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The potential effect and pathway of valsartan: genome-wide and phenome-wide association study from UK Biobank data

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Purpose **Valsartan, an angiotensin II receptor blocker, is widely used for hypertension and heart failure. While its cardiovascular benefits are established, its broader pharmacological effects remain incompletely characterized. This study aimed to identify genetic variants associated with valsartan use and to systematically explore its potential effects and adverse events across a wide range of phenotypes.**

Methods **Using UK Biobank data, we selected participants of European ancestry prescribed valsartan as cases, compared with controls not prescribed any ARBs. A genome-wide association study (GWAS) was conducted to identify suggestive genetic variants associated with valsartan use. These variants were then used as instruments in a phenome-wide association study (PheWAS) to screen for associated traits. Mendelian randomization analyses, including inverse-variance weighted and pleiotropy-robust methods, were employed to assess potential causal relationships.**

Results **The GWAS identified 19 suggestive single nucleotide polymorphisms ($P < 1 \times 10^{-5}$) near genes, including *PREP*, *GCLC*, and *ZNF133*. The PheWAS analysis revealed associations with 14 phenotypes, including lower levels of total cholesterol ($\beta = -0.59$) and low-density lipoprotein cholesterol (LDL-C) ($\beta = -0.56$), and increased risk of cough (odds ratio = 1.67). Mendelian randomization provided genetic evidence consistent with potential causal effects of valsartan in lowering LDL-C ($\beta = -2.34 \times 10^{-3}$) and reducing the risk of transient cerebral ischemic attack.**

Conclusion **Our genetic-based study suggests valsartan use may be associated with lowered LDL-C and reduced risks of certain ischemic cardiovascular events. These findings generate novel hypotheses regarding the drug's pleiotropic effects and potential applications beyond hypertension management, which warrant further clinical investigation.** ***Pharmacogenetics and Genomics*** **36: 134–142**

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Introduction

Cardiovascular disease (CVD) is a contributor to worldwide mortality [1]. Arteriosclerosis is a key factor in the aging of vascular tissue and a reliable indicator of multiple vascular pathologies and mortality, whereas pulse wave velocity is a recognized measure of arteriosclerosis [2–4]. Recent research has shown that angiotensin II receptor blockers (ARBs), which are antihypertensive medications, can increase vascular stiffness via the pulse wave velocity regardless of blood pressure [5,6]. However, no study has explored the association of valsartan with arteriosclerosis risk decrease, and given the multitude of drug types and high incidence of adverse events, selecting the appropriate drug for patients can be challenging [7].

Valsartan belongs to the class of antihypertensive drugs: ARBs, which lower blood pressure while treating heart failure [8]. According to recent studies, valsartan also ameliorates atherosclerosis, cardiac arrhythmia, chronic kidney disease, and other disorders, improving individual treatment effects [9–12]. No studies on the pharmacogenomics (PGx) associated with the adverse events of valsartan have been reported. In Pfeffer *et al.*'s research [13], 83.1% of participants reported adverse events, including hypotension, hyperkalemia, renal dysfunction, cough, and angioedema. We hope to refine the understanding of valsartan adverse events through bioinformatics approaches.

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Genome-wide association studies (GWASs) are frequently employed in PGx research. It has the ability to anticipate polygenic risk scores and potential targets for adverse drug reactions [14–16]. Phenome-wide association studies (PheWASs) invert the idea of a GWAS by searching for phenotypes associated with specific single nucleotide polymorphisms (SNPs) across the range of thousands of human phenotypes [17].

PheWAS improves the understanding of the pleiotropic effects of drug targets, reveals opportunities for drug repurposing, and helps identify potential new drug targets [18–20]. Johnston *et al.* [18] reported that PheWAS was significantly associated with phenotypes, including cardiac dysrhythmia and metabolic syndrome, indicating potential shared mechanisms. This approach provides causal evidence for relevant phenotypes in PheWASs and contributes to the understanding of potential pathways to drug targets. Furthermore, it allows for the investigation of the causal relationship between the reduction in arteriosclerosis and CVD caused by valsartan and the identification of the underlying mechanisms and pathways. However, there is currently a lack of research on the mechanisms underlying the ability of valsartan to reduce arteriosclerosis [21,22].

Valsartan plays crucial roles in the prevention and treatment of CVDs. Our findings that valsartan lowers low-density lipoprotein (LDL) are necessary to improve the existing knowledge of valsartan. We used GWAS to discover valsartan PGx and performed PheWAS to investigate the potential effects of other phenotypes.

Materials and methods

Study design

First, a GWAS was performed to determine the PGx value of valsartan in the UK Biobank (UKB) data. We subsequently performed PheWAS of the significant SNPs from the GWAS, valsartan, and UKB Electronic Medical Record phenotypic data. Finally, we conducted Mendelian randomization analysis utilizing valsartan as the exposure variable, PheWAS results as the intermediate variable, and CVD as the outcome variable.

Sample description

UKB is a prospective study involving approximately 500 000 participants aged 40–69 years at the time of recruitment. Participants were recruited in the UK between 2006 and 2010 and remain of interest. The mean age of the sequenced individuals at recruitment was 56.5 years, and 54% of the sequenced cohort was female. Participant data included regularly updated health records from the UKB, self-report survey information, links to death and cancer registries, urine and blood biomarker collections, imaging data, accelerometer data, and various other phenotypic endpoints. All study participants provided informed consent.

Genome-wide association study

GWAS quality control was performed via PLINK 1.9 [23]. SNP missing rates higher than 5% and missing rates per person higher than 5% were filtered out. A total of 194 681 SNPs were removed, and no individuals were removed. The thresholds of X chromosome heterozygosity rates (*F* values) were 0.2 for females and 0.8 for males, resulting in the removal of 820 individuals. A total of 202 770 SNPs with minor allele frequencies less than 0.01 were filtered out. Hardy–Weinberg equilibrium was calculated for all the SNPs, and 2621 SNPs were terminated (Hardy–Weinberg equilibrium $< 10^{-6}$). A total of 4594 individuals whose heterozygosity was greater than three times the SD were excluded. Finally, an analysis of relatedness was performed, and 23 063 people with PI_HAT > 0.2 were removed.

Multidimensional scaling principal component analysis was performed on the high-quality data, and the top 20 principal components were selected to be used as covariates in the subsequent association analysis. A generalized linear model (GLM) was constructed to explore associated SNPs. In the GLM, the SNPs were used as the dependent variable; valsartan was used as the independent variable; and age, sex, and principal components were used as the covariates. The valsartan-associated SNPs were obtained using 5×10^{-8} and 5×10^{-5} as the stringent and potential *P* value thresholds, respectively. Linkage disequilibrium score regression was subsequently performed to find the SNPs with the smallest *P* value in each significant region.

Functional annotation of genes

With the help of the database and corresponding annotation tool ANNOVAR [24], the SNP information related to valsartan consumption obtained from GWAS will be annotated with gene function from the hg38 database, and its potential association with valsartan consumption will be analyzed in conjunction with gene function.

Enrichment analysis

Using the clusterProfiler, the org.Hs.eg.db, the enrichplot, and the ggplot2 packages in the R language, the obtained genes were subjected to Gene Ontology analyses. The bubble plots of the enrichment results of the three entries of biological process, cellular component, and molecular function.

Identification of shared phenotypes and phenome-wide association study

PheWAS was performed via DeepPheWAS [25], and the analysis process was divided into three parts: phenotype extraction, phenotype creation, and association analysis.

Phenotype extraction: the required phenotypes were extracted from the UKB phenotypic dataset file ID and

streamlined into patient ID, disease code, onset time, and data source. The major phenotype file IDs can be found in the Supplementary materials.

Phenotype creation: First, extract the disease code, and convert codes to specific diseases, convert patient prescription records and clinical phenotypes to corresponding diseases (e.g. taking blood pressure lowering medications recorded as hypertension), and combine multiple diseases/phenotypes to generate composite phenotypes [e.g. hypertension combined with myocardial infarction (MI) as CVD]. Diseases with a prevalence value less than 25 were removed, and phenotypes were stratified by sex and age.

Association analysis: suggestive SNPs obtained from GWASs were extracted via PLINK. To determine whether one carries these SNPs as *y*, one has the disease phenotype as *x*, corrected for age and sex as covariates, and association analysis was performed via the logistic regression model to obtain the potentially relevant phenotypes for taking valsartan, with a *P* value threshold of <0.01.

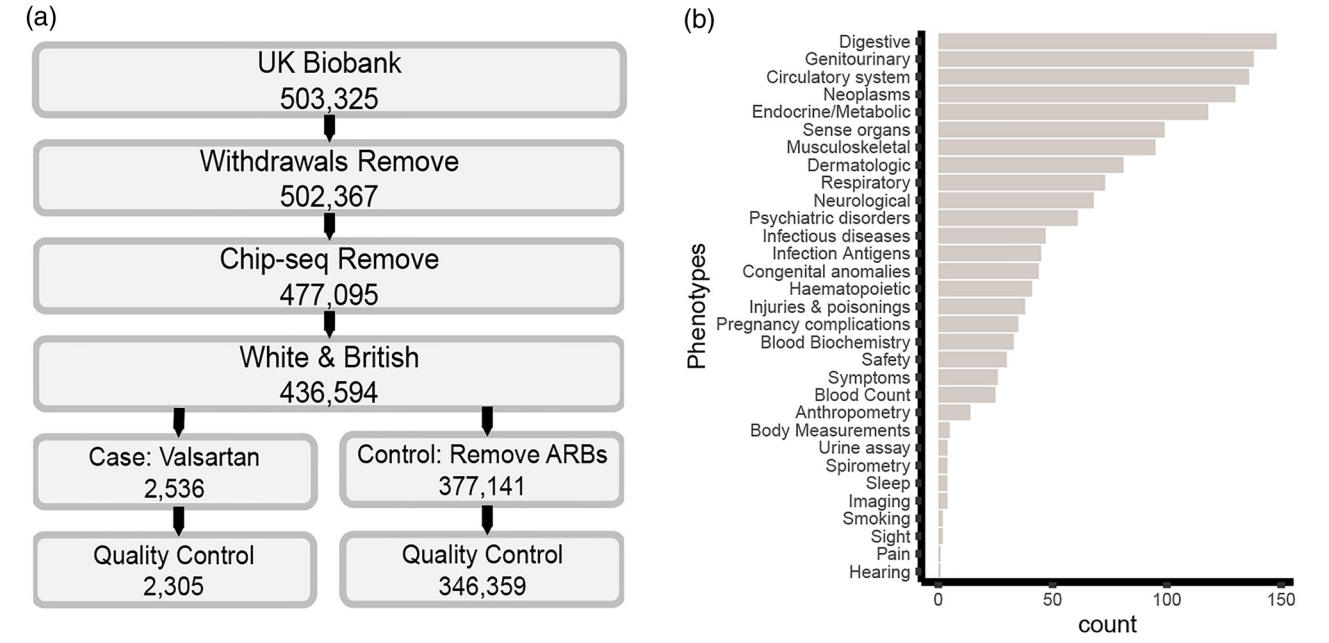
Mendelian randomization

We investigated the causal relationship between valsartan and CVD via phenotype via our PheWAS analysis. We utilized the 'TwoSampleMR' [26] package for the two-step Mendelian randomization analysis, extracted summary data on valsartan from our GWAS results and the IEU GWAS database [27], and extracted summary data on valsartan and CVD. We harmonized the exposure and outcome datasets and performed Mendelian randomization instrumental variable analyses via inverse-variance weighting (IVW). We assessed the R^2 and F value for each instrumental variable to ensure robustness.

Finally, the results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). The Bonferroni correction was applied in the current Mendelian randomization analysis to account for multiple comparisons. Findings for which the *P* value was less than 0.0026 (0.05 divided by 19) indicated a significant causal association. In addition, *P* values between 0.0026 and 0.05 were considered suggestive of a causal association.

A key assumption of Mendelian randomization is that the exposure precedes the outcome. While our genetic instruments are fixed at conception, the measurement of phenotypes like LDL cholesterol (LDL-C) in UKB primarily occurs at baseline assessment. We cannot definitively ascertain that valsartan initiation preceded the LDL-C measurement for all individuals. This introduces a potential for reverse causality, whereby lower LDL-C levels could influence prescribing patterns, although this is less biologically plausible than the drug affecting the trait.

Fig. 1



Study sample exclusion flowchart and phenotype characteristics. (a) Flowchart of study sample exclusion: non-White and British individuals removed and ARBs-using patients removed. (b) All 1612 phenotypes from the UKB EMRs. ARBs, angiotensin II receptor blocker; EMRs, Electronic Medical Records; UKB, UK Biobank.

Results

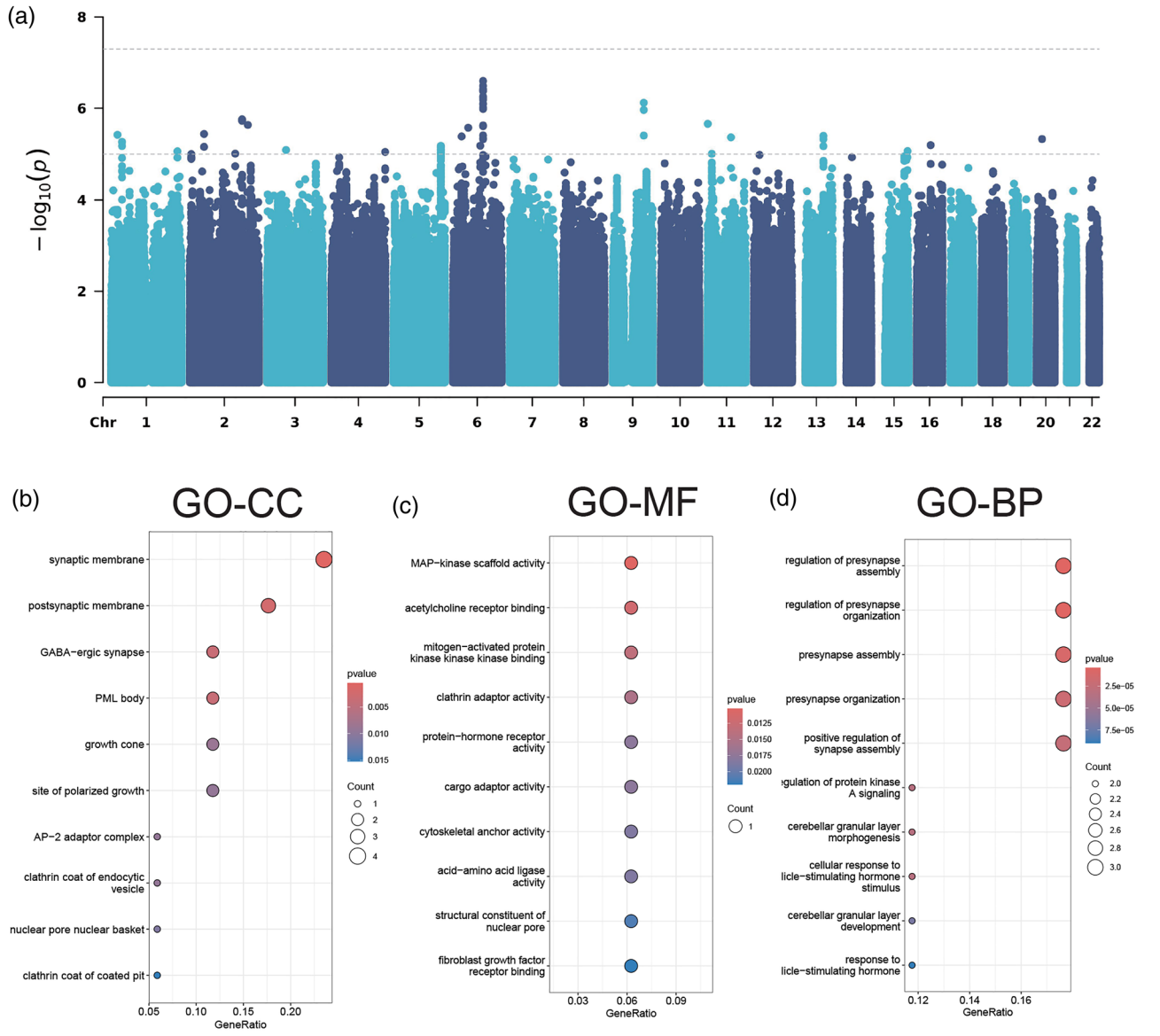
Dataset

This study excluded individuals of non-White race in the UKB sample according to ethnic background ethnicity and those taking ARBs other than valsartan according to the UKB treatment/medication code (Supplementary Table S1, Supplemental digital content 1, *https://links.lww.com/FPC/B537*). The case group consisted of 2305 people taking valsartan and 346 359 controls who did not take ARB drugs (Fig. 1a). The median age was 58 years (interquartile range: 51–63 years), and 43.7% were men. All phenotypes were derived from the UKB data file and UKB Electronic Medical Record, and the remaining 1612 phenotypes were filtered and merged for PheWAS analysis (Fig. 1b).

Genome-wide association study with valsartan

Nineteen suggestive SNPs associated with valsartan administration were obtained through GWAS via the GLM (Fig. 2a). Six introns, 11 intergenic sequences,

Fig. 2



GWAS with valsartan. Manhattan plot of the valsartan GWAS, significance threshold, $P=1 \times 10^{-5}$, and 19 SNPs associated with valsartan. (b)–(d) GO enrichment analysis bar graph, demonstrating the enrichment of valsartan GWAS results. BP, biological process; CC, cellular component; GO, Gene Ontology; GWAS, genome-wide association study; MF, molecular function; SNPs, single nucleotide polymorphisms.

and two noncoding RNA (ncRNA) introns were annotated via ANNOVAR software via the hg38 database (Table 1).

Among them, we found that four SNPs could explain the individual differences in valsartan. rs17065796 ($P = 2.47 \times 10^{-7}$) is in the intron of the *PREP* gene, which transcriptionally and posttranslationally cleaves the peptide bond at the C-terminal end of intrapeptide prolyl residues up to approximately 30 amino acids in length. It is also associated with angiotensin-converting enzyme inhibitor responsiveness; rs17193216 ($P = 2.66 \times 10^{-6}$) is in the intron of the *GCLC* gene, which catalyzes the ATP-dependent ligation of L-glutamate and L-cysteine after transcription and translation and is involved in the first and rate-limiting step of glutathione biosynthesis. It has also been associated with total cholesterol; rs2843443 ($P = 4.69 \times 10^{-6}$) is located in the *ZNF133* gene, which is likely involved in blocking the transcription process, the mechanism of which is currently unknown. It is associated with poor survival and advanced pathological staging of breast carcinomas. rs78502612 is in the intron of the long intergenic ncRNA LINC01505, which contains 13 gene enhancers, such as *SLC44A1*, *FSD1L*, and *FKTN*, in a 1 Mb DNA region in the vicinity of rs78502612. rs2023471 is located in the ncRNA *TRIM31-AS1* (*TRIM31* antisense RNA) intron, which is associated with the erythrocyte count, leukocyte count, and eosinophil-to-leukocyte ratio. However, the GWAS-based Gene Ontology enrichment analysis highlights additional mechanistic layers (Fig. 2b–d). The significant enrichment of SNPs in pathways related to clathrin-mediated endocytosis and cellular polarity suggests that valsartan may also related with dynamic control of angiotensin II type 1 receptor trafficking (via endocytosis-related genes – *CLTC* and *AP2B1* [28]) and vascular remodeling (via polarity-associated pathways).

Phenome-wide association study of valsartan

To explore the pleiotropic effect of valsartan on a variety of complex traits in humans, we performed a PheWAS of 19 GWAS identified significant SNPs associated with valsartan and valsartan usage. The valsartan SNP rs2023471 located in *TRIM31-AS1* intron indicated that white blood cell (leukocyte) count ($P < 6.02 \times 10^{-40}$), lymphocyte count ($P < 1.50 \times 10^{-27}$), neutrophil count ($P < 1.50 \times 10^{-25}$), mean corpuscular hemoglobin ($P < 1.60 \times 10^{-23}$), and 18 other phenotypes were significantly associated with the SNP rs2023471 ($P < 3.10 \times 10^{-5}$; $3.10 \times 10^{-5} = 0.05/1612$) (Fig.3a and b). Among other valsartan SNPs, rs2773159 between *LINC01343* and *LINC01685* was associated with red blood cell (erythrocyte) count ($P < 7.00 \times 10^{-6}$) and hemoglobin concentration ($P < 1.46 \times 10^{-5}$); rs71401392 near *FAM169B* was associated with standing height ($P < 2.08 \times 10^{-8}$) and sitting height ($P < 5.51 \times 10^{-6}$); rs78502612 was associated with sitting height ($P < 6.44 \times 10^{-9}$) and ulcers of the esophagus ($P < 1.12 \times 10^{-5}$); rs11600848 located in *RAB30* was associated with sex hormone binding globulin ($P < 6.29 \times 10^{-8}$); rs2675058 was associated with platelet distribution width ($P < 8.6 \times 10^{-19}$); rs72649484 was associated with alkaline phosphatase ($P < 1.38 \times 10^{-9}$); and rs72723435 was significantly associated with digestive congenital anomalies ($P < 2.93 \times 10^{-5}$) (Supplementary Table S2, Supplemental digital content 1, *https://links.lww.com/FPC/B537*).

With valsartan via PheWAS, we found that the estimated glomerular filtration rate (eGFR) ($P < 6.18 \times 10^{-257}$; $\beta = -0.72$), waist circumference ($P < 1.86 \times 10^{-255}$; $\beta = 0.71$), BMI ($P < 5.31 \times 10^{-234}$; $\beta = 0.69$), urate level ($P < 3.36 \times 10^{-199}$; $\beta = 0.63$), cholesterol level ($P < 2.04 \times 10^{-174}$; $\beta = -0.59$), and 52 other quantitatively measured phenotypes ($P < 3.10 \times 10^{-5}$; $3.10 \times 10^{-5} = 0.05/1612$) were associated with valsartan use

Table 1 Whole-genome sequencing of variants with genome-wide significance

CHR	SNP	ALT	Function	Reference	OR	*P* value
6	rs17065795	T	Intronic	*PREP*	1.406	2.47×10^{-7}
9	rs78502612	C	ncRNA Intronic	*LINC01505*	1.335	7.60×10^{-7}
2	rs2675058	G	Intergenic	*DUSP19*, *NUP35*	1.197	1.74×10^{-6}
11	rs10794344	T	Intronic	*AP2A2*	1.785	2.18×10^{-6}
6	rs17193216	G	Intronic	*GCLC*	1.570	2.66×10^{-6}
2	rs138454785	C	Intergenic	*FSHR*, *NRXN1*	0.4566	3.64×10^{-6}
1	rs72649484	T	Intergenic	*MIR4418*, *ZBTB40*	1.670	3.79×10^{-6}
13	rs7335418	C	Intergenic	*LINC00564*, *SLITRK1*	1.216	4.00×10^{-6}
6	rs2023471	A	ncRNA intronic	*TRIM31-AS1*	0.8262	4.12×10^{-6}
11	rs11600848	C	Intronic	*RAB30*	1.204	4.30×10^{-6}
20	rs2843443	T	Intronic	*ZNF133*	1.351	4.69×10^{-6}
1	rs2773159	A	Intergenic	*LINC01343*, *LINC01685*	1.174	5.30×10^{-6}
16	rs16946901	T	Intergenic	*N4BP1*, *CBLN1*	1.202	6.35×10^{-6}
5	rs58353765	G	Intergenic	*LINC01947*, *TENM2*	0.8549	6.57×10^{-6}
3	rs17188910	C	Intergenic	*LOC105377143*, *KBTBD8*	1.492	8.11×10^{-6}
15	rs71401392	A	Intergenic	*FAM169B*, *IRAIN*	1.534	8.58×10^{-6}
1	rs6666026	G	Intronic	*SLC35F3*	0.8484	8.66×10^{-6}
4	rs72723435	A	Intergenic	*LINC02508*, *LINC01262*	1.181	8.94×10^{-6}
11	rs17418380	G	Intergenic	*INSC*, *LINC02751*	0.8097	9.83×10^{-6}

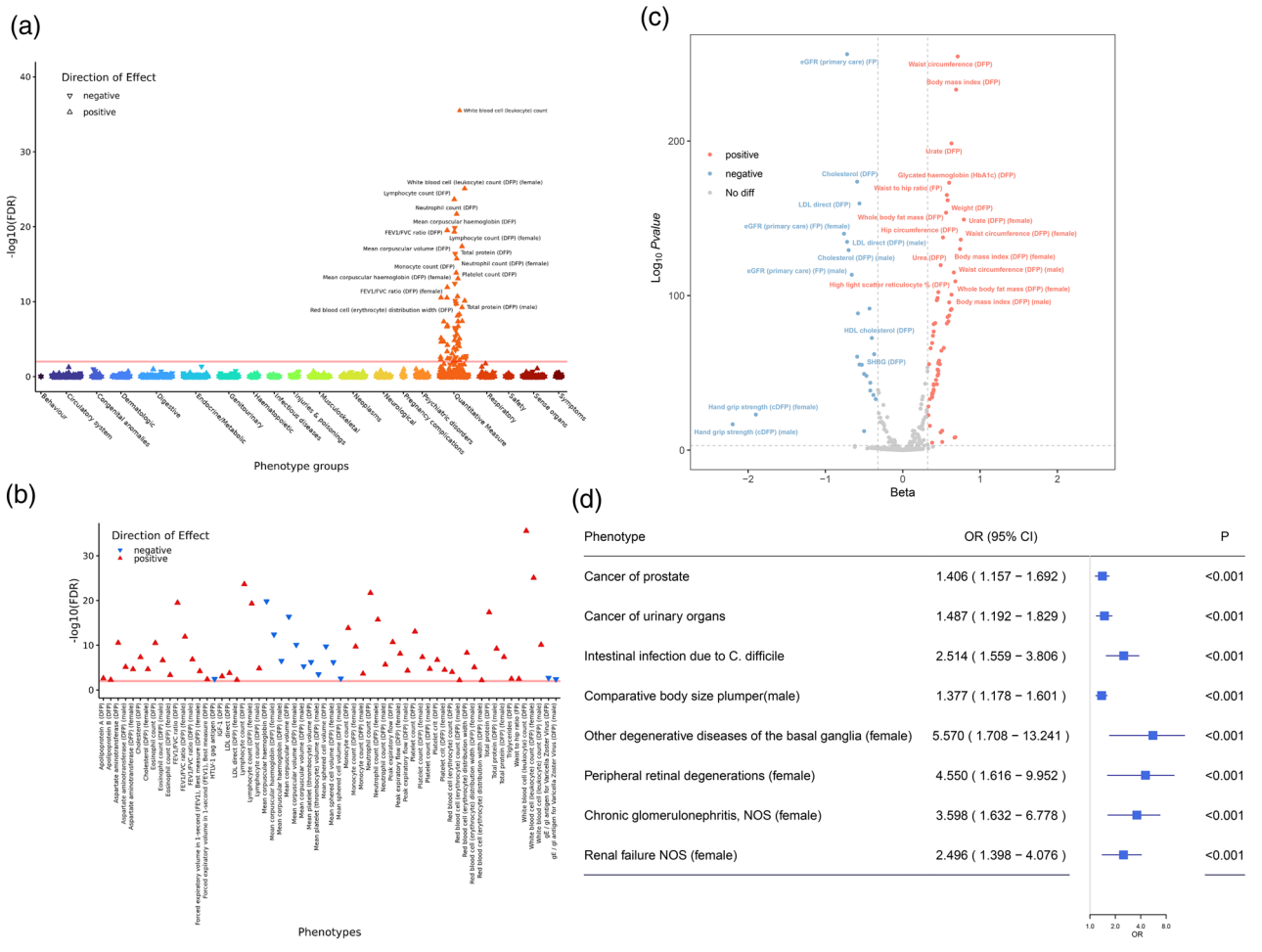
ALT, alternative allele; CHR, chromosome; ncRNA, noncoding RNA; OR, odds ratio; SNP, single nucleotide polymorphism.

(Fig. 3c; Supplementary Table S3, Supplemental digital content 1, *https://links.lww.com/FPC/B537*). We also detected five primary care symptoms associated with valsartan use: snoring ($P < 3.53 \times 10^{-25}$, OR = 1.58), narcolepsy (often) ($P < 6.09 \times 10^{-17}$, OR = 2.25), usual bad sleeper compared with never/sometimes ($P < 1.14 \times 10^{-15}$, OR = 1.43), comparative body size plumper ($P < 3.78 \times 10^{-6}$, OR = 1.28), and cough on most days ($P < 7.37 \times 10^{-6}$, OR = 1.67) (Fig. 3d). Finally, we found that 14 phenotypes, including white blood cell counts, were associated with the valsartan SNPs PheWAS and the valsartan PheWAS (Supplementary Table S3, Supplemental digital content 1, *https://links.lww.com/FPC/B537*).

Mendelian randomization analysis of valsartan

We performed a two-sample Mendelian randomization of the identified PheWAS results on the risk of CVD (Fig. 4a). We found evidence that valsartan increases the platelet distribution width and eosinophil count and decreases LDL-C, aspartate aminotransferase, and peak expiratory flow (Fig. 4b), and all supplementary Mendelian randomization methods yielded effect estimates that were consistent in direction and of similar magnitude to the primary IVW analysis for the association between valsartan and lower LDL-C and other results (Supplementary Table S4, Supplemental digital content 1, *https://links.lww.com/FPC/B537*). Valsartan could benefit from transient cerebral ischemic attack, asthma, and acute transmural MI on the basis of the International Classification of Diseases, Tenth Revision, Mendelian randomization. However, the risk of cholecystitis and urethral stricture increases with valsartan usage (Fig. 4c). These results provide further evidence of the reliability of the PheWAS.

Fig. 3

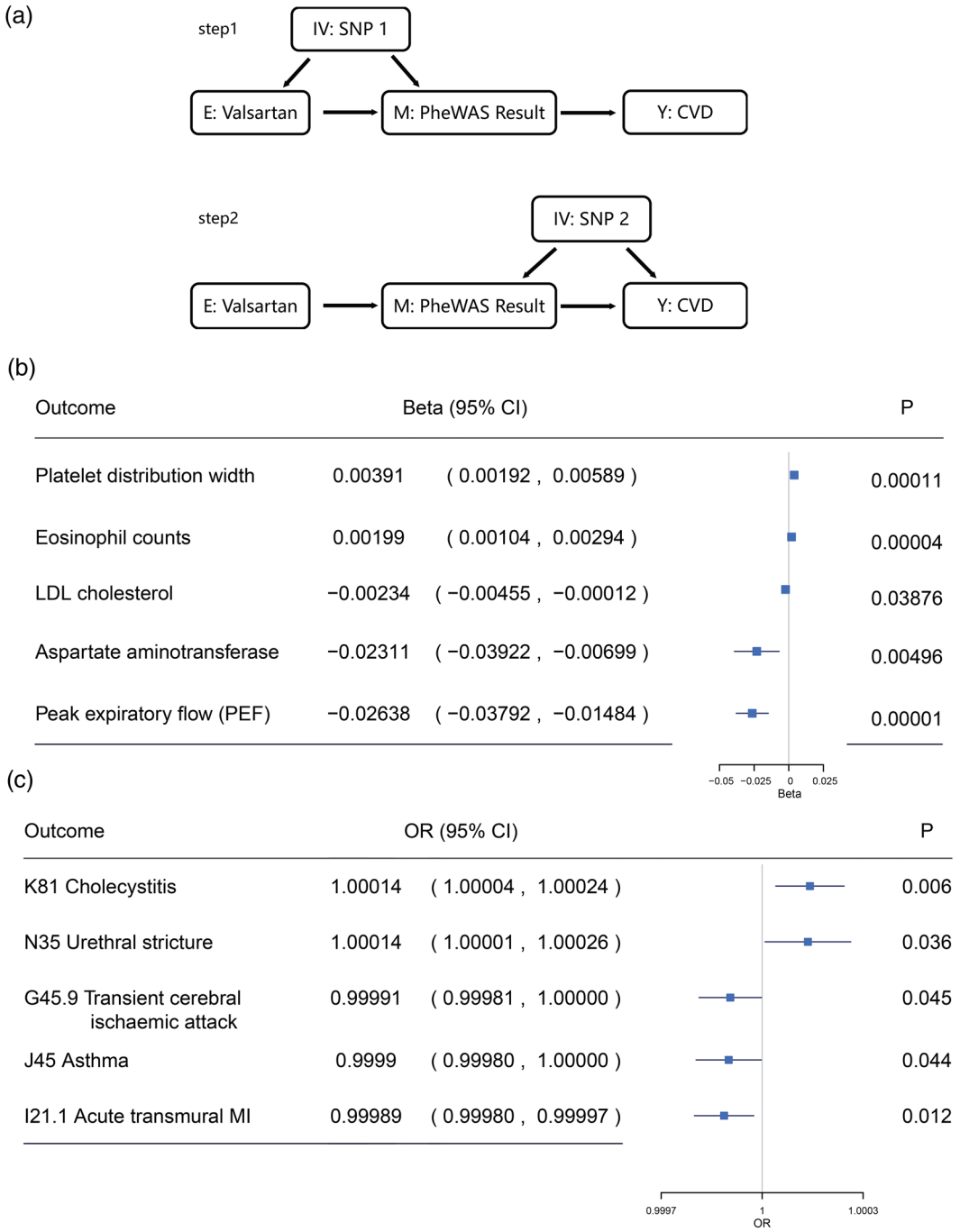


PheWAS of valsartan GWAS SNPs and valsartan use. (a) Manhattan plot of valsartan GWAS SNPs PheWAS, significant phenotypes gathered via quantitative measures. (b) All of the significant phenotypes, including leukocyte and lipid measurements, are shown. (c) Volcano plot of valsartan use PheWAS, waist circumference, and BMI are positively correlated with valsartan, and eGFR and cholesterol are negatively correlated with valsartan. (d) Forest plot of valsartan use PheWAS; valsartan may improve the risk of these symptoms. CI, confidence inteval; eGFR, estimated glomerular filtration rate; FDR, false discovery rate; GWAS, genome-wide association study; NOS, nomen satis; OR, odds ratio; PheWAS, phenome-wide association study.

Discussion

This study employed a multistep genetic approach to investigate the therapeutic effects and potential adverse events associated with valsartan therapy. Our principal findings indicate that valsartan exposure is associated with a reduction in LDL-C and a decreased risk of several cardiovascular outcomes, including transient cerebral ischemic attacks and acute MI. Conversely, we also identified potential associations with increased arterial stiffness and a reduction in eGFR, warranting careful interpretation.

Fig. 4



Mendelian randomization study of valsartan. (a) Mendelian randomization design; E, exposure; M, mediating variable; Y, outcome variable; IV, instrumental variables; (b) Forest plot of clinical data Mendelian randomization; (c) Forest plot of ICD-10 Mendelian randomization. The outcomes from the IEU GWAS database meta-analysis. CI, confidence inteval; CVD, cardiovascular disease; ICD-10, International Classification of Diseases, Tenth Revision; OR, odds ratio; PheWAS, phenome-wide association study; SNP, single nucleotide polymorphism.

The LDL-lowering effect represents a novel and significant finding. This effect was consistently demonstrated across our analytical pipeline, from the initial PheWAS to the confirmatory two-sample Mendelian randomization analysis. This suggests a potential mechanism of action for valsartan beyond its established angiotensin receptor blockade. The identified genetic instrument, the intronic SNP rs17193216 in the *GCLC* gene, offers a potential biological pathway on increasing total cholesterol [29]. *GCLC* encodes the catalytic subunit of glutamate–cysteine ligase, the rate-limiting enzyme in glutathione synthesis. Modulation of this gene could influence oxidative stress pathways, which are intimately linked to lipid metabolism and atherogenesis. While prior clinical evidence, such as the finding from Seferovic *et al.* [30] that the sacubitril/valsartan combination increased HDL cholesterol, hints at valsartan's lipid-modifying potential, our study provides direct genetic evidence specifically implicating valsartan in LDL reduction.

The observed association with decreased eGFR aligns with known pharmacodynamics of renin–angiotensin–aldosterone system inhibitors. An acute drop in eGFR is a recognized hemodynamic effect of these agents, often indicative of effective intraglomerular pressure reduction and not necessarily of intrinsic renal damage. This finding, therefore, may reflect the drug's intended action rather than an adverse event, though long-term clinical monitoring remains prudent [31].

More complex is the association with a higher pulse wave arterial stiffness index. We posit that this likely reflects indication bias or residual confounding rather than a direct causal effect of the drug. Valsartan is prescribed to patients with hypertension, a condition strongly associated with and causative of underlying atherosclerosis and arterial stiffening. Our genetic methodology may not have fully adjusted for the severity of the baseline cardiovascular phenotype in valsartan users. It is highly improbable that valsartan, an antihypertensive agent with demonstrated cardiovascular benefits, directly causes arterial stiffening; a more plausible explanation is that we were unable to accurately obtain the timing of arterial stiffness testing and the duration of valsartan use in the cohort.

Several limitations must be considered when interpreting these results. First, the genetic data were sourced exclusively from the UKB, a cohort of predominantly European ancestry, which restricts the generalizability of our findings to other ethnic populations. Second, while Mendelian randomization strengthens causal inference, our results require validation in dedicated clinical cohorts. Finally, the lack of granular data on medication dosage, duration, and adherence in the source dataset prevents us from exploring dose-response relationships, which may significantly influence the observed outcomes.

In conclusion, our analysis provides genetic support for a novel LDL-lowering effect of valsartan, suggesting it may be a particularly suitable antihypertensive agent for patients with concomitant dyslipidemia. The associations with renal function and arterial stiffness are likely related to its mechanism of action and underlying patient characteristics, respectively. These findings generate important hypotheses regarding the drug's pleiotropic effects but must be confirmed through prospective clinical studies before any implications for clinical practice can be drawn.

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The UK Biobank data were approved by the North West Multicenter Research Ethics Committee (REC reference: 21/NW/0157).

The datasets generated and/or analyzed during the current study are available in the UK Biobank repository, https://www.ukbiobank.ac.uk/.

Conflicts of interest

There are no conflicts of interest.

References

1 Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, *et al.*; GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. *J Am Coll Cardiol* 2020; **76**:2982–3021.

2 Tian X, Zuo Y, Chen S, Zhang Y, Zhang X, Xu Q, *et al.* Hypertension, arterial stiffness, and diabetes: a prospective cohort study. *Hypertension* 2022; **79**:1487–1496.

3 Lu Y, Kiechl SJ, Wang J, Xu Q, Kiechl S, Pechlaner R; Global Pulse Wave Velocity Study Group. Global distributions of age- and sex-related arterial stiffness: systematic review and meta-analysis of 167 studies with 509,743 participants. *EBioMedicine* 2023; **92**:104619.

4 Cohen JB, Mitchell GF, Gill D, Burgess S, Rahman M, Hanff TC, *et al.* Arterial stiffness and diabetes risk in framingham heart study and UK biobank. *Circ Res* 2022; **131**:545–554.

5 Zhu ML, Sun R-L, Zhang H-Y, Zhao F-R, Pan G-P, Zhang C, *et al.* Angiotensin II type 1 receptor blockers prevent aortic arterial stiffness in elderly patients with hypertension. *Clin Exp Hypertens* 2019; **41**:657–661.

6 Cavero-Redondo I, Saz-Lara A, Lugones-Sánchez C, Pozuelo-Carrascosa DP, Gómez-Sánchez L, López-Gil JF, *et al.* Comparative effect of antihypertensive drugs in improving arterial stiffness in adults with hypertension (RIGIPREV study). A network meta-analysis. *Front Pharmacol* 2023; **14**:1225795.

7 Laverty H, Benson C, Cartwright E, Cross M, Garland C, Hammond T, *et al.* How can we improve our understanding of cardiovascular safety liabilities to develop safer medicines? *Br J Pharmacol* 2011; **163**:675–693.

8 Wang S, Wang Y, Deng Y, Zhang J, Jiang X, Yu J, *et al*. Sacubitril/valsartan: research progress of multi-channel therapy for cardiorenal syndrome. *Front Pharmacol* 2023; **14:1167260**.
9 Israili ZH. Clinical pharmacokinetics of angiotensin II (AT1) receptor blockers in hypertension. *J Hum Hypertens* 2000; **14** Suppl 1:S73–S86.
10 Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al*.; ACC/AHA Joint Committee Members. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022; **145**:e895–e1032.
11 Bauersachs J, de Boer RA, Lindenfeld JA, Bozkurt B. The year in cardiovascular medicine 2021: heart failure and cardiomyopathies. *Eur Heart J* 2022; **43**:367–376.
12 Haynes R, Judge PK, Staplin N, Herrington WG, Storey BC, Bethel A, *et al*. Effects of Sacubitril/Valsartan versus irbesartan in patients with chronic kidney disease. *Circulation* 2018; **138**:1505–1514.
13 Pfeffer MA, Claggett B, Lewis EF, Granger CB, Køber L, *et al*. Angiotensin receptor–Neprilysin inhibition in acute myocardial infarction. *N Engl J Med* 2021; **385**:1845–1855.
14 Francis CM, Futschik ME, Huang J, Bai W, Sargurupremraj M, Teumer A, *et al*. Genome-wide associations of aortic distensibility suggest causality for aortic aneurysms and brain white matter hyperintensities. *Nat Commun* 2022; **13**:4505.
15 Zhai S, Zhang H, Mehrotra DV, Shen J. Pharmacogenomics polygenic risk score for drug response prediction using PRS-PGx methods. *Nat Commun* 2022; **13**:5278.
16 Korologou-Linden R, Bhatta L, Brumpton BM, Howe LD, Millard LAC, Kolaric K, *et al*. The causes and consequences of Alzheimer's disease: phenome-wide evidence from Mendelian randomization. *Nat Commun* 2022; **13**:4726.
17 Bastarache L, Denny JC, Roden DM. Phenome-Wide Association Studies. *JAMA* 2022; **327**:75–76.
18 Johnston KJA, Cote AC, Hicks E, Johnson J, Huckins LM. Genetically-regulated gene expression in the brain associated with chronic pain: relationships with clinical traits and potential for drug repurposing. *Biol Psychiatry* 2023; **95** :745.
19 Cao Y, Yang Y, Hu Q, Wei G. Identification of potential drug targets for rheumatoid arthritis from genetic insights: a Mendelian randomization study. *J Transl Med* 2023; **21**:616.
20 Diogo D, Tian C, Franklin CS, Alanne-Kinnunen M, March M, Spencer CCA, *et al*. Phenome-wide association studies across large population cohorts support drug target validation. *Nat Commun* 2018; **9**:4285.
21 Khasawneh LQ, Al-Mahayri ZN, Ali BR. Mendelian randomization in pharmacogenomics: the unforeseen potentials. *Biomed Pharmacother* 2022; **150**:112952.
22 Kim MS, Song M, Kim B, Shim I, Kim DS, Natarajan P, *et al*. Prioritization of therapeutic targets for dyslipidemia using integrative multi-omics and multi-trait analysis. *Cell Rep Med* 2023; **4**:101112.
23 Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MAR, Bender D, *et al*. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* 2007; **81**:559–575.
24 Wang K, Li M, Hakonarson H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. *Nucleic Acids Res* 2010; **38**:e164.
25 Packer RJ, Williams AT, Hennah W, Eisenberg MT, Shrine N, Fawcett KA, *et al*. DeepPheWAS: an R package for phenotype generation and association analysis for phenome-wide association studies. *Bioinformatics* 2023; **39**:btad073.
26 Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, *et al*. The MR-Base platform supports systematic causal inference across the human phenome. *eLife* 2018; **7**:e34408.
27 Elsworth B, Lyon M, Alexander T, Liu Y, Matthews P, Hallett J, *et al*. The MRC IEU OpenGWAS data infrastructure. *bioRxiv*. 2020:2020–08. doi: 10.1101/2020.08.10.244293
28 Kyung JW, Cho IH, Lee S, Song WK, Ryan TA, Hoppa MB, Kim SH. Adaptor Protein 2 (AP-2) complex is essential for functional axogenesis in hippocampal neurons. *Sci Rep* 2017; **7**:41620.
29 MacArthur J, Bowler E, Cerezo M, Gil L, Hall P, Hastings E, *et al*. The new NHGRI-EBI Catalog of published genome-wide association studies (GWAS Catalog). *Nucleic Acids Res* 2017; **45**:D896–D901.
30 Seferovic JP, Claggett B, Seidelmann SB, Seely EW, Packer M, Zile MR, *et al*. Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post-hoc analysis from the PARADIGM-HF trial. *Lancet Diabetes Endocrinol* 2017; **5**:333–340.
31 Zheng CM, Wang J-Y, Chen T-T, Wu Y-C, Wu Y-L, Lin H-T, *et al*. Angiotensin-converting enzyme inhibitors or angiotensin receptor blocker monotherapy retard deterioration of renal function in Taiwanese chronic kidney disease population. *Sci Rep* 2019; **9**:2694.