed the microbiome features in bronchoalveolar lavage fluid (BALF) through metagenomic analysis and found that Prevotella has the highest abun-dance in lung cancer patients [35]. The pulmonary and gut microbiomes interact com-plexly through the gut-lung axis, involving mechanisms such as microbial colonization, immune function modulation, inflammatory responses, and metabolic products, thereby affecting lung health [16,36-39]. Studies on the relationship between the gut microbiome and lung cancer suggest that Firmicutes may play varying roles in different types of lung cancer. For example, the study by Yingchen Li et al. found that the Eubacterium hallii group and Collinsella within the phylum Firmicutes are associated with an in-creased risk of LUAD [15]. Additionally, Actinomycetaceae and Actinomycetales are positively correlated with SCLC, while Christensenellaceae and Lachnospiraceae have a protective effect against SCLC. Additionally, the Ruminococcus torques group within the phylum Firmicutes is associated with an increased risk of LUSC. Similarly, the study by Wenjing Yang et al. also indicates that the Lachnospiraceae family and the E. ruminantium group within the phylum Firmicutes may have a protective effect against SCLC [40]. In summary, the role of the microbiome in different subtypes of lung cancer exhibits diversity and complexity. The specific effects depend not only on the types of microorganisms but also on their location and the biological context of the host. This complex interaction underscores the need to consider these multi-layered differences and mechanisms when studying the relationship between microbiomes and cancer.

Research on skin microbiomes and cancer mainly focuses on their impact on skin can-cer, while the genetic factors that regulate the interactions between skin microbiomes and the host remain insufficiently understood. Kullander et al. found that Staphylococcus aureus is more prevalent in the skin of patients with squamous cell carcinoma than in healthy skin, suggesting that the skin barrier function in squamous cell carcinoma may be weakened or compromised, facilitating the colonization of S. aureus [41]. Another study highlighted that Staphylococcus epidermidis in healthy skin can inhibit the growth of Staphylococcus aureus, potentially helping to reduce the risk of skin tumors [42]. A recent analysis of skin samples from 27 patients with advanced melanoma re-vealed a significant increase in the abundance of Corynebacterium in the skin of ad-vanced melanoma patients [43].

Many microorganisms form symbiotic relationships with their hosts, influencing the host through mechanisms such as modulating immune responses, affecting metabolism, and regulating circadian rhythms [44]. At the same time, the host shapes and maintains the composition and function of its microbiome through diet, lifestyle, and immune sys-tem regulation [45]. Due to the continuous pressure exerted by the skin microbiome on the immune system, the skin contains a vast number of immune cells, approximately 20 billion effector lymphocytes, including a significant population of memory T cells [46]. The skin microbiome not only maintains normal immune system function but also en-hances defense against external threats. It regulates immune responses by influencing local levels of interleukin-1 (IL-1) and affects T cell function, increasing T cell activity and promoting the production of cytokines related to host defense and inflammation, such as IL-17-A and interferon-γ [47]. Additionally, the skin microbiome influences the production of antimicrobial peptides (AMPs) in skin cells. As a crucial component of the innate immune system, AMPs help defend against pathogens, thereby enhancing the host's initial defense against both commensal and foreign pathogens [48]. It also promotes the expression of other key defense mechanisms, such as enhancing components of the complement system, which helps to opsonize pathogens and initiate inflammatory responses, thereby effectively recognizing and clearing pathogens [49]. During wound healing, the skin microbiome plays a crucial role. For example, Staphylococcus epider-midis secretes lipoteichoic acid, which binds to Toll-like receptor 2 (TLR2). This inter-action activates TLR2 signaling pathways in the immune system, aiding in the recogni-tion and response to pathogens. By inhibiting excessive inflammatory responses, it helps prevent wound over-inflammation and promotes faster repair and regeneration [50].

Increasing research evidence suggests that, in addition to the gut-lung axis, there are other important microbiome axes, such as the gut-brain axis, the gut-oral axis, the gut-skin axis, and the recently studied lung-brain axis [51-62]. Some studies have fur-ther revealed interactions between these axes, such as the influence of the gut microbi-ome on the brain and skin through the gut-brain-skin axis [63-65]. These microbiome axes reflect the profound impact that microbiomes have on various organ systems (such as the skin, lungs, brain) and overall health. In these microbiome axes, the immune sys-tem plays a crucial mediating role. Microbiomes influence the health of various organs by modulating both local and systemic immune responses. For example, the gut micro-biome can alter skin immune responses by regulating immune factors and pro-inflammatory molecules, or influence lung inflammation through molecules such as histamine [57,66]. Additionally, microbial metabolites (such as short-chain fatty acids and lipopolysaccharides) not only exert effects within their local environment but can also circulate through the bloodstream to other organs, thereby modulating their func-tion. For example, short-chain fatty acids can influence the severity of lung infections through immune modulation, while metabolites like lipopolysaccharides may impact brain health and function by disrupting the blood-brain barrier [67-69]. These studies indicate that microbiomes, through metabolites, signaling molecules, and im-mune-regulating factors, affect not only the local environment but also interact with other organ systems via various pathways, including blood circulation, neural routes, and the immune system. This cross-system influence reveals that the state of the micro-biome can regulate organ function far from its original environment through complex signaling networks. Recent research has demonstrated that the skin microbiome not on-ly affects skin cancer but may also influence primary liver cancer (PLC) through cross-system mechanisms [70]. Similarly, the skin microbiome may influence lung can-cer through these mechanisms.

However, this study also has certain limitations. Firstly, the GWAS data in the study predominantly come from European populations. While this choice reduces biases due to racial differences, the genetic variation across different ethnic groups limits the generalizability of the findings, especially when applying results to other populations. Addi-tionally, the GWAS data for skin microbiomes are still in the preliminary stages of de-velopment. Limited sample sizes and incomplete strain-level information may affect the ability to detect significant associations, thus reducing statistical power. Finally, our MR analysis reveals a potential causal relationship between skin microbiomes and lung cancer, but the specific biological mechanisms remain unclear. Furthermore, the rela-tionship between microbiomes and host health is complex and involves intricate interac-tions beyond simple causality. Furthermore, the relationship between microbiomes and host health is complex and involves intricate interactions beyond

simple causality. Therefore, future research should focus more on exploring the complex coordination and interactions between the host and skin microbiome to gain a more comprehensive understanding of the role of skin microbiomes in lung cancer development. This ap-proach could provide new perspectives for the prevention and treatment of the disease.

Conclusion

This study, through a two-sample MR analysis, confirmed a causal relationship between the skin microbiome and lung cancer. We found that specific skin microbiome features exhibited significant protective effects or risk factors across different lung cancer subtypes. These findings not only deepen our understanding of the role of the skin micro-biome in the pathogenesis of lung cancer but also provide new potential targets for fu-ture prevention and treatment strategies. Future research should further validate these findings and explore the underlying biological mechanisms and their potential clinical applications. Overall, this study provides valuable insights into the potential relationship between the skin microbiome and lung cancer, advancing the application of microbiome research in cancer studies.

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