Observational Study

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# Obesity, plasma metabolites, and hypertension

## A mediation Mendelian randomization study based on STROBE-MR guidelines

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**Abstract**

Studies have shown the association between obesity and hypertension. Plasma metabolites may have a potential association between the 2. Plasma metabolites mediate the relationship between obesity indicators and hypertension were explored through Mendelian randomization analysis. The inverse variance weighted method was employed as the primary analytical technique, supplemented by Mendelian randomization-Egger, simple mode, weighted median, and weighted mode analysis. Sensitivity analyses were conducted to ensure the robustness of our findings. Furthermore, mediation analysis was utilized to elucidate potential mediating effects of plasma metabolites and obesity. The inverse variance weighted results indicated that obesity indicators served as risk factors for hypertension [odds ratio (OR) = 1.197–1.823; $P < .001$]. In exploring the associations between plasma metabolites and hypertension, 94 significant causal relationships were identified; among these, "propionylglycine levels" (OR = 0.936; $P < .001$) emerged as protective factor while "margarate (17:0) levels" was identified as risk factor (OR = 1.098; $P < .001$). Further mediation analyses suggested the possibility of 19 pairs of mediating effects via plasma metabolites as mediator; notably, "phosphate to asparagine ratio" could reduce the risk effect of obesity on hypertension (1.588%). Sensitivity analyses confirmed the reliability of these results. This study revealed the complex causal relationships between obesity indicators, plasma metabolites, and hypertension, and confirmed the potential mediating role of plasma metabolites between obesity indicators and hypertension. These findings provided new perspectives for the prevention and treatment of hypertension.

**Abbreviations:** BMI = body mass index, CI = confidence interval, CLSA = Canadian longitudinal study on aging, GWAS = genome-wide association study, IVs = instrumental variables, IVW = inverse variance weighted, MR = Mendelian randomization, OR = odds ratio, SNPs = single nucleotide polymorphisms.

**Keywords:** hypertension, mediation analysis, Mendelian randomization, obesity, plasma metabolites

### 1. Introduction

Obesity, characterized by the excessive accumulation of fat or adipose tissue in the body, ranks among the most prevalent noncommunicable diseases globally.[1,2] Over the past few decades, its incidence has risen at an alarming rate, evolving into a global epidemic and a significant public health crisis. Nearly 2 billion adults worldwide are now considered overweight, with over half of them classified as obese.[3,4] Numerous large-scale epidemiological studies have demonstrated a significant association between body mass index (BMI) and blood pressure, with evidence suggesting that obesity is a pathogenic factor for hypertension in obese individuals.[5] Given that obesity and hypertension frequently coexist, it is unsurprising that the incidence of hypertension has also risen in tandem with the increasing prevalence of obesity.[6] Moreover, obesity is recognized as a major risk factor for hypertension across all age groups, including both adults and children, regardless of race, ethnicity, or gender.[7,8] As obesity continues to reach epidemic proportions, the risk and health impact of hypertension are expected to worsen. However, the relationship between obesity and blood pressure is complex, with multiple factors interacting to influence this association.[9] Consequently, elucidating the underlying mechanisms linking obesity to hypertension is crucial for developing more effective prevention and treatment strategies for obesity-related comorbidities.

Advanced techniques like metabolomics allow comprehensive study of metabolites in biofluids and tissues,[10] which can modulate disease risk and serve as key therapeutic targets for interventions.[11] Numerous studies have shown that metabolites and metabolic pathways are closely related to obesity, with obese individuals often exhibiting metabolic disorders.[12] For instance, Lee et al observed that the metabolite profile of obese individuals differs significantly from that of normal-weight individuals.[13] In a study examining the impact of fat-free mass on

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the metabolite profile, Jourdan et al demonstrated that serum metabolite composition is closely related to the stage of obesity.[14] Additionally, the close association between hypertension and certain lipid abnormalities, such as cholesterol and triglycerides, has long been recognized.[15] A recent study based on an obesity-related metabolite score derived from 4 representative plasma metabolites showed an association with hypertension risk and was evaluated as potentially mediating the link between obesity and hypertension risk.[15] However, the mediating role of plasma metabolites between obesity and hypertension is unclear.

Mendelian randomization (MR) is an analytical method that leverages genetic variants as instrumental variables (IVs) to simulate the conditions of a clinical randomized controlled trial. This approach facilitates the inference of causal relationships between risk factors and diseases while mitigating the impact of confounding variables and addressing reverse causality.[16] Based on this, an attempt was made to investigate the association between obesity and hypertension, as well as the potential mediating role of plasma metabolites in their relationship, by employing MR analysis.

## 2. Materials and methods

### 2.1. Study design

The selection of IVs was based on 3 key assumptions: The IV must be significantly associated with the exposure; The IV should not be correlated with any known confounders that may alter the association between the exposure and the outcome; The IV must be independent of the outcome and can only affect the outcome through its influence on the exposure. The Mendelian reporting specifications for randomized studies (STROBE-MR) was completed for this study (Table S1, Supplemental Digital Content, https://links.lww.com/MD/Q999).[16]

### 2.2. Data collection

Genome-wide association study (GWAS) datasets related to obesity indicators and hypertension (finn-b-I9_HYPTENS) were obtained from the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/).[17] The obesity indicators data included 3 datasets: BMI (ukb-b-2303), covering 454,884 European individuals with a total of 9851,867 single nucleotide polymorphisms (SNPs);[18] waist-to-hip ratio adjusted for BMI (ebi-a-GCST90025996), containing 458,349 European samples with 4238,887 SNPs; whole body fat mass (ukb-b-19393), comprising 454,137 European samples with 9851,867 SNPs. The finn-b-I9_HYPTENS dataset had a sample size of 218,754, including 55,917 hypertension cases and 162,837 control samples, with 16,380,466 SNPs, and the ethnicity was European.[17] GWAS data for 1400 plasma metabolites were downloaded from the GWAS catalog (https://www.ebi.ac.uk/gwas/home), involving 8299 unrelated European participants in the Canadian Longitudinal Study on Aging (Table S2, Supplemental Digital Content, https://links.lww.com/MD/Q1000).[19] All the data analyzed in this study are publically accessible, each original GWAS study has received ethical approval. Therefore, no additional ethical approval is required in this study.

### 2.3. Selection of IVs

We limited the inclusion criteria of IVs to ensure the accuracy and validity of the causal relationship between obesity and hypertension. The selection of IVs followed these principles: First, a more lenient significance threshold of $P < 1 \times 10^{-5}$ was applied to select SNPs for the exposure, in order to capture greater exposure variation when the number of available genome-wide significant SNPs was limited.[20,21] Second, the ld_clump() function from the ieugwasr package (v 1.0.0)[22] was used to remove SNPs with linkage disequilibrium ($r^2 = 0.001$; kb = 10,000). Confounders related to the outcome were excluded with $P < 1 \times 10^{-5}$ through the GWAS catalog to avoid violating the third assumption mentioned above. Finally, the strength of the IVs was assessed using the *F*-statistic, we calculated the *F*-statistic of the SNP using the following formula: $F = \frac{N-k-1}{k} \times \frac{R^2}{1-R^2}$, where N represented the number of samples exposed, k represented the number of IVs, and $R^2$ represented the degree of exposure explained by IVs. When the *F*-value is >10, it indicates that strength is sufficient to avoid weak instrument bias in the 2-sample model.[23] In addition, the Steiger filter was applied for IV screening to ensure the unidirectionality of the causal relationship. All palindromic sequences were removed to ensure that the selected SNPs were referenced to the same allele when harmonizing the effects of SNPs on the exposure and the outcome.

### 2.4. MR analysis and mediation MR analyses

In the MR analysis, the inverse variance weighted (IVW)[24] method is the most robust technique for evaluating all IVs,[25] to enhance the reliability of our findings, we also conducted supplementary analyses employing the MR-Egger,[26] weighted median,[27] simple mode,[28] and weighted mode[28] ($P < .05$ indicates a significant causal relationship). Based on the causal effect of the exposure on hypertension, 2 types of causal effects were explored: the causal effect of the mediator on hypertension and the causal effect of the exposure on the mediator. The product c × b represents the mediated effect, and a minus the product of c and b represents the direct effect. The proportion of mediation is calculated by dividing the indirect effect by the total effect (b × c/a). The Delta method was applied to obtain the standard error of the effect estimates.[29]

### 2.5. Statistical analysis

The MR analysis was conducted using the TwoSampleMR (v 0.6.0)[30] and MRPRESSO packages (v 1.0).[31] We conducted sensitivity analysis to evaluate the robustness of the MR results. The mr_heterogeneity() function was used to assess the heterogeneity of the selected IVs. In the presence of heterogeneity, the random-effects IVW was chosen for the initial analysis. The potential impact of directional pleiotropy was assessed by examining the intercept value in the MR-Egger regression, and results with $P < .05$ were excluded. MR PRESSO was used to detect and remove pleiotropy and outliers with $P < .05$. In addition, the presence of pleiotropy was examined using funnel plots to assess the robustness of the results. Subsequently, to evaluate the potential of any single SNP driving the association between the exposure and the outcome, leave-one-out sensitivity analysis was performed by iteratively removing 1 SNP at a time.

## 3. Result

### 3.1. Genetic instruments used in MR analysis

In the study examining the relationship between obesity indicators and hypertension, a total of 771 SNPs were used for subsequent analysis, with *F*-statistics varying from 17.368 to 1306.491. In the analysis exploring the relationship between plasma metabolites and hypertension, 32,682 SNPs were included, with F-statistics fluctuating from 19.503 to 2297.785. In the analysis phase involving obesity indicators and plasma metabolites, 155,173 SNPs were meticulously examined, and potential interference from pleiotropic factors was excluded. To dissect the link between plasma metabolites and obesity indicators, 4822 SNPs were selected, with *F*-statistics spanning from 19.508 to 1845.832. The *F*-statistics

of all SNPs involved in the analysis were above 10, which fully demonstrated the effectiveness and reliability of the analytical methods used.

### 3.2. Investigating the causal links between obesity and plasma metabolites with hypertension

Large-scale epidemiological and longitudinal prospective studies have established a connection between obesity and hypertension.[32] MR was employed to analyze key indicators of obesity, including BMI, waist-to-hip ratio adjusted for BMI, and whole body fat mass, in relation to hypertension. The results found that these obesity indicators were all risk factors for the onset of hypertension [odds ratio (OR) = 1.197–1.823, $P < .001$] (Fig. 1). To further verify whether hypertension would have a causal impact on these obesity indicators that showed a positive significant association, reverse MR analysis was conducted. However, the results of the reverse analysis did not find a significant causal relationship, meeting the requirements for subsequent analysis.

The plasma metabolome is an important method for identifying metabolic biomarkers and pathogens of various diseases.[33] In the population of patients with hypertension, changes in serum metabolic profiles often involve multiple key metabolic pathways, including fatty acid metabolism, glycerophospholipid metabolism, and the metabolism of alanine, aspartate, and glutamate.[34,35] By deeply exploring the potential causal relationships between 1400 plasma metabolites and hypertension, a total of 94 significant causal relationships were ultimately discovered. Among them, 46 were considered protective factors, while 48 were risk factors (Fig. 2). Specifically, the IVW results showed that "2-methoxyresorcinol sulfate levels" [OR = 0.951, 95% confidence interval (CI) = 0.913–0.991, $P = .016$] and "N-acetylneuraminate to N-acetylglucosamine to N-acetylgalactosamine ratio" (OR = 0.947, 95% CI = 0.913–0.981, $P = .003$) had a protective effect on hypertension. In contrast, "adenosine 5'-diphosphate (ADP) to Adenosine 5'-monophosphate (AMP) ratio" (OR = 1.043, 95% CI = 1.005–1.082, $P = .024$) and "carcinoembryonic antigen-related cell adhesion molecule 4" (OR = 1.071, 95% CI = 1.007–1.139, $P = .030$) were risk factors for hypertension. To rule out the potential interference from bidirectional effects, the causal impact of hypertension on these plasma metabolites was assessed. Given that 2 pairs of reverse significant results were found, we excluded them to ensure the accuracy of subsequent analyses (Fig. S1, Supplemental Digital Content, https://links.lww.com/MD/Q999).

### 3.3. The mediating role of plasma metabolites in obesity and hypertension

Previous studies have indicated that 4 representative metabolites may play a potential mediating role between obesity and the risk of hypertension.[15] Based on this, this study was committed to further revealing the complex mechanism by which plasma metabolism regulated its impact on hypertension through obesity indicators. In previous studies, we have successfully identified the causal relationships between 3 key obesity factors and hypertension (Fig. 1), as well as 94 causal links between 1400 plasma metabolites and hypertension (Fig. 2, Fig. S1, Supplemental Digital Content). On this basis, we explored the causal associations between obesity indicators and plasma metabolites, and ultimately found 60 significant associations between 3 categories of obesity indicators and 45 plasma metabolites (Fig. 3). Subsequently, the mediating effects of these associations were estimated and calculated to quantify the specific degree to which obesity indicators affect the risk of hypertension through plasma metabolites. A total of 25 groups of associations with mediating effects were found between 2 obesity indicators and 18 plasma metabolites (Fig. 4). Specifically, these mediating effects covered the regulatory roles of multiple metabolites on the risk of hypertension. For example, "cortolone glucuronide-1 levels" (4.318%), "glutamate to alanine ratio" (4.117%), and "histidine to pyruvate ratio" (3.159%) enhanced the risk effect of whole body fat mass on the onset of hypertension. "glycerol to palmitoylcarnitine (C16) ratio" (4.263%) reduced the risk effect of whole body fat mass on the onset of hypertension. In addition, "glycerol to palmitoylcarnitine (C16) ratio" (3.288%) and "X-25371 levels" (2.181%) weakened the adverse impact of BMI on the risk of hypertension to a certain extent. "1-linoleoyl-gpc (18:2) levels" (2.835%) enhanced the adverse impact of BMI on the risk of hypertension to a certain extent. As some metabolites were unknown, a total of 19 intermediary pairs were screened.These findings enriched the understanding of the complex interactions between obesity, plasma metabolites, and hypertension.

### 3.4. Exploring the role of obesity in the relationship between plasma metabolites and hypertension

Subsequently, further in-depth exploration was conducted on the role of plasma metabolites on hypertension via obesity indicators. Previously, we had identified 94 significant causal links between 1400 plasma metabolites and hypertension (Fig. 2, Fig. S1, Supplemental Digital Content, https://links.lww.com/MD/Q999), as well as the causal relationships between 3 key obesity factors and hypertension (Fig. 1). Building on these foundations, we focused on the causal associations between plasma metabolites and obesity indicators, successfully discovering 26 significant associations between 3 obesity indicators and 22 plasma metabolites (Fig. S2, Supplemental Digital Content, https://links.lww.com/MD/Q999). Then, we further conducted mediation analysis to explore whether these plasma metabolites had an indirect impact on the risk of hypertension through obesity indicators. The results showed 8 significant mediating relationships (X-24546 unknown). Specifically, the obesity indicator "waist-to-hip ratio adjusted for BMI" weakened the risk effect of "glycerol to palmitoylcarnitine (C16) ratio" (2.806%) and "1-methylnicotinamide levels" (2.036%) on the onset of hypertension to a certain extent. In addition, "whole body fat mass" (0.154%) and "BMI" (0.177%) reduced the adverse impact of "glycine to phosphate ratio" on the risk of hypertension (Fig. S3, Supplemental Digital Content, https://links.lww.com/MD/Q999).

| exposure | outcome | method | nsnp | pval | OR(95% CI) | pleio_P |
|---|---|---|---|---|---|---|
| \|\| id:ebi-a-GCST90025996 | Hypertension \|\| finn-b-I9_HYPTENS | IVW | 358 | <0.001 | 1.197 (1.095 to 1.308) | 0.886 |
| \|\| id:ukb-b-19393 | | IVW | 633 | <0.001 | 1.617 (1.507 to 1.735) | 0.661 |
| \|\| id:ukb-b-2303 | | IVW | 672 | <0.001 | 1.823 (1.712 to 1.940) | 0.062 |

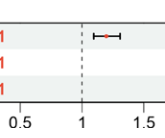


**Figure 1.** The results of MR analysis indicated that 3 obesity indicators were risk factors for hypertension. OR value >1 indicates that exposure is a risk factor for the outcome. CI = confidence interval, IVW = inverse variance weighted, MR = Mendelian randomization, nsnp = number of single nucleotide polymorphism, OR = odds ratio, pleio_P = pleiotropy *P* value, *P* val = *P* value.

| exposure | outcome | method | nsnp | pval | OR(95% CI) | pleio_P |
|---|---|---|---|---|---|---|
| Ribitol levels | Hypertension || finn-b-I9_HYPTENS | IVW | 34 | 0.003 | 1.038 (1.013 to 1.064) | 0.626 |
| Theophylline levels | | IVW | 25 | 0.005 | 1.074 (1.022 to 1.128) | 0.911 |
| 4-methyl-2-oxopentanoate levels | | IVW | 12 | 0.015 | 1.093 (1.017 to 1.175) | 0.684 |
| 3-indoxyl sulfate levels | | IVW | 22 | 0.004 | 1.079 (1.025 to 1.136) | 0.171 |
| N-acetylglycine levels | | IVW | 21 | 0.001 | 0.940 (0.906 to 0.976) | 0.063 |
| Propionylglycine levels | | IVW | 20 | <0.001 | 0.936 (0.904 to 0.970) | 0.625 |
| Stearidonate (18:4n3) levels | | IVW | 27 | 0.025 | 1.058 (1.007 to 1.111) | 0.885 |
| Campesterol levels | | IVW | 20 | 0.031 | 1.039 (1.003 to 1.076) | 0.547 |
| Gamma-glutamylglycine levels | | IVW | 26 | <0.001 | 0.931 (0.902 to 0.960) | 0.530 |
| 1-linoleoyl-gpc (18:2) levels | | IVW | 28 | 0.017 | 0.953 (0.916 to 0.991) | 0.829 |
| Laurylcarnitine levels | | IVW | 26 | 0.022 | 0.947 (0.903 to 0.992) | 0.688 |
| 2-hydroxypalmitate levels | | IVW | 21 | 0.025 | 0.943 (0.896 to 0.993) | 0.961 |
| Octadecanedioate levels | | IVW | 26 | 0.007 | 0.943 (0.904 to 0.984) | 0.466 |
| 1-stearoyl-2-oleoyl-GPE (18:0/18:1) levels | | IVW | 26 | 0.003 | 1.057 (1.019 to 1.097) | 0.233 |
| N-acetyl-3-methylhistidine levels | | IVW | 24 | 0.007 | 1.052 (1.014 to 1.092) | 0.888 |
| N-oleoyltaurine levels | | IVW | 21 | 0.042 | 0.958 (0.919 to 0.998) | 0.644 |
| 2-stearoyl-GPE (18:0) levels | | IVW | 31 | 0.019 | 1.048 (1.008 to 1.090) | 0.854 |
| Mannonate levels | | IVW | 22 | 0.026 | 0.974 (0.952 to 0.997) | 0.285 |
| Sphingomyelin (d18:2/16:0, d18:1/16:1) levels | | IVW | 24 | 0.022 | 1.069 (1.010 to 1.131) | 0.484 |
| 1-(1-enyl-oleoyl)-GPE (p-18:1) levels | | IVW | 18 | 0.006 | 0.940 (0.901 to 0.982) | 0.488 |
| Octadecenedioylcarnitine (C18:1-DC) levels | | IVW | 16 | <0.001 | 0.943 (0.914 to 0.972) | 0.333 |
| 2-methoxyresorcinol sulfate levels | | IVW | 26 | 0.016 | 0.951 (0.913 to 0.991) | 0.440 |
| Octadecanedioylcarnitine (C18-DC) levels | | IVW | 27 | <0.001 | 0.948 (0.921 to 0.977) | 0.699 |
| Umbelliferone sulfate levels | | IVW | 21 | 0.018 | 1.044 (1.007 to 1.082) | 0.736 |
| Sphingomyelin (d18:1/22:2, d18:2/22:1, d16:1/24:2) levels | | IVW | 19 | 0.006 | 0.931 (0.884 to 0.980) | 0.386 |
| Glycodeoxycholate 3-sulfate levels | | IVW | 31 | 0.009 | 0.972 (0.951 to 0.993) | 0.319 |
| 1-(1-enyl-palmitoyl)-2-oleoyl-GPE (p-16:0/18:1) levels | | IVW | 30 | 0.030 | 0.955 (0.916 to 0.995) | 0.334 |
| 1-(1-enyl-stearoyl)-2-linoleoyl-GPE (p-18:0/18:2) levels | | IVW | 21 | 0.018 | 0.949 (0.909 to 0.991) | 0.728 |
| 1-myristoyl-2-arachidonoyl-GPC (14:0/20:4) levels | | IVW | 24 | 0.018 | 0.958 (0.924 to 0.993) | 0.789 |
| N-oleoylserine levels | | IVW | 20 | 0.016 | 0.955 (0.919 to 0.991) | 0.999 |
| Glycosyl ceramide (d18:1/20:0, d16:1/22:0) levels | | IVW | 32 | 0.020 | 0.960 (0.928 to 0.994) | 0.382 |
| Arachidonoylcarnitine (C20:4) levels | | IVW | 34 | 0.042 | 1.027 (1.001 to 1.054) | 0.385 |
| Cortolone glucuronide (1) levels | | IVW | 25 | 0.015 | 1.058 (1.011 to 1.107) | 0.490 |
| Octadecenedioate (C18:1-DC) levels | | IVW | 22 | <0.001 | 0.934 (0.903 to 0.966) | 0.485 |
| 3-hydroxybutyroylglycine levels | | IVW | 27 | 0.001 | 0.944 (0.911 to 0.978) | 0.525 |
| N-lactoyl isoleucine levels | | IVW | 16 | 0.023 | 1.076 (1.010 to 1.146) | 0.317 |
| (2,4 or 2,5)-dimethylphenol sulfate levels | | IVW | 21 | 0.003 | 1.069 (1.023 to 1.118) | 0.075 |
| (2 or 3)-decenoate (10:1n7 or n8) levels | | IVW | 28 | 0.021 | 1.054 (1.008 to 1.101) | 0.247 |
| Thyroxine levels | | IVW | 21 | 0.021 | 1.067 (1.010 to 1.127) | 0.624 |
| Methyl indole-3-acetate levels | | IVW | 22 | 0.015 | 1.058 (1.011 to 1.108) | 0.553 |
| 3-hydroxy-3-methylglutarate levels | | IVW | 21 | 0.011 | 1.071 (1.016 to 1.129) | 0.438 |
| Gamma-glutamylglutamine levels | | IVW | 30 | 0.035 | 0.953 (0.911 to 0.997) | 0.436 |
| 3-hydroxyisobutyrate levels | | IVW | 19 | 0.009 | 1.079 (1.019 to 1.141) | 0.785 |
| Cys-gly, oxidized levels | | IVW | 24 | 0.002 | 1.054 (1.019 to 1.090) | 0.371 |
| Adenosine 3',5'-cyclic monophosphate (camp) levels | | IVW | 28 | 0.019 | 1.049 (1.008 to 1.092) | 0.445 |
| Phosphate levels (UKB data field 30810) | | IVW | 25 | <0.001 | 1.085 (1.039 to 1.133) | 0.072 |
| 1-methylnicotinamide levels | | IVW | 18 | 0.003 | 1.116 (1.037 to 1.201) | 0.113 |
| Myristate (14:0) levels | | IVW | 23 | 0.050 | 1.055 (1.000 to 1.113) | 0.485 |
| Serine levels | | IVW | 36 | 0.032 | 0.962 (0.929 to 0.997) | 0.056 |
| Urea levels | | IVW | 22 | 0.003 | 1.036 (1.013 to 1.061) | 0.503 |
| Plasma free asparagine levels | | IVW | 25 | 0.043 | 1.032 (1.001 to 1.064) | 0.587 |
| Pentadecanoate (15:0) levels | | IVW | 22 | 0.004 | 1.077 (1.024 to 1.132) | 0.363 |
| Margarate (17:0) levels | | IVW | 22 | <0.001 | 1.098 (1.041 to 1.159) | 0.284 |
| X-12816 levels | | IVW | 27 | 0.038 | 1.037 (1.002 to 1.072) | 0.384 |
| X-12729 levels | | IVW | 28 | 0.029 | 1.011 (1.001 to 1.021) | 0.557 |
| X-17653 levels | | IVW | 24 | 0.002 | 0.943 (0.909 to 0.979) | 0.639 |
| X-21364 levels | | IVW | 32 | 0.023 | 0.944 (0.898 to 0.992) | 0.824 |
| X-18922 levels | | IVW | 29 | <0.001 | 0.942 (0.909 to 0.976) | 0.393 |
| X-21807 levels | | IVW | 20 | <0.001 | 0.943 (0.911 to 0.977) | 0.339 |
| X-21829 levels | | IVW | 30 | 0.045 | 1.043 (1.001 to 1.086) | 0.152 |
| X-21471 levels | | IVW | 26 | 0.005 | 0.949 (0.915 to 0.984) | 0.574 |
| X-21470 levels | | IVW | 17 | 0.004 | 0.949 (0.915 to 0.984) | 0.342 |
| X-22520 levels | | IVW | 20 | 0.007 | 0.943 (0.904 to 0.984) | 0.616 |
| X-24546 levels | | IVW | 27 | <0.001 | 0.928 (0.897 to 0.960) | 0.390 |
| X-25371 levels | | IVW | 27 | 0.032 | 0.958 (0.921 to 0.996) | 0.321 |
| X-25810 levels | | IVW | 35 | 0.019 | 0.962 (0.932 to 0.994) | 0.823 |
| N-acetyltyrosine levels | | IVW | 30 | 0.014 | 1.034 (1.007 to 1.063) | 0.553 |
| N-acetylasparagine levels | | IVW | 24 | 0.035 | 1.027 (1.002 to 1.053) | 0.776 |
| N-acetylarginine levels | | IVW | 26 | 0.034 | 1.028 (1.002 to 1.056) | 0.349 |
| N-acetyl-aspartyl-glutamate (naag) levels | | IVW | 18 | 0.023 | 1.040 (1.005 to 1.075) | 0.361 |
| N-acetyl-1-methylhistidine levels | | IVW | 31 | 0.009 | 1.032 (1.008 to 1.057) | 0.669 |
| Glycine levels | | IVW | 22 | 0.002 | 0.956 (0.929 to 0.983) | 0.081 |
| Spermidine to ornithine ratio | | IVW | 15 | 0.037 | 0.948 (0.901 to 0.997) | 0.645 |
| Adenosine 5'-diphosphate (ADP) to Adenosine 5'-monophosphate (AMP) ratio | | IVW | 25 | 0.024 | 1.043 (1.005 to 1.082) | 0.289 |
| Glycine to pyridoxal ratio | | IVW | 15 | 0.008 | 0.942 (0.902 to 0.985) | 0.263 |
| Glycine to alanine ratio | | IVW | 20 | 0.002 | 0.951 (0.921 to 0.982) | 0.707 |
| Phenylalanine to tyrosine ratio | | IVW | 20 | 0.013 | 0.944 (0.902 to 0.988) | 0.640 |
| Glutamine to asparagine ratio | | IVW | 24 | 0.001 | 0.952 (0.925 to 0.981) | 0.780 |
| Histidine to pyruvate ratio | | IVW | 23 | 0.003 | 0.939 (0.901 to 0.979) | 0.060 |
| Carnitine to ergothioneine ratio | | IVW | 21 | 0.002 | 1.074 (1.026 to 1.125) | 0.124 |
| 3-phosphoglycerate to glycerate ratio | | IVW | 18 | 0.002 | 1.101 (1.037 to 1.168) | 0.979 |
| Glycine to phosphate ratio | | IVW | 26 | 0.001 | 0.953 (0.925 to 0.981) | 0.347 |
| Adenosine 5'-monophosphate (AMP) to citrate ratio | | IVW | 22 | 0.007 | 1.076 (1.020 to 1.136) | 0.331 |
| Adenosine 5'-monophosphate (AMP) to glutamine ratio | | IVW | 19 | 0.048 | 1.063 (1.001 to 1.129) | 0.442 |
| Adenosine 5'-monophosphate (AMP) to glycine ratio | | IVW | 24 | 0.009 | 1.059 (1.014 to 1.105) | 0.180 |
| Adenosine 5'-monophosphate (AMP) to asparagine ratio | | IVW | 24 | 0.036 | 0.948 (0.902 to 0.996) | 0.824 |
| phosphate to asparagine ratio | | IVW | 30 | 0.001 | 0.948 (0.917 to 0.979) | 0.830 |
| Salicylate to caprylate (8:0) ratio | | IVW | 23 | 0.017 | 1.055 (1.010 to 1.103) | 0.730 |
| Ornithine to phosphate ratio | | IVW | 16 | 0.018 | 1.081 (1.013 to 1.154) | 0.971 |
| Alpha-ketobutyrate to pyruvate ratio | | IVW | 16 | 0.019 | 1.070 (1.011 to 1.132) | 0.681 |
| Glycerol to palmitoylcarnitine (C16) ratio | | IVW | 21 | <0.001 | 0.865 (0.814 to 0.918) | 0.277 |
| Glutamate to alanine ratio | | IVW | 20 | 0.009 | 1.077 (1.019 to 1.138) | 0.549 |
| N-acetylneuraminate to N-acetylglucosamine to N-acetylgalactosamine ratio | | IVW | 19 | 0.003 | 0.947 (0.913 to 0.981) | 0.367 |
| Adenosine 5'-diphosphate (ADP) to ornithine ratio | | IVW | 23 | 0.035 | 1.039 (1.003 to 1.076) | 0.781 |




**Figure 2.** Results of MR analysis of plasma metabolites on hypertension (including 46 protective factors and 48 risk factors). OR value >1 indicates that exposure is a risk factor for the outcome, OR value <1 indicates that exposure is a protective factor for the outcome. CI = confidence interval, IVW = inverse variance weighted, nsnp = number of single nucleotide polymorphism, OR = odds ratio, pleio_*P* = pleiotropy *P* value, *P* val = *P* value.

### *3.5. Sensitivity analysis*

To avoid excessive bias effects, sensitivity analysis was conducted. There was no evidence of horizontal pleiotropy in the associations obtained from these MR analyses. When conducting MR analysis, random effects had already been used to avoid bias for results with heterogeneity (Table S3, Supplemental Digital Content, https://links.lww.com/MD/Q1000). Moreover, the leave-one-out sensitivity test confirmed the robustness of the results.

| exposure | outcome | method | nsnp | pval | OR(95% CI) | pleio_P |
|---|---|---|---|---|---|---|
| \|\| id:ukb-b-2303 | (2,4 or 2,5)-dimethylphenol sulfate levels | IVW | 672 | 0.047 | 1.118 (1.001 to 1.247) | 0.345 |
| \|\| id:ukb-b-2303 | 1-(1-enyl-oleoyl)-GPE (p-18:1) levels | IVW | 672 | <0.001 | 0.836 (0.767 to 0.912) | 0.713 |
| \|\| id:ukb-b-19393 | 1-linoleoyl-gpc (18:2) levels | IVW | 651 | <0.001 | 0.768 (0.702 to 0.839) | 0.537 |
| \|\| id:ukb-b-2303 | | IVW | 672 | <0.001 | 0.702 (0.644 to 0.765) | 0.212 |
| \|\| id:ukb-b-2303 | 2-hydroxypalmitate levels | IVW | 672 | 0.014 | 0.899 (0.825 to 0.979) | 0.583 |
| \|\| id:ukb-b-19393 | 3-hydroxy-3-methylglutarate levels | IVW | 651 | <0.001 | 1.162 (1.068 to 1.265) | 0.366 |
| \|\| id:ukb-b-2303 | | IVW | 672 | 0.004 | 1.127 (1.038 to 1.222) | 0.284 |
| \|\| id:ukb-b-19393 | 3-indoxyl sulfate levels | IVW | 651 | 0.009 | 1.127 (1.031 to 1.232) | 0.877 |
| \|\| id:ukb-b-2303 | | IVW | 672 | 0.019 | 1.109 (1.017 to 1.208) | 0.876 |
| \|\| id:ukb-b-19393 | Campesterol levels | IVW | 651 | 0.016 | 0.870 (0.777 to 0.975) | 0.860 |
| \|\| id:ukb-b-2303 | | IVW | 672 | 0.007 | 0.861 (0.772 to 0.960) | 0.756 |
| \|\| id:ukb-b-19393 | Carnitine to ergothioneine ratio | IVW | 652 | <0.001 | 1.214 (1.109 to 1.328) | 0.829 |
| \|\| id:ukb-b-2303 | | IVW | 672 | <0.001 | 1.193 (1.093 to 1.301) | 0.122 |
| \|\| id:ukb-b-19393 | Cortolone glucuronide (1) levels | IVW | 652 | <0.001 | 1.448 (1.328 to 1.579) | 0.980 |
| \|\| id:ukb-b-19393 | Gamma-glutamylglutamine levels | IVW | 651 | <0.001 | 0.838 (0.765 to 0.917) | 0.654 |
| \|\| id:ukb-b-2303 | | IVW | 672 | <0.001 | 0.789 (0.723 to 0.861) | 0.077 |
| \|\| id:ukb-b-19393 | Glutamate to alanine ratio | IVW | 652 | <0.001 | 1.307 (1.198 to 1.426) | 0.090 |
| \|\| id:ukb-b-19393 | Glutamine to asparagine ratio | IVW | 651 | 0.001 | 1.161 (1.062 to 1.269) | 0.396 |
| \|\| id:ukb-b-19393 | Glycerol to palmitoylcarnitine (C16) ratio | IVW | 651 | <0.001 | 1.151 (1.064 to 1.246) | 0.733 |
| \|\| id:ukb-b-2303 | | IVW | 672 | <0.001 | 1.145 (1.062 to 1.236) | 0.152 |
| \|\| id:ukb-b-19393 | Glycine levels | IVW | 651 | 0.008 | 0.889 (0.815 to 0.970) | 0.957 |
| \|\| id:ukb-b-2303 | Glycine to phosphate ratio | IVW | 672 | 0.005 | 0.884 (0.811 to 0.964) | 0.072 |
| \|\| id:ukb-b-19393 | Histidine to pyruvate ratio | IVW | 651 | <0.001 | 0.785 (0.717 to 0.859) | 0.265 |
| \|\| id:ukb-b-19393 | Mannonate levels | IVW | 651 | <0.001 | 1.478 (1.357 to 1.610) | 0.589 |
| \|\| id:ukb-b-2303 | | IVW | 672 | <0.001 | 1.430 (1.317 to 1.553) | 0.353 |
| \|\| id:ukb-b-2303 | Margarate (17:0) levels | IVW | 672 | 0.024 | 1.103 (1.013 to 1.201) | 0.890 |
| \|\| id:ukb-b-2303 | Myristate (14:0) levels | IVW | 672 | 0.034 | 1.093 (1.007 to 1.188) | 0.592 |
| \|\| id:ukb-b-19393 | N-acetyl-1-methylhistidine levels | IVW | 651 | 0.014 | 1.123 (1.024 to 1.231) | 0.565 |
| \|\| id:ukb-b-2303 | | IVW | 672 | 0.042 | 1.097 (1.004 to 1.199) | 0.702 |
| \|\| id:ukb-b-19393 | N-acetylglycine levels | IVW | 652 | 0.013 | 0.895 (0.820 to 0.977) | 0.734 |
| \|\| id:ukb-b-19393 | N-acetylneuraminate to N-acetylglucosamine to N-acetylgalactosamine ratio | IVW | 651 | 0.027 | 0.901 (0.822 to 0.988) | 0.201 |
| \|\| id:ukb-b-2303 | | IVW | 672 | 0.008 | 0.888 (0.812 to 0.970) | 0.321 |
| \|\| id:ukb-b-2303 | N-acetyltyrosine levels | IVW | 672 | 0.007 | 1.130 (1.034 to 1.235) | 0.485 |
| \|\| id:ukb-b-19393 | N-lactoyl isoleucine levels | IVW | 651 | <0.001 | 1.181 (1.077 to 1.294) | 0.846 |
| \|\| id:ebi-a-GCST90025996 | N-oleoylserine levels | IVW | 364 | 0.014 | 0.870 (0.779 to 0.972) | 0.670 |
| \|\| id:ukb-b-19393 | N-oleoyltaurine levels | IVW | 651 | 0.015 | 1.124 (1.023 to 1.234) | 0.314 |
| \|\| id:ukb-b-19393 | Octadecanedioate levels | IVW | 651 | 0.049 | 0.914 (0.836 to 1.000) | 0.126 |
| \|\| id:ukb-b-19393 | Octadecenedioate (C18:1-DC) levels | IVW | 651 | 0.003 | 0.874 (0.800 to 0.955) | 0.735 |
| \|\| id:ukb-b-2303 | | IVW | 672 | <0.001 | 0.849 (0.779 to 0.924) | 0.083 |
| \|\| id:ukb-b-2303 | Phenylalanine to tyrosine ratio | IVW | 672 | 0.024 | 0.904 (0.828 to 0.987) | 0.215 |
| \|\| id:ukb-b-19393 | phosphate to asparagine ratio | IVW | 652 | 0.002 | 1.153 (1.055 to 1.259) | 0.417 |
| \|\| id:ukb-b-19393 | Plasma free asparagine levels | IVW | 651 | <0.001 | 0.798 (0.730 to 0.874) | 0.887 |
| \|\| id:ukb-b-19393 | Propionylglycine levels | IVW | 652 | 0.025 | 0.896 (0.814 to 0.986) | 0.697 |
| \|\| id:ukb-b-2303 | Serine levels | IVW | 672 | 0.007 | 0.889 (0.816 to 0.968) | 0.103 |
| \|\| id:ukb-b-2303 | Spermidine to ornithine ratio | IVW | 672 | 0.023 | 0.898 (0.818 to 0.985) | 0.819 |
| \|\| id:ukb-b-19393 | Sphingomyelin (d18:2/16:0, d18:1/16:1) levels | IVW | 651 | 0.008 | 1.119 (1.030 to 1.216) | 0.352 |
| \|\| id:ukb-b-2303 | Urea levels | IVW | 672 | 0.048 | 1.088 (1.001 to 1.183) | 0.817 |
| \|\| id:ukb-b-2303 | X-12729 levels | IVW | 672 | 0.013 | 0.890 (0.811 to 0.976) | 0.815 |
| \|\| id:ukb-b-19393 | X-18922 levels | IVW | 651 | 0.003 | 1.146 (1.047 to 1.255) | 0.598 |
| \|\| id:ukb-b-2303 | | IVW | 672 | <0.001 | 1.177 (1.079 to 1.285) | 0.175 |
| \|\| id:ukb-b-2303 | X-21364 levels | IVW | 672 | 0.011 | 1.113 (1.024 to 1.209) | 0.855 |
| \|\| id:ukb-b-19393 | X-21470 levels | IVW | 651 | 0.050 | 1.096 (1.000 to 1.202) | 0.927 |
| \|\| id:ukb-b-2303 | | IVW | 672 | 0.044 | 1.095 (1.002 to 1.196) | 0.294 |
| \|\| id:ukb-b-2303 | X-21471 levels | IVW | 672 | <0.001 | 1.199 (1.099 to 1.308) | 0.459 |
| \|\| id:ukb-b-2303 | X-21807 levels | IVW | 672 | 0.008 | 0.867 (0.780 to 0.963) | 0.345 |
| \|\| id:ukb-b-19393 | X-21829 levels | IVW | 651 | <0.001 | 1.309 (1.198 to 1.431) | 0.484 |
| \|\| id:ukb-b-2303 | | IVW | 672 | <0.001 | 1.348 (1.237 to 1.468) | 0.129 |
| \|\| id:ukb-b-19393 | X-25371 levels | IVW | 651 | <0.001 | 1.289 (1.179 to 1.409) | 0.108 |
| \|\| id:ukb-b-2303 | | IVW | 672 | <0.001 | 1.355 (1.243 to 1.477) | 0.119 |
| \|\| id:ukb-b-19393 | X-25810 levels | IVW | 651 | 0.017 | 1.115 (1.020 to 1.219) | 0.468 |

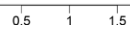


**Figure 3.** Results of MR analysis of obesity indicators on plasma metabolites (60 significant associations between 3 categories of obesity indicators and 45 plasma metabolites). CI = confidence interval, IVW = inverse variance weighted, nsnp = number of single nucleotide polymorphism, OR = odds ratio, pleio_*P* = pleiotropy *P* value, *P* val = *P* value.

## 4. Discussion

The global prevalence and incidence of obesity remain at alarmingly high levels, highlighting the urgent need for safe, effective, and accessible treatments. However, this demand has yet to be fully satisfied.[36] Obesity not only increases the risk of developing various diseases but also contributes to higher mortality rates, with hypertension being a prime example.[37] The close link between obesity and hypertension has been widely confirmed, with obesity being one of the major risk factors for hypertension.[38] Our MR analysis further revealed that 3 key indicators of obesity were all risk factors for hypertension. This finding is consistent with previous studies, such as one that showed a significant causal relationship between BMI and hypertension (OR: 1.13–1.26);[39] childhood obesity has been identified as a risk factor for gestational hypertension (OR = 1.12).[40] These results further emphasize the causal link between obesity and hypertension. Metabolomics has emerged as a powerful tool, capable of revealing the intricate correlations between metabolites or metabolic pathways and physiological or pathological changes. This provides novel perspectives and valuable information for elucidating disease mechanisms.[41] Although prior studies have documented changes in metabolites and their roles in obesity and hypertension, comprehensive research on plasma metabolites in these conditions remains limited. Against this backdrop, MR method was employed to thoroughly investigate the causal relationships between obesity, plasma metabolites, and hypertension. We further analyzed the mediating effects of plasma metabolites between obesity and hypertension. Ultimately, we identified 19 significant pairs of relationships mediated by plasma metabolites, offering new insights into the complex mechanisms underlying the association between obesity and hypertension.

Metabolomics technology enables the comprehensive analysis of intermediates and end products in cellular metabolic

| Outcome(Y) | Expouse(X) | Mediate(M) | beta | nsnp | pval | OR(95% CI) | pleio_P | Mediated effect | Direct effect | Mediated proportion(%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Hypertension | ukb-b-19393 | GCST90199742 | a | 633 | <0.001 | 1.617 (1.507 to 1.735) | 0.661 | c*b | a-c*b | c*b/a |
| | | | c | 651 | <0.001 | 0.768 (0.702 to 0.839) | 0.537 | 1.013 (1.001 to 1.024) | 1.596 (1.486 to 1.714) | 2.649 (0.275 to 5.023) |
| | | | b | 28 | 0.017 | 0.953 (0.916 to 0.991) | 0.829 | pval=0.0287 | pval=8.4e-38 | pval=0.0287 |
| | | GCST90199932 | a | 633 | <0.001 | 1.617 (1.507 to 1.735) | 0.661 | c*b | a-c*b | c*b/a |
| | | | c | 651 | <0.001 | 1.478 (1.357 to 1.610) | 0.589 | 0.990 (0.981 to 0.999) | 1.633 (1.521 to 1.754) | 2.117 (0.203 to 4.031) |
| | | | b | 22 | 0.025 | 0.974 (0.952 to 0.997) | 0.285 | pval=0.0302 | pval=8.88e-42 | pval=0.0302 |
| | | GCST90200156 | a | 633 | <0.001 | 1.617 (1.507 to 1.735) | 0.661 | c*b | a-c*b | c*b/a |
| | | | c | 652 | <0.001 | 1.448 (1.328 to 1.579) | 0.980 | 1.021 (1.003 to 1.039) | 1.584 (1.473 to 1.703) | 4.318 (0.670 to 7.966) |
| | | | b | 25 | 0.015 | 1.058 (1.011 to 1.107) | 0.490 | pval=0.0203 | pval=2.11e-35 | pval=0.0203 |
| | | GCST90200165 | a | 633 | <0.001 | 1.617 (1.507 to 1.735) | 0.661 | c*b | a-c*b | c*b/a |
| | | | c | 651 | 0.003 | 0.874 (0.800 to 0.955) | 0.735 | 1.009 (1.002 to 1.017) | 1.602 (1.492 to 1.720) | 1.911 (0.316 to 3.507) |
| | | | b | 22 | <0.001 | 0.934 (0.903 to 0.966) | 0.485 | pval=0.0189 | pval=7.16e-39 | pval=0.0189 |
| | | GCST90200298 | a | 633 | <0.001 | 1.617 (1.507 to 1.735) | 0.661 | c*b | a-c*b | c*b/a |
| | | | c | 651 | <0.001 | 1.162 (1.068 to 1.265) | 0.366 | 1.010 (1.000 to 1.021) | 1.600 (1.490 to 1.718) | 2.153 (0.046 to 4.261) |
| | | | b | 21 | 0.011 | 1.071 (1.016 to 1.129) | 0.438 | pval=0.0452 | pval=2.28e-38 | pval=0.0452 |
| | | GCST90200578 | a | 633 | <0.001 | 1.617 (1.507 to 1.735) | 0.661 | c*b | a-c*b | c*b/a |
| | | | c | 651 | 0.003 | 1.146 (1.047 to 1.255) | 0.598 | 0.992 (0.984 to 0.999) | 1.630 (1.519 to 1.750) | 1.709 (0.152 to 3.266) |
| | | | b | 29 | <0.001 | 0.942 (0.909 to 0.976) | 0.393 | pval=0.0314 | pval=1.1e-41 | pval=0.0314 |
| | | GCST90200656 | a | 633 | <0.001 | 1.617 (1.507 to 1.735) | 0.661 | c*b | a-c*b | c*b/a |
| | | | c | 651 | <0.001 | 1.289 (1.179 to 1.409) | 0.108 | 0.989 (0.978 to 1.000) | 1.635 (1.522 to 1.755) | 2.276 (0.011 to 4.540) |
| | | | b | 27 | 0.032 | 0.958 (0.921 to 0.996) | 0.321 | pval=0.0489 | pval=1.23e-41 | pval=0.0489 |
| | | GCST90200707 | a | 633 | <0.001 | 1.617 (1.507 to 1.735) | 0.661 | c*b | a-c*b | c*b/a |
| | | | c | 651 | 0.008 | 0.889 (0.815 to 0.970) | 0.957 | 1.005 (1.000 to 1.011) | 1.608 (1.499 to 1.726) | 1.113 (0.007 to 2.218) |
| | | | b | 22 | 0.002 | 0.956 (0.929 to 0.983) | 0.081 | pval=0.0486 | pval=1.04e-39 | pval=0.0486 |
| | | GCST90200787 | a | 633 | <0.001 | 1.617 (1.507 to 1.735) | 0.661 | c*b | a-c*b | c*b/a |
| | | | c | 651 | 0.001 | 1.161 (1.062 to 1.269) | 0.396 | 0.993 (0.987 to 0.999) | 1.629 (1.517 to 1.748) | 1.515 (0.203 to 2.826) |
| | | | b | 24 | 0.001 | 0.952 (0.925 to 0.981) | 0.780 | pval=0.0236 | pval=1.16e-41 | pval=0.0236 |
| | | GCST90200802 | a | 633 | <0.001 | 1.617 (1.507 to 1.735) | 0.661 | c*b | a-c*b | c*b/a |
| | | | c | 651 | <0.001 | 0.785 (0.717 to 0.859) | 0.265 | 1.015 (1.003 to 1.027) | 1.592 (1.483 to 1.710) | 3.159 (0.711 to 5.606) |
| | | | b | 23 | 0.003 | 0.939 (0.901 to 0.979) | 0.060 | pval=0.0114 | pval=2.28e-37 | pval=0.0114 |
| | | GCST90200807 | a | 633 | <0.001 | 1.617 (1.507 to 1.735) | 0.661 | c*b | a-c*b | c*b/a |
| | | | c | 652 | <0.001 | 1.214 (1.109 to 1.328) | 0.829 | 1.014 (1.003 to 1.025) | 1.595 (1.485 to 1.712) | 2.885 (0.551 to 5.218) |
| | | | b | 21 | 0.002 | 1.074 (1.026 to 1.125) | 0.124 | pval=0.0154 | pval=1.17e-37 | pval=0.0154 |
| | | GCST90200866 | a | 633 | <0.001 | 1.617 (1.507 to 1.735) | 0.661 | c*b | a-c*b | c*b/a |
| | | | c | 652 | 0.002 | 1.153 (1.055 to 1.259) | 0.417 | 0.992 (0.986 to 0.999) | 1.629 (1.518 to 1.749) | 1.588 (0.177 to 2.999) |
| | | | b | 30 | 0.001 | 0.948 (0.917 to 0.979) | 0.830 | pval=0.0274 | pval=1.14e-41 | pval=0.0274 |
| | | GCST90200932 | a | 633 | <0.001 | 1.617 (1.507 to 1.735) | 0.661 | c*b | a-c*b | c*b/a |
| | | | c | 651 | <0.001 | 1.151 (1.064 to 1.246) | 0.733 | 0.980 (0.966 to 0.994) | 1.650 (1.536 to 1.773) | 4.263 (1.253 to 7.273) |
| | | | b | 21 | <0.001 | 0.865 (0.814 to 0.918) | 0.277 | pval=0.0055 | pval=1.79e-42 | pval=0.0055 |
| | | GCST90200946 | a | 633 | <0.001 | 1.617 (1.507 to 1.735) | 0.661 | c*b | a-c*b | c*b/a |
| | | | c | 652 | <0.001 | 1.307 (1.198 to 1.426) | 0.090 | 1.020 (1.003 to 1.037) | 1.585 (1.475 to 1.704) | 4.117 (0.708 to 7.526) |
| | | | b | 20 | 0.009 | 1.077 (1.019 to 1.138) | 0.549 | pval=0.0179 | pval=8.51e-36 | pval=0.0179 |
| | ukb-b-2303 | GCST90199742 | a | 672 | <0.001 | 1.823 (1.712 to 1.940) | 0.062 | c*b | a-c*b | c*b/a |
| | | | c | 672 | <0.001 | 0.702 (0.644 to 0.765) | 0.212 | 1.017 (1.002 to 1.032) | 1.792 (1.681 to 1.911) | 2.835 (0.398 to 5.272) |
| | | | b | 28 | 0.017 | 0.953 (0.916 to 0.991) | 0.829 | pval=0.0226 | pval=6.53e-71 | pval=0.0226 |
| | | GCST90199932 | a | 672 | <0.001 | 1.823 (1.712 to 1.940) | 0.062 | c*b | a-c*b | c*b/a |
| | | | c | 672 | <0.001 | 1.430 (1.317 to 1.553) | 0.353 | 0.991 (0.982 to 0.999) | 1.840 (1.727 to 1.960) | 1.551 (0.143 to 2.959) |
| | | | b | 22 | 0.025 | 0.974 (0.952 to 0.997) | 0.285 | pval=0.0308 | pval=5.51e-80 | pval=0.0308 |
| | | GCST90199966 | a | 672 | <0.001 | 1.823 (1.712 to 1.940) | 0.062 | c*b | a-c*b | c*b/a |
| | | | c | 672 | <0.001 | 0.836 (0.767 to 0.912) | 0.713 | 1.011 (1.001 to 1.021) | 1.803 (1.692 to 1.921) | 1.828 (0.230 to 3.426) |
| | | | b | 18 | 0.006 | 0.940 (0.901 to 0.982) | 0.488 | pval=0.025 | pval=1.69e-74 | pval=0.025 |
| | | GCST90200165 | a | 672 | <0.001 | 1.823 (1.712 to 1.940) | 0.062 | c*b | a-c*b | c*b/a |
| | | | c | 672 | <0.001 | 0.849 (0.779 to 0.924) | 0.083 | 1.011 (1.003 to 1.019) | 1.802 (1.692 to 1.920) | 1.865 (0.514 to 3.216) |
| | | | b | 22 | <0.001 | 0.934 (0.903 to 0.966) | 0.485 | pval=0.00683 | pval=6.35e-75 | pval=0.00683 |
| | | GCST90200578 | a | 672 | <0.001 | 1.823 (1.712 to 1.940) | 0.062 | c*b | a-c*b | c*b/a |
| | | | c | 672 | <0.001 | 1.177 (1.079 to 1.285) | 0.175 | 0.990 (0.982 to 0.998) | 1.841 (1.728 to 1.960) | 1.635 (0.305 to 2.964) |
| | | | b | 29 | <0.001 | 0.942 (0.909 to 0.976) | 0.393 | pval=0.016 | pval=2.88e-80 | pval=0.016 |
| | | GCST90200583 | a | 672 | <0.001 | 1.823 (1.712 to 1.940) | 0.062 | c*b | a-c*b | c*b/a |
| | | | c | 672 | 0.008 | 0.867 (0.780 to 0.963) | 0.345 | 1.008 (1.000 to 1.017) | 1.808 (1.697 to 1.925) | 1.396 (0.037 to 2.755) |
| | | | b | 20 | <0.001 | 0.943 (0.911 to 0.977) | 0.339 | pval=0.0441 | pval=1.31e-75 | pval=0.0441 |
| | | GCST90200586 | a | 672 | <0.001 | 1.823 (1.712 to 1.940) | 0.062 | c*b | a-c*b | c*b/a |
| | | | c | 672 | <0.001 | 1.199 (1.099 to 1.308) | 0.459 | 0.991 (0.982 to 0.999) | 1.840 (1.728 to 1.960) | 1.583 (0.218 to 2.947) |
| | | | b | 26 | 0.005 | 0.949 (0.915 to 0.984) | 0.574 | pval=0.023 | pval=4.05e-80 | pval=0.023 |
| | | GCST90200656 | a | 672 | <0.001 | 1.823 (1.712 to 1.940) | 0.062 | c*b | a-c*b | c*b/a |
| | | | c | 672 | <0.001 | 1.355 (1.243 to 1.477) | 0.119 | 0.987 (0.975 to 1.000) | 1.847 (1.733 to 1.968) | 2.181 (0.070 to 4.292) |
| | | | b | 27 | 0.032 | 0.958 (0.921 to 0.996) | 0.321 | pval=0.0428 | pval=3.17e-79 | pval=0.0428 |
| | | GCST90200807 | a | 672 | <0.001 | 1.823 (1.712 to 1.940) | 0.062 | c*b | a-c*b | c*b/a |
| | | | c | 672 | <0.001 | 1.193 (1.093 to 1.301) | 0.122 | 1.013 (1.002 to 1.023) | 1.800 (1.689 to 1.918) | 2.102 (0.365 to 3.839) |
| | | | b | 21 | 0.002 | 1.074 (1.026 to 1.125) | 0.124 | pval=0.0177 | pval=8.59e-74 | pval=0.0177 |
| | | GCST90200826 | a | 672 | <0.001 | 1.823 (1.712 to 1.940) | 0.062 | c*b | a-c*b | c*b/a |
| | | | c | 672 | 0.005 | 0.884 (0.811 to 0.964) | 0.072 | 1.006 (1.000 to 1.012) | 1.812 (1.702 to 1.929) | 0.997 (0.048 to 1.945) |
| | | | b | 26 | 0.001 | 0.953 (0.925 to 0.981) | 0.347 | pval=0.0395 | pval=7.52e-77 | pval=0.0395 |
| | | GCST90200932 | a | 672 | <0.001 | 1.823 (1.712 to 1.940) | 0.062 | c*b | a-c*b | c*b/a |
| | | | c | 672 | <0.001 | 1.145 (1.062 to 1.236) | 0.152 | 0.980 (0.967 to 0.994) | 1.859 (1.744 to 1.982) | 3.288 (0.968 to 5.608) |
| | | | b | 21 | <0.001 | 0.865 (0.814 to 0.918) | 0.277 | pval=0.00547 | pval=2.88e-80 | pval=0.00547 |

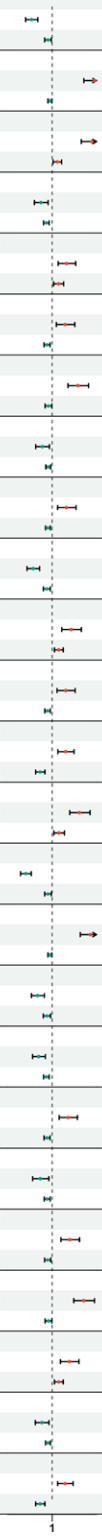


**Figure 4.** Results of mediation analysis of obesity indicators via plasma metabolites for hypertension (25 groups of associations with mediating effects). (A) the total effect of obesity indicators on hypertension; (B) the effect of plasma metabolites on hypertension; (C) the effect of obesity indicators on plasma metabolites. CI = confidence interval, nsnp = number of single nucleotide polymorphism, OR = odds ratio, pleio_P = pleiotropy *P* value, *P* val = *P* value.

processes, covering both exogenous and endogenous small molecules. This approach provides critical molecular-level insights for studying metabolism-related diseases.[42] We found "N-acetylglycine" as a protective factor against obesity and hypertension. N-acetylglycine, an effective signaling molecule, can modulate the expression of multiple genes in adipose tissue that are involved in obesity-related pathways, including immune response, lysosomal function, and tissue remodeling.[43] Moreover, N-acetylglycine levels were found to be significantly negatively correlated with BMI.[44] This finding was

further validated in an obese mouse model, demonstrating its protective role in obesity-related metabolic processes,[42] which is consistent with our study findings. Additionally, another MR analysis confirmed the association between N-acetylglycine and hypertension (OR = 0.946),[45] further supporting our observations. From the perspective of metabolites influencing inflammatory responses, studies have shown that supplementing N-acetylglycine to mice fed a high-fat diet leads to a decrease in the level of Trem2 + macrophages associated with obesity and alters signal transduction in multiple pathways within fat immune cells.[46] This indicates that N-acetylglycine has the function of regulating the obesity-related immune microenvironment. In addition, Trem2 can promote the survival of macrophages in an inflammatory environment and prevent pyroptosis of macrophages by activating the downstream PI3K/AKT signaling pathway of macrophages, thereby expanding the inflammatory response.[47] Notably, more and more evidence indicates a significant relationship between inflammation and hypertension.[48–50] The research by Guzik et al shows that inflammation is an important component affecting the functions of microvessels and macrovessels, triggering a vicious cycle among elevated blood pressure, vascular remodeling, persistent hypertension and its atherosclerotic complications.[51] This indicates that N-acetylglycine may indirectly exert a protective effect on hypertension by influencing the immune microenvironment and thereby affecting pathways related to inflammation. Furthermore, we observed that "Gamma-glutamylglutamine levels" also served as a protective factor against obesity and hypertension. Gamma-glutamyl peptides are a class of important bioactive molecules that play a key role in various physiological functions. Studies have shown that these compounds possess significant anti-inflammatory and antioxidant properties,[52] which may contribute to their protective effects against obesity and hypertension by alleviating metabolic inflammation and oxidative stress. These findings enhance our understanding of the relationship between metabolites and disease.

Given the complexity of the relationship between obesity and hypertension, we further explored potential mediating factors that may attenuate the impact of obesity on hypertension. The mediation analysis results showed that the "glutamine to asparagine ratio" could significantly reduce the risk effect of obesity on hypertension. Subsequently, we investigated the roles of glutamine and asparagine in obesity and hypertension to elucidate the potential protective effects of this mediator in the disease. Glutamine is the most abundant free amino acid in human serum,[53] and its levels are negatively correlated with obesity and other known cardiometabolic disease risk factors.[54,55] Studies have shown that oral glutamine supplements can reduce waist circumference and serum insulin levels in obese patients,[56] indicating a protective role of glutamine in obesity. The research by da Silva AA et al indicates that insulin levels are associated with hypertension. Specifically, hyperinsulinemia may cause an increase in the activity of the sympathetic nervous system and renal sodium retention. If it persists, it may increase blood pressure.[57] Therefore, glutamine can reduce obesity and improve insulin signaling, thereby lowering the risk of hypertension. Moreover, the blood pressure-lowering effect of glutamine may also be partly attributed to its role as a precursor of L-arginine, thereby promoting the synthesis of nitric oxide (NO).[56] NO regulates blood pressure by inhibiting arterial tension, thus exerting a hypotensive effect. Asparagine and glutamine also contribute to the metabolism of arginine and ornithine,[58] and α-difluoromethylornithine can restore endothelial function in spontaneously hypertensive rats and prevent blood pressure elevation,[59] further confirming the potential role of glutamine in preventing hypertension. Asparagine also plays an important role in the metabolic regulation of obesity and hypertension. Circulating asparagine can reduce BMI, abdominal obesity, and insulin resistance.[60,61] Supplementation with asparagine or malate can increase renal L-arginine and NO levels in Dahl salt-sensitive rats, thereby alleviating hypertension.[62] Given the positive roles of glutamine and asparagine in both obesity and hypertension, targeting the "glutamine/asparagine ratio" may emerge as a potential intervention strategy. Modulating this ratio may help improve insulin sensitivity in obese individuals, reduce body weight, and lower the risk of hypertension.

Additionally, we found that the "phosphate to asparagine ratio" could reduce the risk effect of obesity on hypertension. Serum phosphate levels are negatively correlated with obesity indicators.[63] The serum phosphate level in women is negatively correlated with BMI.[64] Low serum phosphate levels are not only associated with obesity itself but may also promote the occurrence of insulin resistance in obese children aged 6 to 12.[65] Insulin resistance can raise insulin levels,[66] and insulin enhances the adrenergic system and increases the activity of the sympathetic nervous system, thereby increasing the risk of blood pressure occurrence.[67] In conclusion, phosphate levels are not only related to obesity itself, but also indirectly participate in the occurrence of hypertension by influencing insulin metabolism. In combination with the aforementioned beneficial effects of asparagine in obesity and hypertension, we hypothesize that modulating the "phosphate/asparagine ratio" may be of significant importance for the prevention and treatment of obesity-related hypertension. Optimizing this ratio may help mitigate the risks associated with obesity and hypertension.

In summary, our study employed the MR approach to thoroughly investigate the complex causal relationships between obesity, plasma metabolites, and hypertension, and for the first time systematically elucidated the mediating role of plasma metabolites in the relationship between obesity and hypertension. This suggests that in clinical practice, doctors should take obesity management as an important part of the prevention and treatment of hypertension, and reduce the risk of hypertension in obese patients through means such as diet, exercise and drug intervention. Furthermore, as plasma metabolites may play a mediating role between obesity and hypertension, this could provide ideas for the development of new prevention and treatment strategies in clinical practice. For instance, the levels of these metabolites can be regulated through dietary intervention or drug treatment, thereby reducing the risk of hypertension. In conclusion, these findings provide novel insights into the underlying mechanisms linking obesity and hypertension and highlight the potential for targeting specific plasma metabolites as a preventive strategy for hypertension. However, our study also has several limitations. The research relied on GWAS data from public databases, which are largely representative of European populations. Due to the differences among various populations in terms of genetic background, lifestyle and environmental exposure, this to some extent limits the universality of the research results to other populations (such as Asian or African populations). In the future, it is necessary to verify its universality in different populations to assess the wide applicability of the research results. Moreover, as this study utilized cross-sectional GWAS data, longitudinal data were not included to monitor the dynamic changes of obesity, plasma metabolites, and hypertension over time. In subsequent studies, we plan to follow up on obese patients and regularly monitor plasma metabolite levels along with blood pressure changes to gain a more comprehensive understanding of the dynamic relationship between these factors. While the mediation analysis identified plasma metabolites that could potentially mitigate the risk effects of obesity on hypertension, these results remain theoretical and require further validation through experimental studies.

## 5. Conclusion

Our comprehensive MR analysis thoroughly explored the causal relationships between obesity indicators, plasma metabolites, and hypertension. The results confirmed that obesity indicators

are significant risk factors for hypertension. Additionally, we identified 94 causal relationships between plasma metabolites and hypertension, as well as 26 causal links between plasma metabolites and obesity. Through mediation analysis, we further elucidated the mediating role of plasma metabolites in the relationship between obesity and hypertension. These findings underscore the intricate interplay among obesity, plasma metabolites, and hypertension, and offer novel insights for the prevention and treatment of hypertension.

## Author contributions

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**Resources:** Honglei Fu.
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**Visualization:** Honglei Fu.
**Writing – original draft:** Honglei Fu.
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