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# Exploring the potential causal relationship between fatty acid metabolism ratios and major salivary gland carcinomas

## A two-sample Mendelian randomization study

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**Abstract**

Major salivary gland carcinomas (MSGCs) is a rare but aggressive cancer, with limited understanding of its metabolic underpinnings. Lipid metabolism, particularly fatty acid metabolism ratios (FAMRs), has been implicated in various cancers, but its role in MSGCs remains unclear. This study aims to explore the potential causal relationships between specific FAMRs and MSGCs using Mendelian randomization (MR) analysis. A 2-sample MR analysis was conducted using summary data from genome-wide association studies. Three FAMRs, including the ratio of diacylglycerol to triglycerides (DAG/TG), total cholesterol (TC) to total lipids (TL) ratio in large very low-density lipoprotein (VLDL; TC/TL in large VLDL), and triglycerides to total lipids ratio in medium VLDL (TG/TL in medium VLDL), were investigated for their potential causal relationships with MSGCs. Sensitivity analyses, including MR-Egger and leave-one-out tests, were performed to assess pleiotropy and the robustness of the results. The DAG/TG and TC/TL ratios in large VLDL were significantly positively associated with an increased risk of MSGCs (OR = 10.921, $P$ = .004 and OR = 2.651, $P$ = .047, respectively). In contrast, the TG/TL ratio in medium VLDL showed a significant negative association with MSGCs risk (OR = 0.460, $P$ = .041). Sensitivity analyses confirmed the robustness of these associations, with no evidence of significant pleiotropy in 2 of the ratios. This study reveals novel insights into the metabolic basis of MSGCs, demonstrating significant associations between specific FAMRs and MSGCs risk. These findings highlight the potential clinical relevance of FAMRs as biomarkers or therapeutic targets in MSGCs. Future studies should focus on diverse populations and mechanistic research to validate these associations and explore their clinical implications.

**Abbreviations:** BWMR = Bayesian weighted Mendelian randomization, DAG = diacylglycerol, FAMRs = fatty acid metabolism ratios, GWAS = genome-wide association study, IVW = inverse-variance weighted, MR = Mendelian randomization, MSGCs = major salivary gland carcinomas, NMR = nuclear magnetic resonance, ORs = odds ratios, SNPs = single nucleotide polymorphisms, TC = total cholesterol, TG = triglycerides, TL = total lipids, VLDL = very low-density lipoprotein.

**Keywords:** lipid metabolism, Mendelian randomization analysis, salivary gland neoplasms

## 1. Introduction

Major salivary gland carcinomas (MSGCs) is rare but highly aggressive head and neck cancers, accounting for approximately 3% to 11% of all malignancies in this region.[1] Although the exact etiology of MSGCs is not well understood, studies suggest that genetic mutations,[2] chronic inflammation, and environmental exposures—such as radiation and viral infections—may play crucial roles in its development. Facial nerve paralysis is observed in up to 63% of cases when MSGCs occurs in the parotid gland.[3] The most common histological subtypes include mucoepidermoid carcinoma and adenoid cystic carcinoma. Established risk factors include advanced age, male gender, smoking, and a family history of cancer.[4] Current treatment strategies primarily involve surgical resection, with the approach varying depending on lesion type and size, often combined with radiation and chemotherapy.[5] Subtotal excision with facial nerve preservation is the most commonly employed therapeutic approach, while total or radical resection may be chosen for larger or more complex malignant lesions.[6]

Due to the complexity and diverse subtypes of MSGCs, its diagnosis and management remain significant challenges for clinicians. Fatty acid metabolism ratios (FAMRs) represent

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*The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.*

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the relative proportions between different types of fatty acids or lipid molecules, such as the ratio of diacylglycerol to triglycerides, or the ratio of triglycerides to total lipids in very low-density lipoprotein (VLDL). These ratios not only reflect the state of lipid metabolism in the body but are also thought to be associated with the development and progression of various diseases.[7] In recent years, increasing attention has been directed toward the potential role of fatty acid metabolism in tumorigenesis.[8] Some studies suggest that abnormal lipid metabolism may promote tumor growth and metastasis by influencing processes such as cell membrane composition, signal transduction pathways, and energy supply.[9] For example, elevated triglyceride ratios have been linked to an increased risk of several malignancies.[10] However, most existing research on the relationship between FAMRs and cancer has focused on breast cancer, non-small cell lung cancer, and prostate cancer,[11] while the relationship between these ratios and MSGCs remains largely unexplored.

Mendelian randomization (MR) is a powerful tool for assessing causal relationships between modifiable exposures or risk factors and clinical outcomes. Compared to traditional epidemiological studies, MR effectively overcomes the limitations posed by confounding factors that may bias causal inference, making it an increasingly popular approach for evaluating and identifying potential causal relationships.[12] MR has provided valuable insights into the causal roles of various diseases.

Although the MR method has been widely applied in research on cardiovascular and metabolic diseases, its use in exploring the causal relationships between FAMRs and specific cancers, including MSGCs, remains underutilized. Therefore, this study utilizes a 2-sample MR approach to explore the potential causal relationship between FAMRs and MSGCs. The goal is to provide a theoretical framework for understanding the role of fatty acid metabolism in the development and progression of MSGCs, thereby establishing a scientific foundation for future prevention and treatment strategies.

## 2. Materials and methods

### 2.1. Research design

MR methods must satisfy 3 core assumptions: association, independence, and exclusion-restriction[13] (Fig. 1). Specifically, the selected instrumental variables must be significantly associated with the exposure (in this study, the FAMRs); the instrumental variables should not be associated with any confounding factors that could influence the exposure-outcome relationship; and the instrumental variables must affect the outcome exclusively through the exposure, which in this study refers to the risk of MSGCs. We strictly adhered to these assumptions and performed a 2-sample MR analysis to ensure the validity of the selected instrumental variables and the robustness of the study findings.

In this study, we conducted a 2-sample MR analysis on 233 circulating metabolic markers, utilizing summary data from genome-wide association studies (GWAS) to evaluate the potential causal relationships between these markers and MSGCs, and to identify metabolic ratios with significant causal associations. Additionally, we performed sensitivity analyses to assess the robustness of the results. The research workflow is illustrated in Figure 2.

### 2.2. Data sources

This study utilized summary statistics from GWAS to investigate the potential causal relationship between specific FAMRs and the risk of MSGCs. For the GWAS data on fatty acid metabolism, we used a study whose univariate summary statistics are available in the GWAS Catalog under accession number GCST90301954. This large-scale study included 136,016 participants and analyzed 233 circulating metabolic markers, 64 of which were related to fatty acid metabolism. These data were obtained using nuclear magnetic resonance spectroscopy, which quantitatively measured various lipids and lipoproteins.[14] The genetic data related to MSGCs were derived from a pan-ancestry genetic analysis in the UK Biobank, which included 456,348 participants of European ancestry and analyzed 2989 binary traits.[15] The UK Biobank is a large-scale prospective study that recruited over 500,000 participants aged 40 to 69 between 2006 and 2010. Its data are widely used in global research across various fields, including cardiovascular disease, cancer, and metabolic disorders, making it a key resource for understanding complex diseases.[16] Since all data used in this study

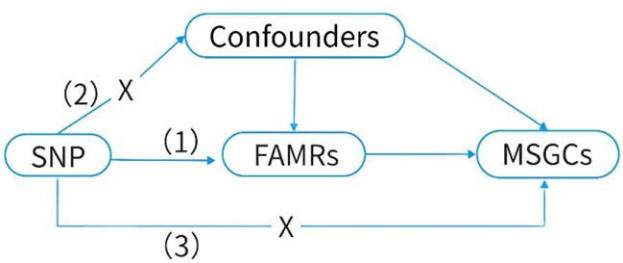


**Figure 1.** The 3 key assumptions of MR research are (1) the SNP is closely associated with specific FAMRs; (2) the SNP is independent of other known confounding factors; and (3) the SNP influences the risk of MSGCs only through FAMRs. The symbol X indicates that the SNP chosen as an instrumental variable is not directly related to confounding factors or outcomes. FAMs = fatty acid metabolism ratios, MR = Mendelian randomization, MSGCs = major salivary gland carcinomas, SNP = single nucleotide polymorphism.

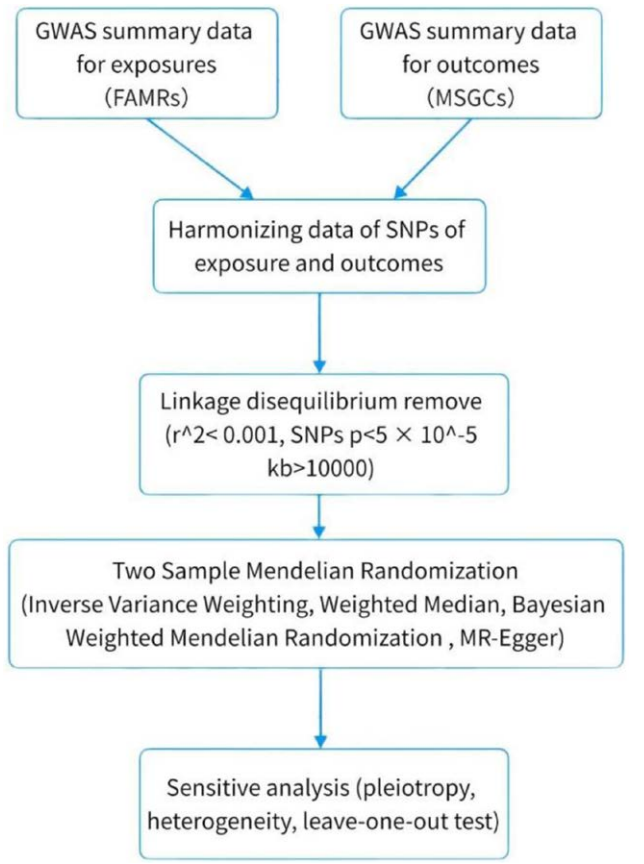


**Figure 2.** Workflow of the study.

are publicly accessible (https://www.ebi.ac.uk/gwas/home) and had received ethical approval from the relevant institutions, no additional ethical approval was required for this analysis.

### 2.3. Selection and validation of instrumental variable SNPs

We selected SNPs associated with the 233 circulating metabolic markers based on 3 criteria. First, SNPs with genome-wide significance ($P$-value < $5 \times 10^{-8}$) were selected. Second, the independence of these SNPs was evaluated using linkage disequilibrium ($r^2 > 0.01$), and SNPs in linkage disequilibrium within 1 Mb of other SNPs with higher $P$-values were excluded. Finally, to control for potential bias, we assessed weak instrument bias in the selected instrumental variables by calculating the $F$-statistic. An $F$-statistic >10 indicated the absence of weak instrument bias, thereby further validating the assumption of association. The $F$-statistic was calculated using the formula $F = [(N - K - 1)/K] \times [R^2/(1 - R^2)]$, where N is the sample size for the exposure, $K$ is the number of instrumental variables, and $R^2$ is the proportion of variance in the exposure explained by the instrumental variables.

### 2.4. Two-sample MR analysis

In this study, we conducted a 2-sample MR analysis using random-effects inverse-variance weighted (IVW), weighted median, and MR-Egger methods to assess the potential causal relationship between specific FAMRs and MSGCs, expressed as odds ratios (ORs). Given that the traditional IVW method may be susceptible to bias from invalid instruments or pleiotropy, we also performed sensitivity analyses to ensure the robustness and accuracy of the IVW results. Additionally, we incorporated Bayesian weighted MR (BWMR) into our analysis. BWMR accounts for the uncertainty in the estimates of weak effects and low-level pleiotropic effects, and it adaptively detects outliers caused by some larger pleiotropic effects.[17] Further validation through BWMR indicated that the results are more robust and reliable.

Our sensitivity analyses involved 3 key steps: assessment of horizontal pleiotropy, heterogeneity tests, and a "leave-one-out" approach. MR-Egger was employed to detect horizontal pleiotropy, with a $P$-value below .05 indicating pleiotropy between the exposure (FAMRs) and the outcome (MSGCs). For heterogeneity, we used Cochran $Q$ test, where a $P$-value > .05 suggests no significant heterogeneity among the instrumental variables, implying that heterogeneity does not influence the study results. In the "leave-one-out" analysis, each SNP was sequentially removed to calculate the meta-effect of the remaining SNPs, allowing us to observe whether the results remained consistent.

All statistical analyses were performed using the "TwoSampleMR" package in R software, version 4.3.2.

## 3. Results

In this study, through a 2-sample MR analysis of 233 circulating metabolic markers, we identified 3 FAMRs with a potential causal relationship to MSGCs. These ratios are the ratio of diacylglycerol to triglycerides (DAG/TG ratio; GCST90301954), the total cholesterol to total lipids ratio in large VLDL (TC/TL ratio in large VLDL; GCST90302020), and the triglycerides to total lipids ratio in medium VLDL (TG/TL ratio in medium VLDL; GCST90302068). The MR analysis results for these markers, including odds ratios (ORs), 95% confidence intervals (CIs), and $P$-values, are presented in Table 1.

The IVW analysis shows a significant positive correlation between the DAG/TG ratio and MSGCs risk ($P$ = .004), with an OR of 10.921. The TC/TL ratio in large VLDL is significantly positively correlated with MSGCs risk ($P$ = .047), with an OR of 2.651. In medium VLDL, the TG/TL ratio shows a significant negative correlation with MSGCs risk ($P$ = .041), with an OR of 0.460.

The BWMR results confirm the correlation between the DAG/TG ratio and the TG/TL ratio in medium VLDL with the risk of MSGCs. However, the TC/TL ratio in large VLDL does not show a significant correlation with MSGCs risk, as shown in Table 2.

**Table 1**

**Associations between FAMRs and the risk of MSGCs.**

| Risk factors | | MR Egger | Weighted median | Inverse variance weighted |
|---|---|---|---|---|
| DAG/TG ratio | OR (95% CI) | 2.256 (0.040 to 127.908) | 9.466 (1.173 to 76.382) | 10.921 (2.100 to 56.786) |
| | *P* value | .695 | .035 | .004 |
| TC/TL ratio in large VLDL | OR (95% CI) | 2.036 (0.386 to 10.748) | 1.909 (0.409 to 8.924) | 2.651 (1.013 to 6.937) |
| | *P* value | .405 | .411 | .047 |
| TG/TL ratio in medium VLDL | OR (95% CI) | 0.193 (0.059 to 0.629) | 0.325 (0.102 to 1.036) | 0.460 (0.219 to 0.970) |
| | *P* value | .007 | .057 | .041 |

DAG = diacylglycerol, FAMRs = fatty acid metabolism ratios, MSGCs = major salivary gland carcinomas, MR = Mendelian randomization, ORs = odds ratios, TC = total cholesterol, TG = triglycerides, TL = total lipids, VLDL = very low-density lipoprotein.

**Table 2**

**Association of the genetically predicted particularly FAMRs with the risk of MSGCs using BWMR.**

| Risk factors | OR (95% CI) | BWMR *P*-value |
|---|---|---|
| DAG/TG ratio | 12.851 (2.501 to 66.028) | .002 |
| TC/TL ratio in large VLDL | 2.549 (0.937 to 6.931) | .067 |
| TG/TL ratio in medium VLDL | 0.454 (0.214 to 0.963) | .039 |

BWMR = Bayesian weighted Mendelian randomization, DAG = diacylglycerol, FAMRs = fatty acid metabolism ratios, MSGCs = major salivary gland carcinomas, ORs = odds ratios, TC = total cholesterol, TG = triglycerides, TL = total lipids, VLDL = very low-density lipoprotein.

**Table 3**

**Pleiotropy test results for selected SNPs.**

| Risk factors | Pleiotropy test beta (SE) | Pleiotropy test *P*-value |
|---|---|---|
| DAG/TG ratio | 0.086 | .406 |
| TC/TL ratio in large VLDL | 0.039 | .704 |
| TG/TL ratio in medium VLDL | 0.027 | .068 |

DAG = diacylglycerol, SNPs = single nucleotide polymorphisms, TC = total cholesterol, TG = triglycerides, TL = total lipids, VLDL = very low-density lipoprotein.

**Table 4**

**Heterogeneity test results for selected SNPs.**

| | Heterogeneity (MR Egger) | | Heterogeneity (IVW) | |
|---|---|---|---|---|
| Risk factors | Cochran *Q* | Heterogeneity test *P*-value | Cochran *Q* | Heterogeneity test *P*-value |
| DAG/TG ratio | 59.371 | .040 | 60.366 | .041 |
| TC/TL ratio in large VLDL | 67.981 | .644 | 68.126 | .670 |
| TG/TL ratio in medium VLDL | 126.921 | .315 | 130.520 | .261 |

DAG = diacylglycerol, IVW = inverse-variance weighted, MR = Mendelian randomization, SNPs = single nucleotide polymorphisms, TC = total cholesterol, TG = triglycerides, TL = total lipids, VLDL = very low-density lipoprotein.

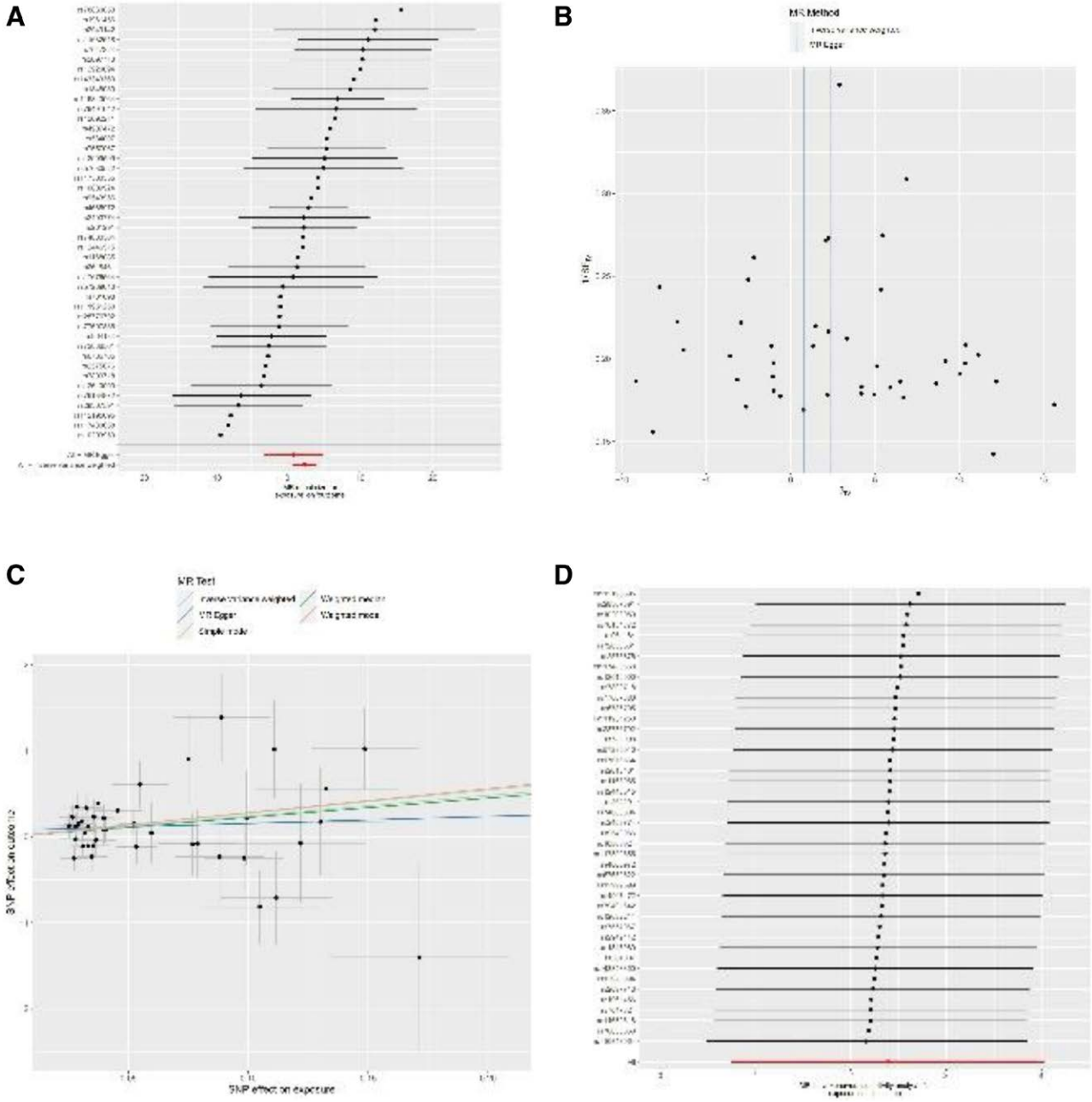


**Figure 3.** The causal effect of DAG/TG ratio levels on the risk of MSGCs. (A–D) Forest plot, funnel plot, scatter plot, and leave-one-out sensitivity analysis of the causal effect of DAG/TG ratio levels on the risk of MSGCs. DAG = diacylglycerol, MSGCs = major salivary gland carcinomas, TG = triglycerides.

To confirm the robustness of these findings, we conducted sensitivity analyses on the 3 FAMRs, with the results presented in Tables 3 and 4. Forest plots, funnel plots, scatter plots, and leave-one-out sensitivity analyses are shown in Figures 3 to 5.

The MR-Egger analysis indicated that none of the 3 markers exhibited significant pleiotropy, suggesting that the selected instrumental variables were relatively robust, and the causal inference between these FAMRs and MSGCs was reliable.

However, in Cochran *Q* test, the *P*-value for the DAG/TG ratio was close to .05, suggesting potential differences in the effect sizes and directions of the SNP instrumental variables used. This could be attributed to various factors, such as unobserved confounders or some SNPs influencing MSGCs risk through different biological pathways. Despite the presence of heterogeneity, the strength of this association remains credible. Both the TC/TL ratio in large VLDL and the TG/TL ratio in medium VLDL did not exhibit significant heterogeneity, indicating a high degree of consistency and reliability in their association with MSGCs.

In the MR-PRESSO test, the global test for the DAG/TG ratio revealed significant pleiotropy ($P = .035$), while the TC/TL ratio in large VLDL ($P = .684$) and the TG/TL ratio in medium VLDL ($P = .277$) did not exhibit any pleiotropy. Notably, no significant outliers were detected in the MR-PRESSO test for the DAG/TG ratio, TC/TL ratio in large VLDL, or TG/TL ratio in medium VLDL, indicating that the SNP instrumental variables were overall robust and reliable. Although the global test for the DAG/TG ratio indicated the presence of pleiotropy, the result was not driven by any individual SNP outliers, suggesting that the significant association with MSGCs risk remained valid. The MR-PRESSO results for the other 2 ratios further supported the reliability of the causal inference.

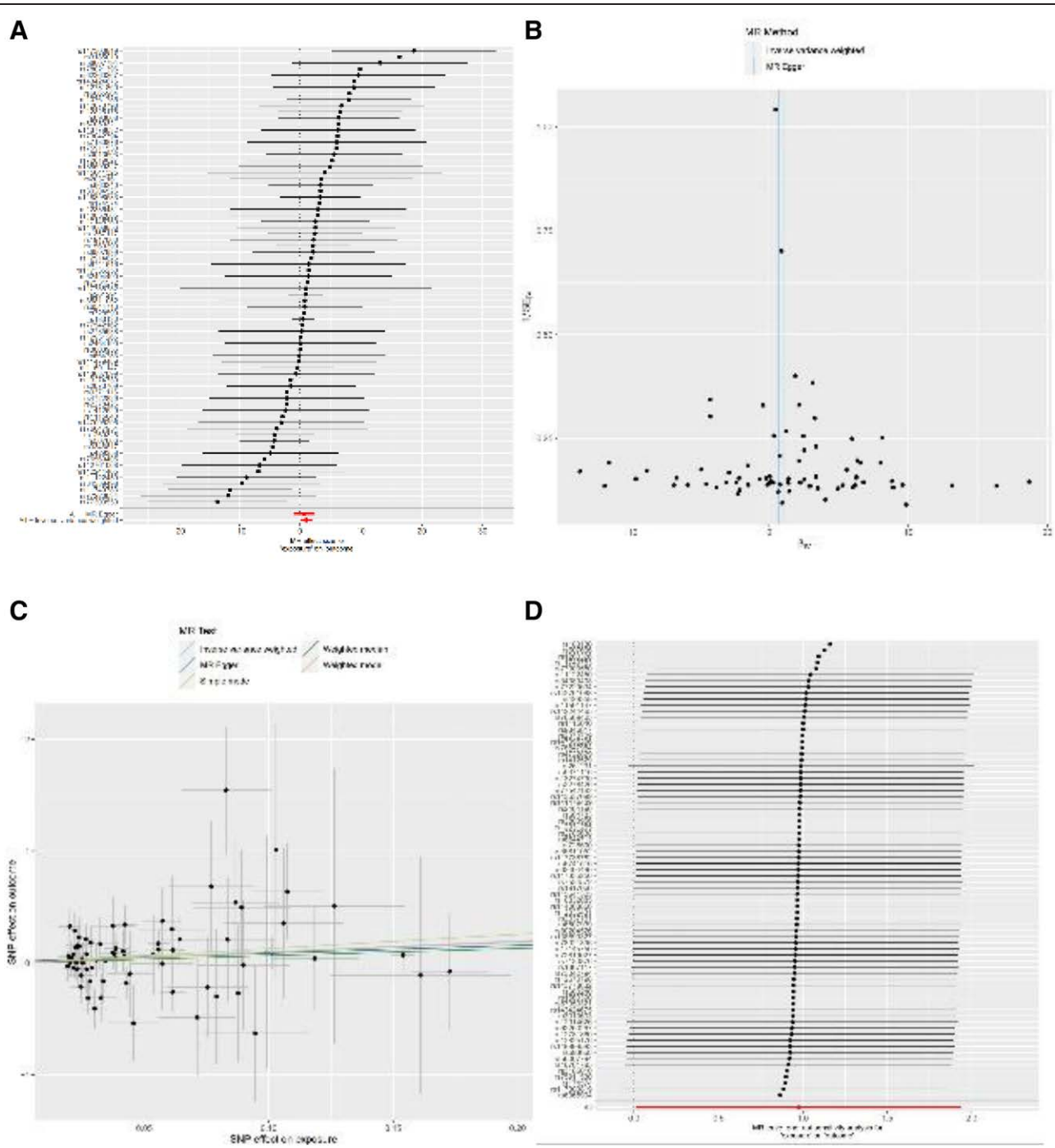


**Figure 4.** The causal effect of TC/TL ratio in large VLDL levels on the risk of MSGCs. (A–D) Forest plot, funnel plot, scatter plot, and leave-one-out sensitivity analysis of the causal effect of TC/TL ratio in large VLDL levels on the risk of MSGCs. MSGCs = major salivary gland carcinomas, TC = total cholesterol, TG = triglycerides, TL = total lipids, VLDL = very low-density lipoprotein.

The results of the leave-one-out sensitivity analysis indicated that the associations between these 3 FAMRs and MSGCs are robust and not unduly influenced by any single genetic variant. This enhances the overall credibility of the analysis, suggesting that these ratios may be important metabolic factors in the development of MSGCs.

## 4. Discussion

This study, through a 2-sample MR analysis, uncovers the potential genetic underpinnings of MSGCs and explores the possible causal relationships between 3 FAMRs and MSGCs. Significant associations were identified between alterations in these FAMRs and the risk of MSGCs. Specifically, the DAG/TG ratio and the TC/TL ratio in large VLDL demonstrated positive associations with MSGCs risk, while the TG/TL ratio in medium VLDL exhibited a significant negative association with MSGC risk. These findings highlight the pivotal role of fatty acid metabolism in the pathogenesis of MSGCs and may provide valuable insights for future prevention and treatment strategies.

In the IVW analysis, the DAG/TG ratio demonstrated a significant positive association with the risk of MSGCs (OR = 10.921, $P$ = .004), suggesting that an elevated DAG/TG ratio may substantially increase the risk of MSGCs.

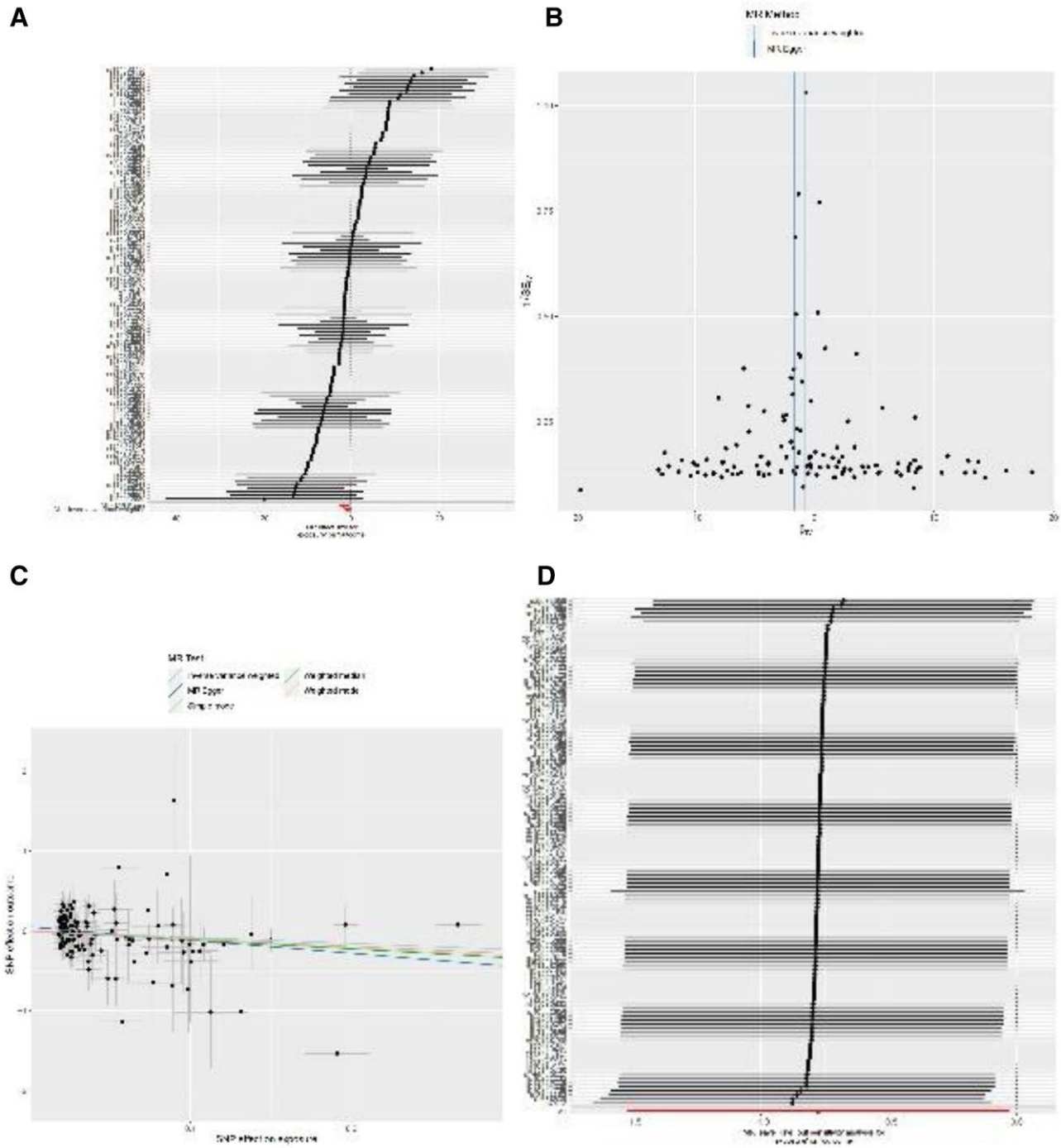


**Figure 5.** The causal effect of TG/TL ratio in medium VLDL levels on the risk of MSGCs. (A–D) Forest plot, funnel plot, scatter plot, and leave-one-out sensitivity analysis of the causal effect of TG/TL ratio in medium VLDL levels on the risk of MSGCs. MSGCs = major salivary gland carcinomas, TC = total cholesterol, TL = total lipids, VLDL = very low-density lipoprotein.

Although the DAG/TG ratio exhibited pleiotropy in the MR-PRESSO test, the other 2 ratios did not, indicating that most instrumental variables are relatively robust. Additionally, the DAG/TG ratio showed overall robustness and reliability in both heterogeneity tests and leave-one-out sensitivity analyses, reinforcing the significance and credibility of this association. These findings suggest that the DAG/TG ratio may serve as an important metabolic marker with potential functional roles in MSGCs development, possibly related to diacylglycerol's role as an intracellular signaling molecule, regulating pathways involved in cell proliferation and survival.[18]

The significant positive association between the TC/TL ratio in large VLDL and the risk of MSGCs (OR = 2.651, $P = .047$) suggests that the TC/TL ratio may play a crucial metabolic role in the development of MSGCs. The ratio of cholesterol to total lipids in large VLDL reflects the metabolic balance of lipid transport, and an abnormal TC/TL ratio may influence cell proliferation and tumor development by regulating lipid metabolism pathways, thereby increasing cancer risk.[19]

In contrast, the significant negative association between the TG/TL ratio in medium VLDL and the risk of MSGCs (OR = 0.460, $P = .041$) indicates that triglyceride imbalance in medium VLDL may be associated with a protective effect

against MSGCs. This protective effect could reduce tumor development by regulating lipid deposition or altering cellular metabolic pathways. These findings provide new insights into potential therapeutic targets for MSGC through lipid metabolism interventions, suggesting possible adjustments in prevention and treatment strategies.

Lipid metabolites such as DAG, TG, and TG in VLDL have been shown to significantly impact cell survival. Certain lipids, such as diacylglycerol[20] and triglycerides in VLDL,[21] appear to promote cell growth and survival, while others may induce cell death or dormancy.[22] This suggests that chronic metabolic imbalances may trigger the production of specific pro-survival molecules and their downstream effects, ultimately influencing tumor initiation and progression.

TG are the primary form of energy storage in cells, and elevated TG levels are frequently observed in individuals with metabolic syndrome and obesity, both of which are associated with an increased risk of cancer. Recent studies have demonstrated that elevated serum TG levels are closely linked to the development of breast cancer,[23] lung cancer,[24] prostate cancer, and ovarian cancer.[25] However, the role of the DAG/TG ratio in cancer, particularly in MSGCs, has not been thoroughly investigated. Our findings suggest that an imbalance in the DAG/TG ratio may contribute to the initiation and progression of MSGCs by disrupting lipid homeostasis and enhancing pro-inflammatory signaling pathways.

VLDL is a type of lipoprotein synthesized by the liver, primarily responsible for transporting triglycerides and cholesterol produced in the liver to other tissues. VLDL is the major carrier of triglycerides in plasma and plays a pivotal role in lipid metabolism. Dysregulation of VLDL metabolism has been linked to various diseases, including cardiovascular disease and cancer.[26] VLDL particles have been shown to promote systemic inflammation and oxidative stress, both of which are key drivers of cancer development.[27]

The TC/TL ratio in large VLDL (TC/TL ratio) reflects the proportion of cholesterol relative to TL within VLDL particles. An abnormal TC/TL ratio may disrupt lipid homeostasis within cells, potentially influencing cell proliferation, survival, and tumor development. It is considered a potential marker of metabolic imbalance and may contribute to tumor progression by altering lipid metabolic pathways.[28] The TG/TL ratio in medium VLDL reflects the relative abundance of TG to TL and may serve as an indicator of metabolic imbalance. An elevated TG/TL ratio is associated with lipid dysregulation and inflammation, both of which are known to create an environment conducive to tumor development.[19]

Despite the promising findings of this study, several limitations must be considered. First, the accuracy of MR analysis depends on the validity of the selected instrumental variables (SNPs), which must be strongly associated with the exposure and influence the outcome solely through the exposure. If alternative pathways, such as horizontal pleiotropy, affect the outcome, bias may be introduced. Second, genetic heterogeneity across populations could influence the relationship between SNPs and the exposure. Since this study primarily uses GWAS data from individuals of European descent, the findings may not be generalizable to other ethnicities or populations. Additionally, MR analysis typically assumes a linear relationship between exposure and outcome, and if the actual relationship is nonlinear, this assumption may lead to erroneous conclusions. The quality and accuracy of MR analysis also depend on the quality of the underlying GWAS data; any errors or deficiencies in the data could affect the results. Furthermore, while MR analysis can suggest a causal relationship, elucidating the specific biological mechanisms remains challenging. MR analysis also cannot determine the magnitude of intervention effects. Therefore, while this study provides valuable insights, these limitations should be considered when interpreting and generalizing the findings. Future research should involve broader populations to verify the generalizability of these associations and be complemented by experimental studies to elucidate the specific mechanisms involved. In-depth mechanistic research and clinical trials will be essential for determining the effectiveness and safety of these metabolic markers as strategies for prevention or treatment.

## 5. Conclusion

Our study is the first to reveal a potential causal relationship between specific FAMRs and MSGCs. The DAG/TG ratio and the TC/TL ratio in large VLDL were significantly positively associated with MSGCs risk, while the TG/TL ratio in medium VLDL showed a significant negative association. These findings provide new insights into the metabolic basis of MSGCs and may have clinical significance in identifying novel biomarkers or therapeutic targets.

## Author contributions

**Conceptualization:** Xiaopo He.
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**Resources:** Kailin Shen.
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**Supervision:** Kailin Shen, Xiaopo He.
**Writing – original draft:** Yongjie Guo, Kailin Shen, Shuqing Ge, Qi Zheng.
**Writing – review & editing:** Yongjie Guo, Kailin Shen, Xiaopo He.

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