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Elevated isoleucine may be a protective factor for primary hypertension

A pooled causal effect study

Ying Shi, MD, PhD[a], Hairun Liu, MD[b], Yi Chen, PhD[c,*]

Abstract

Hypertension continues to pose a huge burden to global public health. Abnormal metabolism not only serves as a risk factor for hypertension but also acts as a driving force in its aggravation. However, there remains a lack of large-scale causal demonstration based on extensive samples. Our study aims to investigate the causal relationship between metabolism and primary hypertension (PH) using Mendelian randomization analysis. We used genome-wide association studies instrumental variables for Mendelian randomization association analysis integrating the diagnosis results of PH in 3 populations from East Asia, the Middle East, and Africa with serum metabolites and metabolite ratios. This allowed us to identify predictive metabolites and metabolic pathways for diagnosing or treating PH. Inverse-variance weighting was the main model for establishing causal associations. In addition horizontal pleiotropy test, linkage disequilibrium test, and sensitivity analysis were employed to test the explanatory power of instrumental variables. A total of 10,922 cases of PH and 8299 cases of metabolomics detection cohorts were included in the study. In East Asian, Middle Eastern, and African populations, we found 36, 57, and 40 known metabolites respectively strongly associated with PH ($P < .05$). Cross-section and meta-analysis of these strongly correlated metabolites across the 3 ethnic groups revealed 7 common metabolites. Notably, elevated isoleucine (odds ratio = 0.74, 95% confidence interval: 0.56–0.96) was demonstrated as a potential protective factor against PH across 3 ethnic groups. The metabolites associated with PH have certain polymorphisms in different populations. Isoleucine may be a promising biomarker for PH diagnosis or treatment, but more clinical validation is needed.

Abbreviations: DBP = diastolic blood pressure, GWAS = genome-wide association study, IVW = inverse-variance weighted, MR = Mendelian randomization, PH = primary hypertension, RCT = randomized-controlled trial, SBP = systolic blood pressure, SNP = single-nucleotide polymorphism.

Keywords: causal association, Mendelian randomization, metabolite, multiple populations, primary hypertension

1. Introduction

Primary hypertension (PH) is one of the most important risk factors for cardiovascular diseases, stroke, chronic kidney disease as well as dementia.[1] The prevalence of elevated blood pressure has declined substantially in Western high-income regions since 1970s, but keeps rising in East, South and Southeast Asia, sub-Saharan Africa, and Oceania.[1] Asian characteristics differed from the West and led to higher stroke incidence.[2] Masked hypertension is a significant clinical entity of target organ damage and cardiovascular disease.[3] The prevalence of masked hypertension for Asians (16.0%) is higher than European (9%).[4] Regarding Africa, hypertension is common in sub-Saharan Africa, the prevalence significantly varies in different African countries, ranging from 37% to 75%.[5] Approximately one-tenth of adolescents have elevated blood pressure across sub-Saharan Africa.[6] The prevalence of hypertension was high in both rural (27.4%) and urban areas

YS and HL contributed to this article equally.

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The datasets generated during and/or analyzed during the current study are publicly available.

This study was conducted based on publicly available data and did not require ethical approval.

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(33.9%) of West Africa.[7] However, the rates of hypertension diagnosis, treatment, and control are markedly low[8] and cause a heavy health and economic burden in both Asia and Africa.[9] The hypertension treatment rates were below 25% for women and less than 20% for men in South Asia and some sub-Saharan African countries. Control rates were lower than 10% in these countries and for men in some countries of North Africa and Central Asia.[10]

PH has been regarded as a disorder of the renin–angiotensin–aldosterone system and the sympathetic nervous system (SNS) in tradition.[11] Yet, current treatments aiming at limiting the effects of renin–angiotensin–aldosterone system or SNS on blood pressure fail in about 40% of cases.[12] This implied that other mechanisms may exist. Previous studies found that immune mechanisms can contribute to the development of hypertension.[13] Flavonoids were reported to possess an underlying mechanism to regulate antihypertensive effects.[14] Genetics can drive the occurrence of hypertension in certain patients.[15] Anxiety diagnosis was also reported can cause development or incidence of hypertension, which might be due to the longer exposure to alterations in autonomic mechanisms.[16] In addition, hypertension has been reported to be associated with impaired metabolic homeostasis and can be considered as a metabolic disorder.[17]

To date, there have been limited cohort-based causal studies examining the relationship between metabolites and PH,[18–22] with a particular lack of research on Asian and African populations. If differentially abundant metabolites are risk factors or protective factors for PH, it is meaningful for the prediction of the disease and auxiliary diagnosis based on specific targets, as well as for further treatment.

Therefore, our study aims to investigate the causal relationship between metabolism and PH in Asian and African populations using Mendelian randomization (MR). We analyzed serum metabolites and metabolite ratios from genome-wide association studies (GWAS). Applying MR analysis, which mimics the design of randomized-controlled trials (RCTs), we explored the causal effects of these metabolites on PH. We used metabolite-associated single-nucleotide polymorphisms (SNPs) as instrumental variables to assess the causal impact and to elucidate the underlying metabolic pathways.

2. Materials and methods

2.1. Study design

The dataset that contains all the data in this study is available to the public on the open website (http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90199001-GCST90200000 and https://gwas.mrcieu.ac.uk/). The GWAS summary statistics have already been published. The ethics committee at each institutional review board authorized all participants' written informed permission in separate cohort studies. No extra ethical approval or informed consent was required in this study.

In the current study, we comprehensively evaluated the relationship between 1091 serum metabolites, 309 metabolite ratios, and PH datasets from East Asian, Middle East, and African populations one by one rigorously based on the MR design. A scientific MR study must include the testing of the following 3 hypotheses: genetic instrumental variables (SNPs) are strongly associated with the serum metabolites level or ratio; genetic instrumental variables should be irrelevant to the PH and independent of any known or unknown confounding factors; and the effect of instrumental variables on the results is mediated only by the serum metabolites level or ratio. Briefly, a causal analysis strategy was employed to select genetically significant SNPs for 1091 human serum metabolites, 309 metabolite ratios, and PH. To avoid sample overlap, metabolites and genetic information of PH were selected from independent GWAS datasets in this study. A schematic of this study is demonstrated in Figure 1.

2.2. GWAS data for human serum metabolites

A genome-wide association aggregate dataset of 1091 human serum metabolites and 309 metabolite ratios involved in this study was obtained by Chen et al[23] These data are publicly available from the GWAS server (http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90199001-GCST90200000). The service platform collects relatively complete human serum metabolomics data. A total of 8299 individuals from the Canadian Longitudinal Study on Aging cohort were included in the GWAS analysis. A total of 248 loci were found to be associated with 690 metabolite levels and 69 loci with 143 metabolite ratios. After integrating metabolite genes and gene expression information, 94 effector genes were identified for 109 metabolites and 48 metabolite ratios. The chemical properties of another 241 unknown or partially characterized metabolites have not been fully determined.

2.3. GWAS data for primary hypertension

The GWAS data of PH among East Asia, Middle East, and Africa populations were obtained from the data of the integrative epidemiology unit open GWAS project (https://gwas.mrcieu.ac.uk/). These summary data were collected from the UK-Biobank cohort in 2020 and GWAS ID were ukb-e-401_EAS, ukb-e-401_MID and ukb-e-401_AFR. In this GWAS meta-analysis, the summary data included 5554 PH cases and 10,922 control cases, yielding a total of 15,530,091 SNPs. We extracted SNPs by analyzing visual component framework files shared by the integrative epidemiology unit platform. The patients with PH were diagnosed according to the standard criteria of the World Health Organization and the International Hypertension Alliance.

2.4. Selection of instrumental variables

In this MR analysis, the selection of instrumental variables was based on 3 basic assumptions. First, we set $P < 1 \times 10^{-5}$ as the genome-wide significance threshold to obtain strongly associated SNPs for each metabolite. Second, a clumping procedure implemented in R software was employed to identify the independent variants. $R^2 < 0.001$ within a 500-kb distance was used to avoid linkage disequilibrium. Third, to quantitatively verify whether the selected SNPs were strongly correlated instruments, we calculated the phenotypic variation explained and the F statistic for each metabolite. Typically, a threshold of $F > 10$ is suggested for the next operation.[24]

2.5. MR analysis

A standard inverse-variance weighted (IVW) method was the prioritized evaluation approach used for causal association exploration between metabolites and PH in this analysis. When the instrumental variables satisfy all 3 major hypotheses, the IVW method can provide a more accurate estimate of the causal effect of metabolite and is considered as the most efficient MR method. However, if some instrument variables do not conform to the instrumental variables hypothesis, the analysis may give inaccurate results. Hence, we conducted the following sensitivity analyses: Q tests were performed using the MR-Egger methods to detect heterogeneity between each instrument variable and the possibility of violating the assumption.[25] The MR–Egger intercept was used to estimate the horizontal pleiotropy, ensuring that the genetic variation was independently related to the metabolite and PH[26]; additional approaches such as the

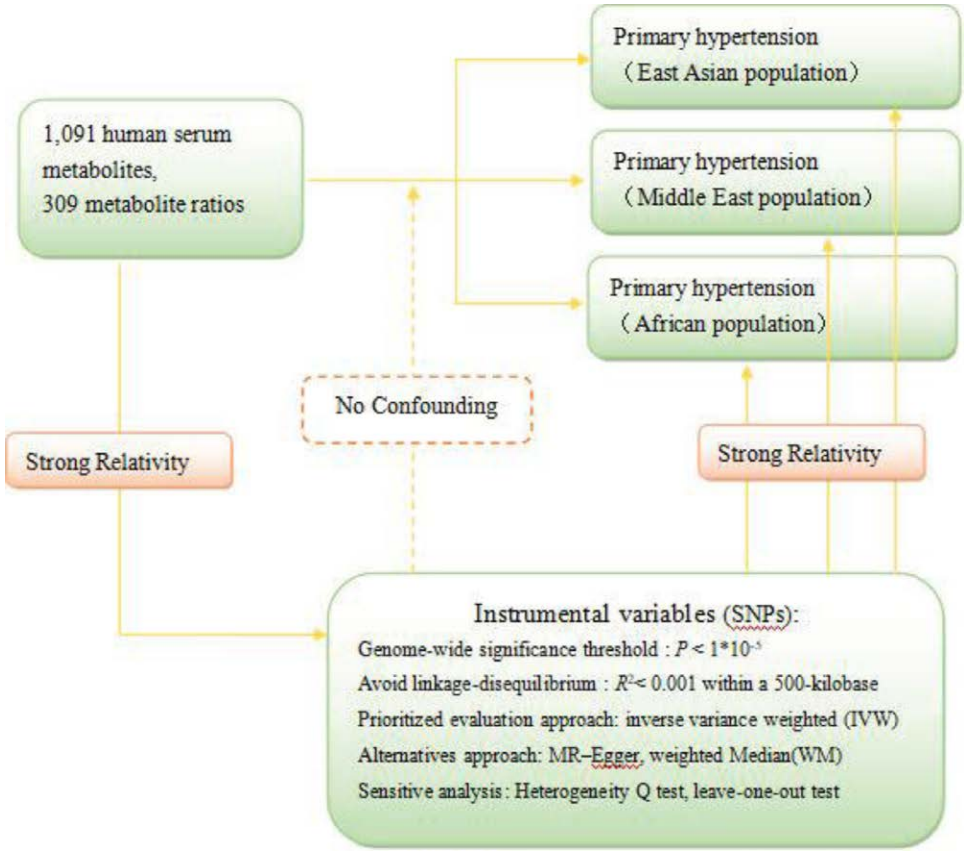

Figure 1. Schematic of the Mendelian randomization analysis. Significant instrumental variables were selected to assess the correlation between metabolites and primary hypertension crossing 3 population. The 3 basic assumptions of Mendelian randomization analysis were illustrated in the acyclic graph. SNP = single-nucleotide polymorphism.

weighted median and weighted mode were applied to enhance the reliability and stability of hypothesis testing; and the individual SNP analysis and leave-one-out test were conducted to estimate the likelihood of relevance observed by individual SNPs. To ensure there was no direct association with PH or other confounding factors, candidate SNPs were compared against the human reference genome database.

2.6. Metabolic pathway analysis

Metabolome enrichment pathways associated with PH were estimated using web-based MetaboAnalyst 5.0. (https://www.Metaboanalyst.ca/, Natural Sciences and Engineering Research Council of Canada, Ottawa, Canada).[27] The pathway and enrichment analysis modules were applied to identify probable metabolite clusters or superpathways that may be associated with metabolic processes and the potential association with PH. The Small Molecule Pathway Database and the Kyoto Encyclopedia of Genes and Genomes database were applied for reference. The significance level of the enrichment pathway was 0.05.

2.7. Intersection analysis

An intersection such as meta-analysis was introduced to analyze the shared metabolites screened by the 3 PH datasets, in conjunction with potential pathway mechanisms, to evaluate the polymorphism of related metabolites in different races.

2.8. Statistical analysis

The MR analysis was conducted using the "TwoSampleMR" package in R (version 4.3.1), developed by Gibran Hemani, Philip Haycock, Jie Zheng, Tom Gaunt, Ben Elsworth, and Tom Palmer (available at https://mrcieu.github.io/TwoSampleMR/). $P < .05$ was considered as statistically significant. The odds ratio was used to estimate the magnitude and direction of the metabolic impact with its corresponding 95% confidence interval. If there was missing data, we have chosen to delete it. The circle heatmap was drawn using ChiPlot (https://www.chiplot.online/) (accessed on September 29, 2023).

3. Results

3.1. Influence of serum metabolites on PH

As the genome-wide significance threshold was $P < 1 \times 10^{-5}$ to select strongly associated SNPs among 1091 human serum metabolites and 309 metabolite ratios, the instrument variables contained 76,267 SNPs in total, with a median of 17 SNPs. Among them, the East Asian population dataset accounted for 28.80%, the Middle East population dataset accounted for 41.63%, and the African population dataset accounted for 29.57%. The F statistic values were all >10, indicating that weak instrumental bias is not detected.

All metabolic analyses used IVW as the primary analytical methodology, with no evidence of heterogeneity and no weak instrument variables.[28] In the East Asian population dataset, 36 significantly associated named metabolites were selected ($P < .05$ for IVW), in which 19 were positively associated with PH and 17 were negatively associated with PH. Carnitine to propionyl carnitine (C3) ratio ($P = .0020$) was the most significant factor, followed by 4-hydroxychlorothalonil levels ($P = .0046$) and histidine to alanine ratio ($P = .0051$) (Fig. 2A). In the Middle East population dataset, 57 significantly associated named metabolites were selected ($P < .05$ for IVW), in which 24 were

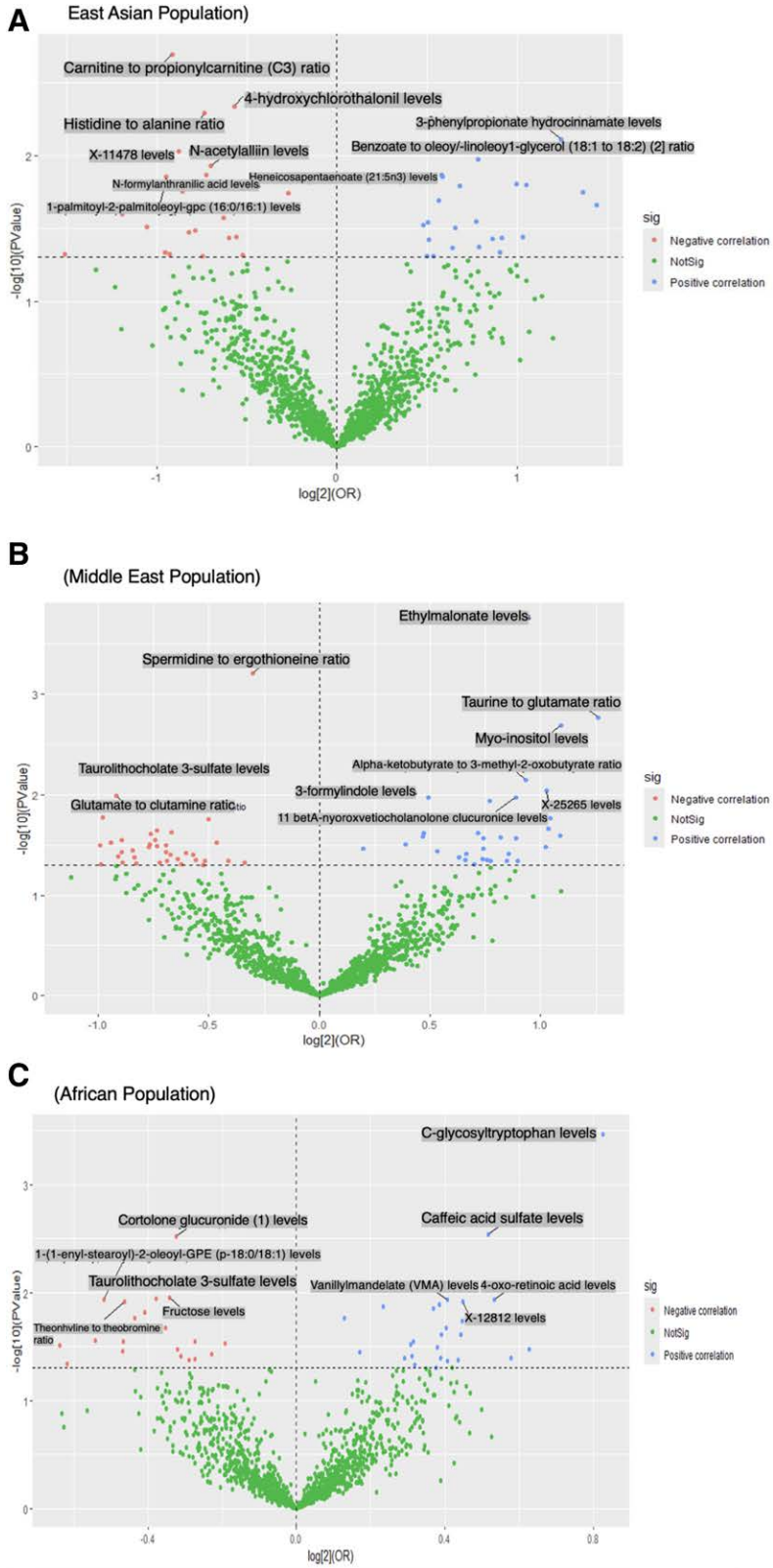

Figure 2. Volcano plots depicting correlations related to the influence of metabolites on primary hypertension. (A–C) Correlation volcano plots among East Asian, Middle East, and African. The plots include both ORs in log 2 scale and *P* values in –log 10 estimated by the inverse variance weighted method for metabolites among 3 populations. OR = odds ratio.

positively associated with PH and 33 were negatively associated with PH. Ethyl malonate levels ($P = .0002$) were the most significant factor, followed by spermidine to ergothioneine ratio ($P = .0006$) and taurine to glutamate ratio ($P = .0017$) (Fig. 2B). In the African population dataset, 40 significantly associated named metabolites were selected ($P < .05$ for IVW), in which 26 were positively associated with PH and 14 were negatively associated with PH. C-glycosyl tryptophan levels ($P = .0003$) were

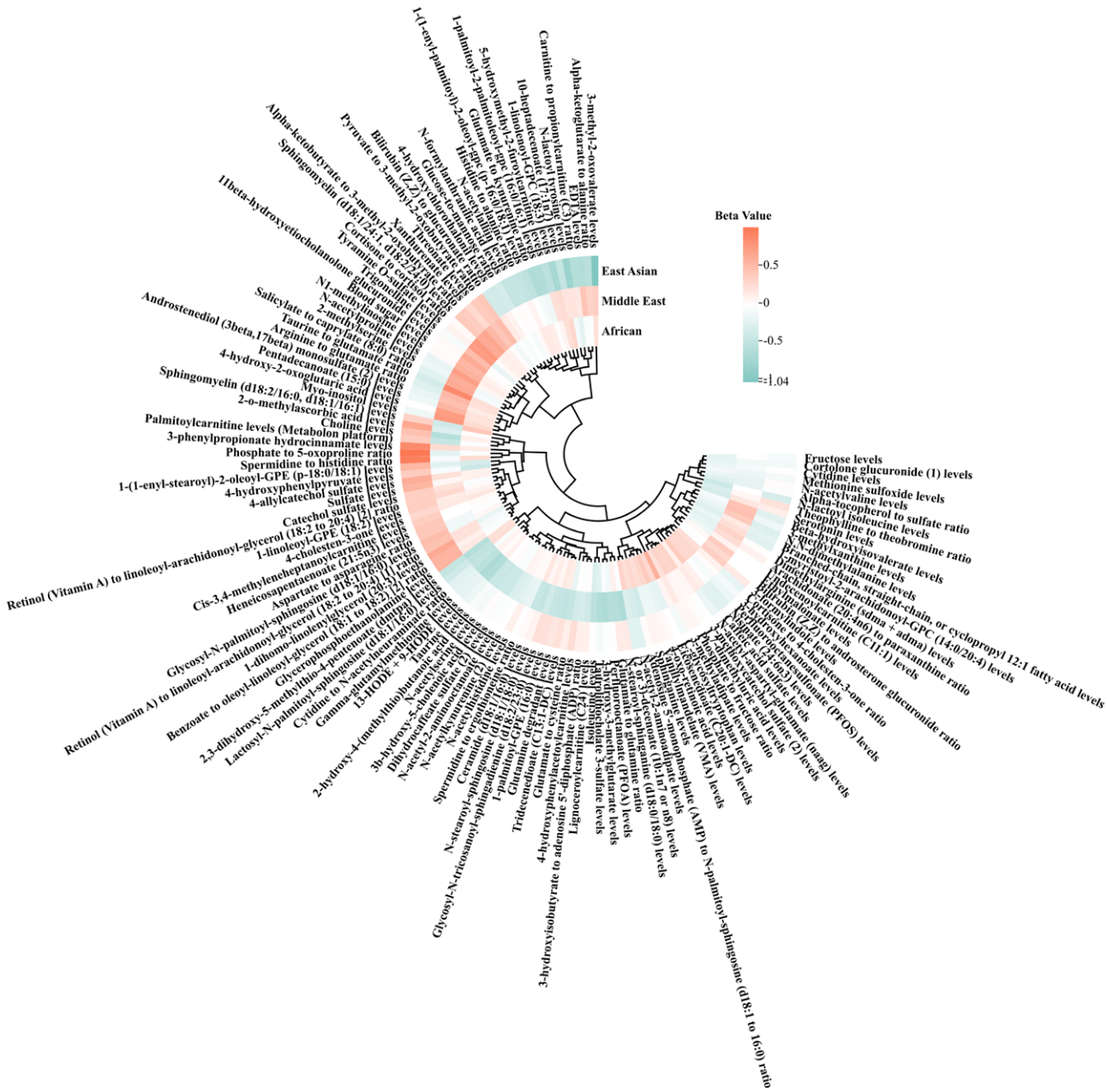

Figure 3. Heat map of the direction of the potential correlation of metabolic involvement in the 3 populations.

the most significant factor, followed by caffeic acid sulfate levels ($P = .0029$) and cortolone glucuronide (1) levels ($P = .0030$) (Fig. 2C). Figure 3 exhibited the direction of the potential correlation of metabolic involvement in the 3 populations. The results of the alternative analysis, Q test, and sensitivity analysis for the known metabolites are shown in Table 1. All instrument variables passed the sensitivity tests ($P > .05$).

The metabolites significantly associated with PH among 3 populations were entered into the MetaboAnalyst 5.0 platform to determine various underlying metabolic pathways involved in the pathogenesis of PH. In the East Asia dataset, histidine, L-aspartic acid, oxoglutaric acid, pyruvic acid, D-glucose, and phosphate were involved in the metabolic enrichment pathway of ammonia recycling, glucose–alanine cycle, urea cycle, alanine metabolism, malate–aspartate shuttle, and glutamate metabolism ($P < .05$). Regarding Middle East dataset, 2-ketobutyric acid, choline, and spermidine were involved in the metabolic enrichment pathway of methionine metabolism ($P < .05$). For Africa dataset, myo-inositol, D-fructose, and phosphate were involved in the metabolic enrichment pathway of galactose metabolism and phosphatidylinositol phosphate metabolism ($P < .05$) (Table 2). The metabolic mechanism formed by the above metabolites may be involved in the pathogenesis of PH. Figure S1A–C, Supplemental Digital Content, http://links.lww.com/MD/O433 exhibits the networks of interactions among the metabolic pathways involved in East Asian, Middle East, and African populations.

3.2. Intersection between East Asian, Middle East, and African populations

Intersection analysis was introduced to analyze the shared metabolites screened by the MR analyses. The cross-sectional and meta-analysis of strongly correlated metabolites across the 3 ethnic groups revealed that 7 metabolites were consistently identified, 5 of which were previously known. Among these, isoleucine (odds ratio = 0.74, 95% confidence interval: 0.56–0.96) emerged as a protective factor for PH across all 3 ethnic groups (Figs. 4 and 5A–E).

Table 1

The 3 Mendelian randomization model estimates of the causal relationships between known metabolites and the risk of primary hypertension and tests for heterogeneity and horizontal pleiotropy

Population	Metabolite	SNP (N)	Method	OR (95% CI)	*P*	Heterogeneity		Pleiotropy	
						Q	*P*	Intercept	*P*
East Asian	Carnitine to propionylcarnitine (C3) ratio	15	IVW	0.53 (0.36–0.79)	.0020	4.5097	.9915	−0.0098	.8702
			MR–Egger	0.56 (0.26–1.24)	.1764	4.4819	.9849		
			WM	0.52 (0.3–0.92)	.0238				
	4-Hydroxychlorothalonil levels	19	IVW	0.67 (0.51–0.89)	.0046	22.1837	.2239	−0.0484	.3908
			MR–Egger	0.80 (0.50–1.26)	.3445	21.2158	.2168		
			WM	0.77 (0.57–1.03)	.0782				
	Histidine to alanine ratio	20	IVW	0.60 (0.42–0.86)	.0051	18.6695	.4782	−0.0315	.4135
			MR–Egger	0.73 (0.41–1.32)	.3108	17.9689	.4577		
			WM	0.65 (0.38–1.10)	.1080				
	3-Phenylpropionate hydrocinnamate levels	12	IVW	2.37 (1.26–4.46)	.0078	10.0966	.5217	−0.0039	.9632
			MR–Egger	2.44 (0.60–9.92)	.2413	10.0943	.4323		
			WM	1.80 (0.76–4.26)	.1838				
	Benzoate to oleoyl-linoleoyl-glycerol (18:1 to 18:2) ratio	22	IVW	1.72 (1.13–2.6)	.0106	10.8147	.9663	0.0189	.7783
			MR–Egger	1.45 (0.41–5.05)	.5685	10.7333	.9528		
			WM	1.54 (0.83–2.88)	.1734				
	N-acetylalliin levels	19	IVW	0.62 (0.42–0.9)	.0119	13.4070	.7669	−0.0165	.8013
			MR–Egger	0.68 (0.28–1.67)	.4146	13.3416	.7130		
			WM	0.56 (0.31–1)	.0511				
	N-formylanthranilic acid levels	14	IVW	0.6 (0.41–0.9)	.0136	9.0650	.7680	−0.0163	.7713
			MR–Egger	0.66 (0.32–1.37)	.2872	8.9767	.7049		
			WM	0.69 (0.4–1.19)	.1784				
East Asian	Heneicosapentaenoate (21:5n3) levels	11	IVW	1.49 (1.09–2.05)	.0136	5.2030	.8772	0.0135	.8113
			MR–Egger	1.43 (0.91–2.25)	.1534	5.1426	.8217		
			WM	1.24 (0.8–1.93)	.3396				
	1-Palmitoyl-2-palmitoleoyl-gpc (16:0/16:1) levels	16	IVW	0.52 (0.31–0.88)	.0140	11.2002	.7383	−0.0306	.6761
			MR–Egger	0.68 (0.18–2.6)	.5815	11.0182	.6846		
			WM	0.63 (0.3–1.3)	.2096				
	Pyruvate to 3-methyl-2-oxobutyrate ratio	18	IVW	1.5 (1.08–2.07)	.0141	15.5724	.5543	0.0481	.3396
			MR–Egger	1.19 (0.68–2.09)	.5563	14.6036	.5538		
			WM	1.41 (0.89–2.22)	.1432				
	Glycosyl-N-palmitoyl-sphingosine (d18:1/16:0) levels	16	IVW	1.6 (1.09–2.35)	.0161	14.6432	.4774	0.0306	.6007
			MR–Egger	1.34 (0.63–2.85)	.4536	14.3493	.4240		
			WM	1.48 (0.89–2.45)	.1288				
	Alpha-ketoglutarate to alanine ratio	15	IVW	0.55 (0.34–0.9)	.0176	12.9394	.5313	0.0400	.6107
			MR–Egger	0.42 (0.14–1.31)	.1581	12.6673	.4738		
			WM	0.44 (0.22–0.88)	.0206				
	Spermidine to histidine ratio	9	IVW	2.58 (1.18–5.66)	.0180	3.2099	.9205	−0.0698	.7116
			MR–Egger	5.55 (0.1–296.53)	.4264	3.0616	.8793		
			WM	1.75 (0.6–5.09)	.3011				
	N-acetyl-aspartyl-glutamate levels	35	IVW	0.83 (0.71–0.97)	.0182	42.2787	.1558	−0.0248	.6239
			MR–Egger	0.89 (0.63–1.26)	.5274	41.9671	.1362		
			WM	0.86 (0.7–1.06)	.1485				

(*Continued*)

Table 1

(*Continued*)

Population	Metabolite	SNP (N)	Method	OR (95% CI)	*P*	Heterogeneity		Pleiotropy	
						Q	*P*	Intercept	*P*
East Asian	Aspartate to asparagine ratio	15	IVW	1.48 (1.06–2.05)	.0202	13.2872	.5040	0.0255	.6275
			MR–Egger	1.32 (0.76–2.3)	.3475	13.0395	.4448		
			WM	1.33 (0.85–2.08)	.2103				
	Phosphate to 5-oxoproline ratio	14	IVW	2.71 (1.16–6.37)	.0218	18.3300	.1454	0.0067	.9643
			MR–Egger	2.52 (0.09–71.57)	.5986	18.3268	.1061		
			WM	2.18 (0.76–6.22)	.1451				
	N-lactoyl tyrosine levels	9	IVW	0.44 (0.21–0.9)	.0251	7.4480	.4892	0.0514	.7739
			MR–Egger	0.26 (0.01–8.33)	.4721	7.3542	.3930		
			WM	0.44 (0.16–1.19)	.1063				
	Sulfate levels	20	IVW	1.71 (1.06–2.76)	.0284	12.0370	.8840	0.0159	.8542
			MR–Egger	1.48 (0.29–7.47)	.6436	12.0022	.8471		
			WM	1.74 (0.87–3.46)	.1149				
	Cis-3,4-methyleneheptanoylcarnitine levels	19	IVW	1.42 (1.04–1.94)	.0289	13.5036	.7608	0.0066	.8707
			MR–Egger	1.38 (0.9–2.13)	.1587	13.4763	.7038		
			WM	1.35 (0.88–2.07)	.1700				
	Catechol sulfate levels	19	IVW	1.4 (1.03–1.89)	.0302	16.8539	.5332	0.0330	.3941
			MR–Egger	1.2 (0.75–1.89)	0.4569	16.0892	.5175		
			WM	1.03 (0.67–1.59)	.8934				
	1-Linolenoyl-GPC (18:3) levels	20	IVW	0.48 (0.25–0.93)	.0307	31.4044	.0364	0.1670	.1000
			MR–Egger	0.1 (0.01–0.66)	.0286	26.9103	.0807		
			WM	0.47 (0.21–1.05)	.0653				
East Asian	1-(1-enyl-palmitoyl)-2-oleoyl-gpc (*P*-16:0/18:1) levels	18	IVW	0.58 (0.35–0.96)	.0328	11.7308	.8162	0.0470	.5484
			MR–Egger	0.36 (0.07–1.79)	.2295	11.3548	.7871		
			WM	0.51 (0.26–1.01)	.0534				
	5-Hydroxymethyl-2-furoylcarnitine levels	17	IVW	0.57 (0.33–0.96)	.0335	21.9405	.1451	0.0916	.3756
			MR–Egger	0.28 (0.06–1.38)	.1389	20.7850	.1438		
			WM	0.79 (0.4–1.56)	.4941				
	Bilirubin (Z,Z) to glucuronate ratio	15	IVW	0.68 (0.47–0.98)	.0364	14.7532	.3952	−0.0056	.9206
			MR–Egger	0.7 (0.35–1.41)	.3352	14.7415	.3238		
			WM	0.65 (0.4–1.06)	.0850				
	2-o-methylascorbic acid levels	15	IVW	1.88 (1.04–3.41)	.0368	14.1081	.4417	0.1629	.1306
			MR–Egger	0.45 (0.07–2.82)	.4092	11.5035	.5687		
			WM	1.66 (0.71–3.89)	.2440				
	4-Allylcatechol sulfate levels	13	IVW	1.82 (1.04–3.2)	.0373	5.8991	.9211	0.0155	.8508
			MR–Egger	1.62 (0.43–6.1)	.4920	5.8620	.8824		
			WM	1.73 (0.82–3.64)	.1500				
	1-Linoleoyl-GPE (18:2) levels	22	IVW	1.42 (1.02–1.98)	.0381	16.6553	.7318	0.0151	.7289
			MR–Egger	1.29 (0.67–2.46)	.4531	16.5317	.6831		
			WM	1.41 (0.91–2.18)	.1201				
	Glycerophosphoethanolamine levels	15	IVW	1.72 (1.02–2.91)	.0422	13.8896	.4580	0.0715	.3092
			MR–Egger	1 (0.32–3.12)	.9994	12.7695	.4658		
			WM	1.23 (0.58–2.59)	.5874				

(*Continued*)

Table 1

(*Continued*)

Population	Metabolite	SNP (N)	Method	OR (95% CI)	*P*	Heterogeneity *Q*	Heterogeneity *P*	Pleiotropy Intercept	Pleiotropy *P*
East Asian	Retinol to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) [1] ratio	18	IVW	1.56 (1.01–2.4)	.0433	24.8466	.0982	0.0755	.2968
			MR–Egger	0.97 (0.37–2.53)	.9575	23.1626	.1095		
			WM	1.54 (0.93–2.56)	.0957				
	1-Dihomo-linolenylglycerol (20:3) levels	13	IVW	1.87 (1.01–3.45)	.0461	15.5200	.2142	0.0803	.5334
			MR–Egger	0.93 (0.1–8.54)	.9502	14.9579	.1844		
			WM	1.38 (0.62–3.1)	.4309				
	Glutamate to kynurenine ratio	16	IVW	0.52 (0.27–0.99)	.0464	23.0616	.0828	0.0963	.3635
			MR–Egger	0.23 (0.04–1.4)	.1329	21.6941	.0851		
			WM	0.35 (0.16–0.78)	.0105				
	3-Methyl-2-oxovalerate levels	5	IVW	0.35 (0.12–0.99)	.0475	0.9170	.9221	−0.3963	.4997
			MR–Egger	30.38 (0–2914355.81)	.6007	0.3312	.9541		
			WM	0.38 (0.11–1.32)	.1269				
	EDTA levels	11	IVW	0.53 (0.28–0.99)	.0479	6.8895	.7358	−0.1059	.3361
			MR–Egger	1.29 (0.2–8.09)	.7950	5.8569	.7542		
			WM	0.64 (0.26–1.57)	.3317				
	Glucose-to-mannose ratio	21	IVW	0.7 (0.48–1)	.0481	22.8218	.2976	−0.0128	.8232
			MR–Egger	0.76 (0.33–1.73)	.5189	22.7604	.2481		
			WM	0.72 (0.44–1.18)	.1967				
	Retinol to linoleoyl- arachidonoyl-glycerol (18:2 to 20:4) [2] ratio	15	IVW	1.41 (1–1.99)	.0489	5.7364	.9727	0.0453	.4605
			MR–Egger	1.08 (0.5–2.33)	.8437	5.1579	.9715		
			WM	1.37 (0.85–2.2)	.1993				
East Asian	Threonate levels	13	IVW	1.45 (1–2.09)	.0492	12.2787	.4236	0.0077	.9157
			MR–Egger	1.4 (0.7–2.8)	.3581	12.2656	.3440		
			WM	1.52 (0.94–2.47)	.0898				
Middle East	Ethylmalonate levels	61	IVW	1.43 (1.19–1.73)	.0002	54.7498	.6674	−0.0005	.9879
			MR–Egger	1.43 (1.07–1.93)	.0208	54.7496	.6328		
			WM	1.37 (1.02–1.82)	.0350				
	Spermidine to ergothioneine ratio	19	IVW	0.81 (0.72–0.91)	.0006	11.2851	.8819	−0.0019	.9517
			MR–Egger	0.81 (0.71–0.93)	.0085	11.2813	.8416		
			WM	0.81 (0.69–0.95)	.0117				
	Taurine to glutamate ratio	20	IVW	2.4 (1.39–4.13)	.0017	9.3095	.9680	−0.0589	.4338
			MR–Egger	3.64 (1.14–11.63)	.0427	8.6685	.9669		
			WM	2.37 (1.09–5.12)	.0287				
	Myo-inositol levels	26	IVW	2.13 (1.32–3.45)	.0020	25.3176	.4447	−0.0759	.2457
			MR–Egger	4 (1.28–12.52)	.0256	23.9018	.4672		
			WM	1.92 (0.98–3.78)	.0587				
	Taurolithocholate 3-sulfate levels	23	IVW	0.52 (0.33–0.83)	.0056	23.1388	.3939	0.0837	.1886
			MR–Egger	0.3 (0.12–0.75)	.0176	21.2686	.4426		
			WM	0.68 (0.37–1.26)	.2218				
	Alpha-ketobutyrate to 3-methyl-2-oxobutyrate ratio	22	IVW	1.91 (1.19–3.06)	.0071	18.2615	.6324	−0.0206	.7526
			MR–Egger	2.19 (0.83–5.81)	.1295	18.1594	.5769		
			WM	2.33 (1.11–4.88)	.0247				

(*Continued*)

Table 1

(*Continued*)

Population	Metabolite	SNP (N)	Method	OR (95% CI)	*P*	Heterogeneity		Pleiotropy	
						Q	*P*	Intercept	*P*
Middle East	Glutamate to glutamine ratio	22	IVW	0.53 (0.33–0.86)	.0102	15.3621	.8044	−0.0492	.5132
			MR–Egger	0.78 (0.23–2.68)	.6962	14.9190	.7810		
			WM	0.53 (0.26–1.06)	.0722				
	11 Beta-hydroxyetiocholanolone glucuronide levels	25	IVW	1.85 (1.15–2.96)	.0106	31.5004	.1399	0.0022	.9741
			MR–Egger	1.82 (0.7–4.73)	.2285	31.4989	.1110		
			WM	1.76 (0.95–3.26)	.0739				
	3-Formylindole levels	34	IVW	1.4 (1.08–1.82)	.0107	17.3762	.9883	−0.0610	.1454
			MR–Egger	1.78 (1.19–2.68)	.0090	15.1488	.9950		
			WM	1.35 (0.94–1.94)	.1053				
	13-HODE + 9-HODE levels	15	IVW	0.51 (0.29–0.88)	.0167	12.9101	.5336	−0.0028	.9674
			MR–Egger	0.52 (0.18–1.49)	.2439	12.9083	.4549		
			WM	0.52 (0.23–1.17)	.1138				
	Tyramine O-sulfate levels	17	IVW	2.06 (1.14–3.73)	.0170	14.4652	.5641	0.0449	.6628
			MR–Egger	1.46 (0.29–7.44)	.6547	14.2673	.5054		
			WM	1.67 (0.71–3.89)	.2369				
	3-Hydroxyisobutyrate to adenosine 5′-diphosphate ratio	21	IVW	0.71 (0.53–0.94)	.0177	15.4088	.7526	−0.0633	.2001
			MR–Egger	0.9 (0.57–1.42)	.6586	13.6465	.8039		
			WM	0.8 (0.53–1.23)	.3109				
	4-Hydroxy-2-oxoglutaric acid levels	25	IVW	2.05 (1.11–3.79)	.0216	39.7832	.0226	0.0246	.7734
			MR–Egger	1.71 (0.43–6.84)	.4581	39.6369	.0169		
			WM	1.41 (0.68–2.90)	.3556				
Middle East	N-Stearoyl-sphingosine (d18:1/18:0) levels	23	IVW	0.6 (0.39–0.93)	.0228	20.8341	.5310	0.0812	.3005
			MR–Egger	0.32 (0.1–1.1)	.0855	19.7073	.5399		
			WM	0.52 (0.28–0.96)	.0363				
	2-Hydroxy-4-(methylthio)butanoic acid levels	26	IVW	0.63 (0.42–0.94)	.0239	21.1211	.6858	0.0009	.9857
			MR–Egger	0.63 (0.28–1.38)	.2560	21.1207	.6316		
			WM	0.8 (0.46–1.4)	.4372				
	Cortisone to cortisol ratio	18	IVW	2.12 (1.1–4.12)	.0256	19.8887	.2800	0.1209	.1697
			MR–Egger	0.73 (0.15–3.59)	.6995	17.6125	.3471		
			WM	2.69 (1.1–6.63)	.0309				
	N1-methylinosine levels	25	IVW	1.76 (1.07–2.91)	.0268	16.8257	.8560	−0.0316	.6595
			MR–Egger	2.36 (0.59–9.41)	.2347	16.6265	.8272		
			WM	1.37 (0.68–2.76)	.3731				
	Salicylate to caprylate (8:0) ratio	17	IVW	1.85 (1.07–3.2)	.0274	14.4466	.5655	0.0041	.9543
			MR–Egger	1.79 (0.49–6.5)	.3921	14.4432	.4922		
			WM	2.17 (1.01–4.7)	.0485				
	2,3-Dihydroxy-5-methylthio-4-pentenoate levels	26	IVW	0.54 (0.31–0.94)	.0283	13.3700	.9716	0.0003	.9970
			MR–Egger	0.54 (0.1–2.97)	.4822	13.3700	.9596		
			WM	0.54 (0.26–1.15)	.1126				
	N-acetyl-2-aminooctanoate levels	36	IVW	0.72 (0.54–0.97)	.0299	36.0884	.4175	−0.0293	.5071
			MR–Egger	0.83 (0.51–1.34)	.4479	35.6174	.3921		
			WM	0.77 (0.52–1.13)	.1852				

(*Continued*)

Table 1

(*Continued*)

Population	Metabolite	SNP (N)	Method	OR (95% CI)	*P*	Heterogeneity *Q*	Heterogeneity *P*	Pleiotropy Intercept	Pleiotropy *P*
Middle East	Taurine levels	14	IVW	0.52 (0.29–0.94)	.0301	7.6962	.8628	0.0072	.9254
			MR–Egger	0.5 (0.16–1.58)	.2591	7.6871	.8091		
			WM	0.62 (0.27–1.43)	.2616				
	Lactosyl-N-palmitoyl-sphingosine (d18:1/16:0) levels	22	IVW	0.59 (0.36–0.95)	.0312	10.7939	.9667	−0.0028	.9729
			MR–Egger	0.6 (0.14–2.6)	.5049	10.7927	.9514		
			WM	0.7 (0.35–1.4)	.3077				
	Bilirubin (Z,Z) to androsterone glucuronide ratio	41	IVW	1.31 (1.02–1.67)	.0313	27.2977	.9370	0.0149	.6637
			MR–Egger	1.23 (0.85–1.78)	.2766	27.1058	.9247		
			WM	1.27 (0.9–1.79)	.1795				
	1-Palmitoyl-GPE (16:0) levels	20	IVW	0.62 (0.4–0.96)	.0320	13.6132	.8058	−0.0001	.9994
			MR–Egger	0.62 (0.19–2.06)	.4439	13.6132	.7539		
			WM	0.56 (0.3–1.02)	.0560				
	N-stearoyl-sphinganine (d18:0/18:0) levels	11	IVW	0.5 (0.27–0.94)	.0320	8.7142	.5594	0.0142	.8818
			MR–Egger	0.45 (0.1–2.11)	.3373	8.6908	.4663		
			WM	0.57 (0.24–1.34)	.1988				
	Glutamine degradant levels	28	IVW	0.6 (0.38–0.96)	.0324	17.6893	.9127	0.0325	.5587
			MR–Egger	0.45 (0.16–1.29)	.1488	17.3384	.8985		
			WM	0.49 (0.26–0.93)	.0289				
	Tridecenedioate (C13:1-DC) levels	22	IVW	0.59 (0.36–0.96)	.0331	11.3832	.9548	0.0512	.4250
			MR–Egger	0.39 (0.13–1.17)	.1083	10.7199	.9532		
			WM	0.46 (0.23–0.92)	.0288				
Middle East	N-acetylproline levels	17	IVW	2.03 (1.06–3.91)	.0333	20.8007	.1863	−0.0571	.6159
			MR–Egger	3.34 (0.45–25.03)	.2586	20.4431	.1556		
			WM	3.58 (1.53–8.36)	.0032				
	N-acetyl-aspartyl-glutamate levels	84	IVW	1.15 (1.01–1.3)	.0342	94.4424	.1837	−0.0309	.4237
			MR–Egger	1.24 (0.99–1.55)	.0680	93.7036	.1774		
			WM	1.22 (1.02–1.45)	.0275				
	Xanthurenate levels	23	IVW	1.67 (1.04–2.69)	.0345	18.4574	.6786	−0.0504	.5280
			MR–Egger	2.44 (0.7–8.55)	.1768	18.0456	.6461		
			WM	1.75 (0.87–3.5)	.1150				
	Perfluorooctanoate levels	21	IVW	0.54 (0.3–0.96)	.0372	23.1113	.2834	0.0217	.8084
			MR–Egger	0.45 (0.1–2.1)	.3223	23.0380	.2357		
			WM	0.75 (0.33–1.7)	.4898				
	Palmitoylcarnitine levels (Metabolon platform)	26	IVW	0.62 (0.39–0.97)	.0377	17.5792	.8597	0.0165	.8023
			MR–Egger	0.55 (0.19–1.6)	.2810	17.5151	.8259		
			WM	0.55 (0.3–1.04)	.0661				
	Lignoceroylcarnitine (C24) levels	25	IVW	0.66 (0.44–0.98)	.0382	26.9693	.3059	−0.0380	.5608
			MR–Egger	0.82 (0.35–1.91)	.6544	26.5671	.2748		
			WM	0.96 (0.55–1.67)	.8812				
	Androstenediol (3 beta, 17 beta) monosulfate (2) levels	28	IVW	1.58 (1.02–2.45)	.0385	15.6267	.9597	0.0506	.3824
			MR–Egger	1.07 (0.4–2.82)	.8940	14.8372	.9602		
			WM	1.52 (0.81–2.85)	.1901				

(*Continued*)

Table 1

(*Continued*)

Population	Metabolite	SNP (N)	Method	OR (95% CI)	*P*	Heterogeneity		Pleiotropy	
						Q	*P*	Intercept	*P*
Middle East	2-Methylserine levels	18	IVW	1.81 (1.03–3.18)	.0392	17.0208	.4530	−0.0879	.3211
			MR–Egger	3.44 (0.89–13.3)	.0925	15.9725	.4549		
			WM	1.37 (0.6–3.13)	.4564				
	N-acetylserine levels	26	IVW	0.63 (0.4–0.98)	.0394	17.2396	.8729	0.0342	.5950
			MR–Egger	0.5 (0.2–1.28)	.1597	16.9493	.8508		
			WM	0.74 (0.4–1.36)	.3266				
	Glycosyl-N-tricosanoyl-sphingadienine (d18:2/23:0) levels	25	IVW	0.67 (0.46–0.98)	.0399	21.2894	.6216	0.0011	.9845
			MR–Egger	0.67 (0.29–1.56)	.3591	21.2890	.5634		
			WM	0.59 (0.34–1.03)	.0618				
	Beta-hydroxyisovalerate levels	25	IVW	1.55 (1.02–2.36)	.0417	21.8935	.5856	−0.0944	.1129
			MR–Egger	2.85 (1.23–6.62)	.0225	19.1771	.6909		
			WM	1.94 (1.08–3.5)	.0277				
	Gamma-glutamylmethionine levels	24	IVW	0.56 (0.32–0.98)	.0421	25.8038	.3102	0.0866	.2922
			MR–Egger	0.24 (0.05–1.23)	.1017	24.5066	.3212		
			WM	0.51 (0.24–1.05)	.0680				
	Dihydrocaffeate sulfate (2) levels	27	IVW	0.64 (0.42–0.99)	.0437	29.3497	.2954	0.0541	.4646
			MR–Egger	0.45 (0.16–1.27)	.1445	28.7161	.2760		
			WM	0.64 (0.35–1.18)	.1553				
	Arginine to glutamate ratio	25	IVW	1.67 (1.01–2.74)	.0438	23.4446	.4937	−0.0188	.7811
			MR–Egger	1.94 (0.6–6.26)	.2780	23.3643	.4397		
			WM	1.42 (0.68–2.95)	.3469				
Middle East	Blood sugar levels	22	IVW	1.69 (1.01–2.82)	.0445	19.2234	.5708	−0.0593	.3712
			MR–Egger	2.75 (0.86–8.79)	.1036	18.3864	.5620		
			WM	1.47 (0.72–3.04)	.2923				
	4-Hydroxyphenylacetoylcarnitine levels	28	IVW	0.68 (0.47–0.99)	.0445	26.0823	.5140	0.0177	.7567
			MR–Egger	0.61 (0.27–1.36)	.2363	25.9843	.4640		
			WM	0.76 (0.44–1.32)	.3269				
	3-Methylxanthine levels	21	IVW	1.58 (1.01–2.47)	.0449	9.8214	.9713	0.0103	.8506
			MR–Egger	1.48 (0.67–3.28)	.3449	9.7849	.9581		
			WM	1.43 (0.72–2.81)	.3048				
	Sphingomyelin (d18:1/24:1, d18:2/24:0) levels	17	IVW	1.86 (1.01–3.41)	.0451	15.5945	.4816	−0.1831	.0597
			MR–Egger	7.33 (1.71–31.32)	.0169	11.4447	.7205		
			WM	2.79 (1.18–6.6)	.0191				
	N-Acetylkynurenine (2) levels	25	IVW	0.75 (0.57–0.99)	.0457	20.9821	.6398	0.0184	.7390
			MR–Egger	0.7 (0.43–1.15)	.1705	20.8683	.5891		
			WM	0.81 (0.56–1.17)	.2603				
	Pentadecanoate (15:0) levels	20	IVW	1.71 (1.01–2.89)	.0457	14.5167	.7528	0.0332	.6385
			MR–Egger	1.36 (0.46–3.99)	.5853	14.2883	.7101		
			WM	1.41 (0.64–3.1)	.3919				
	Ceramide (d18:1/16:0) levels	26	IVW	0.62 (0.39–0.99)	.0457	20.4800	.7212	−0.0039	.9506
			MR–Egger	0.64 (0.22–1.85)	.4168	20.4761	.6694		
			WM	0.66 (0.34–1.28)	.2172				

(*Continued*)

Table 1

(*Continued*)

Population	Metabolite	SNP (N)	Method	OR (95% CI)	*P*	Heterogeneity		Pleiotropy	
						Q	*P*	Intercept	*P*
Middle East	N-acetyl-2-aminoadipate levels	25	IVW	0.7 (0.49–0.99)	.0459	23.3699	.4981	0.0257	.5866
			MR–Egger	0.61 (0.33–1.12)	.1251	23.0649	.4570		
			WM	0.71 (0.43–1.17)	.1765				
	Choline levels	19	IVW	0.54 (0.29–0.99)	.0473	22.3185	.2182	−0.0523	.5829
			MR–Egger	0.85 (0.15–4.68)	.8548	21.9146	.1880		
			WM	0.66 (0.29–1.47)	.3058				
	N-Acetylhistidine levels	27	IVW	0.79 (0.63–1.00)	.0475	23.9955	.5762	−0.0193	.6468
			MR–Egger	0.84 (0.6–1.18)	.3292	23.7803	.5321		
			WM	0.75 (0.54–1.03)	.0710				
	Glutamate to cysteine ratio	28	IVW	0.61 (0.37–0.99)	.0476	25.3018	.5576	0.0914	.3089
			MR–Egger	0.28 (0.06–1.30)	.1166	24.2247	.5631		
			WM	0.47 (0.23–0.97)	.0425				
	Isoleucine levels	20	IVW	0.56 (0.32–0.99)	.0479	17.9483	.5259	−0.0536	.6199
			MR–Egger	0.84 (0.16–4.3)	.8322	17.6936	.4760		
			WM	0.6 (0.27–1.34)	.2116				
	3-Hydroxy-3-methylglutarate levels	19	IVW	0.5 (0.25–1.00)	.0489	21.2300	.2680	0.1611	.1692
			MR–Egger	0.16 (0.03–0.88)	.0504	18.9334	.3324		
			WM	0.5 (0.21–1.21)	.1233				
	3b-Hydroxy-5-cholenoic acid levels	29	IVW	0.65 (0.42–1.00)	.0494	33.2029	.2284	−0.0278	.6598
			MR–Egger	0.78 (0.31–1.99)	.6086	32.9611	.1984		
			WM	0.66 (0.38–1.16)	.1486				
Middle East	Trigonelline levels	23	IVW	1.62 (1–2.64)	.0494	22.9836	.4027	0.0702	.2385
			MR–Egger	1.08 (0.48–2.44)	.8519	21.4779	.4301		
			WM	1.56 (0.79–3.08)	.1982				
Africa	C-glycosyltryptophan levels	19	IVW	1.77 (1.3–2.42)	.0003	22.0007	.2320	0.0448	.4546
			MR–Egger	1.1 (0.31–3.88)	.8838	21.2679	.2145		
			WM	1.53 (1–2.34)	.0522				
	Caffeic acid sulfate levels	16	IVW	1.43 (1.13–1.81)	.0029	7.4223	.9449	−0.0010	.9813
			MR–Egger	1.44 (0.86–2.4)	.1840	7.4217	.9172		
			WM	1.41 (1.01–1.97)	.0418				
	Cortolone glucuronide (1) levels	19	IVW	0.8 (0.69–0.93)	.0030	17.1555	.5124	−0.0219	.3279
			MR–Egger	0.9 (0.68–1.18)	.4504	16.1408	.5139		
			WM	0.82 (0.66–1.01)	.0590				
	Fructose levels	12	IVW	0.79 (0.66–0.95)	.0113	9.8232	.5464	0.0609	.0649
			MR–Egger	0.6 (0.43–0.82)	.0105	5.5254	.8534		
			WM	0.77 (0.58–1.02)	.0712				
	Taurolithocholate 3-sulfate levels	16	IVW	0.77 (0.63–0.94)	.0114	11.7921	.6947	0.0289	.3336
			MR–Egger	0.64 (0.43–0.96)	.0510	10.7890	.7025		
			WM	0.85 (0.63–1.15)	.2922				
	1-(1-Enyl-stearoyl)-2-oleoyl-GPE (*P*-18:0/18:1) levels	11	IVW	0.7 (0.53–0.92)	.0116	8.4359	.5863	0.0813	.0571
			MR–Egger	0.38 (0.2–0.7)	.0130	3.6787	.9313		
			WM	0.58 (0.4–0.86)	.0058				

(*Continued*)

Table 1

(*Continued*)

Population	Metabolite	SNP (N)	Method	OR (95% CI)	*P*	Heterogeneity		Pleiotropy	
						Q	*P*	Intercept	*P*
Africa	Vanillylmandelate levels	20	IVW	1.33 (1.06–1.65)	.0117	13.9439	.7870	0.0368	.2296
			MR–Egger	0.98 (0.58–1.65)	.9463	12.3974	.8261		
			WM	1.23 (0.91–1.66)	.1805				
	4-Oxo-retinoic acid levels	11	IVW	1.45 (1.09–1.93)	.0118	6.7209	.7515	−0.0253	.5887
			MR–Egger	1.77 (0.82–3.83)	.1781	6.4065	.6986		
			WM	1.34 (0.88–2.05)	.1754				
	Theophylline to theobromine ratio	12	IVW	0.73 (0.56–0.93)	.0122	5.7802	.8876	−0.0242	.4159
			MR–Egger	0.85 (0.54–1.33)	.5004	5.0600	.8871		
			WM	0.75 (0.53–1.06)	.0989				
	4-Cholesten-3-one levels	19	IVW	1.18 (1.03–1.34)	.0135	11.9367	.8505	0.0050	.7833
			MR–Egger	1.15 (0.96–1.39)	.1532	11.8586	.8086		
			WM	1.18 (0.99–1.4)	.0697				
	Perfluorooctanesulfonate levels	15	IVW	1.29 (1.05–1.58)	.0140	14.0928	.4428	0.0531	.1679
			MR–Egger	0.93 (0.58–1.51)	.7812	11.9598	.5309		
			WM	1.31 (0.98–1.74)	.0698				
	Branched-chain, straight-chain, cyclopropyl 12:1 fatty acid levels	13	IVW	0.75 (0.6–0.95)	.0153	11.5410	.4832	0.0321	.3730
			MR–Egger	0.6 (0.36–1.01)	.0829	10.6785	.4706		
			WM	0.74 (0.54–1.02)	.0636				
	N-acetyl-aspartyl-glutamate levels	35	IVW	1.09 (1.02–1.18)	.0172	27.7778	.7655	0.0234	.3177
			MR–Egger	1.02 (0.88–1.19)	.7580	26.7483	.7706		
			WM	1.07 (0.96–1.19)	.2124				
Africa	Alpha-tocopherol to sulfate ratio	14	IVW	0.74 (0.58–0.95)	.0173	11.9544	.5314	0.0232	.4976
			MR–Egger	0.64 (0.39–1.03)	.0929	11.4651	.4895		
			WM	0.84 (0.58–1.22)	.3663				
	Phosphate to fructose ratio	9	IVW	1.36 (1.05–1.76)	.0185	12.3296	.1371	−0.0579	.1410
			MR–Egger	1.8 (1.2–2.68)	.0243	8.8489	.2637		
			WM	1.43 (1.04–1.96)	.0293				
	Dimethylarginine (symmetric dimethylarginine + asymmetric dimethylarginine) levels	18	IVW	0.78 (0.64–0.96)	.0212	11.3797	.8362	0.0025	.9211
			MR–Egger	0.77 (0.53–1.13)	.1994	11.3696	.7861		
			WM	0.75 (0.54–1.03)	.0721				
	10-Heptadecenoate (17:1n7) levels	15	IVW	1.32 (1.04–1.68)	.0215	13.2555	.5065	−0.0229	.5864
			MR–Egger	1.57 (0.82–3.04)	.1994	12.9442	.4521		
			WM	1.18 (0.82–1.71)	.3724				
	Nisinate (24:6n3) levels	12	IVW	1.31 (1.04–1.66)	.0244	16.1313	.1363	−0.0531	.3254
			MR–Egger	1.75 (0.96–3.19)	.0959	14.5725	.1484		
			WM	1.47 (1.11–1.94)	.0067				
	3-Methoxycatechol sulfate (2) levels	13	IVW	1.36 (1.04–1.78)	.0248	11.1206	.5186	−0.0433	.3101
			MR–Egger	1.96 (0.95–4.06)	.0967	9.9882	.5315		
			WM	1.56 (1.07–2.28)	.0221				
	Serotonin levels	14	IVW	0.69 (0.49–0.96)	.0280	9.8659	.7049	−0.0572	.4123
			MR–Egger	1.23 (0.31–4.97)	.7721	9.1445	.6905		
			WM	0.7 (0.44–1.13)	.1491				

(*Continued*)

Table 1

(*Continued*)

Population	Metabolite	SNP (N)	Method	OR (95% CI)	*P*	Heterogeneity		Pleiotropy	
						Q	*P*	Intercept	*P*
Africa	Cortisone to 4-cholesten-3-one ratio	21	IVW	1.24 (1.02–1.51)	.0282	19.5209	.4882	0.0149	.6220
			MR–Egger	1.09 (0.63–1.88)	.7524	19.2662	.4399		
			WM	1.17 (0.88–1.56)	.2819				
	1-Myristoyl-2-arachidonoyl-GPC (14:0/20:4) levels	20	IVW	0.83 (0.7–0.98)	.0283	8.1798	.9848	0.0084	.7433
			MR–Egger	0.79 (0.59–1.07)	.1450	8.0692	.9776		
			WM	0.83 (0.66–1.04)	.1102				
	Methionine sulfoxide levels	17	IVW	0.88 (0.78–0.99)	.0299	17.5541	.3506	0.0365	.0457
			MR–Egger	0.8 (0.7–0.92)	.0073	12.8072	.6172		
			WM	0.84 (0.72–0.98)	.0296				
	4-Hydroxyphenylpyruvate levels	9	IVW	0.64 (0.43–0.96)	.0311	7.3750	.4968	−0.0625	.3490
			MR–Egger	1.18 (0.34–4.16)	.8004	6.3676	.4975		
			WM	0.61 (0.34–1.09)	.0963				
	Adenosine 5′-monophosphate to N-palmitoyl- sphingosine (d18:1 to 16:0) ratio	16	IVW	1.3 (1.02–1.66)	.0325	12.3291	.6540	−0.0364	.2336
			MR–Egger	1.75 (1.04–2.96)	.0554	10.7790	.7033		
			WM	1.54 (1.1–2.16)	.0125				
	N,N-dimethylalanine levels	15	IVW	0.8 (0.65–0.98)	.0335	11.0904	.6789	0.0165	.6186
			MR–Egger	0.73 (0.48–1.11)	.1647	10.8303	.6250		
			WM	0.81 (0.62–1.06)	.1244				
	Isoleucine levels	14	IVW	0.72 (0.53–0.98)	.0352	15.2994	.2890	0.0143	.8117
			MR–Egger	0.65 (0.27–1.59)	.3660	15.2241	.2294		
			WM	0.81 (0.54–1.21)	.3007				
Africa	Undecenoylcarnitine (C11:1) levels	28	IVW	0.85 (0.74–0.99)	.0371	32.2583	.2227	−0.0131	.5205
			MR–Egger	0.92 (0.71–1.18)	.5054	31.7404	.2018		
			WM	0.88 (0.72–1.06)	.1794				
	N-acetyl-2-aminoadipate levels	18	IVW	1.24 (1.01–1.52)	.0385	25.6616	.0809	0.0141	.6244
			MR–Egger	1.16 (0.82–1.63)	.4142	25.2680	.0652		
			WM	1.22 (1.00–1.49)	.0532				
	Arachidonate (20:4n6) to paraxanthine ratio	11	IVW	0.81 (0.66–0.99)	.0391	9.4481	.4902	−0.0205	.5073
			MR–Egger	0.89 (0.62–1.28)	.5544	8.9714	.4399		
			WM	0.84 (0.63–1.11)	.2200				
	3-Methyladipate levels	13	IVW	1.22 (1.01–1.48)	.0402	4.6236	.9694	−0.0016	.9553
			MR–Egger	1.24 (0.82–1.86)	.3293	4.6204	.9482		
			WM	1.23 (0.95–1.6)	.1167				
	3-Hydroxyhexanoate levels	12	IVW	1.31 (1.01–1.69)	.0404	11.0169	.4418	0.0387	.3389
			MR–Egger	1.00 (0.55–1.8)	.9938	10.0076	.4398		
			WM	1.26 (0.9–1.78)	.1771				
	Sphingomyelin (d18:2/16:0, d18:1/16:1) levels	12	IVW	1.49 (1.02–2.19)	.0405	9.6401	.5630	0.1771	.1431
			MR–Egger	0.15 (0.01–2.62)	.2230	7.1148	.7146		
			WM	1.50 (0.87–2.59)	.1489				
	Cytidine levels	17	IVW	0.83 (0.69–0.99)	.0411	14.5639	.5568	−0.0028	.9289
			MR–Egger	0.84 (0.58–1.23)	.3826	14.5557	.4839		
			WM	0.82 (0.63–1.07)	.1455				

(*Continued*)

Table 1
(Continued)

Population	Metabolite	SNP (N)	Method	OR (95% CI)	*P*	Heterogeneity		Pleiotropy	
						Q	*P*	Intercept	*P*
Africa	N-acetylvaline levels	11	IVW	0.82 (0.67–0.99)	.0422	7.7614	.6521	–0.0167	.5086
			MR–Egger	0.89 (0.66–1.2)	.4501	7.2877	.6072		
			WM	0.85 (0.67–1.07)	.1619				
	(2 or 3)-decenoate (10:1n7 or n8) levels	16	IVW	1.35 (1.01–1.81)	.0424	16.2002	.3689	0.0041	.9351
			MR–Egger	1.3 (0.5–3.42)	.6008	16.1923	.3018		
			WM	1.29 (0.87–1.93)	.2032				
	1,7-Dimethyluric acid levels	19	IVW	1.33 (1.01–1.74)	.0430	17.2405	.5066	–0.0037	.9463
			MR–Egger	1.37 (0.48–3.93)	.5626	17.2358	.4385		
			WM	1.12 (0.78–1.62)	.5466				
	N-lactoyl isoleucine levels	8	IVW	0.65 (0.43–0.99)	.0455	5.7616	.5678	0.0563	.4147
			MR–Egger	0.39 (0.11–1.34)	.1839	4.9940	.5446		
			WM	0.58 (0.32–1.03)	.0623				
	Sphinganine levels	17	IVW	1.25 (1–1.55)	.0464	15.2364	.5074	–0.0573	.1097
			MR–Egger	1.89 (1.12–3.2)	.0317	12.3449	.6528		
			WM	1.37 (1.02–1.84)	.0344				
	Myo-inositol levels	19	IVW	1.3 (1–1.68)	.0496	12.9993	.7916	0.0095	.7776
			MR–Egger	1.19 (0.62–2.27)	.6041	12.9169	.7417		
			WM	1.24 (0.87–1.78)	.2399				

CI = confidence interval, IVW = inverse-variance weighted, MR–Egger = Mendelian randomization–Egger, OR = odds ratio, SNP = single-nucleotide polymorphism, WM = weighted median.

4. Discussion

Our study found 36, 57, and 40 known metabolites were strongly related to PH in East Asian, Middle Eastern, and African populations, respectively. Histidine, L-aspartic acid, oxoglutaric acid, pyruvic acid, D-glucose, and phosphate were found to be involved in the metabolic enrichment pathway of ammonia recycling, glucose–alanine cycle, urea cycle, alanine metabolism, malate–aspartate shuttle, and glutamate metabolism in East Asian population. 2-Ketobutyric acid, choline, and spermidine were involved in the metabolic enrichment pathway of methionine metabolism among the Middle East population. Myo-inositol, D-fructose, and phosphate were found to be involved in the metabolic enrichment pathway of galactose metabolism and phosphatidylinositol phosphate metabolism for African people. Of the metabolites that were found to be strongly correlated among the 3 races in both cross-sectional and meta-analyses, 7 were consistently identified, 5 of which were previously known with name (N-acetyl-aspartyl-glutamate, taurolithocholate 3-sulfate, isoleucine, N-acetyl-2-aminoadipate, and myo-inositol level) L-aspartic acid, oxoglutaric acid, pyruvic acid, and phosphate were crucial metabolites involved in the enrichment pathways in East Asia population. Isoleucine was demonstrated as a protective factor of PH across the 3 populations. N-acetyl-2-aminoadipate was found to be positively associated with PH in the Africa group, and negatively associated with the East Asian and Middle East populations. Myo-inositol was a risk factor for both African and Middle East groups, but a protective factor for the East Asian population.

Several studies have reported that alanine involved in the glucose–alanine cycle was associated with reduced ammonia excretion and directly affected the ammonia cycle.[29–31] Some studies have found dietary alanine was associated with higher systolic blood pressure (SBP) and diastolic blood pressure (DBP).[32,33] Yet, a cohort study has suggested that alanine tended to diminish the risk of hypertension.[34] Urea cycle disorder can result in hypertension, there is a clear pathophysiological relationship between them.[35] Certain scholars have discovered that the urea cycle may contribute to the availability of precursors for nitric oxide synthesis, ultimately leading to neonatal pulmonary hypertension.[36,37] Hypertension shared common metabolic patterns with dyslipidemia, including alanine metabolism and glutamate metabolism, suggesting potential intervention targets could be provided to patients with both hypertension and dyslipidemia.[38] It was discovered in the Dahl salt-sensitive rat, a model of salt-sensitive hypertension, that aspartate or malate can increase levels of L-arginine and nitric oxide, thereby reducing hypertension.[39] Another study found that a high salt diet can induce hypertension of liver-Yang hyperactivity syndrome by mediating the microbiota associated with the glutamate/γ-aminobutyric acid–glutamine metabolic cycle via the gut–brain axis.[40] Methionine metabolism was involved in endothelial dysfunction, atherosclerosis, and renal fibrosis. It can cause early hypertensive nephrosclerosis.[41] A previous study proposed that methionine-enriched diet could induce elevated SBP.[42,43] Galactose ingestion, like glucose, was reported to result in significantly lesser increases in blood pressure compared with fructose ingestion,[44] indicating its involvement in blood pressure regulation through galactose metabolism. Impaired phosphoinositide metabolism has been found linked to calcium-handling abnormalities associated with hypertension.[45]

L-aspartic acid has been reported to possess notable clinical significance because of its effectiveness in the treatment of hypertension.[46] It has been observed that 2-oxoglutaric acid had abnormal rhythms and contents in hypertension.[47] Plasma pyruvic acid was found to be associated with pulmonary arterial hypertension.[48] Pyruvate acid could change continuously in hypertension progression.[49] Inorganic phosphate might serve as a crucial dietary risk factor for hypertension. The potential mechanisms could be dietary phosphorus excess induces

Table 2

The significant enrichment pathways of the metabolites selected by Mendelian randomization.

Population	Pathway	Metabolite	*P*	FDR
East Asia	Ammonia recycling	Histidine, L-aspartic acid, oxoglutaric acid, pyruvic acid, phosphate	.00685	0.00685
	Glucose–alanine cycle	D-glucose, oxoglutaric acid, pyruvic acid	.00142	0.000699
	Urea cycle	L-aspartic acid, oxoglutaric acid, pyruvic acid, phosphate	.00205	0.000699
	Alanine metabolism	Oxoglutaric acid, pyruvic acid, phosphate	.00448	0.00116
	Malate–aspartate shuttle	L-aspartic acid, oxoglutaric acid	.0217	0.00453
	Glutamate metabolism	L-aspartic acid, oxoglutaric acid, pyruvic acid, phosphate	.0275	0.00483
Middle East	Methionine metabolism	2-Ketobutyric acid, choline, spermidine	.0219	1.000
Africa	Galactose metabolism	Myo-inositol, D-fructose, phosphate	.0237	0.951
	Phosphatidylinositol phosphate metabolism	Myo-inositol, phosphate	.0317	0.951

FDR = false discovery rate.

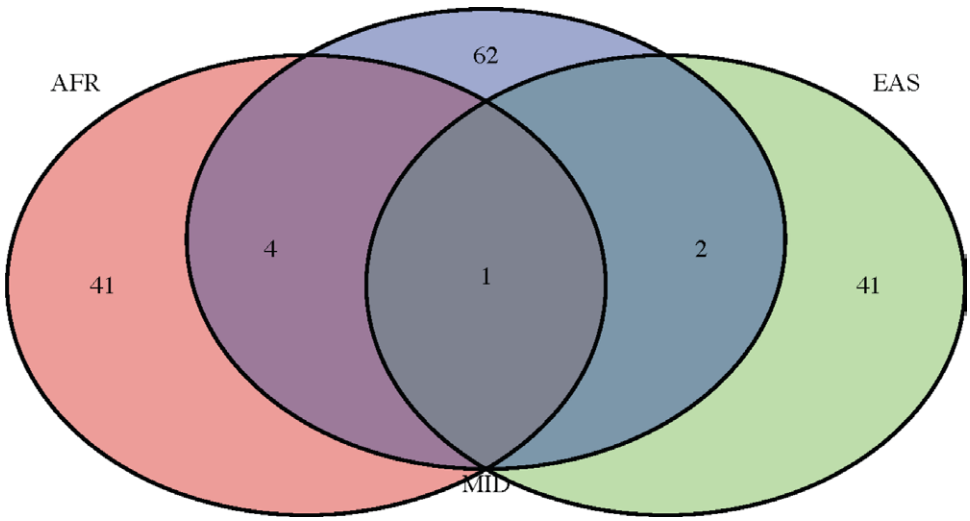

Figure 4. Venn diagram of metabolites' intersection between East Asian, Middle East, and Africa populations.

hypertension including activation of the SNS, impaired endothelial function, increased vascular stiffness, and renal sodium retention.[50] In addition, supplementation of inositol has shown promising results in significantly reducing both SBP and DBP.[51] Moreover, myo-inositol supplementation has demonstrated a notable decrease in the overall incidence of pregnancy-induced hypertension.[52] All these prior findings were aligned with our study, emphasizing these metabolites are really crucial in the enrichment pathways influencing PH.

Numerous studies have stated that isoleucine–proline–proline/valine–proline–proline lactotripeptides can significantly reduce office SBP in both Asian and European populations.[53–55] Another study discovered that the combination of isoleucine–tryptophan with whey protein hydrolysate effectively inhibits plasma angiotensin-1-converting enzyme, leading to antihypertensive effects.[56] These findings highlight the importance of isoleucine as an essential amino acid in managing hypertension. Our study verified the causal correlations between isoleucine and PH among African, Middle East, and East Asian populations based on MR analysis. N-acetyl-2-aminoadipate was found to be a positive predictor on DBP according to another MR analysis focus on the European population.[21] Our study contributes to existing literature by demonstrating that N-acetyl-2-aminoadipate was demonstrated as a risk factor of PH in the African group, but a protective factor in East Asian and Middle East populations. A meta-analysis concluded that inositol supplementation can significantly decrease SBP and DBP, but further large-scale RCTs are still needed to confirm these findings.[51] Interestingly, myo-inositol showed as risk factor in both African and Middle East groups in our study.

There are certain limitations in our study. First, our findings need to be verified by clinical trials or longitudinal studies, particularly large-scale RCTs, to explore their therapeutic potential. Second, we must examine the role of specific metabolites in the development of PH to understand the underlying mechanisms. Our next step will involve using multiomics data to analyze and validate potential mediators. Finally, further research is needed on 2 unidentified metabolites that exhibit overlapping characteristics across different racial groups, as they may have important clinical implications.

5. Conclusion

Our study discovered several metabolites having causal relationships with PH across East Asian, Middle East, and African populations. Isoleucine might be a valuable amino acid in the prevention or treatment for PH.

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Author contributions

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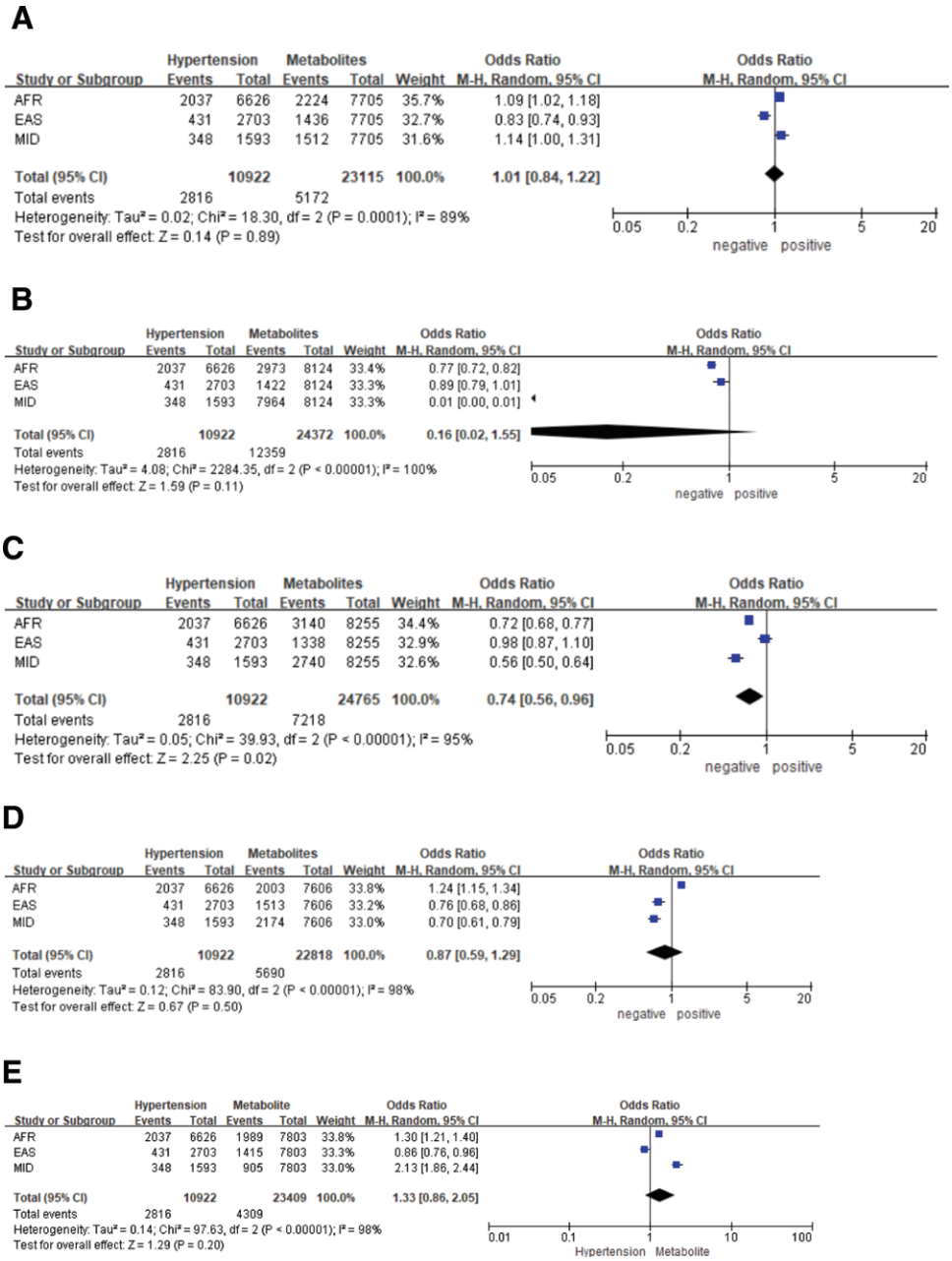

Figure 5. Illustration of the pooled causal effects of 5 known intersecting metabolic factors. (A) The pooled causal effect of N-acetyl-aspartyl-glutamate levels, (B) taurolithocholate 3-sulfate levels, (C) isoleucine levels, (D) N-acetyl-2-aminoadipate levels, and (E) myo-inositol levels. CI = confidence interval, M-H = Mantel-Haenszel, OR = odds ratio.

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