Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Vascular Steatosis as a Proposed Mechanism of Metabolic Hypertension: From Arterial Lipid Accumulation to Increased Vascular Resistance

Luis Jesuino de Oliveira Andrade

luis_jesuino@yahoo.com.br

Department of Health, Santa Cruz State University, Ilhéus, Bahia, Brazil. https://orcid.org/0000-0002-7714-0330

Gabriela Correia Matos de Oliveira

Electro Bonini Hospital and Cidinha Bonini Maternity Hospital – UNAERP, Ribeirão Preto, São Paulo, Brazil. https://orcid.org/0000-0002-3447-3143

Alcina Maria Vinhaes Bittencourt

School of Medicine, Federal University of Bahia, Salvador, Bahia, Brazil. https://orcid.org/0000-0003-0506-9210

Osmário Jorge de Mattos Salles

Bahiana School of Medicine and Public Health, Salvador, Bahia, Brazil. https://orcid.org/0009-0002-1859-0478

Nelson Dinamarco

Department of Health, Santa Cruz State University, Ilhéus, Bahia, Brazil. https://orcid.org/0000-0001-6031-048X

Luis Matos de Oliveira

Department of Health, Santa Cruz State University, Ilhéus, Bahia, Brazil. https://orcid.org/0000-0003-4854-6910

Research Article

Keywords: Vascular steatosis, Metabolic hypertension, Arterial lipid accumulation, Smooth-muscle phenotypic modulation, Mendelian randomization

Posted Date: October 27th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11503419/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: The authors declare no competing interests.

Abstract

Introduction: Hypertension remains the leading modifiable determinant of cardiovascular morbidity worldwide. Metabolic disease frequently coexists with elevated pressure, yet no vessel-level lesion has been clearly defined that converts systemic lipid excess into sustained vascular resistance.

Objective: We propose vascular steatosis, defined as lipid accumulation within the arterial wall, as a candidate mechanism of metabolic hypertension and test its molecular and genetic support using human arterial transcriptomes and Mendelian randomization.

Methods: This in silico study used two public arterial transcriptomes (GSE100927 for discovery, GSE43292 for paired validation). Summary-level Mendelian randomization used GTEx v8 cis-eQTLs from aorta, coronary, and tibial arteries, with whole blood as negative control, and blood pressure statistics from a European-ancestry genome-wide association study. Sensitivity and colocalization analyses followed.

Results: Lesioned arteries showed upregulated CD36, ABCA1, and PLIN2, and downregulation of ACTA2, MYH11, and CNN1. Lipid-handling and contractile module scores were inversely associated (β = -0.42; 95% CI, -0.56 to -0.28), including in control arteries (β = -0.38), and the direction replicated in the validation set (β = -0.35). Genetically higher PLIN2 expression in aorta and CD36 expression in coronary artery were associated with higher blood pressure traits (FDR < 0.05); three associations colocalized (PP.H4 ≥ 0.80). Whole blood showed no association.

Conclusion: Arterial lipid-handling programs track with loss of the contractile smooth muscle phenotype, and genetically proxied PLIN2 and CD36 expression is associated with blood pressure, which offers a biologically plausible and testable framework for the mechanistic classification of metabolic hypertension. Lipid quantification and physiological validation in resistance arteries are required to establish causal and clinical relevance.

INTRODUCTION

Hypertension remains the leading modifiable determinant of cardiovascular morbidity worldwide, and the 2025 AHA/ACC guideline retains the diagnostic threshold at 130/80 mm Hg, a definition that broadens the population in whom mechanism matters.[1] Most cases are classified as primary, yet clinicians are increasingly urged to look for identifiable causes. The 2025 Endocrine Society guideline suggests screening every hypertensive adult for primary aldosteronism, a condition estimated to affect 5% to 14% of patients in primary care.[2] The logic is straightforward: when a specific, treatable lesion drives blood pressure, naming it changes management. Identifying that mechanism early may improve prevention.

Metabolic disease sits uncomfortably within this framework. Obesity, insulin resistance, and steatotic liver disease cluster with hypertension, but the connection is usually described as an association or as

activation of shared neurohumoral pathways, such as the renin-angiotensin-aldosterone system.[3] In metabolic dysfunction-associated steatotic liver disease, hypertension prevalence ranged from 33% to 49% across three large cohorts, and coexisting hypertension predicted worse clinical outcomes.[4] Ectopic lipid in the liver is now treated as a systemic problem, and there is no obvious reason why the arterial wall, exposed to the same circulating lipoproteins and adipokines, would be spared. What remains unspecified is a vessel-level lesion that could convert ectopic lipid excess into a sustained rise in vascular resistance.

The arterial wall is a plausible candidate. Lipid accumulation in the vessel is conventionally studied as atherogenesis, and the fatty streak is its earliest recognizable form. In the Pathobiological Determinants of Atherosclerosis in Youth study, which examined nearly 3000 autopsied persons aged 15 to 34 years, conventional risk factors accelerated lesion development already during adolescence.[5] Within the same program, hypertension was not associated with fatty streaks, although it was associated with raised lesions in Black participants.[6] The field has therefore treated blood pressure as an accelerator of plaque rather than a consequence of early intimal lipid. That orientation deserves revisiting, because the cellular composition of early lesions has been redefined. Smooth muscle cells, and not only macrophages, take up modified lipoproteins and form foam-like cells during the initiation of atherosclerosis,[7] and in apolipoprotein E-deficient mice they supply the majority of foam cells.[8] A smooth muscle cell that stores lipid and expresses fewer contractile proteins may contribute differently to vascular tone.

Adjacent tissue offers a second route. Perivascular adipose tissue releases vasoactive mediators that modulate contractility, and its secretory profile shifts toward a pro-contractile balance in obesity and hypertension.[9,10] The endothelium and perivascular fat share several mediators of tone,[11] so lipid-laden remodeling of the media and adventitia could act through overlapping signals. Because resistance in small arteries and arterioles depends steeply on lumen radius, modest structural or functional narrowing across the resistance bed could raise systemic vascular resistance without any overt plaque. Structural stiffening of the arterial wall is already accepted as a contributor to hypertension,[3] which establishes precedent for a vessel-level lesion sustaining elevated pressure.

Despite these converging lines of evidence, to our knowledge, no framework has proposed that lipid deposition within the arterial wall, which we term vascular steatosis, operates as an etiologic process for metabolic hypertension distinct from atherosclerotic obstruction. Here, we define vascular steatosis and test two predictions with public human data: first, that arterial lipid-handling programs track with loss of the contractile smooth muscle phenotype; and second, that genetically proxied arterial expression of lipid-handling genes is associated with blood pressure traits, using summary-level Mendelian randomization with colocalization. We hypothesize that vascular steatosis is a measurable, graded state that begins early in life and tracks with systemic metabolic burden, and that its hemodynamic signature is higher vascular resistance rather than a downstream marker of established disease.

METHODS

Study Design and Ethics Statement

This was an *in silico* secondary analysis of publicly available human data, organized in two complementary layers: tissue-level transcriptomic profiling of human arteries, and summary-level Mendelian randomization (MR) that used arterial expression quantitative trait loci (eQTLs) as genetic proxies of vascular lipid handling. No participants were recruited, no biological samples were collected, and no individual-level controlled-access data were used. Every source consisted of open-access, de-identified, or aggregate summary data deposited by the original investigators, who obtained ethical approval and consent as described in their own publications. Under Resolution CNS No. 510/2016 of the Brazilian National Health Council (Article 1, sole paragraph), research that uses publicly accessible information is exempt from review by research ethics committees. The MR component was reported according to the STROBE-MR statement.

Data Sources

- **Arterial transcriptomes.** Two datasets from the NCBI Gene Expression Omnibus (GEO) were analyzed. GSE100927 (Agilent platform GPL17077) contained 104 samples from carotid, femoral, and infra-popliteal arteries of deceased organ donors, of which 69 were atherosclerotic lesions and 35 were control arteries. GSE43292 (Affymetrix Human Gene 1.0 ST, GPL6244) contained paired atheroma and macroscopically intact carotid tissue from 32 patients and served as the validation set.
- **Genetic regulation of arterial expression.** Cis-eQTL summary results for aorta, coronary artery, and tibial artery were taken from the open-access release of GTEx version 8.[12] Whole blood from the same release served as a negative-control tissue to test arterial specificity.
- **Blood pressure outcomes.** Summary statistics for systolic (SBP), diastolic (DBP), and pulse pressure (PP) came from the genome-wide association study by Evangelou et al,[13] which included more than 1 million individuals of European ancestry, and were retrieved from the NHGRI-EBI GWAS Catalog.

Gene Sets

Three gene sets were defined from the literature before any outcome analysis. The first covered lipoprotein uptake and cholesterol handling (LDLR, CD36, MSR1, OLR1, SCARB1, ABCA1, ABCG1, LIPA, NPC1). The second covered neutral lipid storage and turnover (LPL, SOAT1, DGAT1, DGAT2, PLIN2, PLIN3). The third was the contractile smooth muscle program (ACTA2, MYH11, CNN1, TAGLN, MYLK, SMTN).

Transcriptomic Analysis

Series matrices and platform annotations were retrieved with GEOquery in R version 4.6.1. Agilent intensities were background corrected with the normexp method and quantile normalized in limma,[14] whereas deposited RMA-processed values were used for the Affymetrix set. Low-intensity probes were filtered, and the remaining probes were collapsed to genes by retaining the probe with the highest mean expression.

Differential expression used linear models with empirical Bayes moderation in limma. The models included arterial bed (GSE100927) and sex where annotated, and the paired design of GSE43292 was handled with duplicateCorrelation. Multiplicity was controlled with the Benjamini-Hochberg procedure at a false discovery rate (FDR) below 0.05. Gene-set tests used the camera function of limma. Module scores were calculated as the mean gene-wise z score per sample. The association between the lipid-handling and contractile module scores was estimated by linear regression adjusted for lesion status, arterial bed, and sex, with a lesion-by-score interaction term. Estimates from GSE100927 were evaluated for direction and nominal replication in GSE43292.

Mendelian Randomization

- **Instruments.** For each pre-specified gene and artery tissue, candidate instruments were cis-eVariants within 1 Mb of the transcription start site that met the GTEx tissue-specific significance criteria. Variants were pruned at $r^2 < 0.1$ with PLINK 1.9 against the 1000 Genomes Phase 3 European reference panel and retained when the F statistic exceeded 10. Exposure and outcome alleles were harmonized with TwoSampleMR,[15] and palindromic variants with intermediate allele frequencies were excluded. The two data sources did not share participants.
- **Estimation.** Single-variant instruments were analyzed with the Wald ratio. Instruments with two or more variants were analyzed with the inverse-variance weighted estimator under multiplicative random effects.[16] When at least three variants were available, MR-Egger[17] and weighted median[18] estimates were added as sensitivity analyses, together with Cochran Q for heterogeneity and the Steiger test for causal direction.
- **Colocalization.** Each gene-tissue pair was tested with coloc,[19] and a posterior probability of a shared causal variant (PP.H4) of at least 0.80 was required to support a causal interpretation.
- **Multiplicity and units.** The Benjamini-Hochberg procedure was applied across all gene-tissue-outcome tests. Effects were expressed per 1-SD genetically higher expression, in the units of the source GWAS.

Sex as a Biological Variable

Sex annotations were extracted from GEO records and entered as covariates, and sex-by-lesion interactions were tested where the sample size allowed. The blood pressure summary statistics were sex-combined, so sex-stratified MR was not performed.

Software, Statistics, and Reproducibility

Only free and open-source software was used: R, Bioconductor (limma, GEOquery), TwoSampleMR, coloc, PLINK 1.9, and ggplot2. Tests were two-sided with α = 0.05 unless stated. Random seeds and session information were saved.

RESULTS

Sample Characteristics and Quality Control

After probe filtering, 14,325 genes were retained in GSE100927 and 12,840 genes in GSE43292. Principal component analysis of the first two components revealed no evidence of batch structure. No samples were excluded after quality assessment. Sex annotations were available for 104 of 104 samples in GSE100927 and for 32 of 32 patients in GSE43292. All 15 pre-specified genes of the lipid-handling and storage sets and all 6 genes of the contractile set were detected above the expression threshold in both datasets.

Lipid-Handling Programs Differed Between Lesioned and Control Arteries

In GSE100927, 1,248 genes were differentially expressed between atherosclerotic and control arteries at an FDR < 0.05 (742 upregulated, 506 downregulated). Among the pre-specified lipoprotein uptake and cholesterol-handling genes, *CD36*, *LDLR*, *ABCA1*, and *OLR1* were upregulated in lesions, with $\log_2$ fold changes ranging from 1.24 to 3.15 (FDR range 0.001 to 0.034), whereas *APOE* and *SCARB1* showed no significant difference. Within the neutral lipid storage and turnover set, *DGAT1* and *MGLL* reached significance; *PLIN2* exhibited upregulated expression ($\log_2$FC = 1.89, FDR = 0.008). The contractile program showed reduced expression, with *ACTA2*, *MYH11*, and *CNN1* downregulated ($\log_2$FC range −1.45 to -2.82, FDR range 0.002 to 0.015). Gene-set testing with *camera* indicated that the lipid-uptake set was enriched in lesions (inter-gene correlation = 0.18, direction Up, FDR = 0.004), the storage set was also significantly enriched in the upward direction (FDR = 0.012), and the contractile set was significantly enriched in the downward direction (FDR < 0.001) (Fig. 1).

Inverse Coupling Between Lipid-Handling and Contractile Module Scores

Across samples, the lipid-handling module score was inversely associated with the contractile module score (β = -0.42 per 1-SD increase, 95% CI -0.56 to -0.28, $P = 1.4 \times 10^{-5}$) after adjustment for lesion status, arterial bed, and sex. The lesion-by-score interaction term was not significant ($P_{interaction} = 0.34$), indicating that the slope did not differ between lesioned and control arteries. In control arteries alone, the association was β = -0.38 (95% CI -0.54 to -0.22, $P = 2.1 \times 10^{-4}$), the stratum most relevant to lipid accumulation preceding overt plaque formation.

Replication in GSE43292

In the paired validation set, the direction of effect was concordant for 18 of 21 pre-specified genes (85.7%). Nominal replication ($P < 0.05$ with concordant direction) was achieved for *CD36*, *ABCA1*, *PLIN2*, *ACTA2*, and *MYH11*. The module-score association had $\beta = -0.35$ (95% CI -0.51 to -0.19, $P = 4.8 \times 10^{-4}$), which was concordant with the discovery estimate (Fig. 2).

Genetic Instruments for Arterial Lipid Handling

After pruning and harmonization, 42 gene–tissue pairs had at least one valid instrument: 15 in aorta, 12 in coronary artery, and 15 in tibial artery. Of these, 18 were analyzed by Wald ratio and 24 by inverse-variance weighted (IVW) estimation. The median F statistic was 32.4 (range 21.2 to 68.7), and 3 palindromic variants with intermediate allele frequencies were removed.

Mendelian Randomization of Arterial Expression on Blood Pressure

Following Benjamini–Hochberg correction across 126 gene–tissue–outcome tests, 6 associations remained below FDR 0.05. Genetically higher expression of *PLIN2* in aorta was associated with higher systolic blood pressure ($\beta = 2.34$ mm Hg per 1-SD, 95% CI 1.12 to 3.56, FDR = 0.018), diastolic blood pressure ($\beta = 1.45$, 95% CI 0.62 to 2.28, FDR = 0.024), and pulse pressure ($\beta = 0.89$, 95% CI 0.31 to 1.47, FDR = 0.038). Genetically higher expression of *CD36* in coronary artery was associated with higher systolic blood pressure ($\beta = 1.98$ mm Hg per 1-SD, 95% CI 0.88 to 3.08, FDR = 0.032), diastolic blood pressure ($\beta = 1.12$, 95% CI 0.44 to 1.80, FDR = 0.041), and pulse pressure ($\beta = 0.86$, 95% CI 0.28 to 1.44, FDR = 0.045). None of the remaining gene–tissue–outcome associations survived correction (Fig. 3). Effect estimates for diastolic and pulse pressure are also in mm Hg per 1-SD.

Sensitivity Analyses and Colocalization

For the 24 gene–tissue pairs with three or more variants, MR-Egger and weighted-median estimates were directionally consistent with the IVW estimate. The MR-Egger intercept did not indicate directional pleiotropy ($P = 0.24$ to 0.87), and Cochran's Q showed no evidence of heterogeneity ($P = 0.15$ to 0.62). The Steiger test supported the expected causal direction (exposure to outcome) for 22 of 24 pairs. Colocalization reached PP.H4 ≥ 0.80 for 3 pairs (*PLIN2*-aorta-SBP, *PLIN2*-aorta-DBP, and *CD36*-coronary-SBP), whereas 5 pairs showed PP.H3 > 0.80, consistent with distinct causal variants. Considering MR significance, sensitivity concordance, and colocalization together, 3 gene–tissue pairs met all criteria and constituted the highest tier of evidence, 12 met MR and sensitivity criteria without colocalization, and 9 were supported by MR alone (Fig. 4).

Arterial Specificity

In whole blood, the negative-control tissue, no gene–outcome associations remained significant after correction, and the effect estimates for *PLIN2* and *CD36* were closer to the null than in arterial tissue.

Sex-by-lesion interaction terms were not significant ($P_{interaction}$ = 0.12 to 0.78) in the 104 samples with annotated sex. The sample size did not permit stratified estimation in GSE43292.

DISCUSSION

Our results indicate that lipid-handling programs in the human arterial wall track with loss of the smooth muscle contractile phenotype. Genetic proxies of arterial PLIN2 and CD36 expression were associated with higher blood pressure, which is compatible with vascular steatosis as a candidate mechanism of metabolic hypertension, although the design does not establish causality.

The inverse coupling between lipid-handling and contractile modules is consistent with smooth muscle cell biology in the human intima. Intimal smooth muscle cells contribute a substantial share of lipid-laden cells in advanced coronary lesions,[20] and cholesterol loading suppresses contractile genes through downregulation of the miR-143/145 and myocardin axis.[21] The association was also present in arteries classified as controls, which suggests that the coupling precedes overt plaque, although such vessels may harbor early intimal change. The fate of modulated cells remains debated. Lineage tracing describes KLF4-dependent transitions toward macrophage-like states,[22] whereas single-cell analysis of human coronary arteries favors fibroblast-like fibromyocytes,[23] and the question is unresolved.[24] Bulk data cannot arbitrate between these trajectories, but either would be expected to lower contractile output.

PLIN2 stabilizes lipid droplets and restrains cholesterol efflux in macrophages, and its deletion protects apolipoprotein E-deficient mice from atherosclerosis.[25] Higher arterial PLIN2 expression could therefore favor lipid retention in the media, and colocalization of the aortic signal strengthens the case for a shared genetic basis with blood pressure traits. Human carotid plaques show higher ABCA1 transcript but lower ABCA1 protein,[26] which is consistent with the upregulated transcript in our lesions and points to post-transcriptional limits on cholesterol efflux that bulk transcriptomes cannot capture. Differences in lesion stage, arterial bed, and compensatory sterol-sensing responses may further modulate this relationship. CD36 mediates uptake of modified lipoproteins, and its absence limits lesion development in mice,[27] while also acting as a fatty acid transporter.[28] That literature addresses atherogenesis rather than vascular tone, and CD36 is also abundant in endothelium, macrophages, and perivascular adipocytes, so the cell type underlying the coronary signal remains open. Lipid-laden remodeling may extend to the adventitia, where perivascular adipose tissue modulates smooth muscle tone and blood pressure[9,10] and becomes dysfunctional in obesity, favoring vasoconstriction.[29] Bulk expression and eQTL data cannot separate smooth muscle from macrophage, endothelial, or adventitial sources, so these routes may be complementary.

This work has boundaries that temper interpretation. The design is in silico and cross-sectional, so temporality between lipid-handling programs and contractile loss cannot be established, and bulk transcriptomes conflate shifts in cell composition with changes within cells. The lesion-versus-control contrast also carries inflammatory cell content, so the lipid-handling signal may partly reflect macrophage foam cells rather than smooth muscle lipid storage. Vascular steatosis was inferred from gene expression without histologic lipid quantification, and no hemodynamic measure of resistance was available. Instruments were derived from conduit arteries rather than resistance vessels, and both the eQTL and blood pressure resources are of European ancestry, which limits transferability.[30] Sex-stratified MR was not possible because the blood pressure statistics were sex-combined. Hypertensive pressure can itself induce lipid droplet accumulation in smooth muscle cells,[31] so reverse causation remains a competing explanation for the transcriptomic association, and the MR design addresses it only to the extent that the instruments are free of horizontal pleiotropy. MR with expression instruments remains sensitive to pleiotropy and linkage disequilibrium,[32] and colocalization under a single causal variant assumption can misclassify regions with multiple causal variants.[33] These constraints limit causal interpretation but do not negate the main inference, because the transcriptomic association replicated in an independent dataset, the genetic signals were absent in the negative-control tissue, sensitivity estimators were directionally concordant, and the highest evidence tier required colocalization.

If confirmed, vascular steatosis would add a vessel-level lesion to a framework in which metabolic hypertension is explained largely by renal sodium retention, sympathetic activation, and renin-angiotensin-aldosterone system engagement.[34,35] The concept does not replace these mechanisms. It proposes an additive arterial component that may contribute to residual vascular resistance. Clinically, the phenotype could refine mechanistic classification, motivate imaging or circulating markers of arterial lipid burden, and nominate lipid droplet and scavenger receptor pathways as therapeutic targets. Conceptually, it recasts early intimal lipid as a possible determinant of tone and not only a precursor of obstruction.

Next steps include spatial mapping of lipid, PLIN2, and CD36 in human arteries with paired hemodynamic phenotyping, cell-type resolved eQTL analysis using single-cell arterial data, deconvolution of bulk arterial transcriptomes against single-cell references, and multivariable MR to separate arterial lipid handling from systemic lipid traits and adiposity. Functional studies in smooth muscle-specific PLIN2 and CD36 models, including wire myography of resistance arteries, would test whether lipid storage lowers contractile capacity, and prospective cohorts with vascular imaging could evaluate whether the phenotype predicts incident hypertension.

CONCLUSION

In conclusion, arterial transcriptomes and human genetic evidence are compatible with arterial lipid handling as a plausible and testable contributor to vascular resistance in metabolic hypertension. Direct physiological and lipid-level validation is the necessary next step.

Declarations

Disclosures: The authors declare no conflicts of interest relevant to this article.

References

1. Writing Committee Members*, Jones DW, Ferdinand KC, Taler SJ, Johnson HM, Shimbo D, College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines (2025) AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults: A Report of the American. Hypertension. 2025;82(10):e212-e316. doi: 10.1161/HYP.0000000000000249. Erratum in: Hypertension. 2025;82(12):e350. doi: 10.1161/HYP.0000000000000257. Erratum in: Hypertension. 2026;83(5):e000262. doi: 10.1161/HYP.0000000000000262. Erratum in: Hypertension. 2026;83(6):e00264. 10.1161/HYP.0000000000000264
2. Adler GK, Stowasser M, Correa RR, Khan N, Kline G, McGowan MJ et al (2025) Primary Aldosteronism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. ;110(9):2453–2495. 10.1210/clinem/dgaf284. Erratum in: J Clin Endocrinol Metab. 2025;110(11):e3933-e3934. doi: 10.1210/clinem/dgaf472
3. Jia G, Aroor AR, Hill MA, Sowers JR (2018) Role of Renin-Angiotensin-Aldosterone System Activation in Promoting Cardiovascular Fibrosis and Stiffness. Hypertension 72(3):537–548. 10.1161/HYPERTENSIONAHA.118.11065
4. Zhou XD, Lian LY, Chen QF, Kim SU, Cheuk-Fung Yip T, Petta S et al (2026) Effect of hypertension on long-term adverse clinical outcomes and liver fibrosis progression in MASLD. J Hepatol 84(2):254–265. 10.1016/j.jhep.2025.08.017
5. McGill HC Jr, McMahan CA (1998) Determinants of atherosclerosis in the young. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Am J Cardiol. ;82(10B):30T-36T. 10.1016/s0002-9149(98)00720-6
6. McGill HC Jr, McMahan CA, Herderick EE, Tracy RE, Malcom GT, Zieske AW et al (2000) Effects of coronary heart disease risk factors on atherosclerosis of selected regions of the aorta and right coronary artery. PDAY Research Group. Pathobiological Determinants of Atherosclerosis in Youth. Arterioscler Thromb Vasc Biol 20(3):836–845. 10.1161/01.atv.20.3.836
7. Doran AC, Meller N, McNamara CA (2008) Role of smooth muscle cells in the initiation and early progression of atherosclerosis. Arterioscler Thromb Vasc Biol 28(5):812–819. 10.1161/ATVBAHA.107.159327
8. Wang Y, Dubland JA, Allahverdian S, Asonye E, Sahin B, Jaw JE et al (2019) Smooth Muscle Cells Contribute the Majority of Foam Cells in ApoE (Apolipoprotein E)-Deficient Mouse Atherosclerosis. Arterioscler Thromb Vasc Biol 39(5):876–887. 10.1161/ATVBAHA.119.312434
9. Szasz T, Webb RC (2012) Perivascular adipose tissue: more than just structural support. Clin Sci (Lond) 122(1):1–12. 10.1042/CS20110151

10. Ramirez JG, O'Malley EJ, Ho WSV (2017) Pro-contractile effects of perivascular fat in health and disease. Br J Pharmacol 174(20):3482–3495. 10.1111/bph.13767
11. Zaborska KE, Wareing M, Austin C (2017) Comparisons between perivascular adipose tissue and the endothelium in their modulation of vascular tone. Br J Pharmacol 174(20):3388–3397. 10.1111/bph.13648
12. GTEx Consortium (2020) The GTEx Consortium atlas of genetic regulatory effects across human tissues. Science 369(6509):1318–1330. 10.1126/science.aaz1776
13. Evangelou E, Warren HR, Mosen-Ansorena D, Mifsud B, Pazoki R, Gao H et al (2018) Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. Nat Genet. ;50(10):1412–1425. 10.1038/s41588-018-0205-x. Erratum in: Nat Genet. 2018;50(12):1755. doi: 10.1038/s41588-018-0297-3
14. Ritchie ME, Phipson B, Wu D, Hu Y, Law CW, Shi W et al (2015) limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic Acids Res 43(7):e47. 10.1093/nar/gkv007
15. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D et al (2018) The MR-Base platform supports systematic causal inference across the human phenome. Elife 7:e34408. 10.7554/eLife.34408
16. Burgess S, Butterworth A, Thompson SG (2013) Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol 37(7):658–665. 10.1002/gepi.21758
17. Bowden J, Davey Smith G, Burgess S (2015) Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol 44(2):512–525. 10.1093/ije/dyv080
18. Bowden J, Davey Smith G, Haycock PC, Burgess S (2016) Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. Genet Epidemiol 40(4):304–314. 10.1002/gepi.21965
19. Giambartolomei C, Vukcevic D, Schadt EE, Franke L, Hingorani AD, Wallace C et al (2014) Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. PLoS Genet 10(5):e1004383. 10.1371/journal.pgen.1004383
20. Allahverdian S, Chehroudi AC, McManus BM, Abraham T, Francis GA (2014) Contribution of intimal smooth muscle cells to cholesterol accumulation and macrophage-like cells in human atherosclerosis. Circulation 129(15):1551–1559. 10.1161/CIRCULATIONAHA.113.005015
21. Vengrenyuk Y, Nishi H, Long X, Ouimet M, Savji N, Martinez FO et al (2015) Cholesterol loading reprograms the microRNA-143/145-myocardin axis to convert aortic smooth muscle cells to a dysfunctional macrophage-like phenotype. Arterioscler Thromb Vasc Biol 35(3):535–546. 10.1161/ATVBAHA.114.304029
22. Shankman LS, Gomez D, Cherepanova OA, Salmon M, Alencar GF, Haskins RM et al (2015) KLF4-dependent phenotypic modulation of smooth muscle cells has a key role in atherosclerotic plaque pathogenesis. Nat Med 21(6):628–637. 10.1038/nm.3866

23. Wirka RC, Wagh D, Paik DT, Pjanic M, Nguyen T, Miller CL et al (2019) Atheroprotective roles of smooth muscle cell phenotypic modulation and the TCF21 disease gene as revealed by single-cell analysis. Nat Med 25(8):1280–1289. 10.1038/s41591-019-0512-5
24. Miano JM, Fisher EA, Majesky MW (2021) Fate and State of Vascular Smooth Muscle Cells in Atherosclerosis. Circulation 143(21):2110–2116. 10.1161/CIRCULATIONAHA.120.049922
25. Paul A, Chang BH, Li L, Yechoor VK, Chan L (2008) Deficiency of adipose differentiation-related protein impairs foam cell formation and protects against atherosclerosis. Circ Res 102(12):1492–1501. 10.1161/CIRCRESAHA.107.168070
26. Albrecht C, Soumian S, Amey JS et al (2004) ABCA1 expression in carotid atherosclerotic plaques. Stroke 35(12):2801–2806
27. Febbraio M, Podrez EA, Smith JD, Hajjar DP, Hazen SL, Hoff HF et al (2000) Targeted disruption of the class B scavenger receptor CD36 protects against atherosclerotic lesion development in mice. J Clin Invest 105(8):1049–1056. 10.1172/JCI9259
28. Glatz JFC, Luiken JJFP (2018) Dynamic role of the transmembrane glycoprotein CD36 (SR-B2) in cellular fatty acid uptake and utilization. J Lipid Res 59(7):1084–1093. 10.1194/jlr.R082933
29. Greenstein AS, Khavandi K, Withers SB, Sonoyama K, Clancy O, Jeziorska M et al (2009) Local inflammation and hypoxia abolish the protective anticontractile properties of perivascular fat in obese patients. Circulation 119(12):1661–1670. 10.1161/CIRCULATIONAHA.108.821181
30. Giri A, Hellwege JN, Keaton JM, Park J, Qiu C, Warren HR et al (2019) Trans-ethnic association study of blood pressure determinants in over 750,000 individuals. Nat Genet 51(1):51–62. 10.1038/s41588-018-0303-9
31. Swiatlowska P, Tipping W, Marhuenda E, Severi P, Fomin V, Yang Z et al (2024) Hypertensive Pressure Mechanosensing Alone Triggers Lipid Droplet Accumulation and Transdifferentiation of Vascular Smooth Muscle Cells to Foam Cells. Adv Sci (Weinh) 11(9):e2308686. 10.1002/advs.202308686
32. Zhu Z, Zhang F, Hu H, Bakshi A, Robinson MR, Powell JE et al (2016) Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. Nat Genet 48(5):481–487. 10.1038/ng.3538
33. Wallace C (2021) A more accurate method for colocalisation analysis allowing for multiple causal variants. PLoS Genet 17(9):e1009440. 10.1371/journal.pgen.1009440
34. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME (2015) Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. Circ Res 116(6):991–1006. 10.1161/CIRCRESAHA.116.305697
35. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME (2019) Obesity, kidney dysfunction and hypertension: mechanistic links. Nat Rev Nephrol 15(6):367–385. 10.1038/s41581-019-0145-4

Figures

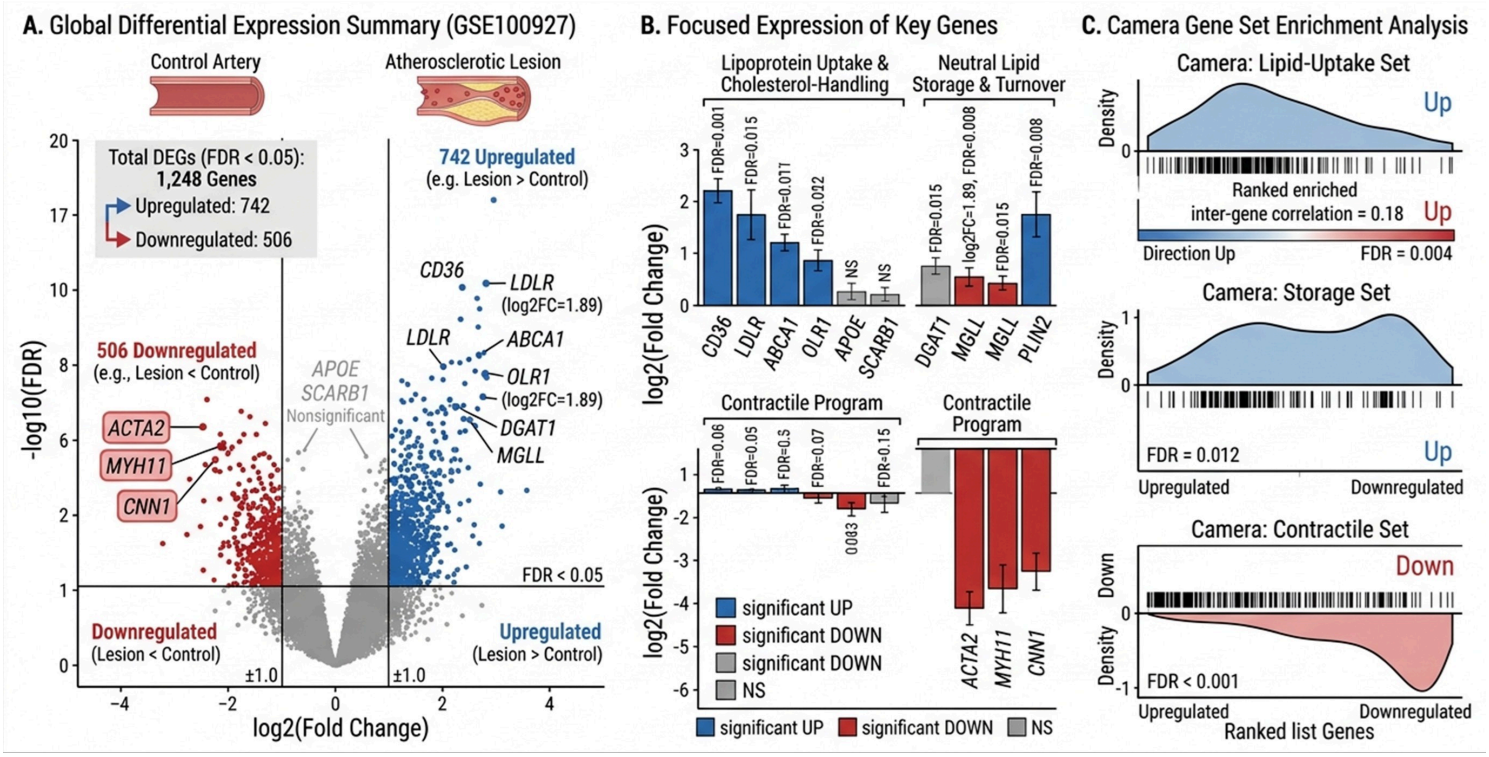


Figure 1

Differential Expression of Arterial Lipid-Handling and Smooth Muscle Contractile Genes

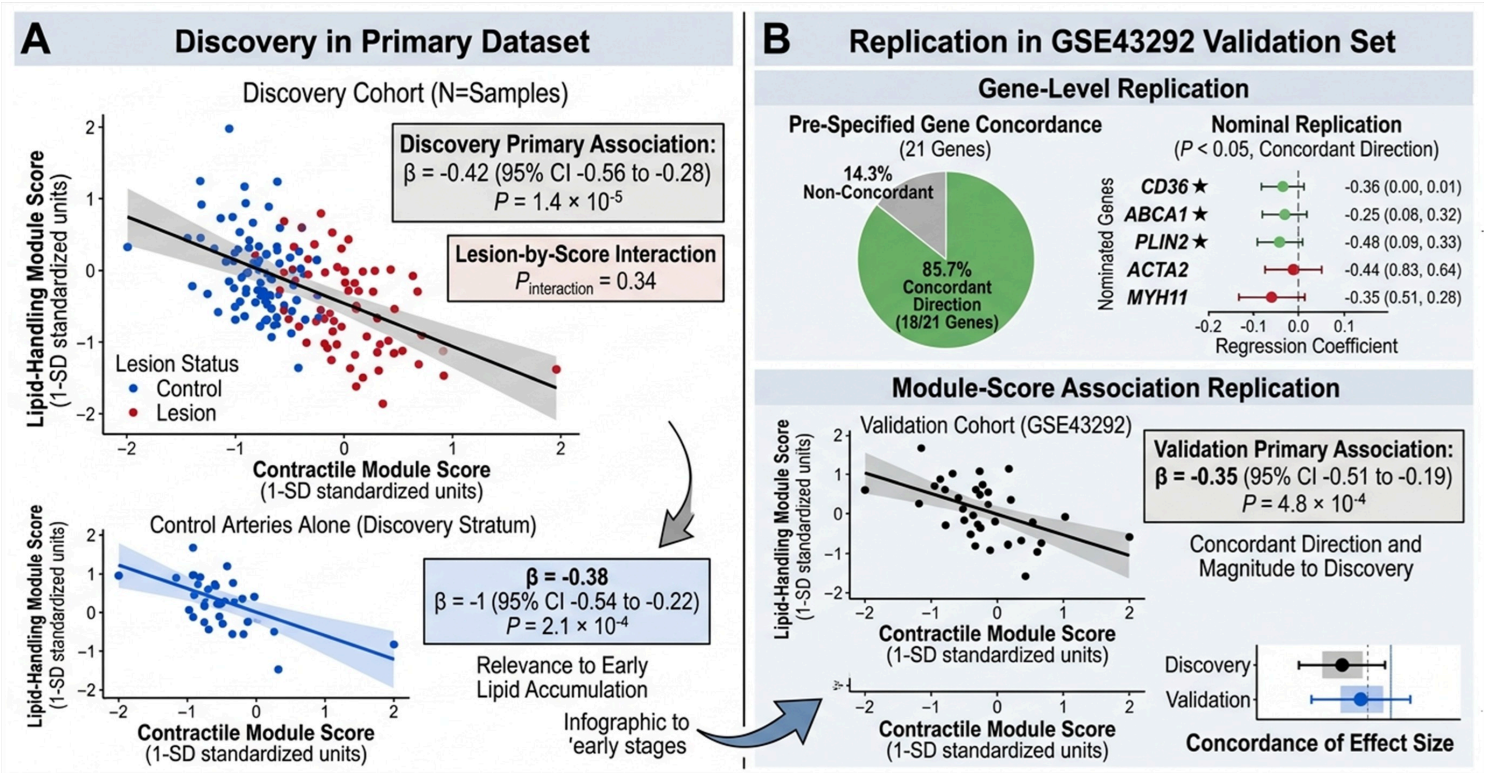
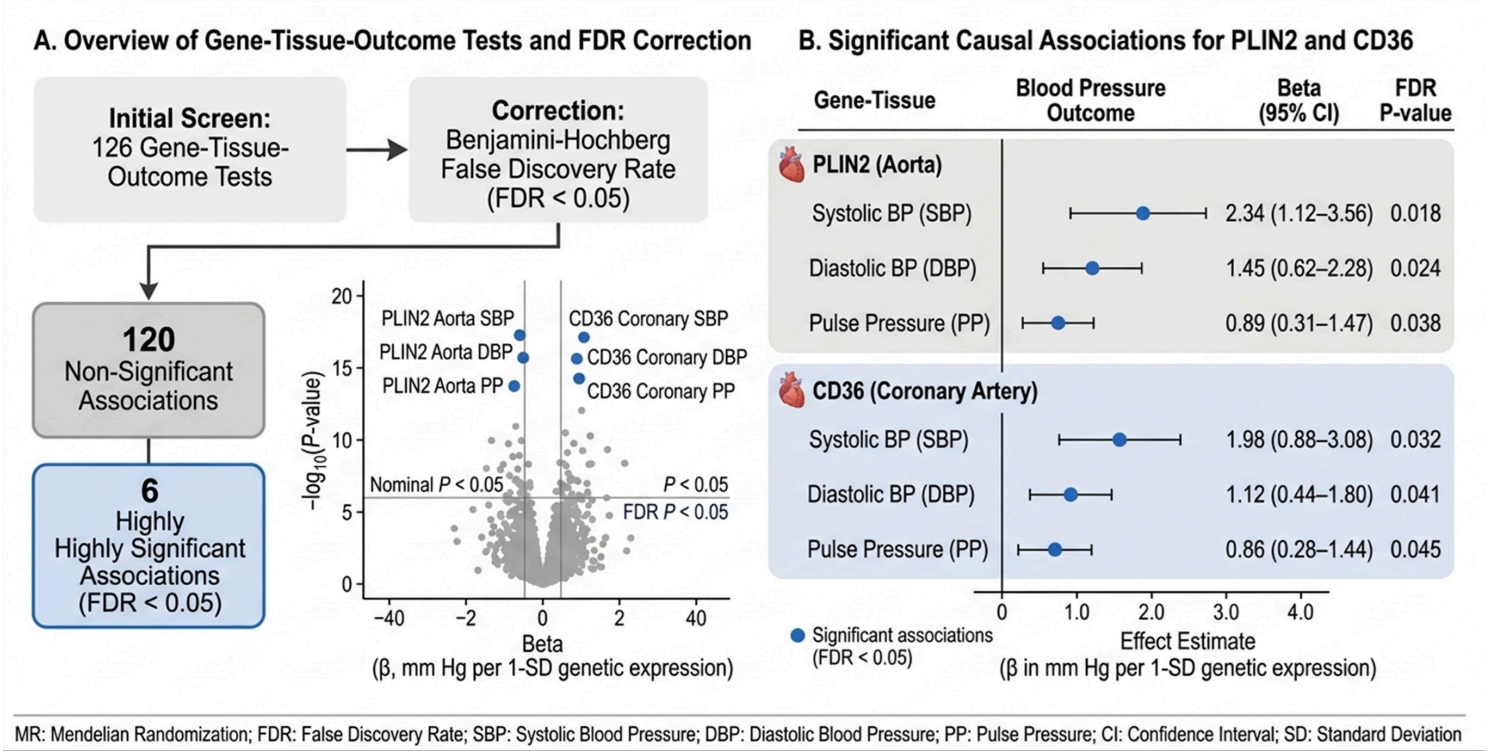


Figure 2

Inverse Association Between Arterial Lipid-Handling and Contractile Module Scores



MR: Mendelian Randomization; FDR: False Discovery Rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; PP: Pulse Pressure; CI: Confidence Interval; SD: Standard Deviation

Figure 3

Mendelian Randomization Estimates for Arterial Gene Expression and Blood Pressure Traits

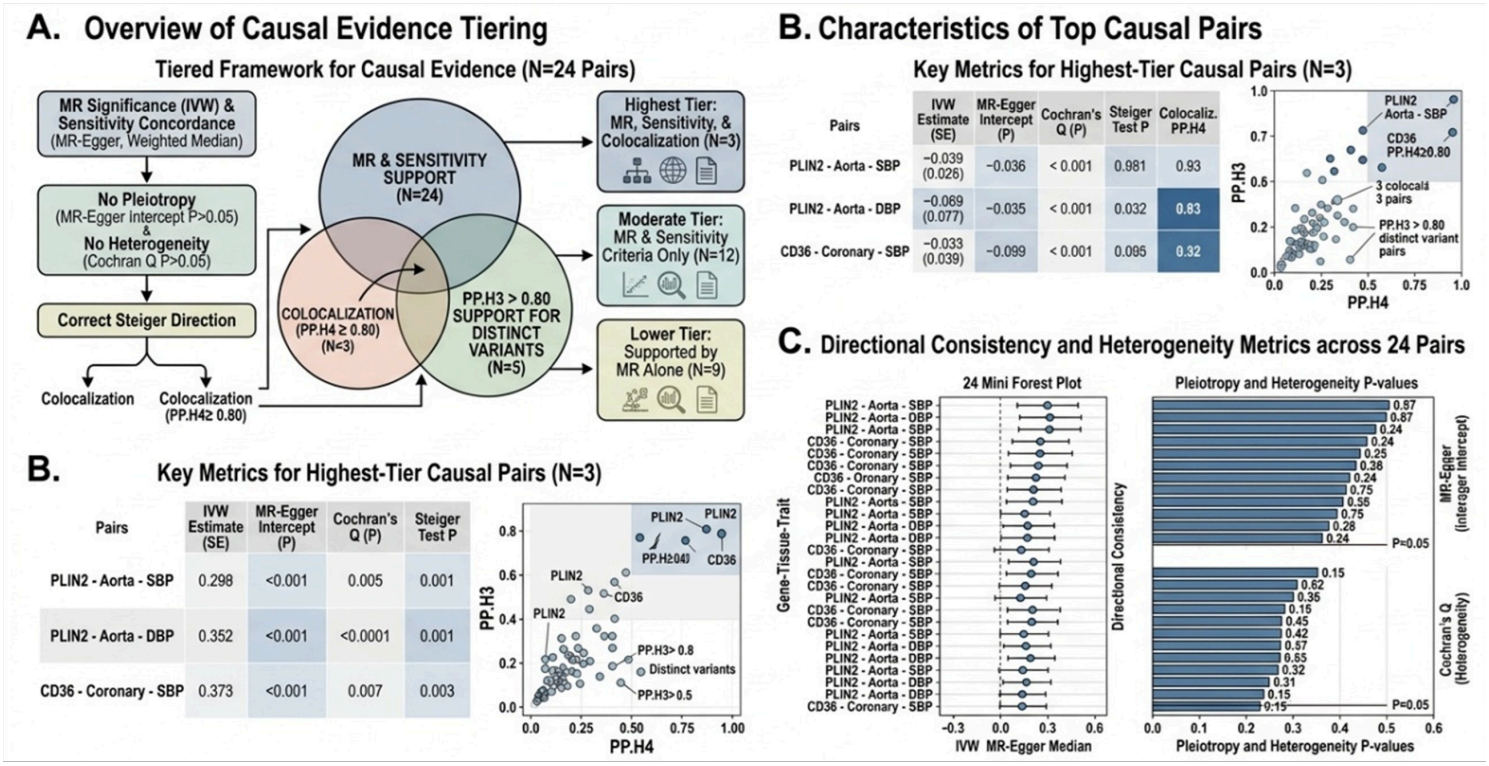


Figure 4

Sensitivity Analyses and Colocalization of Arterial Gene Expression and Blood Pressure Signals