Diabetology & Metabolic Syndrome

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# Unraveling the causal pathway between phosphatidylinositol, metabolites, and metabolic syndrome: a Mendelian randomization study

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## Abstract

**Introduction** Observational studies have increasingly acknowledged the influence of Phosphatidylinositol (PI) on metabolic syndrome (MetS). Nevertheless, the causal association between PI and MetS remains unclear due to the presence of confounding factors and the potential for reverse causation in observational settings. This study seeks to clarify the causal link between PI and MetS while investigating the role of mediating metabolites.

**Methods** A two-sample Mendelian randomization (MR) analysis was performed to examine the association between PI and MetS, utilizing aggregated data from genome-wide association studies (GWAS). Additionally, a two-step MR approach was applied to quantify the mediation effect of metabolites on the PI-MetS relationship. The inverse variance weighted (IVW) method served as the primary analytical approach, complemented by various sensitivity analyses employing alternative techniques.

**Results** A significant positive association was found between genetically predicted PI and a 17% increased risk of MetS. Genetically predicted metabolites, including 4-cholesten-3-one (IVW: OR 1.264, 95% CI 1.076–1.483, $p=0.004$), N-acetylalliin (IVW: OR 1.189, 95% CI 1.008–1.402, $p=0.040$), and the Adenosine 5′-diphosphate to 5-oxoproline ratio (IVW: OR 1.191, 95% CI 1.045–1.357, $p=0.009$), were each significantly associated with an increased risks of MetS, accounting for 14.50, 11.41%, 11.87% and % of the total effect, respectively. Notably, the Retinol to oleoyl-linoleoyl-glycerol ratio (IVW: OR 0.643, 95% CI 0.466–0.887, $p=0.007$) mediated 62.6% of the effect, highlighting its pivotal role in the causal pathway linking PI to MetS. Moreover, 1-palmitoyl-2-dihomo-linolenoyl-GPC (IVW: OR 0.865, 95% CI 0.752–0.995, $p=0.042$) and the Creatine to carnitine ratio (IVW: OR 0.853, 95% CI 0.740–0.983, $p=0.028$) were associated with a reduced risk of MetS, demonstrating inhibitory effects within their respective pathways that accounted to 35.03% and 8.45% reductions in risk, respectively.

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**Conclusions** Our MR analysis demonstrated a positive association between PI and an increased risk of MetS. Furthermore, the metabolite-mediated PI significantly influenced MetS risk. These findings may offer valuable insights into the pathogenesis of MetS and inform future clinical research.

**Keywords** Phosphatidylinositol, Metabolic syndrome, Metabolite, Mendelian randomization

## Introduction

Metabolic syndrome (MetS) is characterized by a constellation of metabolic abnormalities, including dyslipidemia, hypertension, obesity, and insulin resistance, all of which synergistically increase the risk of cardiovascular disease (CVD) [1, 2]. In recent years, the prevalence of MetS has persistently increased, posing a significant public health challenge on a global scale. Epidemiological studies reveal that MetS affects approximately 6–39% of adolescents globally, with prevalence rates in adults ranging from 20–25% [3, 4]. These findings underscore the profound impact of MetS as a widespread public health issue, placing a substantial burden on healthcare systems worldwide. Therefore, a comprehensive investigation into the pathological mechanisms underlying MetS, coupled with the development of potential therapeutic strategies, is of significant scientific and clinical importance.

Phosphatidylinositol (PI) is an essential phospholipid in the human body that produces seven distinct phosphorylated inositol lipids [5]. It functions as a fundamental component of the cell membrane, significantly contributing to cell signaling and membrane transport [6, 7]. PI is intricately linked with insulin resistance, obesity, inflammation, and other critical aspects of MetS, affecting glucose-lipid metabolism through various pathways that facilitate the progression of MetS [8, 9]. Conversely, emerging studies propose that PI might also regulate lipid metabolism and energy homeostasis, potentially exerting an anti-obesity effect by modulating the expression of specific genes involved in hepatic lipid metabolism through diverse metabolic pathways [8]. Derivatives of PI, such as PI3, may serve as insulin sensitizers, offering potential therapeutic benefits in ameliorating metabolic disorders [10–12]. The complex mechanisms through which PI influences MetS underscore the intricate nature of their relationship, with the causal link between them remaining to be fully elucidated.

Previous research has established that metabolites function as pivotal signaling molecules in the pathological processes underlying MetS, impacting mechanisms such as energy homeostasis, glucose metabolism, lipid metabolism, and inflammatory regulation [12, 13]. Phosphatidylinositol 3-phosphate (PI3P) and Phosphatidylinositol 5-phosphate (PI5P), which are principal derivatives of PI, are acknowledged for their regulatory interactions with a broad spectrum of metabolites [14–17]. Consequently, it is apparent that these metabolites are not merely by-products of metabolic processes but also play significant roles in regulating both the onset and progression of MetS. Based on these observations, we hypothesize that metabolites might mediate the effects of PI on MetS.

Mendelian Randomization (MR) is a statistical approach that utilizes genetic variants as instrumental variables (IVs) to mimic the randomization process of controlled clinical trials. This approach inherently mitigates confounding factors such as environmental and behavioral variables, and effectively overcomes the issue of reverse causality [18, 19].Consequently, MR has become a widely accepted strategy for establishing causal inferences in complex disease research. In this study, we applied MR to examine the causal relationships between PI and MetS, and further assessed the mediating effects of candidate metabolic intermediates.

## Methods

### Study design

To elucidate the causal relationship between PI and MetS, this study employed large-scale, publicly available genome-wide association study (GWAS) pooled statistics. This MR study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) guidelines [20].

The study was conducted in three stages. In the initial stage, a univariate Mendelian randomization study (UVMR) was performed to examine the causal relationship between PI and MetS, identifying a positive effect of PI on MetS. To further verify the causal direction and exclude the potential for reverse causation, we conducted a reverse MR analysis to evaluate the influence of MetS on PI. The analysis yielded no evidence of a significant association between MetS and PI. This analytical approach reinforces the robustness of the causal inference and further substantiates the validity of our findings. In the second phase, the causal relationship between PI and metabolites was assessed, resulting in the identification of 81 metabolites as potential mediators. Finally, the impact of metabolites on MetS was examined, leading to the screening of six metabolites and the application of a two-step MR approach to determine the mediator ratio of the compliant metabolites. The MR analysis was conducted under three key assumptions: a strong association between IVs and exposure factors (correlation assumption), the independence of IVs from confounders of the exposure-outcome relationship (independence

assumption), and the effect of IVs on the outcome occurring solely through exposure (exclusivity assumption) [21].

### Data source

PI summary statistics were obtained from FinnGen, which includes 7174 (GeneRISK's 7174 Finns) sample populations of European ancestry [22].The FinnGen study is a large-scale genomics initiative that has analyzed over 500,000 Finnish biobank samples and correlated genetic variation with health data to understand disease mechanisms and predispositions. The project is a collaboration between research organisations and biobanks within Finland and international industry partners.

The GWAS summary statistics for MetS were obtained from The GWAS catalog (GCST90086073). The data was collected from 56,637 individuals of European descent using the comprehensive GWAS strategy GUIDANCE, leading to the identification of 94 genome-wide relevant loci, 26 of which were previously unreported [23]. Metabolite data were sourced from the Canadian Longitudinal Study of Aging (CLSA), which involved 8,299 participants [24]. The CLSA is a large-scale study that encompasses data from 50,000 participants, contributing to a more profound understanding of the disease. Both the GWAS and the CLSA provided the metabolite data used in this study.

Although the PI, MetS, and metabolite data were derived from individuals of European ancestry, differences in sample size, study design, and data acquisition protocols may contribute to population heterogeneity. To minimize the influence of population stratification, only GWAS summary statistics derived from European-ancestry samples were included in the variable selection process. Sensitivity analyses addressing potential bias from population stratification were performed using inverse variance weighting (IVW) and MR-Egger methods, both of which indicated no substantial heterogeneity. Additional information regarding the datasets is provided in Supplementary Table S1.

### Genetic instrumental variable selection

Given the limited number of genome-wide significant variants linked to PI and specific metabolites, we selected SNPs associated with PI, metabolites, and MetS from GWAS datasets using a significance threshold of $P < 1 \times 10^{-5}$. To ensure the independence of selected instrumental variables, we applied a stringent linkage disequilibrium (LD) clumping strategy using a window size of 10,000 base pairs and an $r^2$ threshold of $< 0.001$. This approach effectively minimizes covariance-induced bias in MR estimates and addresses instrument non-independence caused by LD, thereby reducing the risk of false-positive results. We then calculated the F-statistic for each SNP and excluded those classified as weak IVs ($F < 10$). In addition, allelic harmonization was performed to align effect alleles and prevent strand mismatches, thereby improving the accuracy of causal inference. To account for potential pleiotropic bias, we conducted sensitivity analyses using methods such as MR-Egger and MR-PRESSO to detect horizontal pleiotropy and confirm the robustness of our findings. Detailed characterization of SNPs associated with PI, Metabolites, and MetS, respectively, can be found in the online Supplementary Material, Tables S2-S5.

### Statistical analysis

#### *UVMR analysis*

In the UVMR analysis, the IVW method was primarily used to estimate causal effects. This approach provides the highest statistical power under the assumption that all instrumental variables are valid and not affected by horizontal pleiotropy. Recognizing the potential for pleiotropic bias in empirical settings, we additionally employed MR-Egger regression, the weighted median method, as well as the simple and weighted mode-based estimators to validate the robustness of causal inference. The weighted median method yields consistent causal estimates even when up to 50% of the instruments are invalid, whereas MR-Egger regression enables detection and adjustment of directional pleiotropy [25, 26]. MR-Egger intercept tests were further used to assess global pleiotropy, and heterogeneity was quantified using Cochran's Q statistic. Additionally, MR-PRESSO was utilized to detect potential outlier IVs and correct for any bias they may introduce. The reliability of IVW-derived estimates is reinforced when results from multiple methods demonstrate directional concordance and sensitivity analyses reveal no evidence of substantial pleiotropy or heterogeneity.

### Mediator MR analysis

In this study, a two-step MR analysis was conducted to investigate potential intermediate factors that may mediate the causal relationship between PI and MetS [27]. Initially, the study evaluated the causal impact of PI on selected mediators ($\beta_1$), followed by an assessment of the mediators' causal effect on MetS ($\beta_2$). Subsequently, utilizing the 'product of coefficients method,' the study calculated the mediating effect of PI on MetS through the mediator ($\beta_1{}^*\beta_2$) and determined the mediation ratio by dividing the mediating effect by the total effect (the causal effect of PI on MetS) (Fig. 1).

### Sensitivity analysis

In this study, we assessed the robustness of the IVW results using MR-Egger, weighted median, simple mode, and weighted mode. Cochran's Q statistic and funnel

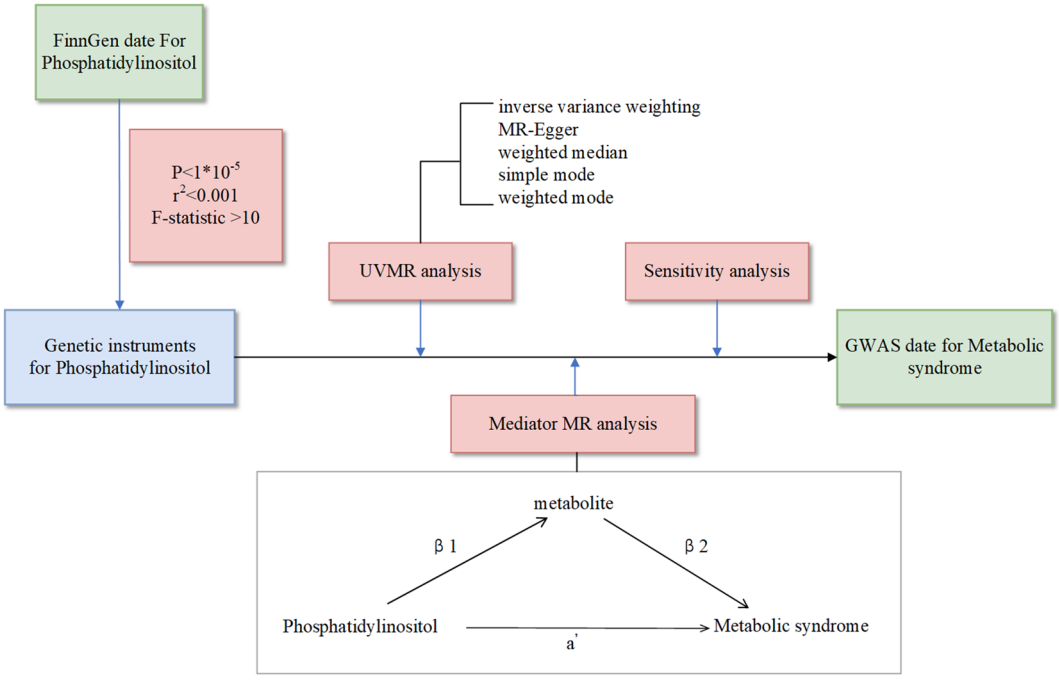


**Fig. 1** Study protocol

plots were used to test for heterogeneity [21, 28].MR-Egger assesses the multiplicity of genetic variants based on the magnitude of the intercept term [29]. We used the MR polytomous residuals and outliers (MR-PRESSO) method to detect possible outliers and calculated causal estimates after removing identified outliers [30]. In addition, forest plots and leave-one-out plots were drawn for sensitivity analysis. All MR analyses were performed using the R packages "Two Sample MR", "MR. raps" in R software (version 4.2.3; https://www.r-project.org), "MR-PRESSO".

## Results

### Causal relationship between PI and MetS

A bidirectional MR analysis was conducted to investigate the relationship between PI and MetS. When PI was considered as the exposure, nine single nucleotide polymorphisms (SNPs) were selected as IVs for the MR analysis (see Supplementary Table S2). The primary IVW analysis indicated a positive association between PI and the risk of MetS, revealing a 17% increase in MetS risk for each 1 standard deviation increase in PI (OR: 1.173; 95% CI: 1.039–1.324). These findings were further confirmed by other sensitivity analysis methods. No heterogeneity among the IVs was detected, as indicated by Cochran's Q statistic, and instrument validity tests confirmed strong instrument strength ($F > 10$) with no evidence of horizontal pleiotropy. Funnel plot analysis did not reveal any asymmetry. Results from the leave-one-out analysis demonstrated that causality estimates remained stable, with no significant changes observed after the exclusion of any single SNP. When MetS was treated as the exposure, thirty-three SNPs associated with MetS were identified (see Supplementary Table S3). However, substantial evidence indicated no association between MetS and PI, with the IVW estimate being 0.972 (95% CI: 0.900–1.050, $P = 0.475$) (Fig. 2).

### Causal relationship between PI and metabolites

A total of 81 out of 1400 metabolites met all initial screening criteria (Fig. 3). These IVW estimates have been confirmed by at least one sensitivity analysis. Possible heterogeneity between some of the IVs in this study. the MR-Egger pleiotropy test showed horizontal pleiotropy between PI and metabolites such as 1-palmitoyl-GPI, while the MR-PRESSO method was used to exclude isolated SNPs. After excluding these outlier SNPs, IVW estimates for the majority of metabolites remained largely unchanged. Minor adjustments were observed for a few metabolites (e.g., ROL/GLY), although the direction of the effects was preserved. These findings underscore the robustness of our analytical approach. Furthermore, although slight asymmetry was observed in a subset of funnel plots, most remained directionally consistent with IVW estimates. Causal effect estimates also showed minimal variation during the stepwise removal of individual SNPs (Supplementary Tables S4–S7).

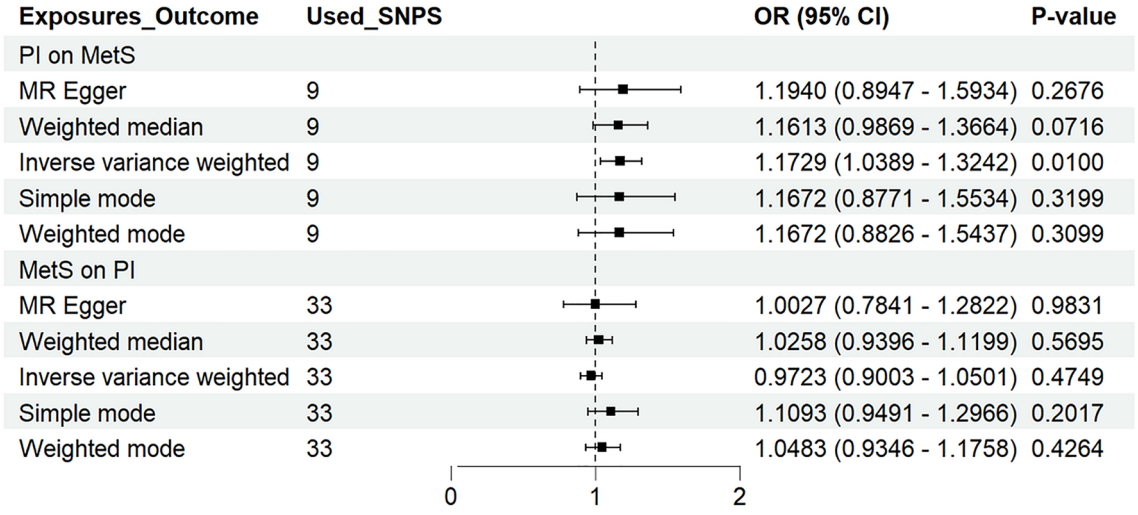


**Fig. 2** Causal effect of PI on MetS

### Causality of metabolites on MetS

Among the 81 metabolites assessed, six metabolites fulfilled all screening criteria. Notably, 4-cholesten-3-one (4C3O), N-acetylalliin (NAA), and the ratio of adenosine 5'-diphosphate to 5-oxoproline (ADP/OP) demonstrated a positive correlation with the risk of MetS, leading to a 18–26% increase in risk per 1 SD increase. Conversely, 1-palmitoyl-2-dihomo-linolenoyl-GPC (PDL-GPC), the creatine to carnitine ratio (CCR), and the retinol to oleoyl-linoleoyl-glycerol ratio (ROL/GLY) were associated with a 13–36% reduction in MetS risk per 1 standard deviation (SD) increase. In sensitivity analyses of metabolite causality with MetS, the MR-Egger intercept method revealed no significant directed pleiotropy in any of the analyses. Analysis using Cochran's Q statistic revealed potential heterogeneity among the partial IVs. Additionally, deviations from symmetry were noted in several funnel plots. Following the exclusion of potential pleiotropic SNPs, the MR-PRESSO method produced results consistent with the IVW analysis, with the exception of ROL/GLY (supplementary material online, document 1).

### Mediating role of metabolites between PI and MetS

This study identified that ROL/GLY (mediating effect percentage: 62.59%), 4C3O (14.50%), ADP/OP (11.87%), and NAA (11.41%) mediated the effect of PI on MetS. Furthermore, the study demonstrated that PDL-GPC and CCR exerted inhibitory effects on the promotion of MetS by PI. Specifically, PDL-GPC exhibited a 35.03% inhibitory effect, whereas CCR demonstrated an 8.45% inhibitory effect (Figs. 4 and 5).

## Discussion

This MR study reveals a positive causal effect of PI on MetS and elucidates the mediating pathways involved. We observed that each standard deviation (SD) increase in genetically determined PI corresponded to a 17% increase in MetS risk. Concurrently, we identified that 4C3O, NAA, ADP/OP, and ROL/GLY facilitated PI-promoted MetS development, with ROL/GLY exerting the most substantial effect at 62.59%. Notably, PDL-GPC and the CCR played an inhibitory role in this pathway.

PI is synthesized from inositol and phosphatidic acid in the endoplasmic reticulum, serving as a minor phospholipid closely linked to insulin levels. Its phosphorylation acts as a crucial cell signaling mechanism involved in various biological processes like cell growth, differentiation, migration, and apoptosis. PI can be phosphorylated at different positions on the inositol ring, generating diverse phosphorylation products such as PI3P, PI4P, PI5P, PI (3,4)P2, PI(4,5)P2, and PI(3,4,5)P3, each with distinct biological functions [5, 30, 31]. For instance, PI3P is pivotal in activating the PI3K/Akt signaling pathway, which influences the homeostatic and metabolic functions of adipose tissue [32]. In cases of obesity and MetS, reduced cellular response to insulin can inhibit the PI3K/AKT pathway, impacting glucose and lipid metabolism. Additionally, MetS often involves low-grade systemic inflammation, where the PI signaling pathway contributes to the inflammatory response, potentially leading to increased production of inflammatory factors that block the IRS-PI3K/AKT pathway, worsening metabolic disturbances and contributing to the prevalence of MetS [33, 34]. PI4P as one of its derivatives, is important for maintaining many cellular functions and has been closely associated with diseases such as obesity and type 2 diabetes [35, 36]. PI(4,5)P2 is an interesting and important phospholipid in the human body, which is mainly enriched in the plasma membrane and affects the function of organelles by regulating the localization and activity of proteins on the organelles and has an important role in the development of diabetes mellitus [37, 38].

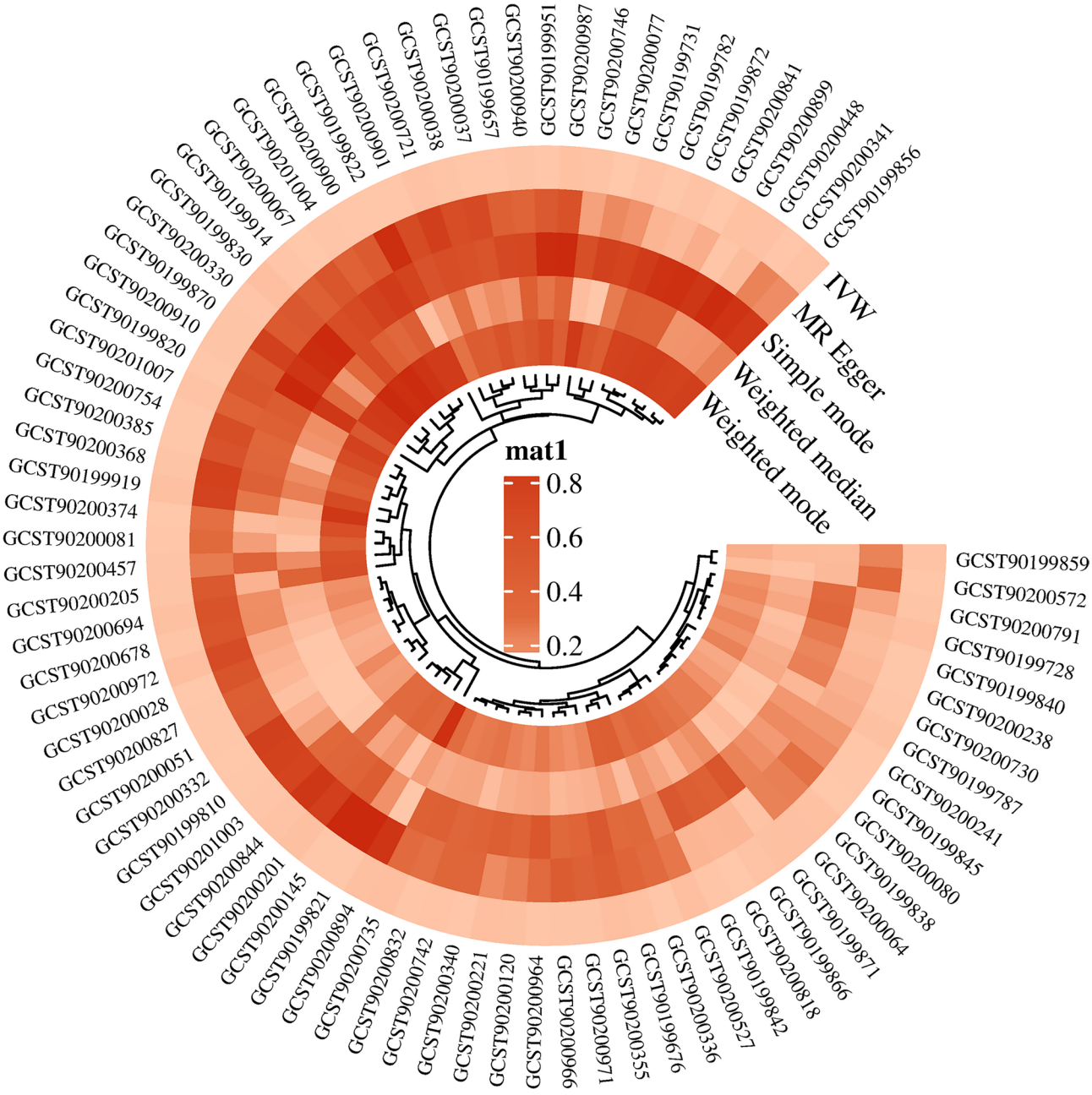


**Fig. 3** The selection process of Metabolites as causal mediators of PI and MetS

Verma et al. [39]. highlighted the pivotal role of the PI3K/AKT pathway in MetS progression, showing its association with lipid levels, atherosclerosis, and insulin levels. Phosphorylated PI derivatives serve as intracellular signaling molecules, interacting with proteins through specific structural domains like PH, FYVE, and PX domains, thereby transmitting signals within the cell. Ratke et al. [40]. investigated the signaling mechanism behind leptin-induced tumor cell migration and identified PI3K activation by leptin as a key factor in this process, which has implications for the management of obesity-related colorectal cancer. Using MR methods, the relationship between PI and MetS was explored, revealing that elevated PI levels contribute to MetS development, underscoring the importance of long-term PI effects on MetS and offering potential clinical strategies for its prevention and treatment.

Previous research has established a strong relationship between metabolites, MetS, and PI, emphasizing their crucial role in the development of metabolic disorders [13]. This study seeks to identify potential metabolite mediators that influence the causal effects of PI on

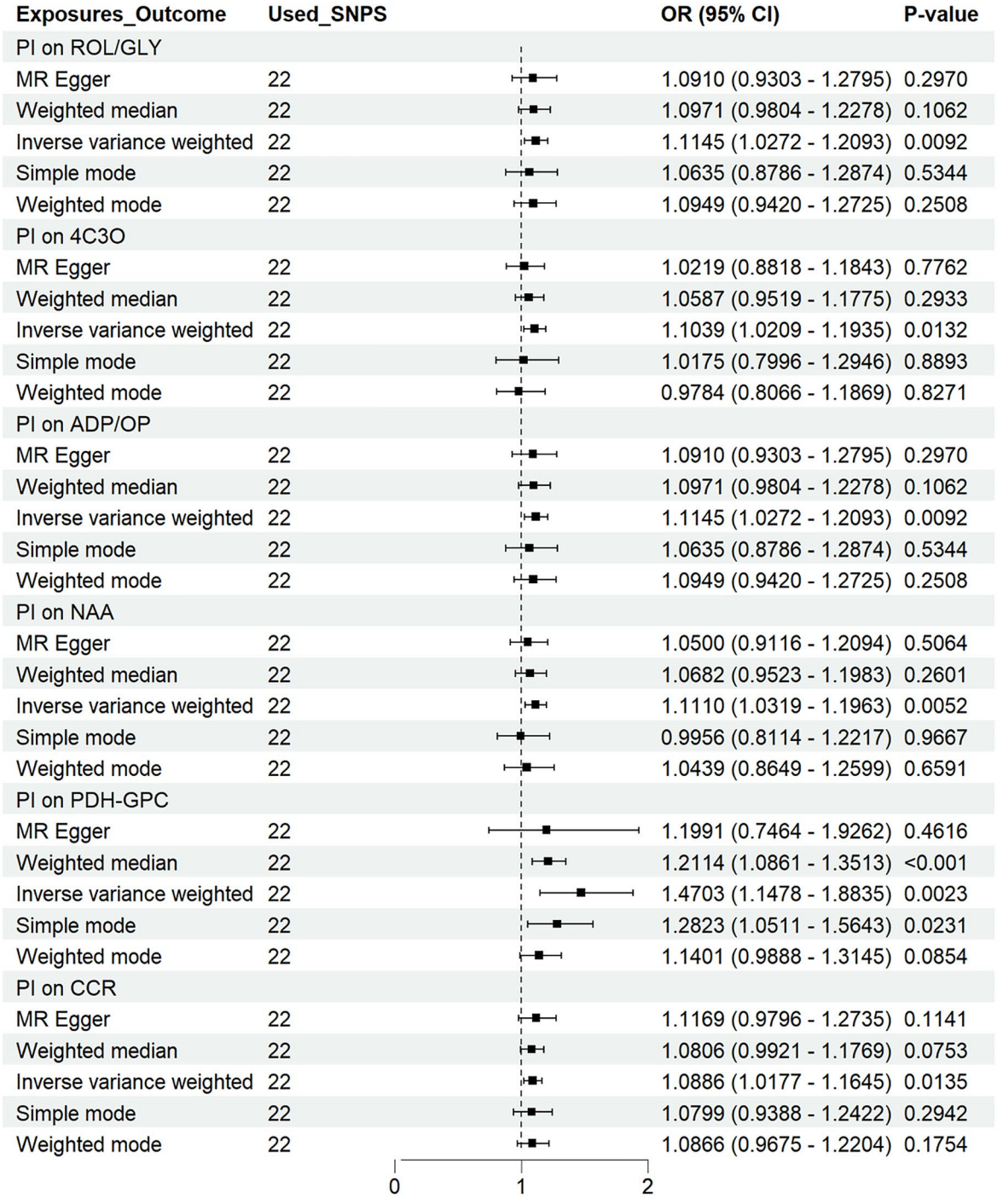


**Fig. 4** Causal effect of PI on metabolites

the progression of MetS. The analysis identified that the ratio of retinol to glyceryl (ROL/GLY) predominantly mediates the pathway through which elevated PI levels increase the risk of MetS, accounting for 62.59% of the effect. Retinol has been demonstrated to affect the phosphoinositide 3-kinase (PI3K)/AKT signaling pathway, which plays a role in vascular endothelial function and neuroprotection [41, 42]. Additionally, elevated levels of retinol have been associated with insulin resistance, increased triglyceride (TG) levels, and an elevated risk of type 2 diabetes [43]. Further, retinol-binding protein 4 (RBP4) has been implicated in the development of hypertriglyceridemia and MetS in multiple studies [44]. Reay et al. [45]. reported that retinol may causally influence inflammation, obesity, ocular phenotypes, gut microbiota composition, and MRI-derived brain structures.

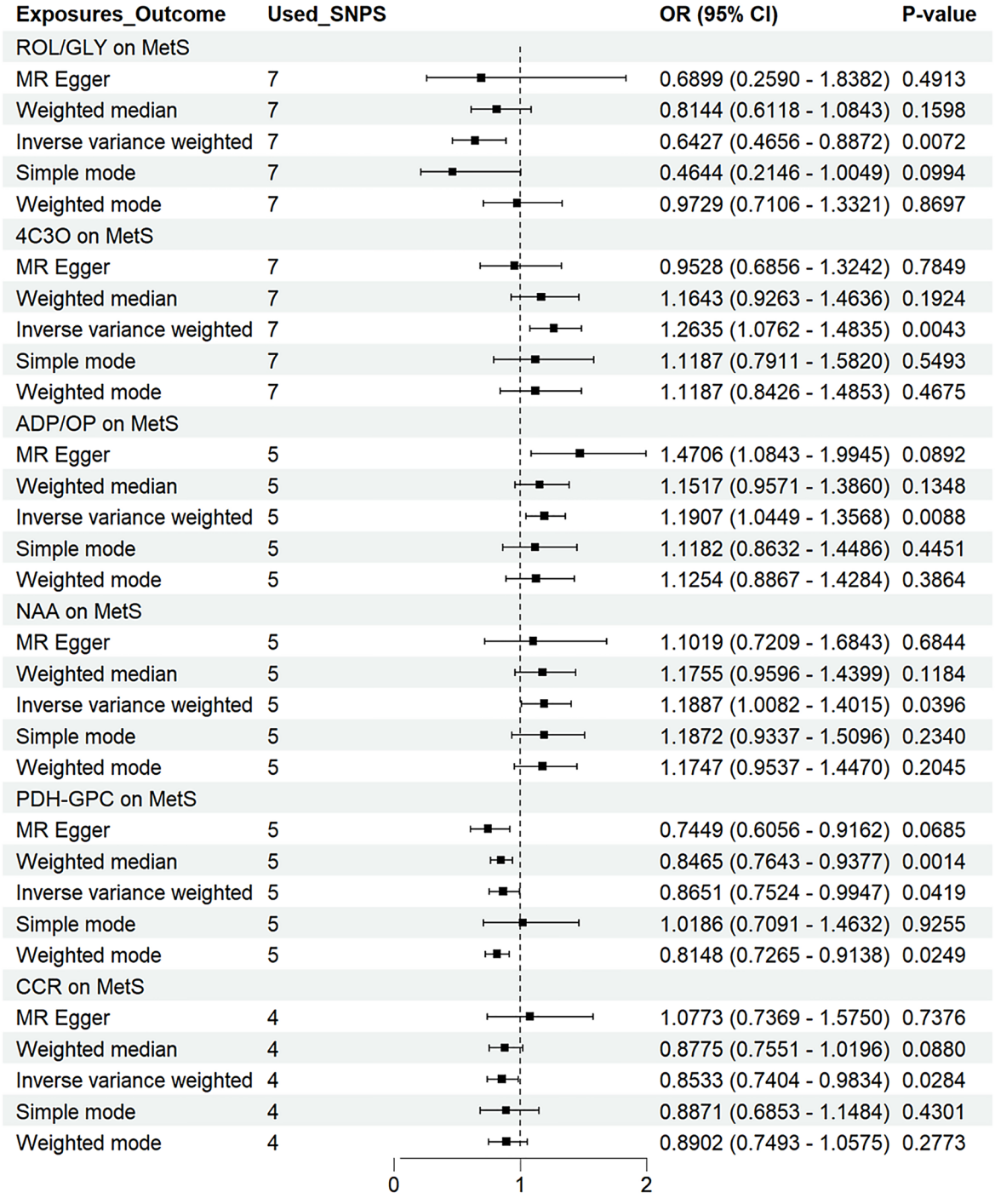


**Fig. 5** Causal effect of metabolites on MetS

Conversely, circulating retinol levels may themselves be causally influenced by lipid profiles and serum creatinine concentrations. Shin et al. [46]. demonstrated that cytosolic retinol homeostasis dysregulation is closely linked to RBP4 overproduction and hepatic inflammation in diabetic livers, ultimately impairing hepatic metabolic function. Moreover, Tian et al. [47]. found that exogenous retinyl acetate remodels the cellular lipidome by elevating phosphatidylcholine and TG levels while reducing PI content. Collectively, these findings support the potential utility of the ROL/GLY ratio as an early biomarker for metabolic dysregulation.

Another notable mediator identified was 4C3O, contributing 14.50% to the causal pathway. This cholesterol oxidation product, predominantly metabolized in the liver, interacts with motor proteins in conjunction with

PI, demonstrating anti-obesity and lipid-lowering effects [48]. Elia et al. [49]. demonstrated that 4C3O exerts antitumor effects by modulating lipid metabolism and suppressing adipogenesis in breast cancer cells. Liu et al. [50]. conducted a meta-analysis and systematic review of ten studies involving 1,034 patients with irritable bowel syndrome and 232 healthy controls. The analysis revealed significantly elevated serum 4C3O levels in irritable bowel syndrome patients compared to healthy individuals. Delle Bovi RJ et al. [51]. demonstrated that elevated levels of 4C3O could further exacerbate metabolic abnormalities by influencing cell membrane structure or insulin receptor function. Furthermore, a cohort study by Pang et al. [52]. found that metabolic markers, including 4C3O, were associated with the risk of non-alcoholic fatty liver disease in relatively lean Chinese adults, suggesting a potential role for these biomarkers in mediating the link between metabolic dysregulation and non-alcoholic fatty liver disease.

Notably, our study also demonstrated that PDL-GPC and CCR significantly inhibit the development of MetS exacerbated by elevated PI levels. Creatine plays a role in antioxidant and anti-inflammatory responses and supports metabolic processes. Conversely, fluoride has been demonstrated to decrease levels of creatine and other metabolites by activating signaling pathways such as FoxO and PI3K/Akt. In conclusion, our research highlights the critical role of metabolites in mediating the promotion of MetS by elevated PI levels. These findings suggest that modifying dietary habits and lifestyle to regulate metabolite levels of retinol, creatine, and other compounds may help mitigate the impact of elevated PI levels on MetS.

Additionally, we identified that NAA and the ADP/OP mediates the causal relationship between PI and MetS, thereby contributing to disease progression. NAA, a sulfur-containing compound, is potentially associated with antioxidant properties. Its elevation may be implicated in the development of insulin resistance through the regulation of oxidative stress and inflammatory responses. Insulin resistance is commonly associated with chronic inflammation, and elevated oxidative stress may exacerbate this condition, thus contributing to the development of MetS [53]. Increased ADP levels are linked to a reduced cellular energy supply, whereas the metabolism of 5-oxoproline may be associated with antioxidant functions within the glutathione cycle. Additionally, NAA and ADP/OP were found to mediate the relationship between PI and the progression of MetS [54, 55]. The PI3K-mediated Kkt1 pathway plays a pivotal role in the release of platelet al.pha granules induced by ADP, thereby affecting platelet function during the inflammatory response. Consequently, alterations in this ratio may indicate dysregulation of metabolic and antioxidant defense systems, further influencing the effects of PI on MetS [56, 57]. Research has indicated that the Kkt1 pathway, mediated by PI3K, is crucial for ADP-induced platelet α-granule release and plays a significant role in orchestrating platelet-mediated inflammatory responses [58].

Interestingly, we also observed that the ratio of 1-palmitoyl-2-dihomo-linolenoyl-GPC to creatine and carnitine plays a significant role in inhibiting the development of MetS accelerated by PI. This finding suggests that specific molecules associated with lipid and energy metabolism may play a role in the metabolic protective mechanism. The creatine to carnitine ratio is involved in antioxidant and anti-inflammatory responses that support metabolic processes. Additionally, fluoride decreases the levels of creatine and other metabolites by activating signaling pathways such as FoxO and PI3K/Akt [59]. By enhancing cellular energy metabolism, creatine, as a component of the energy buffer system, improves ATP regeneration efficiency, while carnitine is essential for fatty acid oxidation. The synergistic effects of these compounds may inhibit PI-induced metabolic disorders by improving energy supply and fatty acid metabolism [60].

In conclusion, our findings support a positive causal relationship between PI and MetS, offering new insights into metabolic regulatory networks mediated by diverse biomarkers. While elucidating the underlying mechanisms of PI action in metabolic diseases, these findings highlight several potential targets for intervention, particularly in retinol metabolism, cholesterol metabolism, and energy metabolism pathways. However, we acknowledge that the robustness of our results may be influenced by the inherent limitations of the MR methodology, including the limited generalizability due to reliance on European population samples and the inability of MR to capture potential nonlinear relationships. Consequently, these results should be interpreted with caution and necessitate validation in both experimental and population-based settings. Future research should continue to investigate the mechanisms of these metabolic markers in metabolic disorders, aiming to provide a more robust scientific foundation for prevention and treatment strategies for MetS.

A major strength of this study lies in the implementation of a rigorously designed MR approach, leveraging genetic variants as instrumental variables to investigate the potential causal relationship between PI and MetS, and to further examine possible metabolite-mediated pathways. We utilized large-scale, publicly available GWAS summary statistics for genetic instruments related to exposures, outcomes, and mediators, with rigorous allelic harmonization to ensure strand and effect alignment. Comprehensive sensitivity analyses including MR-Egger regression, weighted median and mode

estimators, and MR-PRESSO were conducted to assess potential horizontal pleiotropy and evaluate the robustness of the causal inferences. Nonetheless, this study has several notable limitations. First, our focus on individuals of European ancestry was aimed at ensuring genetic consistency, which may restrict the generalizability of our findings to other racial and ethnic groups. Second, given the two-sample MR design, we assumed a linear relationship between PI and MetS; thus, individual-level data will be essential for future research to investigate potential nonlinear causality. Third, although we employed methods to address abnormal variability, the potential impact of horizontal pleiotropy and the heterogeneity of IVs on our results cannot be fully excluded. Fourth, due to the use of pooled statistics in this study, we are unable to determine causal relationships within subgroups, such as between females and males. Fifth, the limited data on PIs and metabolites within the GWAS datasets underscores the need for more comprehensive data in future studies to facilitate further validation. Finally, this study employed a two-step MR approach to perform mediation analysis, estimating the proportion mediated via the "product of coefficients" method. However, this approach generally assumes theoretically that there is no interaction between exposure and the mediating variable, which may not always hold true in real biological mechanisms. Although we initially assessed potential interaction effects in our sensitivity analyses, the current analyses failed to systematically incorporate modeling of the interaction terms, which may have led to underestimation or bias of the mediating effects.

## Conclusion

The study demonstrated a positive causal relationship between PI and MetS, with key mediators identified as the ROL/GLY, 4C3O, NAA, and ADP/OP. Conversely, PDL-GPC and the CCR were found to play an inhibitory role in this pathway. These findings offer new insights into the pathogenesis of MetS, highlighting the importance of dietary and weight management in lipid regulation.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01731-7.

Supplementary Material 1

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**Author contributions**
YYG was involved in data download and analysis, as well as manuscript writing and editing. MYL and LM contributed to writing the first draft and creating the images. HYB and LL played key roles in manuscript editing, verification, and program/project development. All authors have reviewed and approved the final manuscript.

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

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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