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Mendelian randomization analysis of the causal association between metabolite and skin cancer

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Availability of data and materials: all the data for this article are available in the GWAS and UK Biobank database.

Abstract

Skin cancer (SC) is a significant public health issue, with increasing incidence rates globally. Although environmental factors such as ultraviolet (UV) 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 revealed a total of 76 metabolites associated with SC risk. Of them, leucine to N-palmitoyl-sphingosine ratio, glycerol to palmitoylcarnitine ratio, oleoyl-linoleoyl-glycerol levels, and hypotaurine-to-taurine ratio were strongly associated with SC. Notably, leucine to N-palmitoyl-sphingosine ratio and glycerol to palmitoylcarnitine ratio were linked to increased risk factors for SC. However, oleoyl-linoleoyl-glycerol levels and hypotaurine-to-taurine 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.[1] 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.[2] SC is primarily classified into three types: basal cell carcinoma, squamous cell carcinoma, and melanoma.[2] While environmental factors, especially ultraviolet radiation (UVR) exposure, are well-established risk factors,[3] recent research has begun to uncover the potential role of metabolic processes in SC pathogenesis. Specifically, certain metabolites may influence tumor development and progression.[4]

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.[5] Notably, specific lipid metabolites, such as prostaglandins and leukotrienes, significantly contribute to SC development by modulating the inflammatory response.[6] Metabolites associated with lipid, amino acid, and carbohydrate metabolism have been implicated in various cancers, affecting critical pathways regulating cell proliferation, inflammation, and apoptosis.[7]

Despite these associations, establishing a causal relationship between metabolites and SC remains complex due to confounding factors and the potential for reverse causation.[8] Traditional observational studies often struggle to disentangle these intricacies, underscoring the need for more robust methodological approaches.[9] 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.[10] 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 1400 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.

Materials and Methods

Study design

We assessed the cause-and-effect relationship between 1400 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 1×10^5 from the outcome during our MR analysis. To address the third assumption, we employed methodologies, such as MR Egger and 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 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 ($p<5\times10^{-8}$) for metabolite traits, we implemented stricter correlation thresholds ($p<5\times10^{-9}$) 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

5×10^{-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-Pleiotropy RESidual Sum and Outlier (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 were valid. When over 50% of variants are affected by horizontal pleiotropy, we assessed the strength of our genetic instruments using F-statistics, where a mean F-statistic of less than 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", were tailored for MR analysis.

Results

Causal association between metabolites and SC 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-linoleoyl-glycerol levels (OR=0.889, 95% CI=0.829-0.953, p=0.001), and the hypotaurine to taurine 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.[11] 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.[12] Additionally, tumor cells can enhance biofilm formation and increase membrane lipid saturation through metabolic reprogramming, promoting rapid proliferation and tumor progression.[13] 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 relationship 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 metabolites 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-taurine 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.[14] Moreover, studies using mouse models of breast cancer and melanoma have found that microbiota from 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 cell (PMN-MDSC), a phenomenon linked to poor clinical outcomes.[15] Leucine is a crucial element of the mTORC1 signaling pathway, which promotes protein translation and cell proliferation.[16] However, dysregulation of the PI3K/Akt/mTOR pathway and related components is frequently observed in various cancers, including melanoma and non-melanoma SC types.[17] 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.[18] 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,[19] 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.[20] 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.[21] 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.[22] 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 β-oxidation and the tricarboxylic acid (TCA) cycle. Among these, palmitic acid-derived palmitoylcarnitine constitutes about 80% of the total fatty acids synthesized in cells.[23] Previous studies have reported significantly 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.[24] Interestingly, research by Patrick C. 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.[25] 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.[26] 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.[27] This process gives hypotaurine potent hydroxyl radical scavenging properties.[28] 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.[29] Previous studies have demonstrated that hypotaurine can exert antitumor effects by enhancing antioxidant capacity, modulating immune responses, and inducing apoptosis in tumor cells.[30] Our study found that the risk of developing skin cancer decreased when the hypotaurine-to-taurine ratio increased. Since 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 UK Biobank database. This approach effectively addresses the limitations of traditional observational studies by minimizing 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 (RCTs). 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 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

In summary, this study provides evidence for a causal association between specific metabolites and SC risks using MR approaches. 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.

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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 instrumental variables (IVs) influence the outcome solely through exposure. Key abbreviations include SNPs for single-nucleotide polymorphisms, LD for linkage disequilibrium, and IVW (inverse variance weighted), weighted median, MR-Egger, and MR-PRESSO.

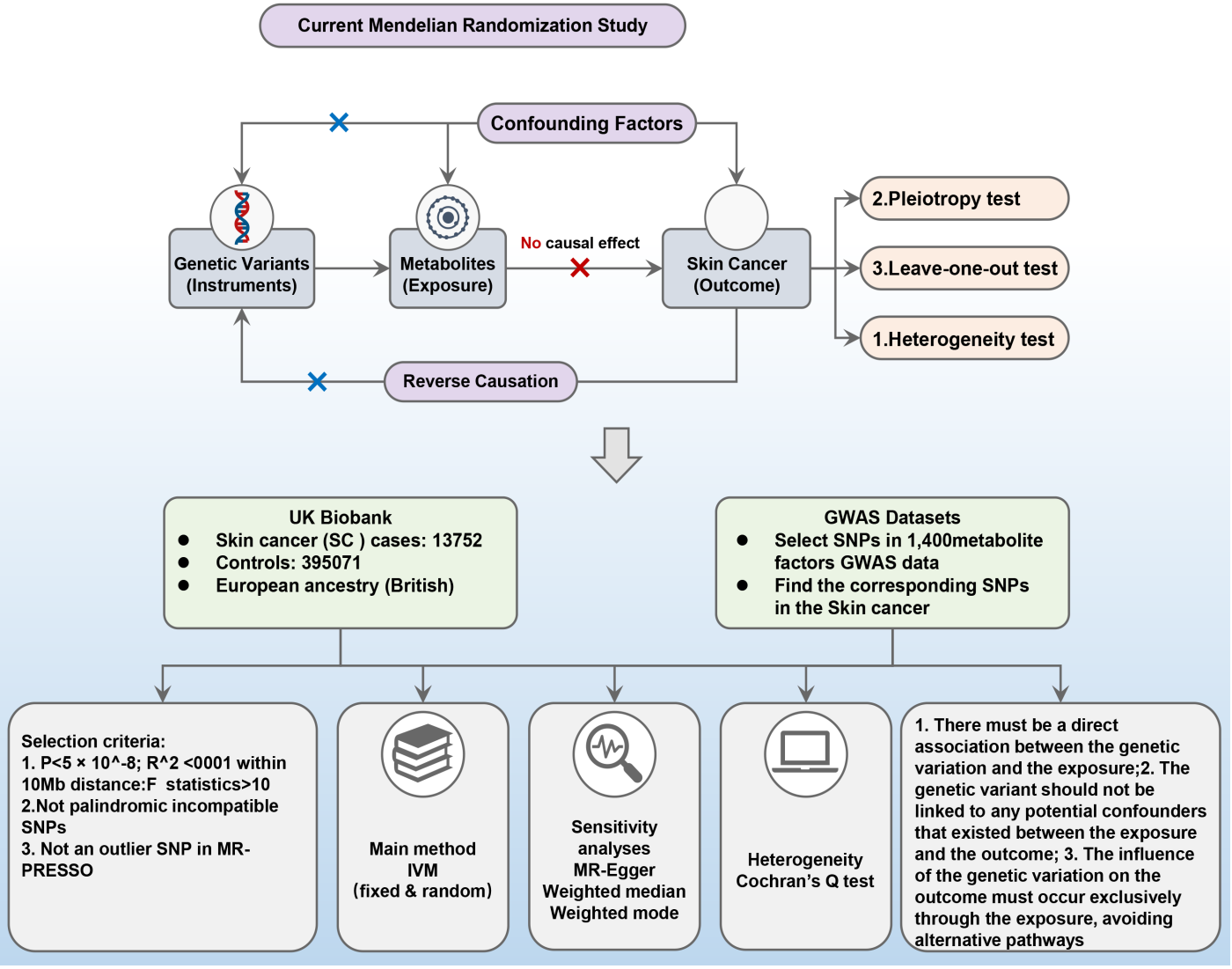
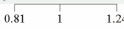


Figure 2. The causal association between all metabolites and skin cancer (SC) risks. **A**) Protective factors against SC. **B**) Risk factors of SC. We selected IVW as a primary method; p<0.05 showed statistical significance; OR value >1 indicated a risk factor, while OR value <1 indicated a protective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

A

Exposure	Method	No.of SNP	OR(95% CI)	P
Oleoyl−linoleoyl−glycerol levels	Inverse variance weighted	29	0.889 (0.829 to 0.953)	0.001
Hypotaurine to taurine ratio	Inverse variance weighted	25	0.893 (0.834 to 0.957)	0.001
Glucose to fructose ratio	Inverse variance weighted	14	0.894 (0.815 to 0.981)	0.017
3−indoxyl sulfate levels	Inverse variance weighted	20	0.895 (0.827 to 0.969)	0.006
Palmitoleoylcarnitine levels	Inverse variance weighted	19	0.896 (0.813 to 0.988)	0.028
1−linoleoyl−GPI levels	Inverse variance weighted	21	0.898 (0.836 to 0.965)	0.003
1−palmitoyl−2−linoleoyl−gpc levels	Inverse variance weighted	33	0.899 (0.842 to 0.959)	0.001
2−naphthol sulfate levels	Inverse variance weighted	21	0.903 (0.827 to 0.985)	0.022
3−ethylcatechol sulfate levels	Inverse variance weighted	20	0.905 (0.833 to 0.984)	0.019
1−stearoyl−2−linoleoyl−gpc levels	Inverse variance weighted	20	0.909 (0.834 to 0.992)	0.032
Behenoylcarnitine levels	Inverse variance weighted	28	0.910 (0.858 to 0.964)	0.001
N−stearoyl−sphinganine levels	Inverse variance weighted	13	0.912 (0.840 to 0.990)	0.027
Isoursodeoxycholate levels	Inverse variance weighted	19	0.913 (0.833 to 1.000)	0.050
Cysteinylglycine levels	Inverse variance weighted	19	0.915 (0.855 to 0.979)	0.010
Sarcosine levels	Inverse variance weighted	20	0.918 (0.850 to 0.991)	0.029
Uridine levels	Inverse variance weighted	19	0.918 (0.856 to 0.986)	0.018
Sulfate of piperine metabolite C18H21NO3 levels	Inverse variance weighted	20	0.919 (0.856 to 0.987)	0.020
Citrate to oxalate (ethanedioate) ratio	Inverse variance weighted	15	0.920 (0.848 to 0.999)	0.046
5alpha−androstan−3beta,17alpha−diol disulfate levels	Inverse variance weighted	23	0.921 (0.866 to 0.979)	0.008
Lignoceroylcarnitine levels	Inverse variance weighted	24	0.923 (0.876 to 0.973)	0.003
tryptophan to tyrosine ratio	Inverse variance weighted	25	0.924 (0.862 to 0.991)	0.028
1−stearoyl−GPG levels	Inverse variance weighted	22	0.926 (0.870 to 0.985)	0.015
Hydroxy−cmpf levels	Inverse variance weighted	21	0.926 (0.861 to 0.996)	0.039
Phosphate to mannose ratio	Inverse variance weighted	24	0.926 (0.861 to 0.997)	0.041
Gamma−tocopherol/beta−tocopherol levels	Inverse variance weighted	23	0.927 (0.863 to 0.996)	0.037
Carboxyethyl−gaba levels	Inverse variance weighted	22	0.928 (0.869 to 0.991)	0.025
Adenosine 5'−diphosphate (ADP) to pantothenate ratio	Inverse variance weighted	16	0.928 (0.868 to 0.992)	0.029
Sulfate of piperine metabolite C16H19NO3 levels	Inverse variance weighted	23	0.929 (0.865 to 0.998)	0.043
N−oleoyltaurine levels	Inverse variance weighted	20	0.929 (0.871 to 0.992)	0.028
1−palmitoleoyl−2−linolenoyl−GPC levels	Inverse variance weighted	19	0.930 (0.873 to 0.991)	0.025
Caffeine to theophylline ratio	Inverse variance weighted	28	0.931 (0.869 to 0.997)	0.041
Campesterol levels	Inverse variance weighted	21	0.933 (0.889 to 0.979)	0.005
Cysteinylglycine to taurine ratio	Inverse variance weighted	30	0.936 (0.880 to 0.995)	0.034
Oleoyl−linoleoyl−glycerol to linoleoyl−arachidonoyl−glycerol ratio	Inverse variance weighted	24	0.938 (0.891 to 0.987)	0.014
Etiocholanolone glucuronide levels	Inverse variance weighted	20	0.939 (0.899 to 0.982)	0.005
Ethyl beta−glucopyranoside levels	Inverse variance weighted	19	0.947 (0.899 to 0.997)	0.039
Benzoate to linoleoyl−arachidonoyl−glycerol ratio	Inverse variance weighted	26	0.948 (0.900 to 0.998)	0.043



B

Exposure	Method	No.of SNP	OR(95% CI)	P
Linoleoyl−arachidonoyl−glycerol levels	Inverse variance weighted	34	1.047 (1.002 to 1.093)	0.042
Andro steroid monosulfate C19H28O6S levels	Inverse variance weighted	38	1.049 (1.001 to 1.100)	0.047
Erythritol levels in elite athletes	Inverse variance weighted	21	1.049 (1.001 to 1.099)	0.044
1−methylxanthine levels	Inverse variance weighted	29	1.049 (1.000 to 1.101)	0.049
16a−hydroxy DHEA 3−sulfate levels	Inverse variance weighted	24	1.050 (1.004 to 1.099)	0.034
Glucuronate to androsterone glucuronide ratio	Inverse variance weighted	20	1.051 (1.002 to 1.102)	0.041
1−arachidonoyl−gpc levels	Inverse variance weighted	28	1.056 (1.013 to 1.101)	0.011
Adenosine 5'−diphosphate (ADP) to fructose ratio	Inverse variance weighted	32	1.058 (1.005 to 1.115)	0.032
Arachidonate to oleate to vaccenate ratio	Inverse variance weighted	16	1.060 (1.008 to 1.115)	0.022
Stearoyl sphingomyelin levels	Inverse variance weighted	32	1.064 (1.004 to 1.128)	0.037
Glutamine to alanine ratio	Inverse variance weighted	35	1.067 (1.006 to 1.132)	0.032
Glycolithocholate sulfate levels	Inverse variance weighted	21	1.070 (1.002 to 1.143)	0.045
Phosphate to oleoyl−linoleoyl−glycerol ratio	Inverse variance weighted	31	1.071 (1.010 to 1.136)	0.022
Palmitoylcarnitine levels	Inverse variance weighted	29	1.072 (1.004 to 1.144)	0.037
Eicosapentaenoate levels	Inverse variance weighted	27	1.074 (1.003 to 1.151)	0.042
Ergothioneine levels	Inverse variance weighted	25	1.077 (1.001 to 1.159)	0.045
Uridine to 2'−deoxyuridine ratio	Inverse variance weighted	27	1.078 (1.015 to 1.145)	0.015
Benzoate to oleoyl−linoleoyl−glycerol ratio	Inverse variance weighted	30	1.078 (1.021 to 1.139)	0.007
Arachidonate to linoleate ratio	Inverse variance weighted	25	1.081 (1.032 to 1.133)	0.001
N−methylproline levels	Inverse variance weighted	22	1.083 (1.006 to 1.165)	0.033
4−allylphenol sulfate levels	Inverse variance weighted	22	1.084 (1.010 to 1.165)	0.026
Adenosine 5'−monophosphate (AMP) to proline ratio	Inverse variance weighted	19	1.085 (1.005 to 1.171)	0.037
Plasma lactate levels	Inverse variance weighted	19	1.085 (1.001 to 1.176)	0.046
Arachidonate to pyruvate ratio	Inverse variance weighted	16	1.090 (1.013 to 1.174)	0.021
Phenylacetylcarnitine levels	Inverse variance weighted	24	1.093 (1.023 to 1.169)	0.009
Phenylalanine to tyrosine ratio	Inverse variance weighted	17	1.095 (1.019 to 1.176)	0.013
3−methyl−2−oxovalerate to 3−methyl−2−oxobutyrate ratio	Inverse variance weighted	20	1.098 (1.016 to 1.188)	0.019
Sebacate levels	Inverse variance weighted	16	1.099 (1.011 to 1.193)	0.026
Arachidonate levels	Inverse variance weighted	28	1.105 (1.049 to 1.164)	0.000
Cortisol to 4−cholesten−3−one ratio	Inverse variance weighted	21	1.107 (1.034 to 1.186)	0.004
Docosapentaenoate levels	Inverse variance weighted	25	1.108 (1.035 to 1.187)	0.003
Margarate levels	Inverse variance weighted	20	1.108 (1.020 to 1.204)	0.015
N−methyl−2−pyridone−5−carboxamide levels	Inverse variance weighted	16	1.112 (1.017 to 1.215)	0.020
Aspartate to phosphate ratio	Inverse variance weighted	17	1.119 (1.033 to 1.213)	0.006
2−hydroxybutyrate/2−hydroxyisobutyrate levels	Inverse variance weighted	16	1.123 (1.028 to 1.226)	0.010
Adenosine 5'−monophosphate (AMP) to phenylalanine ratio	Inverse variance weighted	24	1.124 (1.048 to 1.205)	0.001
Aspartate to citrulline ratio	Inverse variance weighted	18	1.129 (1.046 to 1.219)	0.002
Glycerol to palmitoylcarnitine ratio	Inverse variance weighted	19	1.132 (1.030 to 1.245)	0.010
Leucine to N−palmitoyl−sphingosine ratio	Inverse variance weighted	23	1.137 (1.036 to 1.248)	0.007

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 value >1 indicated a risk factor, while OR value <1 indicated a protective factor.

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

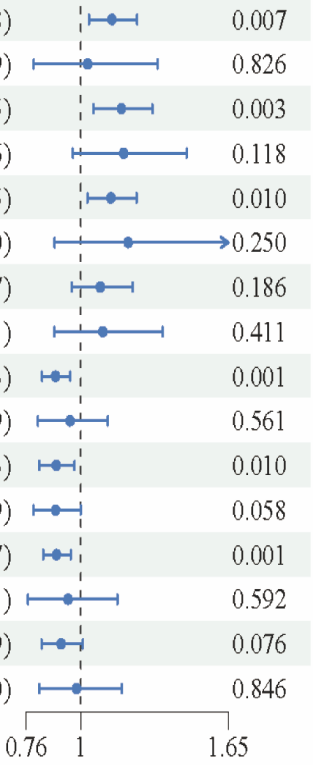


Figure 4. Scatter plot showing the relationship between four metabolites and the SC risk. **A)** Leucine to N-palmitoyl-sphingosine ratio in SC. **B)** Glycerol to palmitoylcarnitine ratio in SC. **C)** Oleoyl-linoleoyl-glycerol levels in SC. **D)** Hypotaurine to taurine ratio in SC.

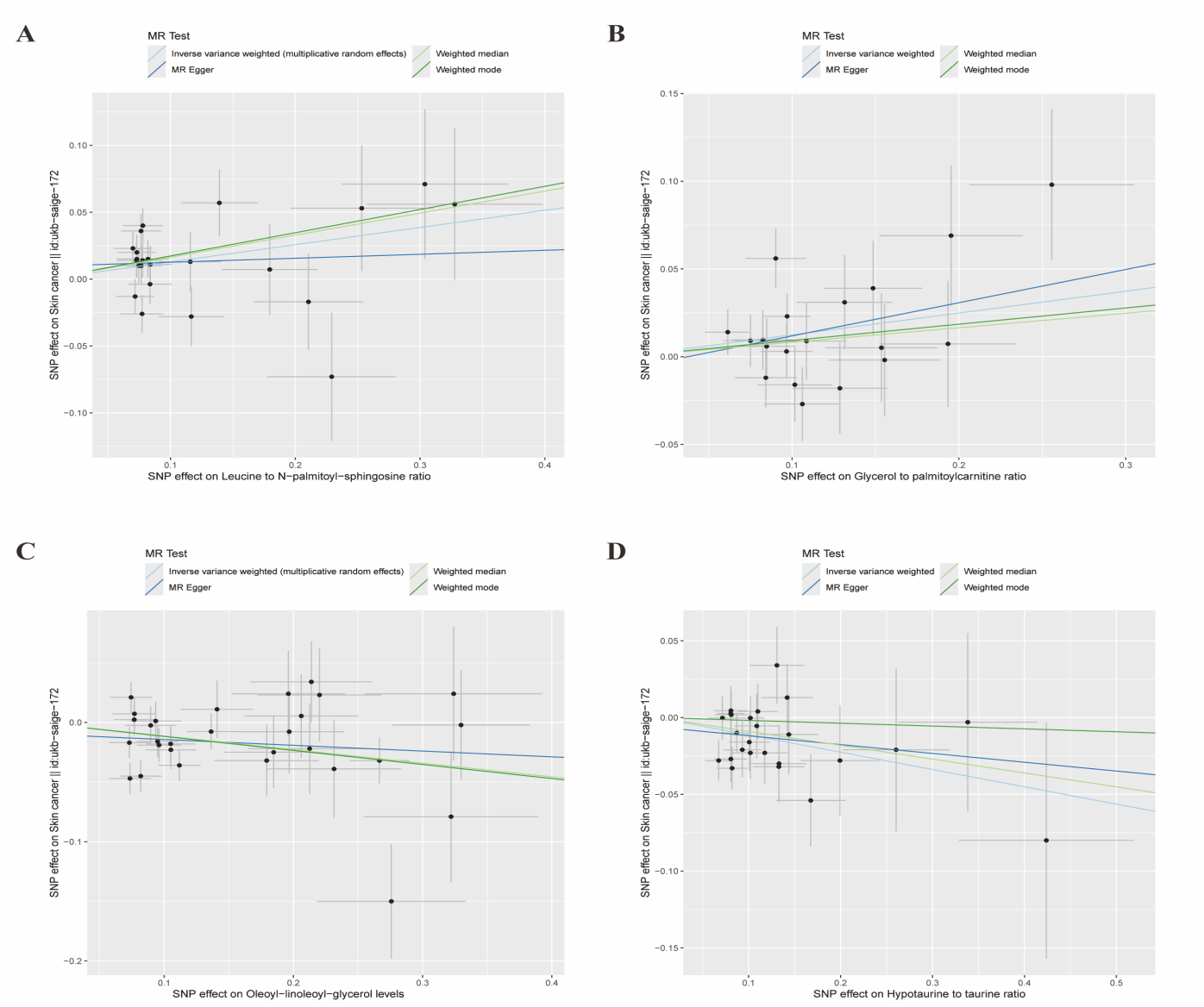


Figure 5. A funnel plot showing IVs for each significant causal association between four metabolites and the SC risk. **A)** Leucine to N-palmitoyl-sphingosine ratio in SC. **B)** Glycerol to palmitoylcarnitine ratio in SC. **C)** Oleoyl-linoleoyl-glycerol levels in SC. **D)** Hypotaurine to taurine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

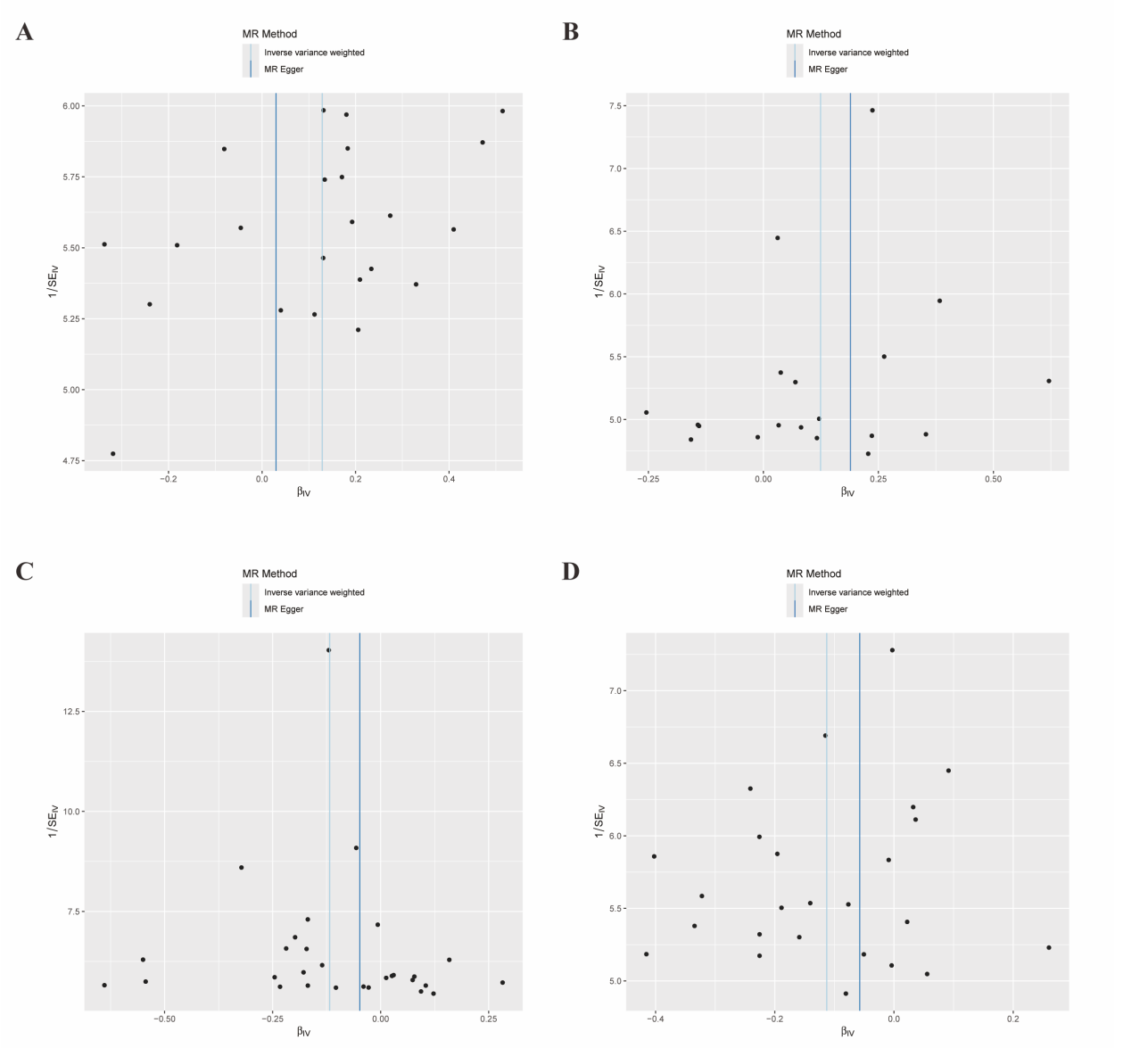
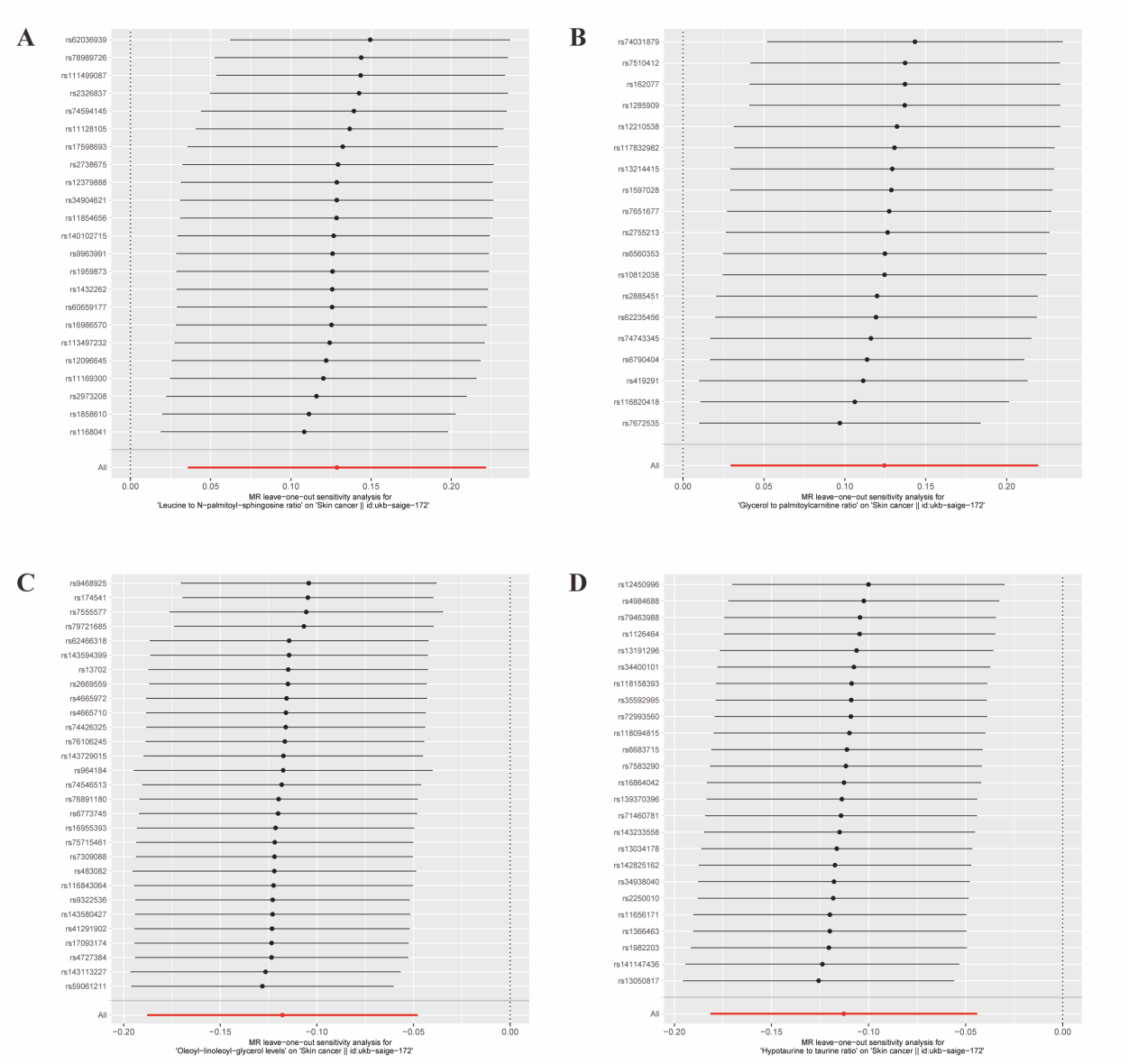


Figure 6. Leave-one-out plot showing the genetic associations of four metabolites with the SC risk. **A)** Leucine to N-palmitoyl-sphingosine ratio in SC. **B)** Glycerol to palmitoylcarnitine ratio in SC. **C)** Oleoyl-linoleoyl-glycerol levels in SC. **D)** Hypotaurine to taurine ratio in SC.



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 no significant pleiotropy effects were found.*