

# Mendelian randomization analysis of the causal association between metabolites and skin cancer

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## Abstract

Skin cancer (SC) is a significant public health issue, with increasing incidence rates globally. Although environmental factors such as ultraviolet radiation (UVR) exposure are recognized risk factors, the impact of metabolites on SC development has not been thoroughly examined. This study seeks to explore the causal association between metabolites and SC risks using a Mendelian randomization (MR) approach. Our analysis identified 76 metabolites associated with SC risk. Of them, the leucine-to-N-palmitoyl-sphingosine ratio, glycerol-to-palmitoylcarnitine ratio, oleoyl-linoleoyl-glycerol levels, and hypotaurine-to-aurine ratio were strongly associated with SC. Notably, the leucine-to-N-palmitoyl-sphingosine ratio and the glycerol-to-palmitoylcarnitine ratio were associated with increased risk factors for SC. However, oleoyl-

linoleoyl-glycerol levels and hypotaurine-to-aurine ratio served as the protective indicators of SC. This study highlights the potential role of metabolites in skin cancer etiology, suggesting that metabolic factors may serve as important targets for prevention and risk assessment strategies.

## Introduction

Skin cancer (SC) is one of the most severe health challenges of this decade, currently ranking as the fifth most prevalent type of cancer worldwide.<sup>1</sup> It is projected to surpass heart disease as the leading cause of death and a significant obstacle to increasing life expectancy in the coming years.<sup>2</sup> SC is primarily classified into three types: basal cell carcinoma, squamous cell carcinoma, and melanoma.<sup>2</sup> While environmental factors, especially ultraviolet radiation (UVR) exposure, are well-established risk factors,<sup>3</sup> recent research has begun to uncover the potential role of metabolic processes in SC pathogenesis. Specifically, certain metabolites may influence tumor development and progression.<sup>4</sup>

Metabolites, the end products of cellular metabolism, play essential roles in various biological functions, including energy production, signaling, and cellular homeostasis. Emerging evidence suggests that alterations in metabolite levels could be linked to cancer risk and progression.<sup>5</sup> Notably, specific lipid metabolites, such as prostaglandins and leukotrienes, significantly contribute to SC development by modulating the inflammatory response.<sup>6</sup> Metabolites associated with lipid, amino acid, and carbohydrate metabolism have been implicated in various cancers, affecting critical pathways regulating cell proliferation, inflammation, and apoptosis.<sup>7</sup>

Despite these associations, establishing a causal relationship between metabolites and SC remains complex due to confounding factors and the potential for reverse causation.<sup>8</sup> Traditional observational studies often struggle to disentangle these intricacies, underscoring the need for more robust methodological approaches.<sup>9</sup> Mendelian randomization (MR) offers a promising alternative by employing genetic variants as instrumental variables (IVs) to assess the causal effects of exposures, such as the effect of altered metabolite levels on health outcomes.<sup>10</sup> This method effectively minimizes confounding and reverse causation, providing clearer insights into the causal pathways involved.

In this study, we aim to investigate the causal association between 1,400 metabolites and SC phenotypes using an MR framework. By leveraging publicly available genetic data and metabolite measurements, we will identify potential metabolic pathways that may contribute to SC risks. Our findings can enhance understanding of the biological mechanisms underlying SC and inform preventive strategies targeting metabolic pathways.

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## Materials and Methods

### Study design

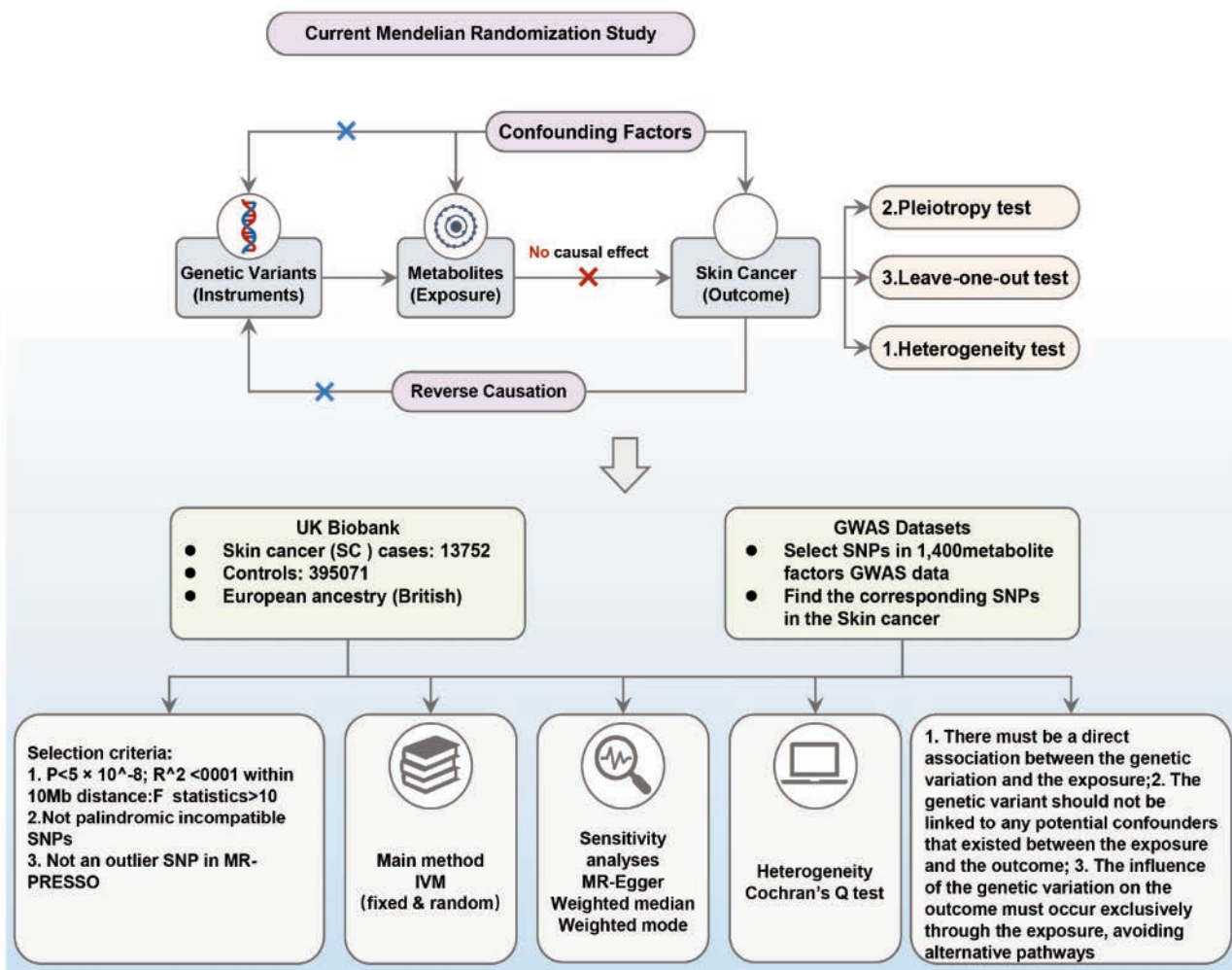
We assessed the cause-and-effect relationship between 1,400 types of metabolites and SC phenotypes using two-sample MR analyses, which leverage genetic variations as proxies for risk factors. To ensure reliable causal inference, IVs in MR must satisfy three key assumptions: i) a direct association must exist between the genetic variation and the exposure; ii) the genetic variant should not be associated with any confounders that could influence the relationship between the exposure and the outcome; and iii) the effect of the genetic variation on the outcome must operate exclusively through the exposure, avoiding alternative pathways.

Specifically, our MR analyses adhered to these major assumptions. First, there should be a strong correlation between the IV (G) and the exposure factor (P). Second, there should be no direct correlation between G and the outcome variable (Y), ensuring that G does not influence Y through any pathway other than P. Additionally, G should not be correlated with known confounding

factors (U). To meet the second assumption, we excluded points with p-values less than  $1 \times 10^5$  from the outcome during our MR analysis. To address the third assumption, we employed methodologies, such as MR-Egger and MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO), to test for pleiotropy and found no evidence of such effects in our results. Furthermore, we reviewed the Genome-Wide Association Study (GWAS) catalog for relevant single-nucleotide polymorphisms (SNPs) and eliminated those with pleiotropic effects prior to the MR analysis. While our study indicates a potential association, further large-scale research is necessary to explore this relationship in depth (Figure 1).

### Data sources for exposure and outcome

The statistical summary of GWAS data for each metabolite is publicly available from the European GWAS repository (accession numbers: GCST90199621-90201020) at <https://gwas.mrcieu.ac.uk/>. Specifically, we selected the United Kingdom (UK) Biobank SAIGE (ukb-saige-172) dataset, using “skin cancer” as a keyword for identification. This comprehensive



**Figure 1.** Study design flowchart. The first assumption is that the instrumental variables strongly correlate with the exposure. The second assumption posits that these instrumental variables are not associated with confounding factors. The third assumption asserts that the IVs influence the outcome solely through exposure.

GWAS database, encompassing a wide range of genetic variations and their associations with various traits and diseases, serves as a valuable resource for researchers and clinicians aiming to understand the genetic underpinnings of complex traits and diseases. Subsequently, we downloaded relevant data from the UK Biobank PheWeb database (<https://pheweb.org/UKB-SAIGE/>), focusing on SC, which included a cohort of 408,823 European individuals (n=13,752 cases and 395,071 controls) for SC. The UK Biobank represents a large-scale biomedical database that compiles genetic, health, and lifestyle information from over 500,000 participants across the UK. Its goal is to enhance the prevention, diagnosis, and treatment of various diseases by facilitating research into the relationships between genetic factors and health outcomes. GWAS typically involves collecting and analyzing DNA samples from participants to identify genetic variations associated with specific traits or diseases. The biological materials used in these studies often include DNA extracted from blood, saliva, or other tissues. Researchers isolate DNA from these samples and apply genotyping methods to pinpoint genetic variations, such as SNPs, that may be linked to the trait or disease under investigation.

### Instrument selection

Given the substantial number of SNPs demonstrating genome-wide significance ( $p < 5 \times 10^{-8}$ ) for metabolite traits, we implemented stricter correlation thresholds ( $p < 5 \times 10^{-9}$ ) for selecting genetic IVs. These IVs were categorized using the reference panel for linkage disequilibrium (LD) from the 1000 Genomes Project, applying a threshold of  $R^2 < 0.001$  within a distance of 1,000 kilobases (kb). Due to the relatively small size of the GWAS data for metabolites, we also employed a p-value cutoff of  $5 \times 10^{-8}$  along with a more lenient clustering threshold ( $R^2 < 0.001$  at a distance of 1,000 kb). To ensure the robustness of our analysis, we selected IVs with F-statistics greater than 10, designating them as strong instruments for further investigation. These IVs were extracted from summary statistics related to SC outcomes, with any SNPs exhibiting potential pleiotropic effects ( $p < 10^{-5}$ ) on SC being excluded, following established methodologies from prior research. To maintain consistency in our analysis, we synchronized SNPs between the exposure and outcome datasets, ensuring uniform effect estimates for the same effect allele.

### Statistical analysis

In our study, we utilized a range of genetic variants as IVs rather than relying solely on an allele score. This approach allowed us to rigorously test key assumptions, identify potential pleiotropy, and conduct more effective sensitivity and multivariable MR analyses. We employed four distinct MR methodologies: inverse variance weighted (IVW) using a random-effects model, weighted median, MR-Egger, and MR-PRESSO. These methodologies helped assess the consistency of our findings under varying assumptions regarding heterogeneity and pleiotropy, with the IVW method serving as the primary analysis framework for all four sets of IVs. Heterogeneity was quantified using Cochran's Q statistic.

Our study also included analyses under more stringent conditions. While the IVW method assumes that all genetic variants are valid, it may be biased if a substantial number of SNPs are influenced by horizontal pleiotropy. In contrast, the weighted median approach is robust when less than 50% of variants exhibit horizontal pleiotropy, assuming that most genetic variants are valid. When over 50% of variants are affected by horizontal pleiotropy, we assessed the strength of our genetic instruments using F-statistics; a mean F-statistic below 10 indicates weak IVs.

Furthermore, the MR-Egger method was applied to evaluate potential directional pleiotropy, with a significant intercept suggesting directional pleiotropy. Additionally, the MR-PRESSO method was implemented to minimize heterogeneity in causal effect estimates by excluding disproportionately influential SNPs (NbDistribution=1,500). In addition, we conducted Steiger-filtering analyses to identify and eliminate genetic variants that were more strongly associated with the outcome than with the exposure, indicating possible reverse causality.

All statistical analyses were performed using R version 4.3.1 (R Foundation) and specific R packages, including "TwoSampleMR" and "MR", for MR analysis.

## Results

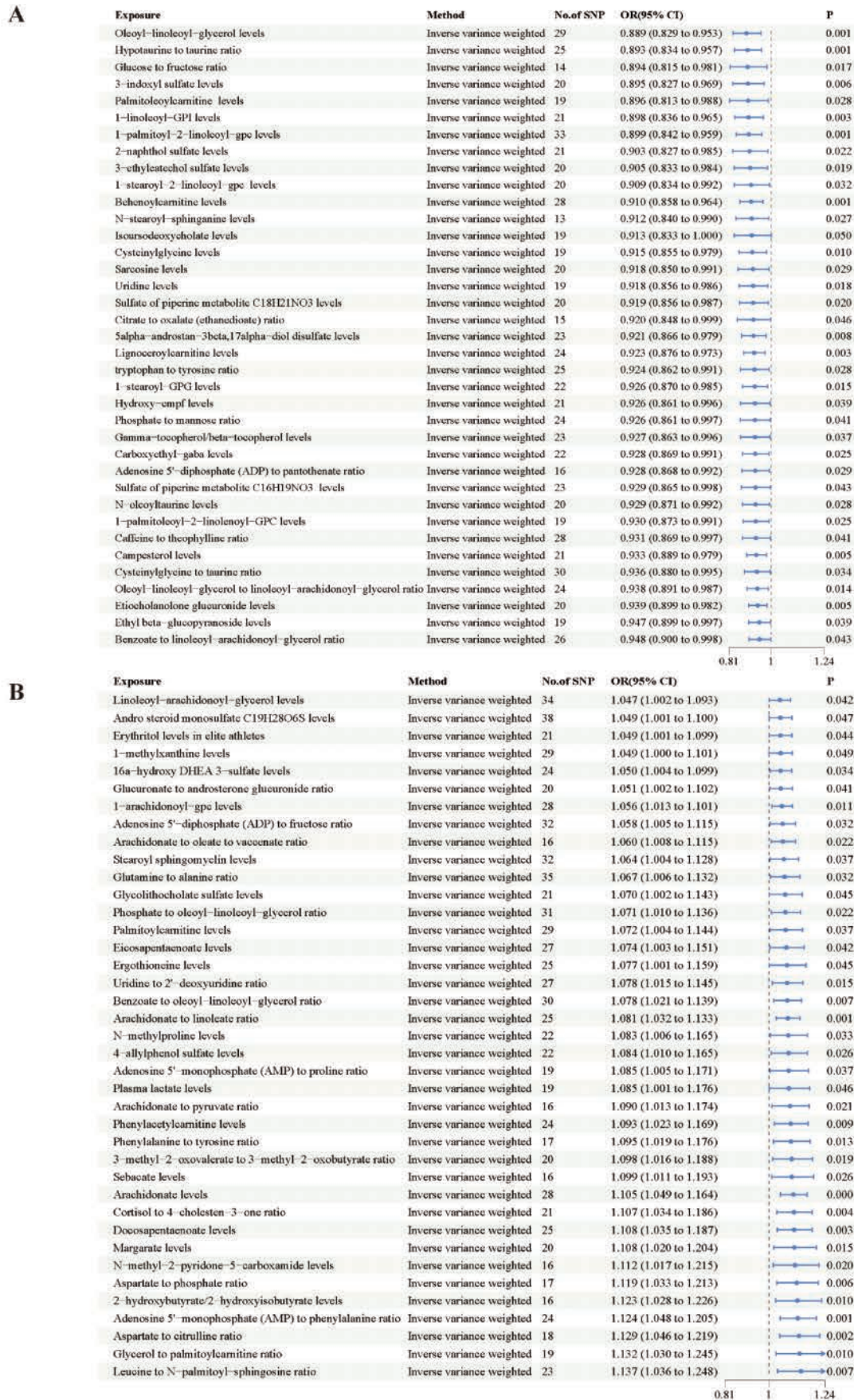
### Causal association between metabolites and skin cancer pathogenesis

To investigate the causal effect of various metabolites on SC, we conducted a two-sample MR analysis employing IVW as the primary method. Our findings revealed significant associations between 76 metabolites and SC risks (Figure 2). Notably, SC risk was strongly associated with the leucine-to-N-palmitoyl-sphingosine ratio (odds ratio [OR]=1.137, 95% confidence interval [CI]: 1.036-1.248,  $p=0.007$ ), the glycerol-to-palmitoylcarnitine ratio (OR=1.132, 95% CI: 1.030-1.245,  $p=0.010$ ), oleoyl-linoleoylglycerol levels (OR=0.889, 95% CI: 0.829-0.953,  $p=0.001$ ), and the hypotaurine-to-aurine ratio (OR=0.893, 95% CI: 0.834-0.957,  $p=0.001$ ) (Figure 3). We also performed a sensitivity analysis to assess the robustness of our findings. While some heterogeneity was observed, indicated by significant results from Cochran's Q test ( $p < 0.05$ ), the causal estimates remained stable when analyzed using the random-effects IVW model (*Supplementary Table 1*). The p-values for the MR-Egger intercept were above 0.05, indicating no significant pleiotropic effects (*Supplementary Table 2*). Furthermore, we evaluated the data through scatter plots (Figure 4), funnel plots (Figure 5), and leave-one-out plots (Figure 6), which helped mitigate the potential influence of outliers and horizontal pleiotropy on the key metabolites identified.

## Discussion

Cancer has long been viewed as a hereditary disease linked to mutations in oncogenes and tumor-suppressor genes. However, a growing body of research indicates that metabolic disturbances in cancer cells may be not only a hallmark of the disease but also a fundamental cause.<sup>11</sup> In cancer patients, various metabolic abnormalities often co-exist, exemplified by the Warburg effect, which demonstrates that cancer cells consume significantly more glucose than normal cells.<sup>12</sup> Additionally, tumor cells can enhance biofilm formation and increase membrane lipid saturation through metabolic reprogramming, promoting rapid proliferation and tumor progression.<sup>13</sup> With the recent advancements in metabolomics, research into cancer-related metabolites, particularly blood metabolites, has deepened. These metabolites are easily accessible and detectable, offering potential for early cancer screening and prevention. Understanding the relationships between blood metabolites and cancer and their biological mechanisms can help identify new therapeutic targets.

In our study, we investigated the correlation between 76 metabolites and SC risks through MR and identified 39 metabo-



**Figure 2.** The causal association between all metabolites and SC risks. **A)** Protective factors against SC; **B)** risk factors of SC. We selected IVW as a primary method;  $p < 0.05$  showed statistical significance;  $OR > 1$  indicated a risk factor, while  $OR < 1$  indicated a protective factor.

lites that showed a significant positive correlation with SC risk, with the strongest associations being the leucine-to-N-palmitoyl-sphingosine and glycerol-to-palmitoylcarnitine ratio. Conversely, 37 metabolites were significantly negatively correlated with SC, serving as protective factors, particularly oleoyl-linoleoyl-glycerol levels and the hypotaurine-to-aurine ratio.

Leucine, a branched-chain amino acid known for its bulky side chains, plays a critical role in cancer metabolism. Our findings suggest that a higher leucine-to-N-palmitoyl-sphingosine ratio correlates with increased SC risks; as blood leucine levels rise and N-palmitoyl-sphingosine levels decrease, the risk of developing SC increases. This aligns with previous research showing that circulating leucine levels are positively associated with squamous cell lung cancer risk.<sup>14</sup> Moreover, studies using mouse models of breast cancer and melanoma have found that microbiota from a high-fat diet (HFD) release abundant leucine, which can activate the rapamycin complex 1 (mTORC1) signaling pathway in myeloid progenitor cells, promoting differentiation into polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs), a phenomenon linked to poor clinical outcomes.<sup>15</sup> Leucine is a crucial element of the mTORC1 signaling pathway, which promotes protein translation and cell proliferation.<sup>16</sup> However, dysregulation of the PI3K/Akt/mTOR pathway and related components is frequently observed in various cancers, including melanoma and non-melanoma SC types.<sup>17</sup> N-palmitoyl-sphingosine, a major component of ceramide, constitutes 50-63% of total sphingomyelin and plays various roles in cellular signaling, including apoptosis, proliferation, cell cycle arrest, cell differentiation, and induction of cytokine synthesis.<sup>18</sup> While elevated ceramide levels have been associated with adverse cardiovascular events, the relationship between N-palmitoyl-sphingosine and

cancer remains less explored. Only one study performed a comprehensive metabolomic analysis of fecal samples from patients with advanced adenomas and colorectal cancer. It concluded that a composite indicator containing lactosyl-N-palmitoyl-sphingosine would be potentially valuable for the future diagnosis and prevention of colorectal cancer,<sup>19</sup> highlighting the need for further research into its role in SC pathogenesis. We also found that an elevated glycerol-to-palmitoylcarnitine ratio is a risk factor for SC. Elevated glycerol and reduced palmitoylcarnitine levels in the blood may promote SC. Glycerol is a small molecule that serves as a key intermediary in carbohydrate and lipid metabolism. It is primarily stored in adipose tissue as the backbone for triglycerides (TG). In adipose tissue, glycerol can be effluxed *via* aquaporin 7 (AQP7), and the liver takes up glycerol *via* AQP9.<sup>20</sup> In a study by Zheng Li *et al.*, the expression of AQP3 was positively associated with the glycerol level in human gastric cancer tissues. When the glycerol level was decreased, the cellular uptake was reduced, resulting in compromised energy production and impaired proliferation of cancer cells.<sup>21</sup> Research has shown that during the early stages of liver cancer, glycerol metabolism is reprogrammed to enhance its utilization for gluconeogenesis, providing a critical energy source for hepatocellular carcinoma cells.<sup>22</sup> However, the role of glycerol in promoting skin cancer development has not been thoroughly investigated. We hypothesize that elevated glycerol levels in the body may support the rapid proliferation of skin cancer cells. Acylcarnitines, which are intermediates in fatty acid oxidation, can accumulate when there is metabolic dysfunction, particularly due to poor integration between  $\beta$ -oxidation and the tricarboxylic acid cycle. Among these, palmitic acid-derived palmitoylcarnitine constitutes about 80% of the total fatty acids synthesized in cells.<sup>23</sup> Previous studies have reported significantly

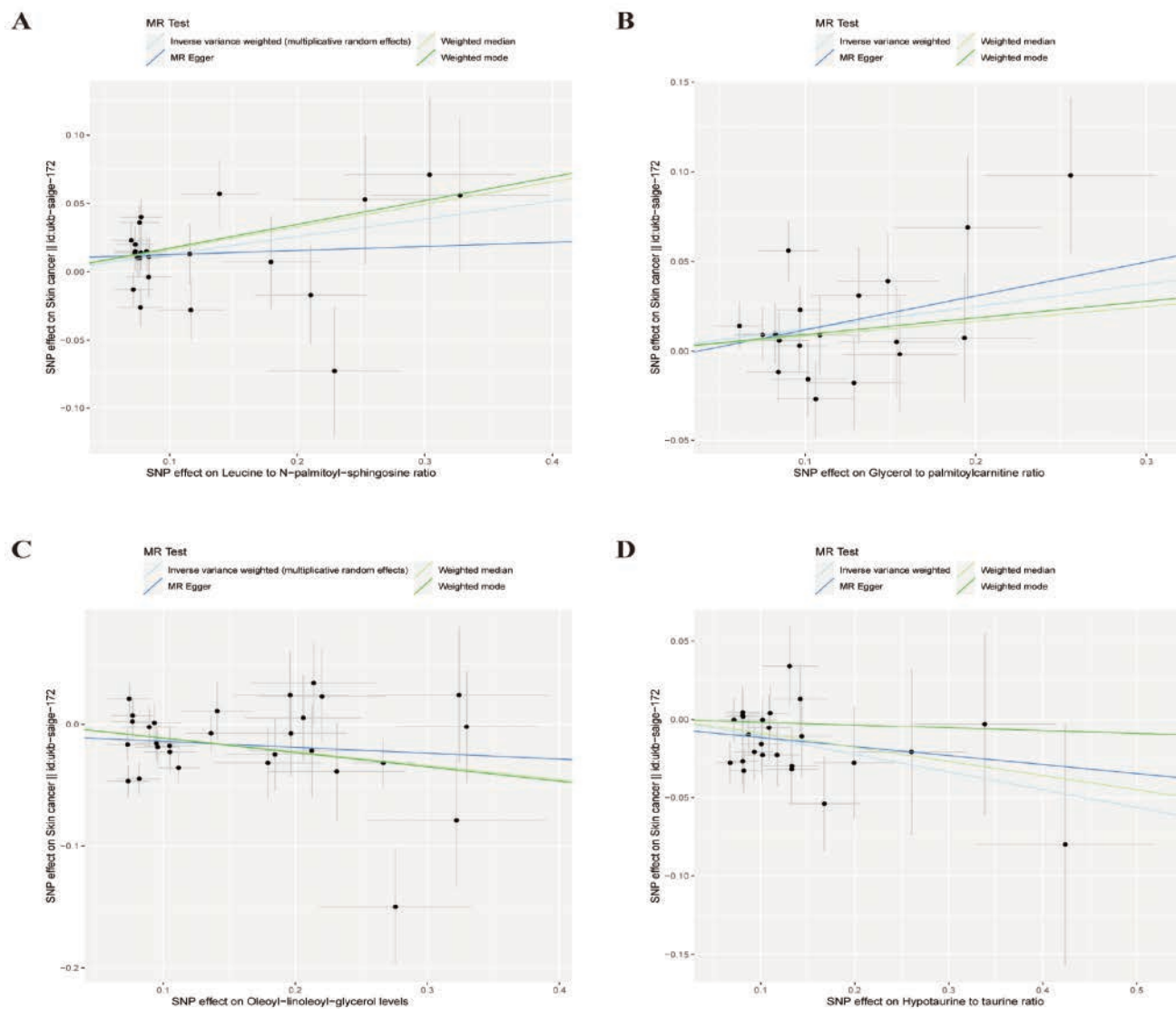
Exposure	Method	No. of SNP	OR(95% CI)	P
Leucine to N-palmitoyl-sphingosine ratio	Inverse variance weighted	23	1.137 (1.036 to 1.248)	0.007
Leucine to N-palmitoyl-sphingosine ratio	MR Egger	23	1.030 (0.793 to 1.339)	0.826
Leucine to N-palmitoyl-sphingosine ratio	Weighted median	23	1.179 (1.057 to 1.315)	0.003
Leucine to N-palmitoyl-sphingosine ratio	Weighted mode	23	1.189 (0.965 to 1.466)	0.118
Glycerol to palmitoylcarnitine ratio	Inverse variance weighted	19	1.132 (1.030 to 1.245)	0.010
Glycerol to palmitoylcarnitine ratio	MR Egger	19	1.208 (0.885 to 1.650)	0.250
Glycerol to palmitoylcarnitine ratio	Weighted median	19	1.086 (0.961 to 1.227)	0.186
Glycerol to palmitoylcarnitine ratio	Weighted mode	19	1.097 (0.884 to 1.361)	0.411
Oleoyl-linoleoyl-glycerol levels	Inverse variance weighted	29	0.889 (0.829 to 0.953)	0.001
Oleoyl-linoleoyl-glycerol levels	MR Egger	29	0.953 (0.811 to 1.119)	0.561
Oleoyl-linoleoyl-glycerol levels	Weighted median	29	0.892 (0.818 to 0.973)	0.010
Oleoyl-linoleoyl-glycerol levels	Weighted mode	29	0.889 (0.791 to 0.999)	0.058
Hypotaurine to taurine ratio	Inverse variance weighted	25	0.893 (0.834 to 0.957)	0.001
Hypotaurine to taurine ratio	MR Egger	25	0.944 (0.768 to 1.161)	0.592
Hypotaurine to taurine ratio	Weighted median	25	0.914 (0.827 to 1.009)	0.076
Hypotaurine to taurine ratio	Weighted mode	25	0.982 (0.817 to 1.180)	0.846

**Figure 3.** The causal associations between four metabolites and SC risks. We selected IVW as a primary method;  $p < 0.05$  showed statistical significance;  $OR > 1$  indicated a risk factor, while  $OR < 1$  indicated a protective factor.

elevated levels of palmitoylcarnitine in prostate cancer tissues, where high concentrations are associated with increased expression and secretion of the pro-inflammatory cytokine IL-6, potentially promoting cancer progression.<sup>24</sup> Interestingly, research by Turnbull *et al.* demonstrated that palmitoylcarnitine reduced the survival of colorectal cancer cells (HT29 and HCT116) by inhibiting their ability to mitigate oxidative stress through glutathione-redox coupling, thus sensitizing them to elevated hydrogen peroxide levels, which have a cancer-suppressive effect.<sup>25</sup> Our study found that palmitoylcarnitine acts as a protective factor against skin cancer, aligning with Turnbull's findings. However, the precise mechanism remains unclear, suggesting that the effects of palmitoylcarnitine may be bidirectional and vary across different cancer types.

We found that elevated levels of oleoyl-linoleoyl-glycerol and an increased hypotaurine-to-taurine ratio are protective factors against skin cancer, with higher concentrations of both associated

with a lower incidence of the disease. Although oleoyl-linoleoyl-glycerol has been less extensively studied, it is suggested to be linked to the sodium-glucose cotransporter protein 2 (SGLT2), and it may also help reduce the risk of major depression.<sup>26</sup> Hypotaurine, a sulfur amino acid, is oxidized to taurine through a non-enzymatic reaction when it interacts with reactive oxygen species (ROS), such as hydroxyl radicals.<sup>27</sup> This process gives hypotaurine potent hydroxyl radical scavenging properties.<sup>28</sup> Skin cancer is primarily caused by cumulative exposure to UVR, which generates ROS and contributes to oxidative damage, leading to cell death and potentially carcinogenesis. The protective role of hypotaurine against skin cancer may be attributed to its antioxidant activity.<sup>29</sup> Previous studies have demonstrated that hypotaurine can exert antitumor effects by enhancing antioxidant capacity, modulating immune responses, and inducing apoptosis in tumor cells.<sup>30</sup> Our study found that the risk of developing skin cancer decreased when the hypotaurine-to-taurine ratio increased. Since



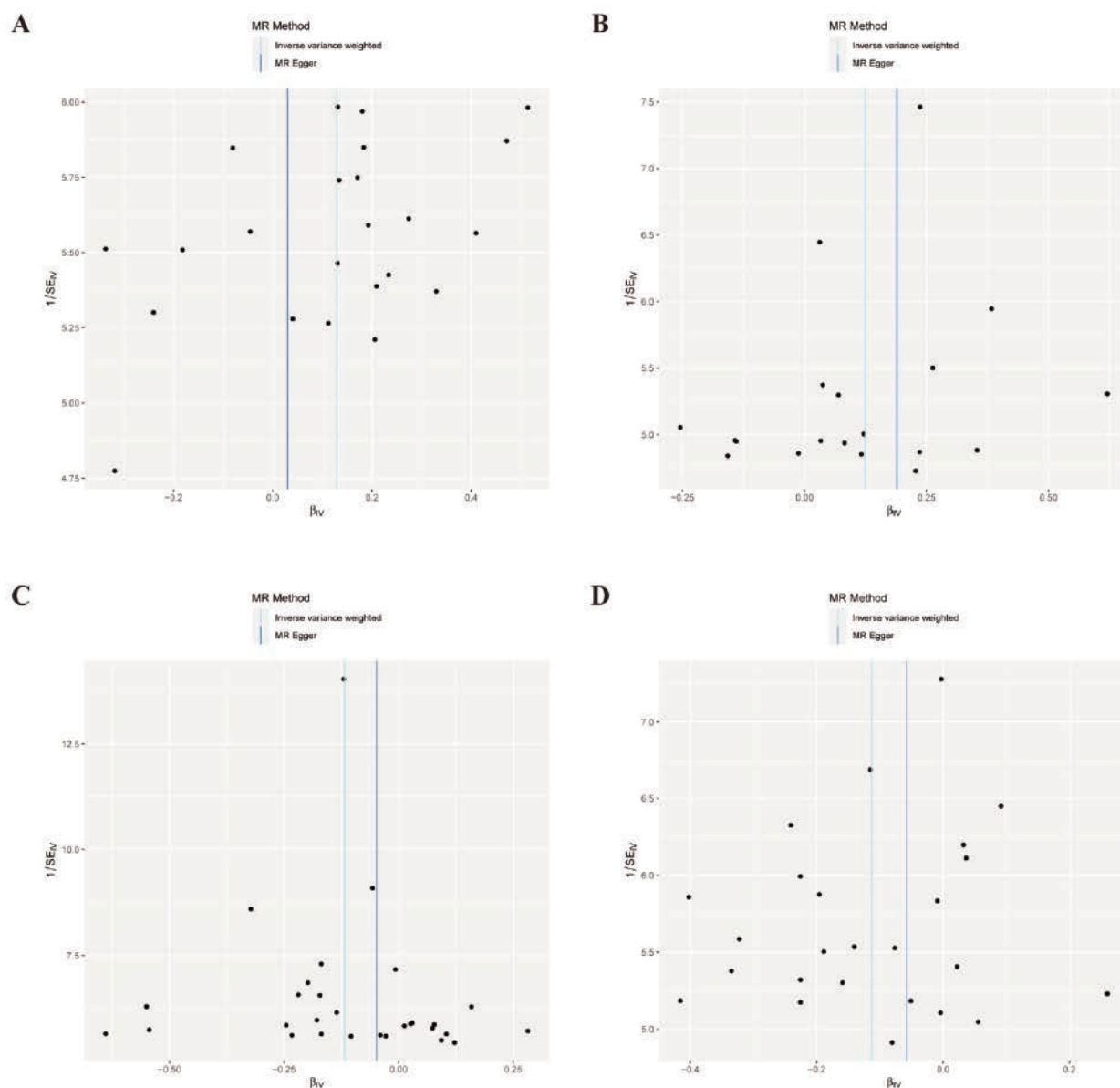
**Figure 4.** Scatter plot showing the relationship between four metabolites and the SC risk. **A)** Leucine-to-N-palmitoyl-sphingosine ratio in SC; **B)** glycerol-to-palmitoylcarnitine ratio in SC; **C)** oleoyl-linoleoyl-glycerol levels in SC; **D)** hypotaurine-to-taurine ratio in SC.

taurine is produced from the oxidation of hypotaurine, a decrease in hypotaurine coincides with an increase in taurine, resulting in a lower hypotaurine-to-*taurine* ratio associated with an increased risk of skin cancer. We speculate that hypotaurine may have stronger anticancer properties than taurine, and its conversion to taurine could weaken the overall anticancer effect. This hypothesis warrants further experimental investigation.

### Strengths and limitations

Our MR study aimed to assess the causal correlation between altered metabolite levels and SC risks using a large-scale GWAS and the UK Biobank database. This approach effectively addresses the limitations of traditional observational studies by minimiz-

ing confounding factors and reducing the risk of reverse causality. Additionally, MR mitigates the issues of representativeness and feasibility that often arise in randomized controlled trials. However, this study has several limitations. First, we used non-fasting plasma samples for metabolomics profiling. While we adjusted for the time since the last meal or beverage, some residual variability may still exist. Second, our analysis concentrated on gene-metabolite pairs deemed most relevant based on existing expression data and biological understanding, particularly those involving effector genes. Nonetheless, the potential significance of other metabolites or ratios with high heritability related to SC should not be overlooked. Future research should incorporate additional expression data and metabolic insights to identify effector genes for these other metabolites and ratios. Third, the MR



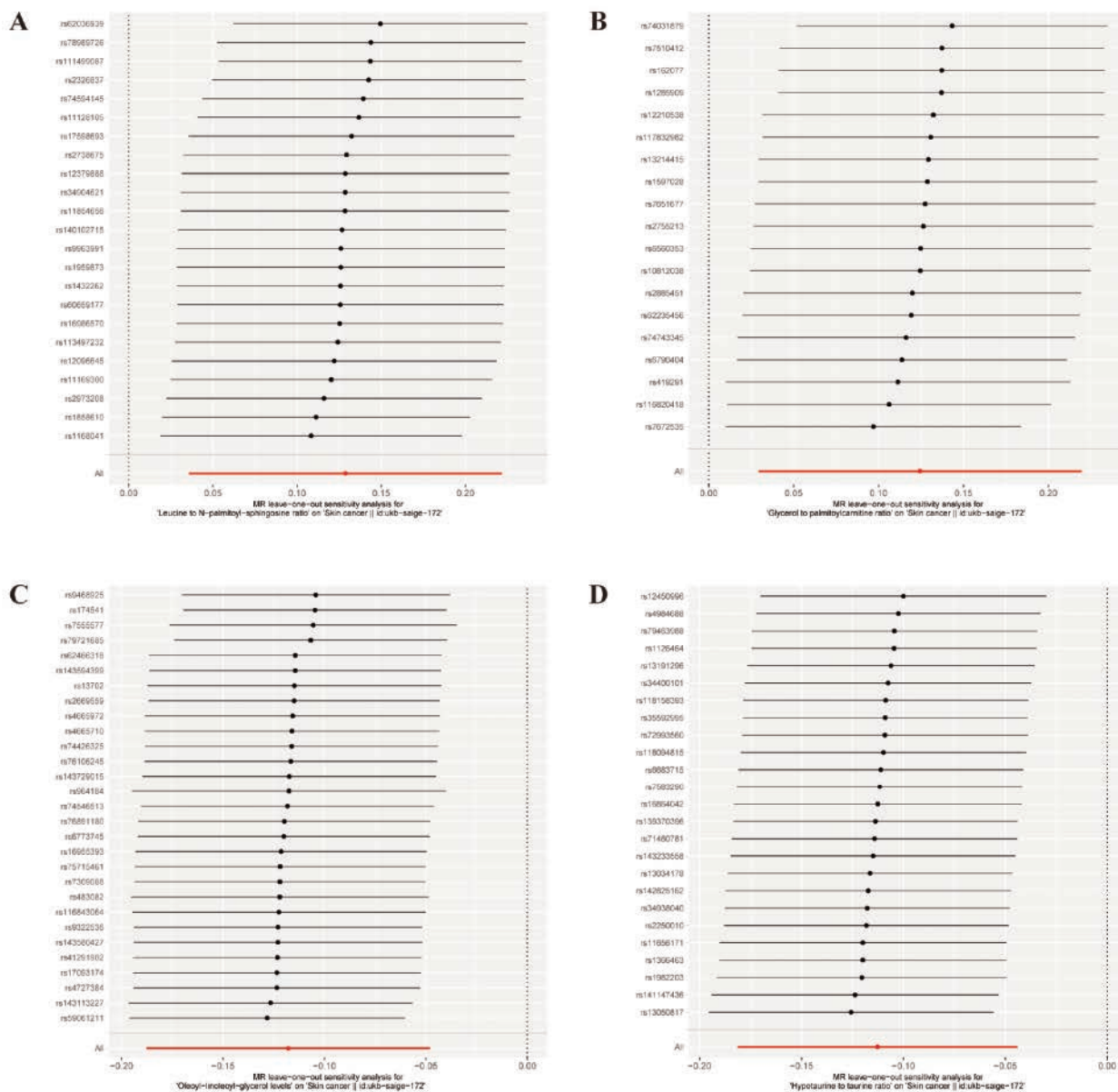
**Figure 5.** A funnel plot showing IVs for each significant causal association between four metabolites and the SC risk. **A)** Leucine-to-N-palmitoyl-sphingosine ratio in SC; **B)** glycerol-to-palmitoylcarnitine ratio in SC; **C)** oleoyl-linoleoyl-glycerol levels in SC; **D)** hypotaurine-to-*taurine* ratio in SC.

analysis faced limitations as most metabolites and metabolite ratios were correlated with only a single IV. This constraint limited the applicability of common MR sensitivity tests, such as MR-Egger, which require multiple IVs. Nevertheless, our approach reduced the risk of horizontal pleiotropy by utilizing IVs closely linked to effector genes that influence metabolite levels. We also performed manual assessments of metabolic pleiotropy, excluding IVs correlated with multiple metabolites that were not part of the same metabolic pathways. While these measures helped minimize potential biases, we recognize that some may persist due to limitations in metabolome profiling and gaps in databases of metabolite-protein interactions. Further research with a more comprehensive assessment of the metabolome is essential for a better understanding of the genetic influences on metabolites. Lastly, this study primarily involved elderly individuals of European descent.

Exploring the effects of the identified genetic variations on metabolites and their ratios across diverse demographic groups represents a promising direction for future research.

## Conclusions

This study provides evidence of a causal association between specific metabolites and SC risk using MR methods. The findings highlight the role of metabolic factors in SC etiology and suggest that targeting modifiable metabolites may offer opportunities for prevention. Further research is needed to validate these associations and explore their clinical implications, ultimately contributing to improved SC risk assessment and management strategies.



**Figure 5.** A funnel plot showing IVs for each significant causal association between four metabolites and the SC risk. **A)** Leucine-to-N-palmitoyl-sphingosine ratio in SC; **B)** glycerol-to-palmitoylcarnitine ratio in SC; **C)** oleoyl-linoleoyl-glycerol levels in SC; **D)** hypotaurine-to-aurine ratio in SC.

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Online Supplementary Material:

Supplementary Table 1. The heterogeneity of causal association between all metabolites and SC risks. The *p*-values for Cochran's *Q* were above 0.05, suggesting that no significant heterogeneity effects were found.

Supplementary Table 2. The pleiotropy of causal association between all metabolites and skin cancer. The *p*-values for the MR-Egger intercept were above 0.05, suggesting that no significant pleiotropy effects were found.