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ORIGINAL RESEARCH

Causal Association Between Skin Microbiota and Malignant Melanoma: Genetic Insights From Mendelian Randomization

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Background: Malignant melanoma (MM) is an extremely aggressive type of skin cancer that represents a major risk to human health. Earlier observational research has indicated that skin microbiota could play a role in the development and advancement of MM. Nevertheless, the causal link between skin microbiota and MM is still unclear.

Methods: Utilizing data from genome-wide association studies (GWAS) conducted on a European cohort, we applied Mendelian randomization (MR) to evaluate the causal link between skin microbiota and MM. The analysis involved various MR methodologies, including inverse variance weighting (IVW), MR-Egger regression, weighted median, weighted mode and simple mode. Furthermore, we performed sensitivity analysis employing the intercept test of MR-Egger, the Cochran's Q test, the MR-PRESSO approach, and a leave-one-out method.

Results: By conducting MR analysis on the KORA FF4 cohort, we identified several skin microbiotas (ASV003 [Staphylococcus (unc).], ASV016 [Enhydrobacter (unc).], and ASV021 [Micrococcus (unc).]) related with an elevated risk of MM. Conversely, genus: Finegoldia and class: Alphaproteobacteria were shown to inhibit the occurrence of MM. Additionally, MR analysis of the PopGen cohort revealed that ASV021 [Micrococcus (unc).] and family: Moraxellaceae were identified as possible risk factors for MM.

Conclusion: Our research offers new insights into the connection between skin microbiota and MM, indicating that skin microbiota might affect the onset and advancement of MM. Therefore, focusing on skin microbiota could be a valuable strategy for the prevention, identification, and management of MM.

Keywords: Skin microbiota, Malignant melanoma, Genome-wide association study, Mendelian randomization

Introduction

Malignant melanoma (MM), a type of malignant tumor originating from melanocytes, represents the most lethal form of skin cancer.[1] Although the incidence of MM is lower compared to other skin cancers, it accounts for more than 90% of skin cancer-related deaths due to its highly aggressive nature.[2] Epidemiological studies indicate that potentially 325,000 new cases of MM will occur in 2020, leading to approximately 57,000 fatalities attributed to the disease. If the incidence rate remains constant throughout 2020, it is estimated that the worldwide impact of melanoma could rise to about 510,000 new cases and 96 million deaths by the year 2040, which represents an alarming fiCgure[3].Surgery is currently the most important method to treat MM, and its early surgical resection rate is high (>90%).[4] However, many patients are already in the middle and advanced stages when MM is discovered, and treatment options are limited.[5] As a result, identifying novel markers and possible interventions holds substantial importance for the prompt diagnosis, management, and therapy of MM.

As the organ that occupies the greatest surface area in the human body, the skin plays a key role in executing several physiological functions such as safeguarding against external harm and regulating homeostasis.[6] The functions of the skin can be primarily attributed to the diverse array of microbiota that inhabit its surface. Research indicates that there are

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intricate relationships between the skin microbiota and the skin of the organism, which are crucial for sustaining the skin's barrier function and overall health. These interactions suggest that a balanced and varied microbiome is fundamental for protecting the skin from external threats and maintaining its integrity, thereby highlighting the significance of these microbial communities in dermatological well-being.[7,8] However, if human skin is continuously exposed to various harmful internal and external environments, this balance will be disrupted, leading to a variety of skin diseases,[9] which is similar to intestinal flora.[10] Compared to normal human skin tissue, patients with squamous cell carcinoma and actinic keratosis exhibit a higher prevalence of Staphylococcus aureus and a reduced abundance of commensal microorganisms.[11] In their examination of the skin microbiota within a melanoma model, Mrazek et al[12] discovered substantial differences in both the bacterial composition and the diversity of microbiota on the skin surface of the melanoma model when compared to normal skin. Giese et al[13] demonstrated that Staphylococcus aureus can enhance melanoma cell aggregation and invasion through lipids generated by the lipase Sal2. These suggest that skin microbiota could be crucial in influencing the development and progression of MM. Another study revealed that a significant presence of Corynebacterium spp. exists in the extremities of patients with stage III/IV multiple myeloma. This bacterium stimulates the production of IL-17, which, in turn, can enhance the proliferation and invasion of MM cells by the IL-6–Stat3 signaling pathway.[14,15] However, current research on skin microbiota and MM is limited, and their correlation needs to be further investigated.

Mendelian randomization (MR) represents a method in epidemiology that evaluates the causal relationships between exposures and outcomes.[16] In comparison to randomized controlled trials, the MR design is primarily devoid of confounding and reverse causation, as genes are assigned randomly at conception, significantly minimizing the potential biases associated with observational studies.[17] In this research, we examined skin microbiota as a factor of exposure and MM as an outcome variable to explore the causal association between skin microbiota and the occurrence of MM using MR analysis. This approach aims to offer new strategies for the prevention and management of malignant melanoma.

Materials and Methods

Study Design

The design of our study is depicted in Figure 1. In this research, single nucleotide polymorphisms (SNP), which signify genetic variations, were chosen as instrumental variables for MR analysis. This analysis is based on three key

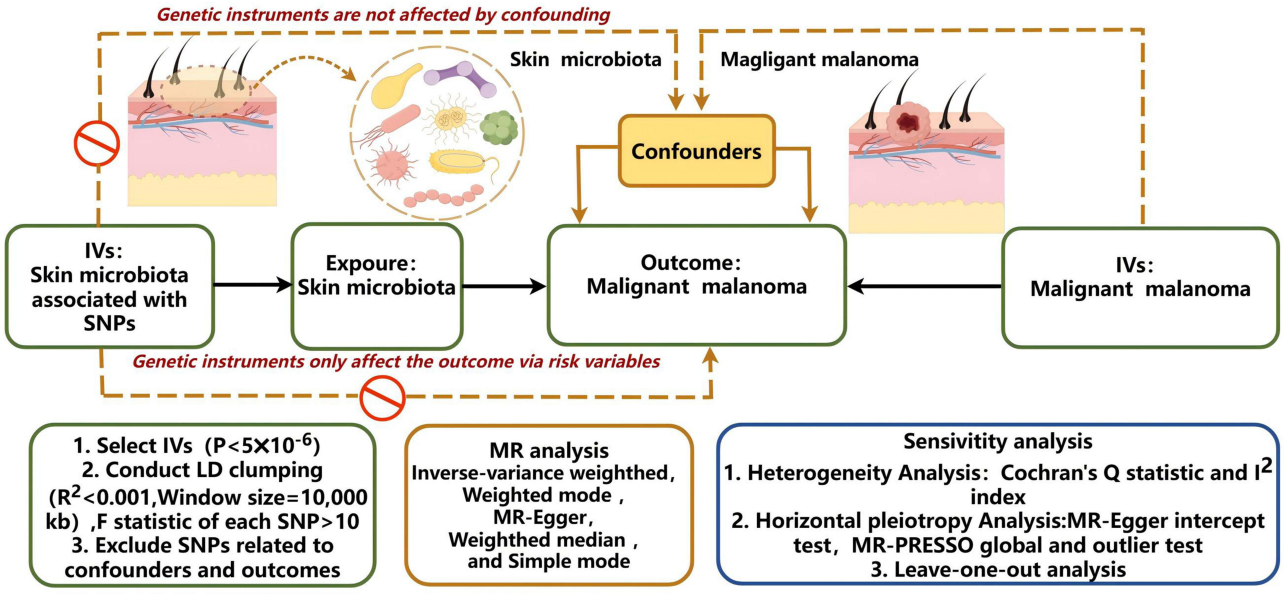

Figure 1 The design of Mendelian randomization (MR) study by Figdraw.

assumptions: (1) The instrumental variable has a direct relationship with the exposure factor; (2) The instrumental variable is not influenced by any confounding factors; and (3) The instrumental variable affects the outcomes exclusively through the exposure factor.[18]

Data Collection

Summary statistics for MM were extracted from various GWAS databases. MM genetic variation data (GWAS ID: ieu-b-4969) was publicly accessed at https://www.ebi.ac.uk/gwas, comprising of 375,767 samples (3,751 cases and 372,012 controls). Data concerning skin microbiota have been obtained from research initiatives led by the Biobank PopGen and the KORA Study Center. This study involved a total of 597 participants drawn from two distinct cohorts, all of whom are of German descent. The primary focus of the sequencing efforts was the V1-V2 region of the 16S rRNA gene, which enabled the creation of detailed microbial community profiles. Furthermore, comprehensive genome-wide association analyses were conducted on individual bacterial taxa at multiple, non-redundant taxonomic levels, which ranged from amplicon sequence variants (ASVs) to the phylum level. This multi-tiered approach allowed for a nuanced understanding of the microbiota present on the skin. In addition to this, the research explored the relationship between the composition of polybasic microbial communities and variations in the host's genetic makeup, thereby shedding light on how genetic diversity may influence the skin microbiota.[19]

The Selection Of instrumental Variables

This research undertook a comprehensive series of SNP screening procedures to validate the causal connection between skin microbiota and MM. The criterion for selection was set at $P = 5.0\times10^{-6}$. To mitigate the effects of linkage disequilibrium, the threshold was determined at $r^2 < 0.001$ and kb = 10,000 for choosing independent instrumental variables. The PhenoScanner platform was employed to pinpoint and eliminate variables linked to confounding factors. Furthermore, palindromic SNPs, as well as those absent from the outcome dataset or displaying allelic discordance between the exposure and outcome, were removed. Ultimately, the F value for the instrumental variable was computed, with only those variables having an F value exceeding 10 being included in the MR analysis. Outliers were identified through the MR-PRESSO model; any detected outliers were discarded, and the analysis was re-evaluated using the remaining SNP.[20,21]

Statistical Analysis

A total of five approaches were utilized to carry out an MR analysis aimed at exploring the potential causal link between skin microbiota and MM. These approaches comprised IVW, weighted median, weighted model, simple model, and MR-Egger regression. To evaluate the heterogeneity among SNPs, Cochrane's Q statistic was computed. A p-value greater than 0.05 indicates a likelihood of weak genetic pleiotropy, which can be considered negligible.[22] The MR-PRESSO approach was employed to identify and evaluate abnormal outliers. After eliminating these outliers, we examined if the results of the MR analysis were affected by an individual SNP.[23]

Results

As demonstrated in Figure 2A and B and Figure 3A and B, along with Supplementary Tables S1 and S2, our MR analysis of the KORA FF4 cohort has identified five skin microbiotas associated with the incidence of MM using IVW method. Specifically, we found that ASV003 [Staphylococcus (unc).] (OR = 1.0004, 95% CI = 1.0000–1.0008, p = 0.038), ASV016 [Enhydrobacter (unc).] (OR = 1.0007, 95% CI = 1.0002–1.0012, p = 0.007), and ASV021 [Micrococcus (unc).] (OR = 1.0008, 95% CI = 1.0003–1.0014, p = 0.002) are linked with an increased incidence of MM. Conversely, the genus: Finegoldia (OR = 0.9995, 95% CI = 0.9990–0.9996, p = 0.031) and the class: Alphaproteobacteria (OR = 0.9993, 95% CI = 0.9987–0.9999, p = 0.032) are found to decrease the risk of MM. Furthermore, our MR analysis of the PopGen cohort identified ASV021 [Micrococcus (unc).] (OR = 1.0005, 95% CI = 1.0001–1.0010, p = 0.021) and the family: Moraxellaceae (OR = 1.0006, 95% CI = 1.0000–1.0012, p = 0.043) as potential risk factors for MM. In Figure 4A–E and Figure 5A and B, We use the scatter plots to illustrate the causal link between skin microbiota and MM.

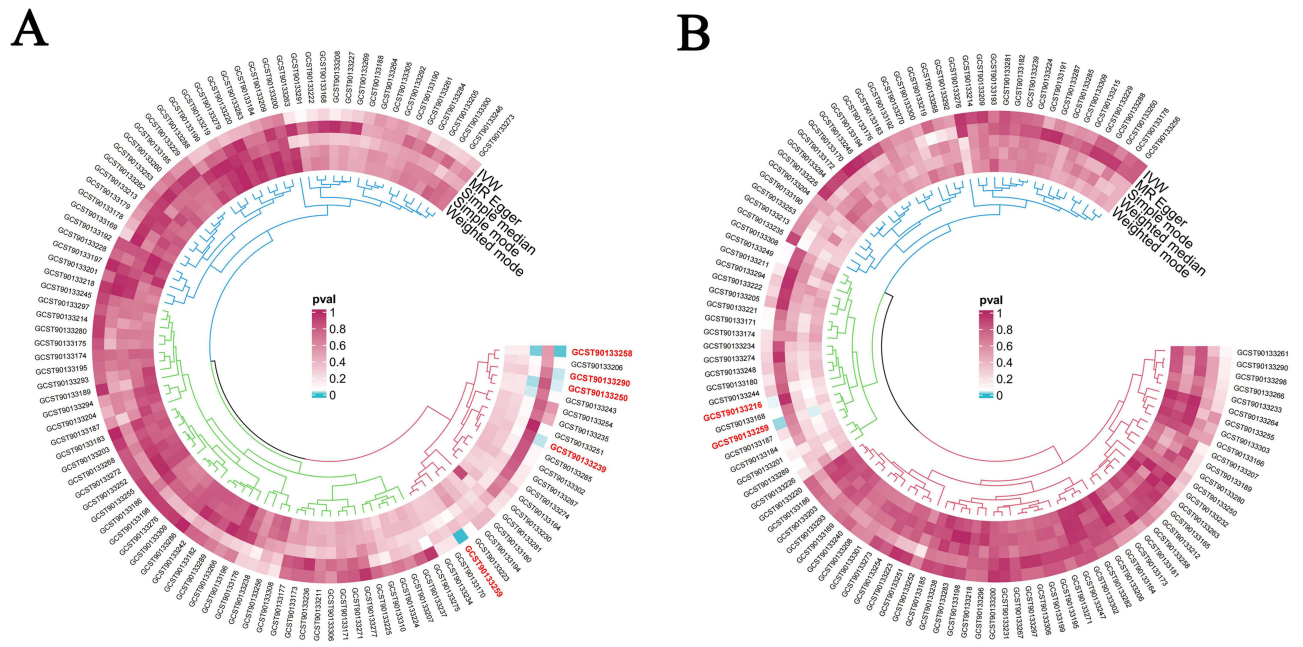

Figure 2 The causal connection between skin microbiota and MM. (**A**) KORA FF4 cohort; (**B**) PopGen cohort.

Sensitivity Analysis

In order to assess the potential bias within the MR analysis, we performed a comprehensive sensitivity analysis. The results obtained from the tests for heterogeneity and pleiotropy are detailed in Tables S3-S6. Notably, the MR-Egger intercept test revealed no evidence of horizontal pleiotropy in the skin microbiota under examination. This finding is further corroborated by the application of both the leave-one-out approach and the MR-PRESSO method, as depicted in Figure S1A–E, Figure S2A and B, and Tables S7-S8. Additionally, the results of the heterogeneity test indicated an absence of significant heterogeneity among the skin microbiota studied, as evidenced by a P-value exceeding 0.05.

Discussion

Based on the GWAS data, we conducted an MR analysis to investigate the causal relationship between skin microbiota and MM. Our findings indicate that ASV003 [Staphylococcus (unc).], ASV016 [Enhydrobacter (unc).], ASV021 [Micrococcus (unc).], and the family: Moraxellaceae are risk factors for MM, while genus: Finegoldia and class: Alphaproteobacteria serve as protective factors. This MR analysis substantiates the causality between skin microbiota and MM, indicating that skin microbiota may play a significant role in the onset and advacement of MM.

Staphylococcus are a diverse group of Gram-positive cocci, including Staphylococcus epidermidis, Staphylococcus albus, Staphylococcus aureus.[24] Previous studies have suggested that Staphylococcus is closely associated with the development and progression of various diseases, such as infections, tumors, and poisonings. Compared with normal skin tissue, MM tissue has a higher abundance of Staphylococcus aureus, which may lead to significantly enhanced ribosome, DNA repair and recombinant protein, pyrimidine metabolism, purine metabolism and other activities in tumor cells, promoting the progression of MM.[25] In addition, Wang et al[26] found that lipoteichoic acid derived from Staphylococcus epidermidis can promote the viability of MM cells by increasing the expression levels of multiple proteins such as TRAF1, CASP14 and CASP5 under UV exposure. This is consistent with our MR analysis results. However, there are also studies showing that Staphylococcus epidermidis can reduce the incidence of UV-induced tumors and inhibit the growth by producing N-hydroxyaminopurine (6-HAP).[27] Therefore, the role of Staphylococcus aureus in the pathogenesis of MM needs to be further explored.

Endohydrobacter is a genus of rod-shaped, gram-negative bacteria classified within the order Pseudomonas.[28] This genus has potential diagnostic significance in the early detection of colon cancer and might play a role in the

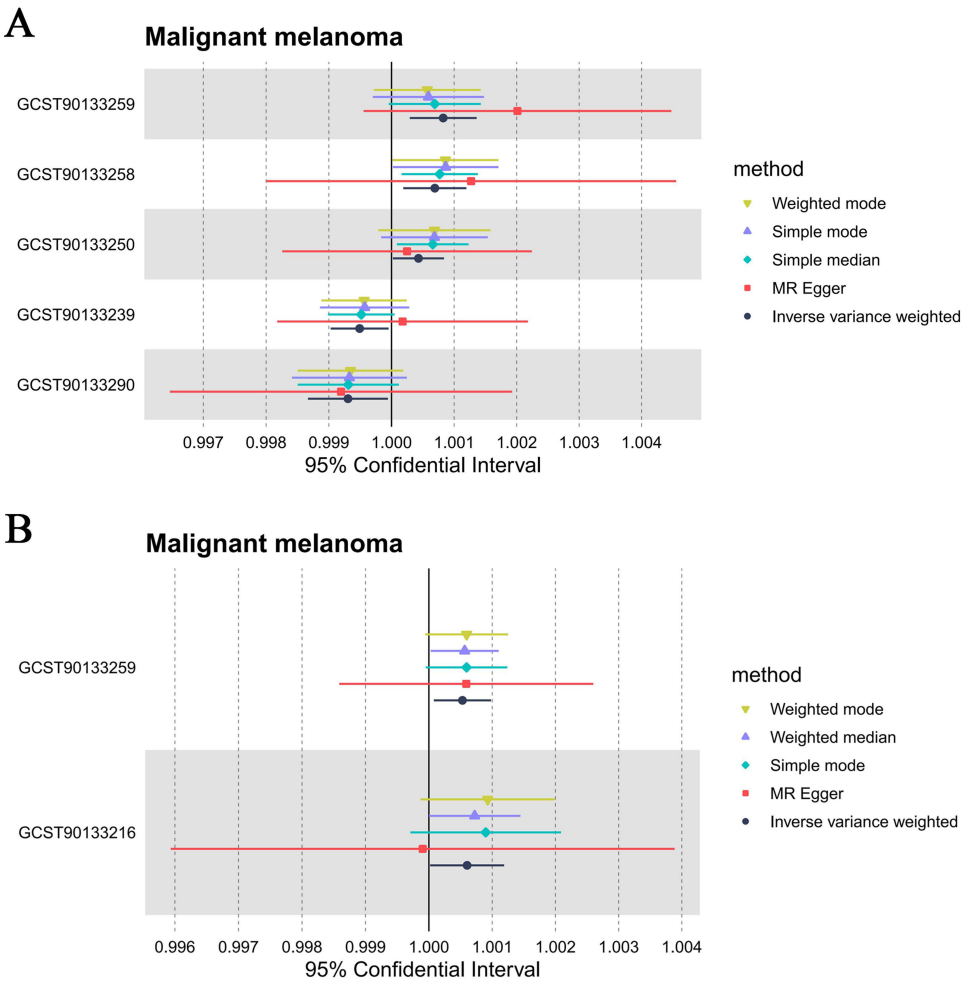

Figure 3 Forest plot of the causal relationship between skin microbiota and MM. (**A**) KORA FF4 cohort, ID for skin microbiota, GCST90133259: ASV021 [Micrococcus (unc.)]; GCST90133258: ASV016[Enhydrobacter (unc.)]; GCST90133250: ASV003 [Staphylococcus (unc.)]; GCST90133239: genus: Finegoldia; GCST90133290: class: Alphaproteobacteria. (**B**) PopGen cohort, ID for skin microbiota, GCST90133259: ASV021 [Micrococcus (unc.)]; GCST90133216: family: Moraxellaceae.

development and advancement of this disease.[29] Additionally, in individuals with locally advanced rectal cancer, the quantity of Enhydrobacter was notably elevated when compared to those who showed a positive response to neoadjuvant treatment.[30] However, the current research on Enhydrobacter in skin malignant tumors has not yet been reported, and further exploration by researchers is needed. Alphaproteobacteria are oligotrophic bacteria that inhabit not only the surface of human skin but also thrive in low-nutrient environments, such as deep-sea sediments, glacial ice, and deep underground soil.[31] Parrot etal[32] found that compounds extracted from the Alphaproteobacterium strain MOLA1416, isolated from marine lichen, can produce significant anti-tumor effects on B16 melanoma cells. This may be one of the reasons for its inhibitory effect on the occurrence of MM. Micrococcus are commonly found in different environments, including skin, soil, and air.[33] Moraxellaceae is an obligate anaerobic Gram-positive coccus that can colonize the mucous membranes of the skin, genitourinary tract, upper respiratory tract, gastrointestinal tract and oral cavity.[34] Finegoldia is an anaerobic Gram-positive coccus capable of causing serious infections in the skin, joints, gastrointestinal tract, and other parts of the body.[35] While the involvement of these three bacteria in MM has not been extensively explored, it has been noted that they are essential for preserving skin health. Disruption of their bacterial balance can lead to various skin issues, including atopic dermatitis, psoriasis, and acne.[36,37]

This study is the first to use MR analysis to investigate the causal link between human skin microbiota and MM. The results of our study indicate that skin microbiota could potentially function as a novel biomarker for the diagnosis of malignant melanoma. The fact that skin microbiota can be easily and conveniently sampled further enhances the implications of our

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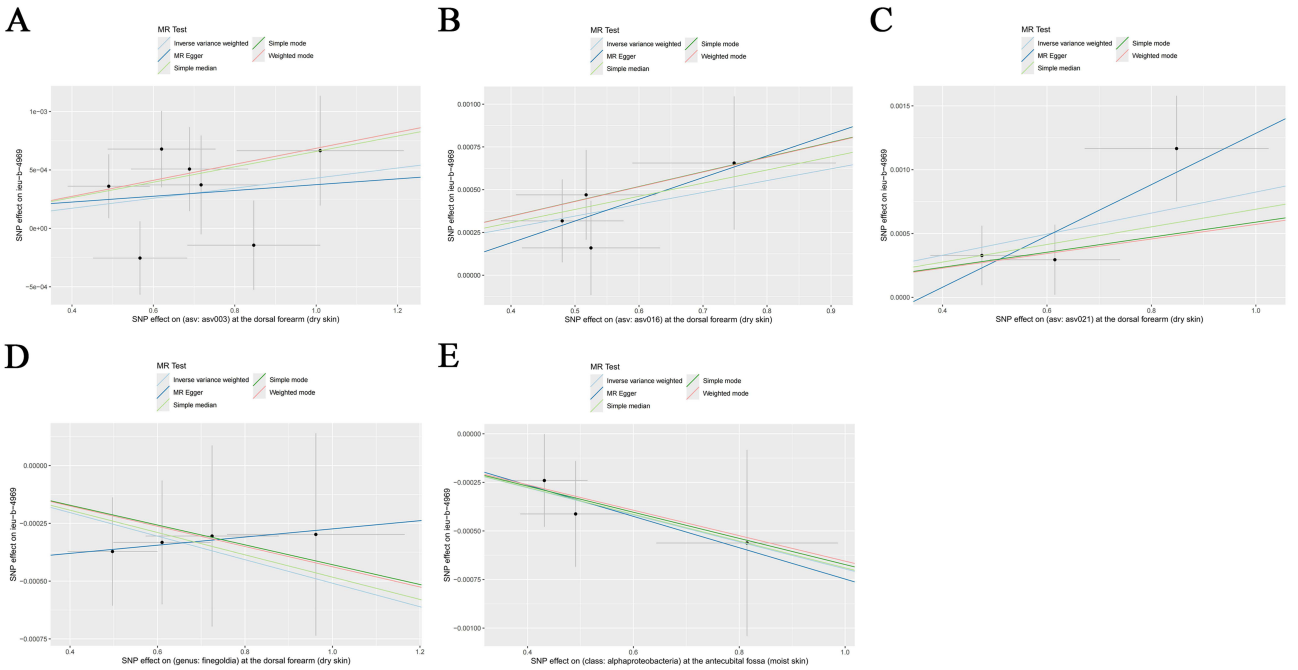

Figure 4 Scatter plots illustrating the causal relationship between five skin microbiota (KORA) and MM. (**A**) ASV003 [Staphylococcus (unc.)]; (**B**) ASV016[Enhydrobacter (unc.)]; (**C**) ASV021 [Micrococcus (unc.)]; (**D**) genus: Finegoldia; (**E**) class:Alphaproteobacteria.

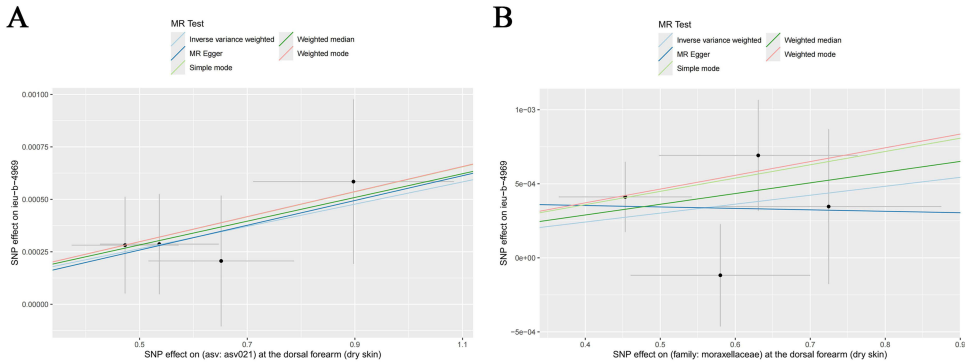

Figure 5 Scatter plots illustrating the causal relationship between two skin microbiota (PopGen) and MM. (**A**) ASV021 [Micrococcus (unc.)]; (**B**) family: Moraxellaceae.

findings, suggesting that they could lead to innovative approaches in the diagnosis, prevention, and treatment of skin-related diseases going forward. However, our study is not without its limitations. One notable constraint is that the dataset utilized in our GWAS is primarily derived from individuals of European descent. This limitation raises concerns regarding the potential for biased estimations and may restrict the applicability of our findings to diverse ethnic populations. Additionally, although we have pinpointed several specific skin microbiotas related to risk of MM, the precise underlying molecular mechanisms driving this association remain unclear and require further exploration. Moreover, it is important to acknowledge that our conclusions are largely based on statistical analyses, which underscores the need for additional validation through comprehensive basic and clinical research to solidify and corroborate our findings.

In addition, our study demonstrates an association between skin microbiota and the incidence of MM in situ. However, it remains unclear whether skin microbiota plays a role in invasive MM. In contrast to MM in situ, invasive MM exhibits a more malignant character and has the potential to progress to metastatic melanoma, which can spread to other organs and is associated with a poorer prognosis.[38] Therefore, it is essential to investigate the involvement of skin microbiota in the development and progression of metastatic melanoma in future studies.This will be crucial for enhancing our understanding of the pathogenesis of invasive MM and for informing treatment strategies.

Conclusion

In conclusion, this research highlights the importance of skin microbiota in relation to the risk associated with MM. It also identifies particular strains of microbiota that could potentially affect an individual's susceptibility to MM. The implications of these discoveries are profound, as they provide valuable insights that could enhance both the preventive strategies and diagnostic approaches for MM. Nevertheless, to fully understand the mechanisms that underpin these observations and to explore the therapeutic possibilities they may offer for MM, additional research is essential.

Date Availability Statement

The data utilized in this study was obtained from the MiBioGen repository, which can be accessed at: https://mibiogen.gcc.rug.nl/. Additionally, data concerning MM is available for download through the IEU Open GWAS project. Individuals interested in acquiring this data can navigate to the following link: https://gwas.mrcieu.ac.uk/ and use the ID: ieu-b-4969 to facilitate their download.

Ethics Statements

According to Article 32 of the Ethical Review Measures for Life Science and Medical Research Involving Human Beings of the People's Republic of China, the data used in this study will not cause any form of harm to human beings, nor will it touch sensitive personal privacy or trade secrets, so the ethical review can be exempted. In addition, the database used in this study was publicly available and legally available.

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Disclosure

The authors declare no conflicts of interest in this work.

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