Major lipids and lipoprotein levels and risk of blood pressure elevation: a Mendelian Randomisation study

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Summary

Background Quantitative nuclear magnetic resonance (NMR) metabolomics techniques provide detailed measurements of lipoprotein particle concentration. Metabolic dysfunction often represents a cluster of conditions, including dyslipidaemia, hypertension, and diabetes, that increase the risk of cardiovascular diseases (CVDs). However, the causal relationship between lipid profiles and blood pressure (BP) remains unclear. We performed a Mendelian Randomisation (MR) study to disentangle and prioritize the potential causal effects of major lipids, lipoprotein particles, and circulating metabolites on BP and pulse pressure (PP).

Methods We employed single-nucleotide polymorphisms (SNPs) associated with major lipids, lipoprotein particles, and other metabolites from the UK Biobank as instrumental variables. Summary-level data for BP and PP were obtained from the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort. Two-sample MR and MR Bayesian model averaging approaches (MR-BMA) were conducted to analyse and rank causal associations.

Findings Genetically predicted TG was the most likely causal exposure among the major lipids to increase systolic blood pressure (SBP) and diastolic blood pressure (DBP), with marginal inclusion probabilities (MIPs) of 0.993 and 0.847, respectively. Among the majority of lipoproteins and their containing lipids, including major lipids, genetically elevated TG in small high-density lipoproteins (S_HDL_TG) had the strongest association with the increase of SBP and DBP, with MIPs of 0.416 and 0.397, respectively. HDL cholesterol (HDL_C) and low-density lipoprotein cholesterol (LDL_C) were potential causal factors for PP elevation among the major lipids (MIP = 0.927 for HDL_C and MIP = 0.718 for LDL_C). Within the sub-lipoproteins, genetically predicted atherogenic lipoprotein particles (i.e., sub-very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and LDL particles) had the most likely causal impact on increasing PP.

Interpretation This study provides genetic evidence for the causality of lipids on BP indicators. However, the effect size on SBP, DBP, and PP varies depending on the lipids' components and sizes. Understanding this potential relationship may inform the potential benefits of comprehensive management of lipid profiles for BP control.

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Abbreviations: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; BP, blood pressure; CVDs, cardiovascular diseases; DBP, diastolic blood pressure; *DGAT2*, diacylglycerol O-acyltransferase 2; EB-RAPS, Empirical Partially Bayes Robust Adjusted Profile Score; *ELOVL4*, elongation of very long chain fatty acids protein 4; GERA, Genetic Epidemiology Research on Adult Health and Aging; GWAS, genome-wide association study; HDL, high-density lipoprotein; HDL_C, HDL cholesterol; IDL_P, intermediate-density lipoprotein particles; IVW, inverse-variance weighted; LD, linkage disequilibrium; LDL, low-density lipoprotein; LDL_C, LDL cholesterol; LDL_P, LDL particles; *LPL*, lipoprotein lipase; MACE, model-averaged causal effect; MIP, marginal inclusion probability; MR, Mendelian Randomisation; MR-BMA, MR Bayesian model averaging approach; MR-PRESSO, MR pleiotropy residual sum and outlier method; NMR, nuclear magnetic resonance; PP, pulse pressure; *PP*, posterior probability; *PPARA*, peroxisome proliferator-activated receptor alpha; SBP, systolic blood pressure; SD, standard deviation; S_HDL_P, small HDL particles; S_HDL_TG, TG in small HDL; SNPs, single-nucleotide polymorphisms; TG, triglycerides; VLDL, very low-density lipoprotein; VLDL_P, VLDL particles; XXL_VLDL_P, concentration of chylomicrons and extremely large VLDL particles

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Research in context

Evidence before this study

Several observational and Mendelian Randomisation (MR) studies have found that among the routinely measured lipid parameters (low-density lipoprotein cholesterol [LDL_C], high-density lipoprotein cholesterol [HDL_C], and triglycerides [TG]), HDL_C and TG are risk factors for hypertension or systolic blood pressure (SBP) elevation. The current consensus on the comprehensive management of blood pressure (BP) and dyslipidaemia also focuses only on major lipids, with LDL_C as the primary intervention target. However, the three indicators of BP, i.e., SBP, diastolic blood pressure (DBP), and pulse pressure (PP), differ in susceptibility populations, mechanisms, and prognosis, and they may have distinct sub-lipoprotein contributors. The causal relationship between lipid profiles and the risk of BP rise has not been fully determined. Quantitative nuclear magnetic resonance (NMR) metabolomics techniques provide detailed measurements of lipoprotein particle concentrations, relevant lipoprotein subclasses classified by particle size, and other metabolic markers.

Added value of this study

Based on large-scale genome-wide association study (GWAS) summary data, we performed a two-sample MR study and MR Bayesian model averaging approach (MR-BMA) to disentangle and prioritize the potential causal effects of major lipids, lipoprotein particles, and circulating metabolites on BP indicators. Among major lipids, we found that genetically predicted TG was the most likely causal exposure to increase SBP and DBP. Among lipoproteins and their containing lipids, genetically elevated TG in small high-density lipoproteins (S_HDL_TG) had the strongest association with the increase of SBP and DBP. HDL_C and LDL_C were potential causal factors for PP elevation. In sub-lipoproteins, genetically predicted atherogenic lipoprotein particles (i.e., sub-very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and LDL particles) had the most likely causal impact on increasing PP. Meantime, we performed a series of sensitivity analyses to confirm the robustness of the results.

Implications of all the available evidence

Our study comprehensively characterizes and ranks the potential causal relationship of lipoprotein particles, lipid sub-components, and multiple metabolites, with BP indicators. This study provides genetic evidence for the causality of lipids on BP indicators. However, the effect size on SBP, DBP, and PP varies depending on the lipids' components and sizes. Understanding this potential relationship may inform the potential benefits of comprehensive management of dyslipidaemia for BP control. Further interventional research is necessary to elucidate these relationships.

Introduction

Hypertension remains the primary driver of cardiovascular diseases (CVDs) and mortality.[1–5] For the prevention and treatment of hypertension, firstly, it is necessary to maintain a normal level of systolic blood pressure (SBP) and diastolic blood pressure (DBP), as recommended by the current guidelines.[6,7] Elevated SBP is highly prevalent in the elderly population and increases in importance with advancing age for the occurrence and progression of adverse CVD events.[1–5,8] Elevated DBP is more common in young individuals, has a high probability of transitioning to future systolic hypertension,[9] and is the predominant predictor of CVDs below middle age.[8] Whereas DBP reduction is associated with an increased risk of all-cause mortality in older adults and individuals taking antihypertensive medications.[10,11] Therefore, pulse pressure (PP), a proxy for arterial stiffness, which is defined as the difference between SBP and DBP, is also highlighted for its importance, particularly with increasing age.[12] Elevated PP has been approved as a strong predictor of hypertension, CVDs, and overall mortality.[12,13] Control of the level of PP has been considered a new therapeutic strategy independent of reductions in blood pressure (BP).[12] Since the three indicators of BP differ in susceptibility populations, mechanisms, and prognosis, they may have distinct contributors.

Dyslipidaemia is a common risk factor for CVDs in hypertensive patients, and the coexistence of the two significantly increases the risk of CVDs.[14] Therefore, joint management of BP and lipids has become the cornerstone of the prevention and treatment of CVDs. The current consensus on the comprehensive management of BP and dyslipidaemia focuses on major lipids, with low-density lipoprotein cholesterol (LDL_C) as the primary intervention target.[15,16] However, some studies have shown that in patients with well-controlled LDL_C levels, there is still a residual risk of CVDs.[17] Prior

studies assessing the association between hypertension and major lipids measured by conventional clinical chemistry have reported inconsistent findings regarding the association with LDL_C.[18–20] Few studies have explored the association between PP and lipids. Moreover, traditional measures of circulating lipids cannot distinguish lipoprotein size, concentration, and subfractions, which may vary extensively between the associations with the risk of SBP, DBP, and PP. The quantitative Nuclear Magnetic Resonance (NMR) metabolomics technology provides detailed measurements of lipoprotein particle concentrations, relevant lipoprotein subclasses classified by particle size, and other metabolic markers.[21] The application of novel metabolic biomarkers enhances the understanding of traditional disease etiology studies and risk prediction and management.[22,23] However, little is known about the causal molecular reflections between SBP, DBP, and PP and whether they are different.

A two-sample Mendelian Randomisation (MR) approach based on large-scale genome-wide association study (GWAS) summary data uses exposure-associated genetic variants as instrumental variables to estimate the potential causal relationship between exposure and outcome. In this study, based on the MR approach, we sought to gradually deepen and uncover which one or more of the genetically predicted metabolites are most likely to be associated with the elevation risk of SBP, DBP, and PP. Identifying these refine causal biomarkers will substantially refine risk stratification and aid in managing patients with hypertension and co-management of BP and lipids in high-risk populations. Moreover, this information can help guide the target validation for pharmacological and clinical interventions to reduce the risk of disease.

Methods

Two-sample MR data sources

This two-sample MR study was based on publicly available summary datasets, as detailed in Supplemental Table S1A. Briefly, we used GWAS conducted among individuals of mostly European ancestry in the UK Biobank as data sources for exposure, including five major lipids measured by standard clinical chemistry assays and 249 metabolic biomarkers measured by high-throughput NMR spectroscopy.[24,25] The UK Biobank is a prospective cohort database of approximately 500,000 participants aged 40–69 across the United Kingdom, and its detailed procedures for genotyping, imputation, and quality control of the genetic information have been previously described.[26] The GWAS of five major lipids measured by standard clinical chemistry assays was performed using BOLT-LMM linear mixed models adjusted for age, sex, and a binary variable denoting the genotyping chip individuals were allocated to in UK Biobank.[24] The GWAS of 249 metabolites was performed on 115,078 European-ancestry participants in the UK Biobank by Nightingale Health 2020.[25] The metabolic biomarkers contained detailed lipid subfractions, such as 14 size categories of lipoprotein particles ranging from small high-density lipoprotein particles (S_HDL_P) to chylomicrons and extremely large very low-density lipoprotein particles (XXL_VLDL_P), as well as total cholesterol, triglyceride (TG), etc., contained in each lipoprotein, and other metabolites such as amino acids, fatty acids, glycolytic metabolites, etc. Lipid-related traits and NMR measurements in the UK Biobank were inverse rank-based normal transformed.

Our outcomes include SBP, DBP, and PP, where PP = SBP-DBP. Summary-level data for BP and PP were obtained from the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort, also of predominantly European ancestry, which started at an average age of 60.9 years and was followed for 4 years.[27] The GERA cohort comprises longitudinal electronic health records from 99,785 individuals, providing 1,342,814 measurements of systolic, diastolic, and pulse blood pressure for a genome-wide association study on long-term average systolic, diastolic, and pulse pressure. The majority of genome-wide significant loci identified in the GERA cohort have been replicated in the International Consortium for Blood Pressure (ICBP) study (n = 69,396) and the UK Biobank study (n = 152,081).[27] Anti-hypertensive medication treatment was assessed via electronic health record prescription filling information; once an individual started a drug, they were considered treated on all subsequent measurements. To correct for the treatment effect, an increase of 15 mmHg was added to the treated SBP value, and an increase of 10 mmHg was added to the treated DBP value, similar to previous BP GWAS.[27–29] The GWAS for BP and PP adjusted for age, body mass index, sex, and principal components and its detailed procedures for genotyping, imputation, and quality control of the genetic information have been previously described.[27]

Two-sample MR study design

We included two non-overlapping populations to conduct the two-sample MR analysis. A summary of our study design is given in Fig. 1. Firstly, we used univariable MR methods to explore the potential causal relationship between major lipid traits, lipoprotein particle concentrations, and their cholesterol and TG concentrations, as well as other non-lipid-related metabolites such as amino acids, glycolysis-related metabolites, ketone bodies, inflammation, and fatty acids, and SBP, DBP, and PP. Major lipids included apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), HDL cholesterol (HDL_C), LDL_C, and total TG, measured by NMR spectroscopy and standard clinical chemistry assays. Secondly, we conducted multivariable MR Bayesian model averaging approach (MR-BMA) analyses to detect

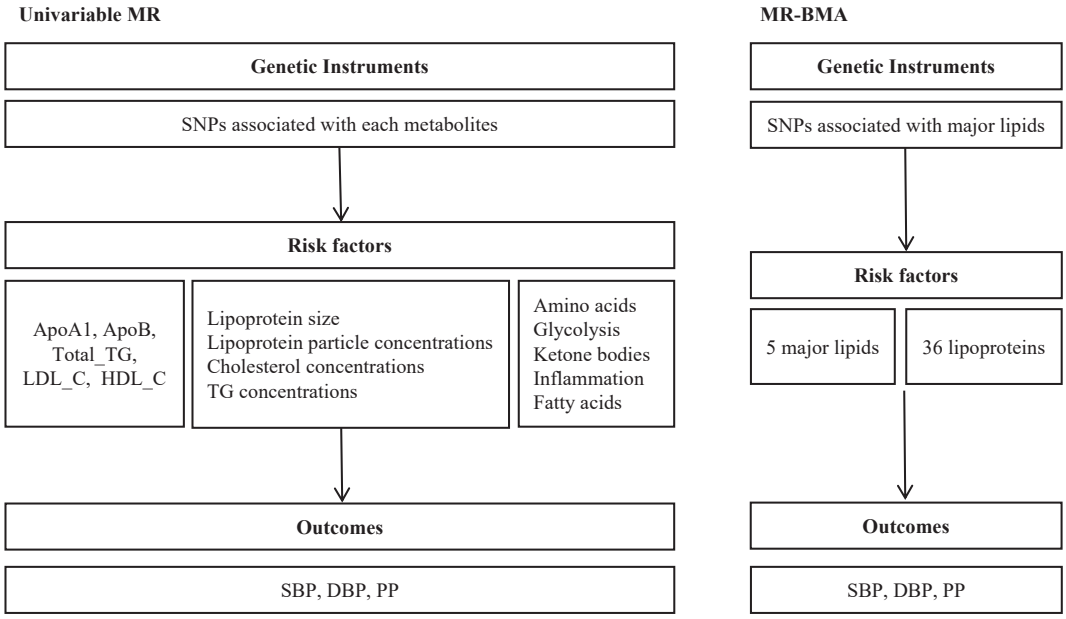

***Fig. 1:* The summary of the study design.** MR, Mendelian Randomisation; MR-BMA, multivariable MR Bayesian model averaging approach; SNPs, single-nucleotide polymorphisms; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; TG, triglycerides; LDL_C, low-density lipoprotein cholesterol; HDL_C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

the most likely causal risk factors associated with the risk of BP and PP elevations among major lipids and highly correlated candidate lipoproteins with shared genetic variation.

Two-sample MR analyses

Genetic instruments

Compared with traditional multivariate regression methods, MR methods are less susceptible to measurement errors, confounding factors, and reverse causal association under the following three assumptions: (1) the genetic variants are strongly associated with exposure (relevance); (2) the genetic variants are not related to the confounding factors of the exposure-outcome relationship (independence); and (3) the genetic variants do not affect the outcome through pathways other than the exposure (exclusion restriction). Based on this, we selected single-nucleotide polymorphisms (SNPs) strongly associated with exposures as instrumental variables based on the following conditions: (1) identified SNPs at the level of genome-wide statistical significance ($P < 5 \times 10^{-8}$). (2) Clumped with a 10,000 kB window to a linkage disequilibrium (LD) threshold of $R^2 < 0.1$ using 1000 Genomes European Ancestry as a reference panel to ascertain independence between genetic variants. For those variants in LD, we chose the one with the lowest *P*-value. (3) With a strong *F* statistic to avoid weak instrument bias (the cutoff was set to an *F* statistic ≥10). (4) Filtered SNPs using Steiger filtering. This test allows assessing the direction of causality for each SNP with the assumption that a valid IV should explain more variance in the exposure than the outcome and removes those genetic variants that do not satisfy this criterion.

To measure the strength of instrumental variables and the degree of explanation for phenotypes, we calculated the *F* statistic and R^2 for instrumental variables. The *F* statistic is related to the degree of interpretation for phenotype by genetic variation (R^2), sample size (N), and the number of instrumental variables (k), with the following calculation formula: $F = R^2$ (N-k-1)/k $(1–R^2)$.[30] The R^2 for an instrument is calculated using the approximation $R^2 = 2\text{EAF}\ (1–\text{EAF})\ \beta^2$, where EAF is the effect allele frequency and β is the estimated genetic effect on exposure.[31] In the derivation of this formula, we assume that the standard deviation of the phenotype is approximately one, as the original GWAS data standardized the phenotype through normalization transformation. The *F* statistic ≥10 indicates a relatively low risk of weak instrument bias.[32] All the SNPs used as instrumental variables were listed in Supplemental Tables S2–S4.

Univariable MR

We conducted univariable MR analyses for the association of each exposure with SBP, DBP, and PP. We used the inverse-variance weighted (IVW) method as the principal analysis, which is a robust MR method under the assumption of valid instrumental variables and balanced pleiotropy.[33]

Multivariable MR: MR-BMA

While it is plausible that each lipoprotein particle alone plays a causal role, it is also possible that a particular subclass of lipoproteins predominates and ultimately accounts for the relationship between lipoprotein particles and BP and PP. So, we further used the multivariable MR method, which permits the appraisal of multiple risk factors simultaneously.[34] Existing multivariable MR methods are applicable to a small number of risk factors and cannot be extended to the dimension of high-throughput experiments. We used a recently proposed MR-BMA that can be extended to the dimensions of high-throughput experiments and can detect true causal risk factors from a large number of highly correlated candidate risk factors (up to $|r| = 0.99$) with shared genetic variation better and more consistently than traditional multivariable IVW regression or other methods.[35] Details of the method have been reported previously.[22,23,35] Briefly, formulated in a Bayesian framework, MR-BMA uses independence priors and closed-form Bayes factors to evaluate the posterior probability (*PP*) of specific models (i.e., one risk factor or a combination of multiple risk factors). In high-dimensional variable selection, the evidence for one particular model can be small because the model space is very large and many models might have comparable evidence. MR-BMA uses Bayesian model averaging (BMA) and computes for each risk factor its marginal inclusion probability (MIP), which is defined as the sum of the *PP* of all models in which the risk factor exists and represents the probability that the risk factor is a causal determinant of disease risk. Risk factors are prioritized and ranked according to MIP. MR-BMA also reported the model-averaged causal effect (MACE), which represents a conservative estimate of the average direct causal effect of this risk factor on the outcome in these models. The specific method used in calculating the MACE is based on model averaging (weighted averaging), where the weights are derived from the *PP* of the potential models. It is worth noting that the purpose of MR-BMA is to correctly detect (by ranking) the true causal risk factors rather than to provide an unbiased estimate of the direct causal effect.

We used SNPs associated with five major lipids as instruments ($P < 5 \times 10^{-8}$, $R^2 < 0.1$ in the 1000 Genomes European Ancestry Reference Panel). Firstly, we performed a ranking analysis among the five major lipids. We computed the genetic correlation between the five major lipids, as shown in Supplemental Table S5. Genetic correlations were computed using the beta-coefficients of genetic associations for the genetic variants and the available metabolites, which is consistent with previous literature that has utilized the MR-BMA method.[23,35] The genetic correlations were estimated using the Pearson correlation method. No pair of risk factors included in the five major lipid analyses was more highly correlated than $|r| > 0.99$. Then, we prepared a ranking analysis among 43 lipoproteins and their containing lipids (including apolipoprotein, lipoprotein size, cholesterol, and TG concentrations in different size categories of lipoprotein particles) (Supplemental Table S6). We computed the genetic correlation between them based on the above-mentioned instrumental variables and randomly excluded one of each pair of metabolites with a stronger correlation than $|r| > 0.99$ (Supplemental Table S7). Finally, the remaining 36 lipoproteins were available for ranking analysis (Supplemental Table S6).

Sensitivity analysis

Univariable MR

In the univariable MR analyses, as the IVW estimates might be biased by invalid instrument bias or horizontal pleiotropy, we conducted a series of sensitivity analyses to ensure the robustness of the results. Firstly, we assessed invalid instrument bias using the weighted median method, which assumes more than 50% of the weight provided by valid SNPs.[36] Second, MR-Egger regression was conducted, which allows instruments to have horizontal pleiotropic effects under the assumption that each genetic variant's association with exposure is independent of the variant's pleiotropic effects.[37] Third, we used the MR-Egger intercept to estimate directional pleiotropy,[37] and the Cochrane's *Q* statistic to test for the presence of heterogeneity, and if $P \leq 0.5$, we applied the multiplicative random-effects IVW method for analysis.[33] Fourth, we used the MR pleiotropy residual sum and outlier method (MR-PRESSO) to identify outlying SNPs that may have horizontal pleiotropy and correct the estimated causal effect by removing outlier SNPs if the MR-Egger intercept test indicated pleiotropic effects.[38] Among them, the global test can detect whether horizontal pleiotropy exists, the outlier test is used to eliminate outliers and estimate the corrected causal effect, and the distortion test is used to detect whether there is a significant difference between the results before and after adjustment.

Furthermore, we performed a sensitivity analysis using a more stringent LD threshold of $R^2 < 0.001$ to further assess the robustness of our results. The SNPs used as instrumental variables for this section are listed in Supplemental Table S8.

Three-sample MR

Considering that the exclusion of weak instrumental variables may introduce selection bias and selection based on the dataset in which genetic associations with the exposure are estimated may lead to "winner's curse"—genetic associations tend to be overestimated in the dataset in which they were first discovered, in order to further improve the robustness of the analysis, we performed an additional sensitivity analysis using the three-sample genome-wide MR design and utilized the Empirical Partially Bayes Robust Adjusted Profile Score

(EB-RAPS) method proposed by Zhao et al.[39,40] Briefly, variants are identified in one dataset, and the genetic associations with exposure and outcome are estimated in separate datasets. Our study design makes use of three non-overlapping GWAS:

1. Instrumental variable selection dataset: GWAS for serum metabolomics (Nightingale NMR was used to quantify 230 serum metabolic biomarkers from 37,359 INTERVAL participants).[41]
2. SNP-exposure correlation dataset: GWAS for serum metabolomics (Nightingale NMR was used to quantify 249 serum metabolic biomarkers from 115,078 UK Biobank participants).[25]
3. SNP-outcome correlation dataset: GWAS for BP indicators (99,785 GERA cohort participants).[27]

Following the principles of three-sample MR, we selected independent SNPs associated with exposures in the selection dataset as instrumental variables, typically around 1000. Specifically, SNPs were selected based on the level of statistical significance at $P < 5 \times 10^{-2}$ and LD clumping ($R^2 < 0.001$) using 1000 Genomes European ancestry reference panel. The exposure and outcome datasets provide estimates of the genetic effects and standard errors of the SNPs on exposure and outcome, respectively.

The EB-RAPS method models SNP effects using a spike-and-slab prior, performs empirical Bayes estimation and adaptive shrinkage of effect sizes, constructs robust estimating equations to jointly estimate the causal effect and overdispersion parameter, and finds the solution. We performed the analysis with and without accounting for overdispersion variance. Causal effect estimates using robust loss functions (Huber or Tukey) were reported in the sensitivity analysis to ensure stable inferences. More details of the method have been reported previously.[39]

Multivariable MR

In the MR-BMA's analysis, in order to check the model fit, we used the *Q*-statistic to quantify the outlier and the Cook's distance to quantify the influential variants in the best model with *PP* >0.02 for each result.[22,23,35] Any genetic variation with a *Q*-statistic greater than 10 or a Cook's distance greater than the median of a central F-distribution with d and n–d degrees of freedom was removed and reanalysed, where d is the number of risk factors and n is the number of genetic variants.[35] Our primary analysis was performed after model diagnostics.

To further validate the robustness of our MR-BMA results, we conducted a conventional multivariable MR analysis by randomly excluding one metabolite from each pair of metabolites with a correlation greater than 0.8 (Supplemental Table S5). When analysing the five major lipids, a total of four models were selected by randomly excluding one metabolite from each of the two pairs. Meanwhile, out of the 43 lipoproteins, only eight lipoproteins were ultimately available for the conventional multivariable analysis (Supplemental Table S6).

Drug-target MR

To investigate the influence of TG-lowering on the risk of elevated BP indicators, we conducted further drug-target MR analysis. The cis-eQTL summary statistics used in the drug-target MR analysis were sourced from the eQTLGen Consortium (detailed information is available in Supplemental Table S1B).[42]

Our initial phase involved a comprehensive search within the DrugBank database (https://go.drugbank.com/) to identify drugs associated with the treatment of hypertriglyceridemia. Based on the drug's primary pharmacological mechanism, our focused investigation centered on genes encoding the pharmacological targets of fenofibric acid and omega-3-carboxylic acids. This choice aligns with the 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia, which indicates that in patients with severe hypertriglyceridemia, advocating for the use of medications like prescription omega-3 fatty acids or fibrates in severe hypertriglyceridemia cases to mitigate the risk of acute pancreatitis.[43] Considering the availability of cis-eQTL data, our final analysis encompassed the following loci: peroxisome proliferator-activated receptor alpha (*PPARA*) (identified as the primary pharmacological target for fenofibric acid), alongside diacylglycerol O-acyltransferase 2 (*DGAT2*), lipoprotein lipase (*LPL*), and elongation of very long chain fatty acids protein 4 (*ELOVL4*) (recognized as the primary pharmacological targets for omega-3-carboxylic acids). Supplemental Table S1C contains detailed information for target genes.

Next, we selected SNPs located within the upstream or downstream 100 kb of the identified targets that showed statistical significance ($P < 5 \times 10^{-8}$) at the genome-wide level and clumped for an LD threshold of $R^2 < 0.1$ from the eQTLGen Consortium database. We identified three variants in the *PPARA* locus, four variants in the *DGAT2* locus, 18 variants in the *LPL* locus, and 12 variants in the *ELOVL4* locus (Supplemental Table S9). Similar to univariable MR, we performed IVW, weighted median, MR-Egger regression, MR-Egger intercept, and Cochrane's *Q* statistic as the analysis methods.

Statistical analysis

Results were reported as the β ± SE mmHg change in BP and PP measurements per one standard deviation (SD) increase in the genetically predicted circulating metabolite level. In the conventional MR analysis, we used the Bonferroni correction to account for multiple testing considering the number of risk factors in

different groups (P value = 0.05/the number of risk factors). $P < 0.05$, but not significant after Bonferroni correction, were defined as potential associations. The P-value significance thresholds for each exposure group are shown in Supplemental Table S10. In MR-BMA analysis, P-values are calculated for each risk factor using a permutation method (we perform 1000 permutations), with adjustment for multiple testing via the Benjamini and Hochberg false-discovery rate (FDR) procedure.[22,23] Two-sample MR and a series of sensitivity analyses were performed using the TwoSampleMR and MRPRESSO packages; three-sample MR was performed using the mr.raps packages; and the code for the MR-BMA method was obtained from the cited literature.[35] All analyses were performed using R software version 4.2.2 (R Foundation for Statistical Computing).

Ethics

The datasets used in this study are publicly available summary datasets and can be found in cited papers. All original GWAS studies were approved by the ethics committee with informed consent from all participants.

Role of funders

The funding institutions had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Results

Association of genetically predicted major lipid profiles with BP and PP

In univariable MR analysis, the causal risk estimates of the genetically predicted five major lipids, measured by NMR spectroscopy and conventional clinical chemistry methods, on BP and PP were similar (Fig. 2). Genetically elevated total TG was positively associated with SBP and DBP, with β (SE) of 0.580 (0.124), $P < 0.001$, and 0.205 (0.078), $P = 0.009$, respectively, for the NMR spectroscopy method, and β (SE) of 0.743 (0.101), $P < 0.001$, and 0.310 (0.066), $P < 0.001$, respectively, for the clinical chemistry method. Inverse relations were observed for genetically predicted ApoB and LDL_C on DBP, with β (SE) of –0.292 (0.090), $P = 0.001$, and –0.306 (0.087), $P < 0.001$ for the NMR spectroscopy method, and –0.220 (0.059), $P < 0.001$, and –0.259 (0.071), $P < 0.001$ for the clinical chemistry method. For PP, positive relationships were observed for genetically elevated ApoB, LDL_C, and total TG (β (SE) = 0.391 (0.078), 0.411 (0.078), and 0.373 (0.085) for the NMR spectroscopy method, 0.404 (0.059), 0.420 (0.069), and 0.429 (0.072) for the clinical chemistry method, all $P < 0.001$); a negative relationship was observed for HDL_C (β (SE) = –0.339 (0.078) for the NMR spectroscopy method, and –0.518 (0.060) for the clinical chemistry method, all $P < 0.001$) (Fig. 2 and Supplemental Table S11). These findings were consistent with causality in the weighted median and MR Egger methods for violations of assumptions. For the results with pleiotropy, we used the MR-PRESSO to identify and remove the outlier SNP with horizontal pleiotropy, and the conclusion was still consistent. The Cochrane's Q statistic showed heterogeneity in most of the results ($P \leq 0.001$), which were analysed using the multiplicative random-effects IVW method (Supplemental Table S11).

Prioritizing the role of major lipid profiles on BP and PP

MR-BMA assigns to each lipid risk factor a probability score (MIP) and assigns to each model that includes a risk factor or a combination of risk factors a model score (PP), quantifying how well the risk factor associations with BP indicators are explained (Table 1 and Supplemental Table S12). Our primary analysis was performed after model diagnostics, which removed influential and outlying genetic variants (Supplemental Table S13, Supplemental Figures S1 and S2). The raw

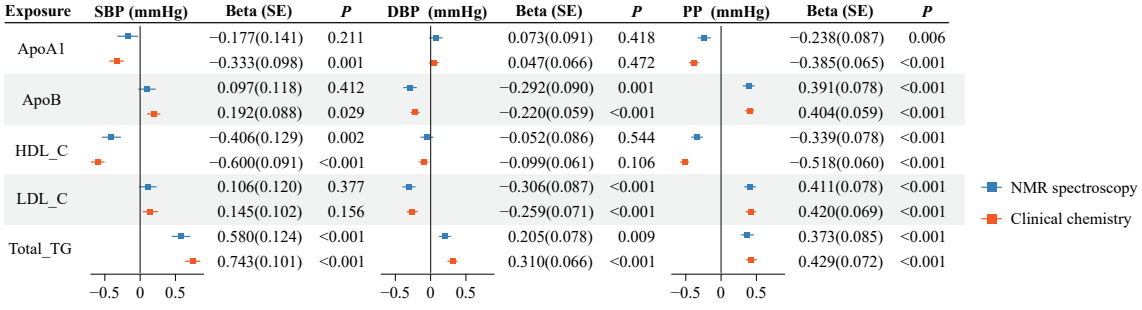

Fig. 2: **The causal effects of major lipids on BP and PP.** Causal estimates are obtained using the inverse-variance weighted method. Results are presented as beta (SE) mmHg changes for BP and PP traits per one SD increase in genetically predicted lipid levels. NMR, nuclear magnetic resonance; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

Exposure	MIP	MACE (mmHg)	Empirical *P*-value	FDR
Systolic blood pressure				
Total_TG	0.993	0.554	0.001	0.005
HDL_C	0.228	−0.066	0.278	0.694
ApoA1	0.115	−0.013	0.921	1.000
ApoB	0.029	0.003	0.998	1.000
LDL_C	0.024	0.000	1.000	1.000
Diastolic blood pressure				
Total_TG	0.847	0.261	0.007	0.020
LDL_C	0.602	−0.172	0.008	0.020
ApoB	0.259	−0.038	0.230	0.383
ApoA1	0.147	0.107	0.797	0.797
HDL_C	0.145	−0.104	0.772	0.797
Pulse pressure				
HDL_C	0.927	−0.354	0.001	0.005
LDL_C	0.718	0.329	0.003	0.007
ApoB	0.325	0.135	0.086	0.143
Total_TG	0.141	0.026	0.750	0.832
ApoA1	0.135	−0.012	0.832	0.832

Abbreviations: BP, blood pressure; MR-BMA, Mendelian Randomisation Bayesian model averaging approach; MIP, marginal inclusion probability; MACE, model-averaged causal effect; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; HDL_C, high-density lipoprotein cholesterol; LDL_C, low-density lipoprotein cholesterol; Total_TG, total triglycerides. Risk factors are ranked by the MIP in the primary analysis after model diagnostics. Causal effects are beta mmHg for BP indicators per 1 standard deviation increase in the risk factor. Empirical *P*-values are computed using 1000 permutations and adjusted for multiple testing using the false-discovery rate (FDR) procedure.

Table 1: **Ranking of most likely causal exposures among major lipids for BP indicators using MR-BMA.**

results before SNP removal are presented in Supplemental Table S14, consistent with the results of the primary analysis. For SBP, the strongest risk factor was total TG, with a MIP of 0.993 and a FDR of 0.005, while other risk factors had MIPs <0.250 (Table 1). The top-ranked model also revealed that total_TG (*PP* = 0.646) has the highest association with SBP, not other lipids (Supplemental Table S12). The top risk factor related to the DBP increase was also total TG, with MIP = 0.847 and FDR = 0.020 (Table 1). The top-ranked model also showed that total_TG and LDL_C (*PP* = 0.515) have the highest association with DBP rise (Supplemental Table S12). The top risk factors associated with PP increase were HDL_C and LDL_C, with MIPs of 0.927 and 0.718 and FDRs of 0.005 and 0.007, respectively (Table 1). Similarly, HDL_C and LDL_C remain the highest risk factors in the top-ranked model, with a *PP* of 0.512 (Supplemental Table S12).

Association of genetically predicted lipoprotein particles and concentrations with BP and PP

Genetically predicted VLDL particles (VLDL_P) and their sub-particles of different sizes showed a positive relationship with SBP levels (Fig. 3 and Supplemental Table S15). For DBP, genetically predicted LDL_size presented a negative association, with a β (SE) of −0.571 (0.165), P = 0.001. In addition, genetically elevated intermediate-density lipoprotein particles (IDL_P), LDL particles (LDL_P), and their sub-particles showed a negative causal association with DBP levels (Fig. 3 and Supplemental Table S16). Genetically predicted HDL_size showed a negative relationship with PP levels (β (SE) = −0.296 (0.069), P < 0.001). The majority of atherogenic lipoprotein particles, including sub-VLDL, IDL, and LDL particles, have positive associations with PP, which were demonstrated at the multiple test significant level (Bonferroni correction) (Fig. 3 and Supplemental Table S17).

The causal effect of genetically elevated cholesterol components in individual lipoprotein particles on outcomes was consistent with that of total lipoprotein particles (Supplemental Tables S15–S17). Notably, the genetically elevated TG component of the majority of lipoprotein particles was found to have a positive or suggestive positive association with SBP, DBP, and PP (Fig. 4, Supplemental Tables S15–S17).

The sensitivity analysis results for causal effects using different methods were presented in Supplemental Tables S15–S17. The results obtained from the weighted median, MR Egger, and MR-PRESSO methods remained unchanged.

Prioritizing the role of multiple lipoproteins on BP and PP

To further clarify the varying impacts of individual lipoproteins, including the five major lipids, on BP and PP levels, we performed ranking analysis on the following 36 lipoproteins using MR-BMA. These lipoproteins include apolipoprotein, lipoprotein size, cholesterol, and TG concentrations in different size categories of lipoprotein particles, and their details can be found in Supplemental Table S6.

In the MR-BMA analysis for SBP and DBP, the top exposure was genetically predicted TG in small HDL (S_HDL_TG), with MIPs of 0.416 and 0.397 and FDRs of 0.036 and 0.024, respectively (Table 2). Consistent with this, the ranking of the models also showed that the model containing S_HDL_TG was the first-ranked model for both SBP and DBP (*PP* = 0.055 and 0.056, respectively) (Supplemental Table S18). The sensitivity analysis results for detecting influential or outlying genetic variants can be seen in Supplemental Table S19, Supplemental Figures S3 and S4. The results were consistent before and after SNP removal (Supplemental Table S20). When analysing the relationship between lipoprotein and PP, all models have a *PP* of around 0.1 (10%), meaning that these models represent similar feature sets. In this case, this could be interpreted as one of these 10 models taking 100% of the weight (but the algorithm cannot decide which is truly correct). Consequently, we refrained from conducting subsequent ranking analyses due to the lack of sufficient statistical support for any specific model (Supplemental Table S18).

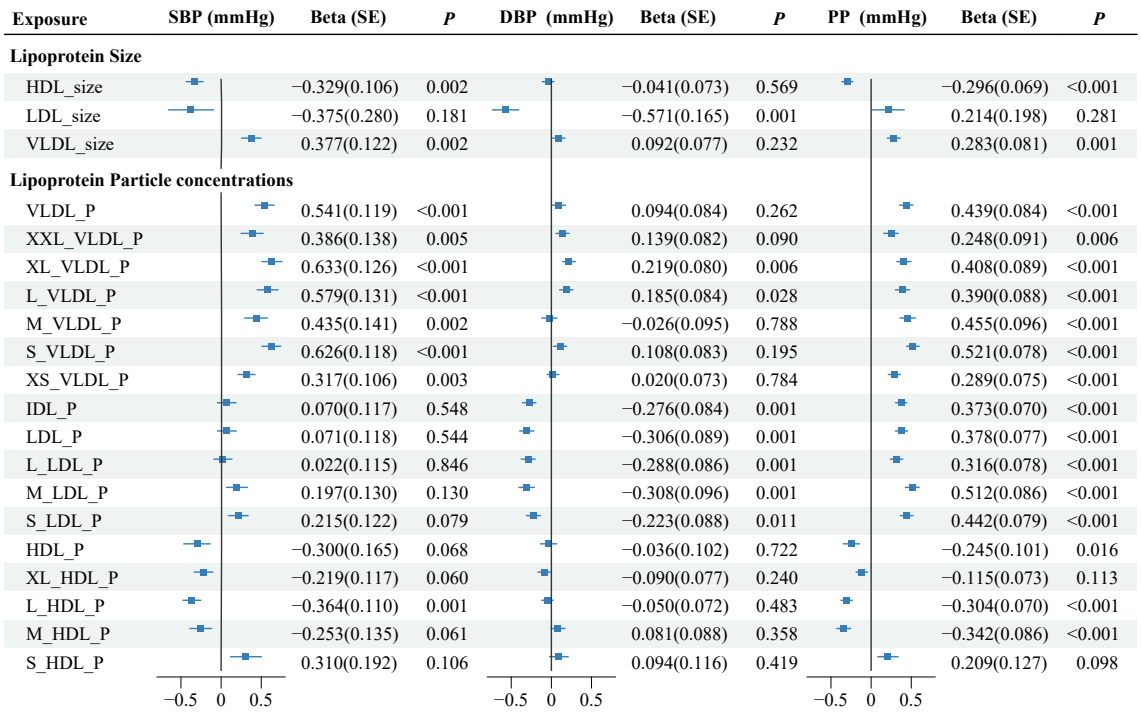

***Fig. 3:* The causal effects of lipoprotein size and lipoprotein particle concentrations on BP and PP.** Causal estimates are obtained using the inverse-variance weighted method. Results are presented as beta (SE) mmHg changes for BP and PP traits per one SD increase in genetically predicted lipid levels. HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; HDL_size, average diameter for HDL particles; LDL_size, average diameter for LDL particles; VLDL_size, average diameter for VLDL particles; VLDL_P, VLDL particles; XXL_VLDL_P, chylomicrons and extremely large VLDL particles; XL_VLDL_P, very large VLDL particles; L_VLDL_P, large VLDL particles; M_VLDL_P, medium VLDL particles; S_VLDL_P, small VLDL particles; XS_VLDL_P, very small VLDL particles; IDL_P, intermediate-density lipoprotein particles; LDL_P, LDL particles; L_LDL_P, large LDL particles; M_LDL_P, medium LDL particles; S_LDL_P, small LDL particles; HDL_P, HDL particles; XL_HDL_P, very large HDL particles; L_HDL_P, large HDL particles; M_HDL_P, medium HDL particles; S_HDL_P, small HDL particles; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

Association of genetically predicted amino acids, fatty acids, ketone bodies, glycoprotein acetyls, and other traits with BP and PP

In the analysis of the association between other non-lipid metabolites and BP indicators, we found that genetically predicted glycine was negatively associated with SBP and PP (β (SE) = –0.220 (0.079), P = 0.005, and –0.189 (0.050), P < 0.001). In addition, genetically predicted glucose levels were negatively associated with DBP and positively associated with PP, with an β (SE) of –1.138 (0.197), P < 0.001 for DBP, and 1.527 (0.299), P < 0.001 for PP. The results of sensitivity analyses using other methods were stable, and no excessive pleiotropy or heterogeneity was observed (Supplemental Tables S21–S23).

Sensitivity analysis

To further validate the robustness of our univariable MR results, we conducted sensitivity analyses using a stricter threshold for LD, with an R^2 < 0.001. Interestingly, under the IVW method, genetically predicted Total_TG and S_HDL_TG remained positively correlated with SBP, DBP, and PP levels (Supplemental Tables S24–S26). Additionally, genetically predicted VLDL_P's sub-particles showed a positive relationship with SBP levels (Supplemental Table S24). For DBP, genetically predicted LDL size demonstrated a negative correlation (Supplemental Table S25). The association between atherogenic lipoprotein particles (sub-VLDL particles) and PP was positively confirmed under the IVW method (Supplemental Table S26). The above results under the IVW method were all confirmed at the multiple test significance level (Bonferroni correction), although these findings were only potentially relevant or no longer significant under the additional method analysis (Supplemental Tables S24–S26).

To address the potential for selection bias resulting from the exclusion of weak instrumental variables, we conducted additional three-sample MR analyses. The results of these analyses, presented in Supplemental Tables S27–S29, remained consistent with our main findings. Specifically, we observed positive correlations between Total_TG, S_HDL_TG, and elevated blood pressure indicators.

Exposure	SBP (mmHg)	Beta (SE)	*P*	DBP (mmHg)	Beta (SE)	*P*	PP (mmHg)	Beta (SE)	*P*
Triglycerides concentrations									
VLDL_TG		0.478(0.130)	<0.001		0.165(0.078)	0.035		0.312(0.088)	<0.001
XXL_VLDL_TG		0.254(0.133)	0.056		0.075(0.085)	0.376		0.179(0.088)	0.043
XL_VLDL_TG		0.588(0.135)	<0.001		0.198(0.083)	0.017		0.384(0.091)	<0.001
L_VLDL_TG		0.514(0.137)	<0.001		0.121(0.089)	0.172		0.391(0.092)	<0.001
M_VLDL_TG		0.464(0.133)	0.001		0.104(0.085)	0.220		0.359(0.089)	<0.001
S_VLDL_TG		0.537(0.117)	<0.001		0.182(0.074)	0.014		0.359(0.080)	<0.001
XS_VLDL_TG		0.461(0.104)	<0.001		0.223(0.067)	0.001		0.239(0.070)	0.001
IDL_TG		0.474(0.098)	<0.001		0.228(0.063)	<0.001		0.247(0.071)	<0.001
LDL_TG		0.515(0.111)	<0.001		0.216(0.072)	0.003		0.300(0.075)	<0.001
L_LDL_TG		0.497(0.105)	<0.001		0.198(0.069)	0.004		0.297(0.072)	<0.001
M_LDL_TG		0.579(0.116)	<0.001		0.222(0.075)	0.003		0.358(0.078)	<0.001
S_LDL_TG		0.520(0.113)	<0.001		0.209(0.075)	0.005		0.315(0.078)	<0.001
HDL_TG		0.475(0.104)	<0.001		0.290(0.068)	<0.001		0.183(0.074)	0.014
XL_HDL_TG		0.296(0.098)	0.002		0.158(0.062)	0.011		0.137(0.070)	0.053
L_HDL_TG		0.284(0.091)	0.002		0.230(0.058)	<0.001		0.049(0.066)	0.463
M_HDL_TG		0.461(0.101)	<0.001		0.354(0.067)	<0.001		0.106(0.078)	0.172
S_HDL_TG		0.799(0.114)	<0.001		0.316(0.075)	<0.001		0.476(0.078)	<0.001

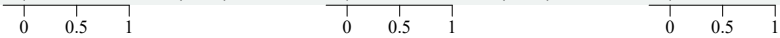

Fig. 4: **The causal effects of TG concentrations in lipoprotein particles on BP and PP.** Causal estimates are obtained using the inverse-variance weighted method. Results are presented as beta (SE) mmHg changes for BP and PP traits per one SD increase in genetically predicted lipid levels. TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; XXL_VLDL_TG, chylomicrons and extremely large VLDL TG; XL_VLDL_TG, very large VLDL TG; L_VLDL_TG, large VLDL TG; M_VLDL_TG, medium VLDL TG; S_VLDL_TG, small VLDL TG; XS_VLDL_TG, very small VLDL TG; IDL_TG, intermediate-density lipoprotein TG; L_LDL_TG, large LDL TG; M_LDL_TG, medium LDL TG; S_LDL_TG, small LDL TG; XL_HDL_TG, very large HDL TG; L_HDL_TG, large HDL TG; M_HDL_TG, medium HDL TG; S_HDL_TG, small HDL TG; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

To further validate the robustness of our MR-BMA results, we conducted conventional multivariate MR analysis. When analysing the five major lipids, in all models correcting for the remaining variables, genetically predicted Total_TG remained positively associated with SBP and DBP levels (Supplemental Table S30A). HDL_C, or ApoA1, is negatively associated with PP, and LDL_C, or ApoB, is positively associated with PP (Supplemental Table S30B). Meanwhile, when analysing multiple lipoproteins and their containing lipids, S_HDL_TG remained positively associated with SBP, but its association with DBP was no longer significant (Supplemental Table S30C). Genetically predicted LDL_C levels still remained positively associated with elevated PP in the multivariate models (Supplemental Table S30D).

The results derived from the drug-target MR analysis are presented in Supplemental Table S31. The investigation focused on understanding the effects of specific drug targets, namely *PPARA*, *DGAT2*, *ELOVL4*, and *LPL*, acting as proxies for TG-lowering on BP indices. For the treatment proxy of fenofibric acid acting via *PPARA*, significant associations were observed with SBP and PP, displaying a notable decrease (β (SE) = −1.354 (0.540), $P = 0.012$ for SBP; β (SE) = −1.225 (0.356), $P = 0.001$ for PP). Conversely, no significant associations were found between *PPARA* and DBP. Omega-3-carboxylic acids, as represented by *LPL*, demonstrated a notable decrease in association with SBP and PP (β (SE) = −0.225 (0.091), $P = 0.014$ for SBP; β (SE) = −0.253 (0.081), $P = 0.002$ for PP), but not DBP. *ELOVL4* and *DGAT2* showed varying associations with SBP, DBP, and PP, yet were not consistently significant across all outcomes, warranting further exploration. The weighted median analysis also confirmed the above association; the pleiotropy test by MR Egger and the Cochran's *Q* test were employed to ensure the robustness of the associations observed.

Discussion

Our study comprehensively characterizes and ranks the causal relationship between genetically predicted lipoprotein particles, lipid sub-components, multiple metabolites, and BP indicators. Total_TG was the top risk factor among the major lipids, potentially causing SBP and DBP increases. Among multiple lipoproteins and their containing lipids, TG in small HDL, namely S_HDL_TG, became the top factor leading to the increase in BP. For PP, HDL_C and LDL_C were the potential exposure foci among the major lipids. Among the various lipoproteins and their containing lipids, genetically elevated atherogenic lipoproteins are causally associated with PP. Therefore, our data suggests that comprehensive management of lipid profiles may benefit blood pressure control.

Exposure	MIP	MACE (mmHg)	Empirical *P*-value	FDR
Systolic blood pressure				
S_HDL_TG	0.416	0.310	0.001	0.036
L_LDL_TG	0.325	0.187	0.002	0.036
L_HDL_C	0.188	−0.069	0.003	0.036
IDL_TG	0.184	0.092	0.004	0.036
HDL_C	0.164	−0.060	0.009	0.054
HDL_size	0.125	−0.042	0.025	0.112
XXL_VLDL_C	0.121	−0.058	0.009	0.054
XS_VLDL_TG	0.117	0.057	0.011	0.057
XL_HDL_C	0.111	−0.037	0.034	0.136
XXL_VLDL_TG	0.105	−0.043	0.040	0.144
Diastolic blood pressure				
S_HDL_TG	0.397	0.216	0.001	0.024
M_HDL_TG	0.302	0.105	0.002	0.024
S_LDL_C	0.175	−0.054	0.007	0.036
L_VLDL_C	0.161	−0.076	0.002	0.024
LDL_C	0.145	−0.041	0.008	0.036
XS_VLDL_TG	0.134	0.043	0.004	0.036
Non_HDL_C	0.130	−0.036	0.007	0.036
ApoB	0.124	−0.036	0.007	0.036
Total_C	0.110	−0.030	0.029	0.095
Remnant_C	0.098	−0.024	0.025	0.090

Abbreviations: BP, blood pressure; MR-BMA, Mendelian Randomisation Bayesian model averaging approach; MIP, marginal inclusion probability; MACE, model-averaged causal effect; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; S_HDL_TG, small HDL TG; L_LDL_TG, large LDL TG; L_HDL_C, large HDL cholesterol; IDL_TG, intermediate-density lipoprotein TG; HDL_C, HDL cholesterol; HDL_size, average diameter for HDL particles; XXL_VLDL_C, chylomicrons and extremely large VLDL cholesterol; XS_VLDL_TG, very small VLDL TG; XL_HDL_C, very large HDL cholesterol; XXL_VLDL_TG, chylomicrons and extremely large VLDL TG; M_HDL_TG, medium HDL TG; S_LDL_C, small LDL cholesterol; L_VLDL_C, large VLDL cholesterol; LDL_C, LDL cholesterol; non_HDL_C, total cholesterol minus HDL-C; ApoB, apolipoprotein B; Total_C, Total cholesterol; Remnant_C, Remnant cholesterol (non-HDL, non-LDL-cholesterol). Risk factors are ranked by the MIP in the primary analysis after model diagnostics. Causal effects are beta mmHg for BP indicators per 1 standard deviation increase in the risk factor. Empirical *P*-values are computed using 1000 permutations and adjusted for multiple testing using the false-discovery rate (FDR) procedure.

Table 2: **Ranking of most likely causal exposures among 36 lipoproteins for BP indicators using MR-BMA.**

These findings are consistent with previous clinical trials that have investigated the effects of such treatment regimens on mortality rates and major adverse cardiovascular events in hypertensive patients. A 16-year follow-up randomized trial investigated the long-term cardiovascular and all-cause mortality effects of hypertensive patients receiving combined antihypertensive and lipid-lowering therapy. The findings demonstrated that a treatment regimen based on calcium channel blockers for blood pressure control and statins for cholesterol reduction had sustained beneficial effects on mortality.[44] Another study, the Heart Outcomes Prevention Evaluation (HOPE)-3 study, considered the impact of combined therapy on major adverse cardiovascular events in intermediate-risk individuals with no apparent clinical cardiovascular disease.[45] The study showed that in participants with elevated baseline BP (SBP >143 mmHg), the combination of candesartan (16 mg daily) and hydrochlorothiazide (12.5 mg daily) significantly reduced the incidence of major adverse cardiovascular events after 5.6 years of treatment, compared to placebo.[46] Moreover, it is worth noting that the benefits of combined antihypertensive and lipid-lowering therapy extend beyond the active treatment phase. Subsequent investigations revealed that these benefits continued to accumulate for at least 3 years after discontinuation of the treatment in patients initially randomized to both BP lowering and rosuvastatin, when compared with those receiving double placebo.[47] These findings contribute to the growing body of evidence supporting the long-term benefits of this treatment strategy.

Our results highlight the similarities in the effects of lipids and lipoproteins on SBP and DBP. Genetically predicted TG is the common top risk factor for the increase in SBP and DBP. Consistent with our findings, a previous observational study with a mean follow-up of 8.49 years also showed that TG and TG-related parameters were associated with new-onset hypertension.[48] Some MR studies also demonstrated a causal relationship between TG and SBP/hypertension.[18–20] However, our study ranked the causal relationship between the five major lipids currently routinely measured in clinical practice and three different dimensions of BP indicators (SBP, DBP, and PP) and found that TG is the top risk factor for both SBP and DBP, rather than other lipids.

We further ranked the causal relationship between BP and 36 different lipoproteins and their containing lipids, including five major lipids. The results showed that S_HDL_TG was the common potential factor for the increase in SBP and DBP. A previous study involving 17,527 initially healthy women with a follow-up of 8 years found that the lipoprotein pattern of hypertension was consistent with ours, i.e., higher concentrations of small LDL, small HDL, and large VLDL particles.[49] However, their study was limited to women and did not prioritize the many risk factors. Our study not only draws causal association conclusions based on MR methods, but also ranks many factors, which may provide more information for looking for new and additional drug targets.

Our results also highlight the differences in the effects of lipids and lipoproteins on BP and PP. For PP, the protective effect of HDL_C and the dangerous effect of LDL_C bear the brunt among the major lipids. Upon further analysis of the various lipoprotein subclasses, genetically elevated atherogenic lipoprotein particles (i.e., sub-VLDL, IDL, and LDL particles) were highlighted. There have been no previous studies on the association of PP with lipid profiles. Our study analysed the lipid and lipoprotein particles that play a causal role in PP increases and found that the focus is different from that of BP, which may provide extra clues for the prevention and management of hypertension and adverse prognosis in the elderly.

Additionally, we observed a correlation between TG-lowering genetic variants in the *PPARA* locus and a lower risk of SBP and PP elevation by drug-target MR analysis. However, given the limited scope of our drug target selection, the strength of the evidence remains to be supported by interventional studies.

The mechanism behind our findings on the role of TG in BP rise may include endothelial dysfunction, atherosclerosis, inflammation, and insulin resistance.[50–52] In addition, in the hypertriglyceridemic state, the transfer of TG from TG-rich lipoproteins (VLDL and chylomicrons) to HDL particles and the transfer of cholesteryl esters from HDL to TG-rich lipoproteins are enhanced. This process results in the formation of TG-rich and cholesteryl ester-core-depleted HDL particles, which are the preferred substrate for the enzyme hepatic lipase, resulting in an increase in S_HDL_P and a decrease in the anti-atherogenic HDL sub-fractions.[53] Our study also found a negative correlation between HDL_size and BP indicators, which may highlight the more dangerous role of S_HDL_P than HDL of other sizes. In addition, TG-rich HDL, especially S_HDL_TG, may also alter the anti-atherosclerotic capacity of HDL itself, including its antioxidant and anti-inflammatory capacity.[53,54] These reasons may explain why S_HDL_TG is the top-ranked causal factor for SBP and DBP increases. More studies on different populations and drug targets are needed to verify whether it is more beneficial to recommend TG and finer S_HDL_TG lipoprotein particles as new anti-hypertensive targets and anti-hypertensive combined lipid-lowering drug targets.

Elevated PP, as a proxy for arterial stiffness, has been approved to be a strong predictor of hypertension, CVDs, and overall mortality.[12,13] Our study highlights the causal role of atherosclerosis-associated lipoprotein particles on PP, which is mainly reflected in the decrease of anti-atherogenic HDL_C and the increase of atherogenic particles (i.e., sub-VLDL, IDL, and LDL particles), especially S_VLDL_P, M_LDL_P, and S_LDL_P. Atherosclerosis results in changes in arterial stiffness that affect BP control over time and facilitate the transition from mixed hypertension to isolated systolic hypertension, a form that is more difficult to treat.[51] Atherosclerosis is also associated with an inflammatory status, which may also contribute to hypertension.[50] Smaller particles are more likely to penetrate the arterial wall through the intima and interact with proteoglycans, leading to subendothelial retention of lipoproteins—an early step in the development of atherosclerosis.[55] Furthermore, native LDL particles do not induce cholesterol accumulation induced by oxidized LDL, which is a critical step in atherosclerosis as it contributes to foam cell production, endothelial dysfunction, and inflammatory processes. In contrast, small and dense LDL particles are more susceptible to oxidation.[56]

Our study had some limitations, thus, interpreting estimates of the effect of metabolites on the risk of elevated BP and PP requires caution. First, the GWAS data population used in our study was primarily European-ancestry, which may limit the generalizability of our conclusions to non-European-ancestry populations. Second, our exposure and outcome GWAS data are distributed in the age range of 40–69 years, which may limit the applicability of our findings to the younger or older population. Third, although we tried to eliminate possible pleiotropic effects using the MR-Egger and MR-PRESSO methods, we cannot exclude the possibility that lipid-related genetic variations may affect other metabolic traits. Fourth, in our study, the MR-BMA method identified the most likely causal factor among the highly correlated lipid-related risk factors associated with the outcome, which does not rule out the possibility that additional unanalysed risk factors may also be causal factors.

To conclude, our study provides genetic evidence for the causal effects of lipids on BP indicators. TG and the TG component of small HDL particles have the greatest impact on SBP and DBP levels. Atherogenic lipoproteins are causally associated with PP. This evidence may provide an important rationale for the comprehensive management of lipid profiles when improving BP control. Further research is warranted to elucidate the underlying mechanisms and optimize the implementation of such therapeutic interventions in clinical practice.

Contributors

W.-F.L. and C.-Z.Y. designed the study, collected, reviewed, analysed data, and wrote the manuscript. F.L. and X.H. verified data and contributed to data analysis. J.C. revised the manuscript and provided valuable suggestions for study design and data analysis. S.-Z.C., Z.-G.S., and H.L. contributed equally, designed the project, edited the manuscript, and supervised the study. All authors have approved the final version of this paper.

Data sharing statement

The datasets used in this study are publicly available summary datasets and can be found in cited papers, in the IEU OpenGWAS Project repository [https://gwas.mrcieu.ac.uk/], or in the GWAS Catalogue repository [https://www.ebi.ac.uk/gwas/home]. There are no restrictions on data availability other than those imposed by the corresponding data committee.

Declaration of interests

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2023.104964.

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