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ORIGINAL RESEARCH

Cardiometabolic, Lifestyle, and Nutritional Factors in Relation to Varicose Veins: A Mendelian Randomization Study

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BACKGROUND: We conducted a 2-sample Mendelian randomization study to assess the associations of cardiometabolic, lifestyle, and nutritional factors with varicose veins.

METHODS AND RESULTS: Independent single-nucleotide polymorphisms associated with height (positive control), body mass index, type 2 diabetes, diastolic and systolic blood pressure, smoking, alcohol and coffee consumption, 7 circulating vitamins (A, B6, B9, B12, C, 25-hydroxyvitamin D, and E), and 5 circulating minerals (calcium, iron, magnesium, selenium, and zinc) at the genome-wide significance level were used as instrumental variables. Summary-level data for the genetic associations with varicose veins were obtained from the UK Biobank (8763 cases and 352 431 noncases) and the FinnGen consortium (13 928 cases and 153 951 noncases). Genetically predicted higher height, body mass index, smoking, and circulating iron levels were associated with an increased risk of varicose veins. The odds ratios (ORs) per 1-SD increase in the exposure were 1.34 (95% CI, 1.25–1.43) for height, 1.39 (95% CI, 1.27–1.52) for body mass index, 1.12 (95% CI, 1.04–1.22) for the prevalence of smoking initiation, and 1.24 (95% CI, 1.16–1.33) for iron. Higher genetically predicted systolic blood pressure and circulating calcium and zinc levels were associated with a reduced risk of varicose veins, whereas the association for systolic blood pressure did not persist after adjustment for genetically predicted height. The OR was 0.75 (95% CI, 0.62–0.92) per 1-SD increase in calcium levels and 0.97 (95% CI, 0.95–0.98) for zinc.

CONCLUSIONS: This study identified several modifiable risk factors for varicose veins.

Key Words: lifestyle ■ Mendelian randomization ■ metabolic ■ mineral ■ varicose veins

Varicose veins as a common manifestation of chronic venous disease affects >23% of adults in the United States.[1] Its high prevalence along with complications, such as chronic venous ulcers, impose a large burden on health care systems and society.[2] Recent studies showed that patients with varicose veins had a substantially greater risk of developing deep vein thrombosis[3] and suffered from impaired quality of life.[4]

Modifiable factors, including obesity, blood pressure, and lifestyle and nutritional factors have been shown to influence vascular health and to be associated with vascular-related diseases.[5,6] Epidemiological studies have associated age, sex (more common in women), obesity, pregnancy, and prior deep vein thrombosis to an increased risk of varicose veins.[7,8] A recent study based on data from 502 619 UK adults additionally proposed smoking and hypertension as potential modifiable risk factors for varicose veins.[9] Data on other modifiable factors, such as alcohol and coffee consumption and nutritional factors (eg, circulating levels of vitamins and minerals changed with dietary intake[10,11]), in relation to varicose veins are limited.[12] An exploration of the

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CLINICAL PERSPECTIVE

What Is New?

- Genetically predicted height, body mass index, smoking, and circulating iron levels were positively associated with risk of varicose veins, whereas genetically predicted systolic blood pressure and circulating calcium and zinc levels were inversely associated with the disease.
- The association for genetically predicted systolic blood pressure did not remain after adjustment for height.
- Genetically predicted coffee consumption and circulating vitamin B12 and magnesium levels were suggestively associated with varicose veins.
- There was no association of genetically predicted type 2 diabetes, alcohol consumption, circulating vitamin A, vitamin B6, folate, vitamin C, 25-hydroxyvitamin D, vitamin E, and selenium with varicose veins.

What Are the Clinical Implications?

- Strategies targeting the above-mentioned modifiable factors, such as lowering body mass index, reducing smoking initiation and encouraging smoking cessation, and avoiding excessive iron intake may prevent varicose veins and reduce corresponding disease burden.

Nonstandard Abbreviations and Acronyms

MR	Mendelian randomization

causal associations between these modifiable factors and varicose veins is of great importance in preventing or delaying disease progression.

Mendelian randomization (MR) analysis can strengthen causal inference in an exposure–outcome association by leveraging genetic variants as instrumental variables for a modifiable exposure.[13] The approach can diminish unobserved confounding because genetic variants are randomly assorted at conception and therefore unassociated with self-adapted lifestyle factors and behaviors. The method can also minimize reverse causation, because the onset and progression of a disease are unlikely to modify germline genotype. Previous MR studies have shown potential causal links of blood iron and several anthropometric traits, including weight and height, with risk of varicose veins.[9,14–16] However, MR evidence on other modifiable factors in relation to varicose veins is limited. Here, we conducted a 2-sample MR study to confirm previously established associations for varicose veins and to further explore the associations of other metabolic, lifestyle, and nutritional factors with risk of varicose veins.

METHODS

All data analyzed in this study are available in the Open Science Framework data respiratory (https://osf.io/9s3hd/).

Genetic Instrument Selection

Single-nucleotide polymorphisms (SNPs) associated with cardiometabolic (body mass index,[17] type 2 diabetes,[18] and systolic and diastolic blood pressure[19]), lifestyle (smoking initiation,[20] smoking index [defined by the method outlined by Leffondré et al,[21] taking into account smoking status as well as smoking duration, heaviness, and cessation in ever smokers],[22] alcohol,[20] and coffee consumption[23]) and nutritional factors (circulating vitamin A,[24] vitamin B6,[25] folate [vitamin B9],[26] vitamin B12,[26] vitamin C,[27] 25-hydroxyvitamin D,[28] vitamin E,[29] calcium,[30] iron,[31] magnesium,[32] selenium,[33] and zinc[34]) at the genome-wide significance threshold ($P<5\times10^{-8}$) were identified from corresponding genome-wide association studies. Linkage disequilibrium among SNPs for one exposure was estimated based on the 1000 Genomes European reference panel. Independent SNPs (SNPs without linkage disequilibrium, defined by $r^2<0.01$ and clump distance >10 000 kb) were selected as instruments. Information on used genome-wide association studies is presented in Table S1.

Positive Control

Standing height was used as a positive control for varicose veins.[9] Independent SNPs ($r^2<0.01$ and clump distance >10 000 kb) associated with height at the genome-wide significance level were used as instrumental variables from the Genetic Investigation of Anthropometric Traits consortium with 253 288 individuals of European ancestry.[35]

Data Sources

Summary-level data on the associations of exposure-associated SNPs with varicose veins were obtained from the UK Biobank study (8763 cases and 352 431 noncases) and the FinnGen consortium (13 928 cases and 153 951 noncases). Incident and prevalent cases of varicose veins were defined by the *International Classification of Diseases, Eighth and Ninth Revision (ICD-8/9)* code 454 and the *International Classification of Diseases, Tenth Revision* (*ICD-10*) code I83. The UK Biobank is a cohort study including 500 000 adults,

aged 40 to 69 years, across the UK from 2006 to 2010. In this study, data in UK Biobank were extracted from the second wave of genome-wide association analyses by the Neale Lab, where individuals of non-European ancestry, closely related individuals, individuals with sex chromosome aneuploidies, and individuals who had withdrawn consent were excluded.[36] The FinnGen consortium is a growing project studying genetic variation in relation to disease trajectories. We used data from the R4 release of genome-wide analysis results in FinnGen including a total of 218 792 individuals after the exclusion of individuals with ambiguous gender, high genotype missingness (>5%), excess heterozygosity (±4 SDs), and non-Finnish ancestry.[37]

Statistical Analysis

For exposures instrumented by at least 3 SNPs, the inverse-variance–weighted method under a multiplicative random-effects model was used as the primary statistical method; otherwise, the inverse-variance–weighted fixed-effects method was applied. Estimates from UK Biobank and FinnGen were combined using the fixed-effects meta-analysis method. Three sensitivity analyses, including the weighted median,[38] MR-Egger (Mendelian randomization-Egger),[39] and MR-PRESSO (Mendelian Randomization Pleiotropy Residual Sum and Outlier)[40] methods, were conducted to examine the robustness of the associations and to test for horizontal pleiotropy for exposures instrumented by ≥3 SNPs. The weighted median method provides consistent causal estimates when >50% of the weight comes from valid instruments.[38] The MR-Egger regression can detect unbalanced horizontal pleiotropy by its intercept and provides estimates after correction for pleiotropic effects but is limited by low statistical power.[39] The MR-PRESSO method can detect outlying SNPs and provides causal estimates after the removal of corresponding outliers.[40] For vitamins and minerals associated with varicose veins at $P<0.05$ in the inverse-variance–weighted analysis based on UK Biobank and FinnGen combined data, we performed colocalization analysis (calcium only because of lack of summary-level data for the other nutrients),[41] leave-one-out analysis,[42] and supplementary MR analysis using SNPs mapping to genes with a proximal biological link to the risk factor. Given that blood pressure and height are inversely correlated,[43] we performed multivariable MR analyses to assess the association between genetically predicted blood pressure and varicose veins with the adjustment for genetically predicted standing height and vice versa. Given sample overlap between exposure and outcome data sets for analysis in UK Biobank, we calculated the *F* statistic for all studied traits in UK Biobank (Table S2).[44] Conditional *F* statistic for systolic blood pressure (*F* statistic=34.2) in multivariable MR analysis was calculated using the MVMR (multivariable Mendelian randomization) package.[45] A Cochrane *Q* value was used to assess heterogeneity among estimates of individual SNPs in the analysis of one exposure. The false discovery rate method was used to correct for multiple testing (Table S3). Power was estimated using an online tool (Table S2).[46] All tests were 2-sided and performed using the TwoSampleMR,[47] MR-PRESSO,[40] Coloc,[41] and MendelianRandomization[48] packages in the R software (version 4.0.2).

Ethical Approval

All studies included in cited genome-wide association studies had been approved by a relevant review board. All participants had given informed consent. The MR analyses were approved by the Swedish Ethical Review Authority (2019-02793).

RESULTS

Higher genetically predicted height and body mass index was associated with an increased risk of varicose veins in both UK Biobank and FinnGen (Figure 1). For a 1-SD increment of genetically predicted height and body mass index, the combined odds ratio (OR) of varicose veins was 1.34 (95% CI, 1.25–1.43; $P<0.001$) and 1.39 (95% CI, 1.27–1.52; $P<0.001$), respectively. Genetically predicted systolic but not diastolic blood pressure was inversely associated with varicose veins (Figure 1). The combined ORs of varicose veins were 0.87 (95% CI, 0.79–0.96; $P=0.007$) and 0.92 (95% CI, 0.78–1.08; $P=0.315$) per 10-mm Hg increases in genetically predicted systolic and diastolic blood pressure, respectively. The associations were stable in sensitivity analyses (Table S4). However, the association for genetically predicted systolic blood pressure did not persist in the multivariable MR analysis with adjustment for genetically predicted height (Figure 1). Genetic liability to type 2 diabetes was not associated with varicose veins (Figure 1).

Among 3 studied lifestyle factors, genetic predisposition to smoking initiation showed a robust positive association with varicose veins risk (Figure 2). For a 1-SD increase in the log-transformed OR of genetic predisposition to smoking initiation, the OR of varicose veins was 1.12 (95% CI, 1.04–1.22; $P=0.004$) in the meta-analysis of UK Biobank and FinnGen. The positive association was replicated in the analysis of genetically predicted lifetime smoking index (combined OR, 1.31 [95% CI, 1.09–1.57]; $P=0.003$, for a 1-SD increase in the genetically predicted index). Higher genetically predicted coffee consumption was associated with a lower risk of varicose veins in UK Biobank (OR, 0.70 [95% CI, 0.58–0.84]; $P=0.002$, for a 50% increase in genetically predicted coffee

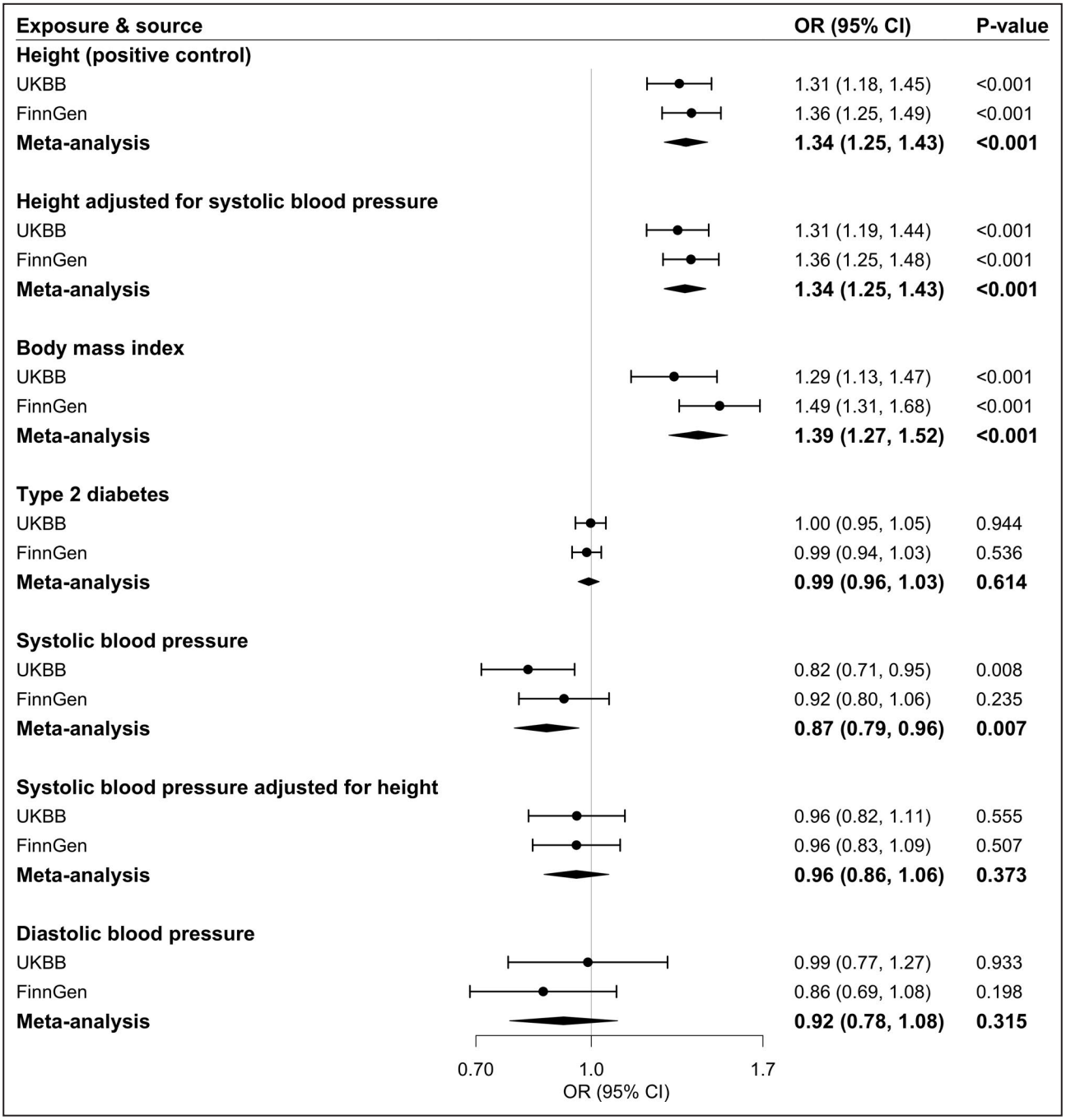

Figure 1. Associations of genetically predicted metabolic factors with risk of varicose veins.
Estimates were obtained from the univariable and multivariable inverse-variance–weighted method. ORs were scaled to a 1-SD increase in genetically predicted height and body mass index, 1-unit increase in log-transformed OR of type 2 diabetes, and 10-mm Hg increase in genetically predicted blood pressures. Circles represent the study-specific OR, and horizontal lines represent the 95% CI of the OR. Diamonds represent the meta-analysis OR estimate with it 95% CI. OR indicates odds ratio; and UKBB, UK Biobank.

consumption) but not in FinnGen (Figure 2). Genetically predicted alcohol consumption was not associated with varicose veins (Figure 2). The associations remained consistent in sensitivity analyses (Table S4).

Higher genetically predicted vitamin A (retinol) and vitamin B12 levels were associated with an elevated risk of varicose veins in UK Biobank; however, only the association for genetically predicted vitamin B12 was directionally replicated in FinnGen (Figure 3). For a 1-SD increase in genetically predicted vitamin B12 levels, the combined OR of varicose veins was 1.07 (95% CI, 1.01–1.14; P=0.032), whereas the combined

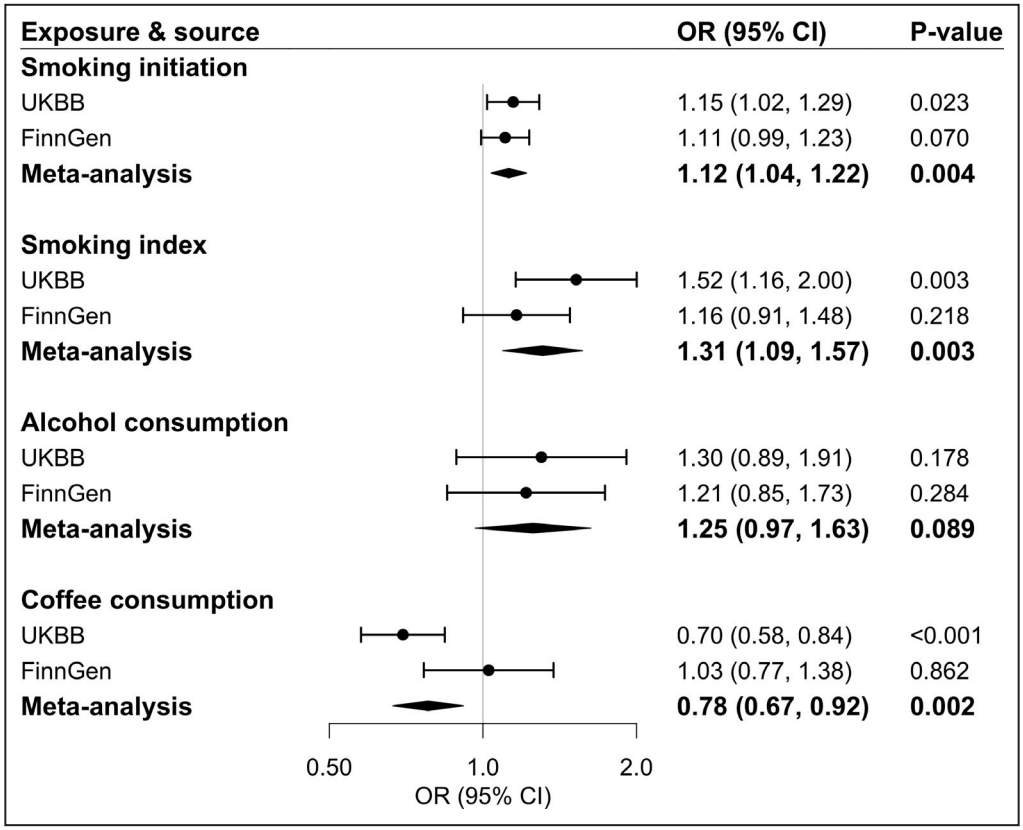

Figure 2. Associations of genetically predicted lifestyle factors with risk of varicose veins. Estimates were obtained from the inverse-variance–weighted method. ORs were scaled to a 1-SD increase in log-transformed OR of smoking initiation,1-SD increase in genetically predicted lifetime smoking index (equivalent to an individual smoking 20 cigarettes a day for 15 years and stopping 17 years ago or an individual smoking 60 cigarettes a day for 13 years and stopping 22 years ago), 1-SD increase in log-transformed alcoholic drinks per week, and 50% increase of genetically predicted coffee consumption. Circles represent the study-specific OR, and horizontal lines represent the 95% CI of the OR. Diamonds represent the meta-analysis OR estimate with it 95% CI. OR indicates odds ratio; and UKBB, UK Biobank.

association for genetically predicted vitamin B12 did not survive multiple testing correction. The association for vitamin B12 was consistent in leave-one-out analysis (Table S5) and in the analysis based on rs602662 in *FUT2* (Table S6), which plays a role in vitamin B12 absorption.[49] Genetically predicted vitamin C levels were positively associated with risk of varicose veins in FinnGen (OR, 1.24 [95% CI, 1.05–1.48]; *P*=0.014, for a 1-SD increase in genetically predicted vitamin C levels) but not in UK Biobank (Figure 3). Genetically predicted vitamin B6, folate, 25-hydroxyvitamin D, and vitamin E were not associated with varicose veins (Figure 3).

Higher genetically predicted calcium and zinc levels were associated with a decreased risk of varicose veins, whereas genetically predicted iron levels were positively associated with the disease (Figure 4). The combined ORs per 1-SD increase in genetically predicted circulating levels of these minerals were 0.75 (95% CI, 0.62–0.92; *P*=0.005) for calcium, 0.97 (95% CI, 0.95–0.98; *P*<0.001) for zinc, and 1.24 (95% CI, 1.16–1.33; *P*<0.001) for iron (Figure 4). The association remained consistent in leave-one-out analysis (Table S5). The association for calcium persisted in the analysis based on rs1801725 located in the *CASR* gene that encodes the calcium-sensing receptor, and the association for iron remained in the analysis based on SNPs in *HFE* and *TMPRSS6* genes that regulate iron homeostasis (Table S6). The colocalization analysis of calcium did not have adequate power to detect a causal link with varicose veins (Table S7). Genetically predicted selenium and magnesium levels were not associated with varicose veins (Figure 4). However, the inverse association between genetically predicted magnesium and varicose veins became clearer in the weighted median and MR-Egger analyses (Table S4).

We detected moderate heterogeneity in the analyses of height, body mass index, blood pressure, smoking initiation, lifetime smoking index, and

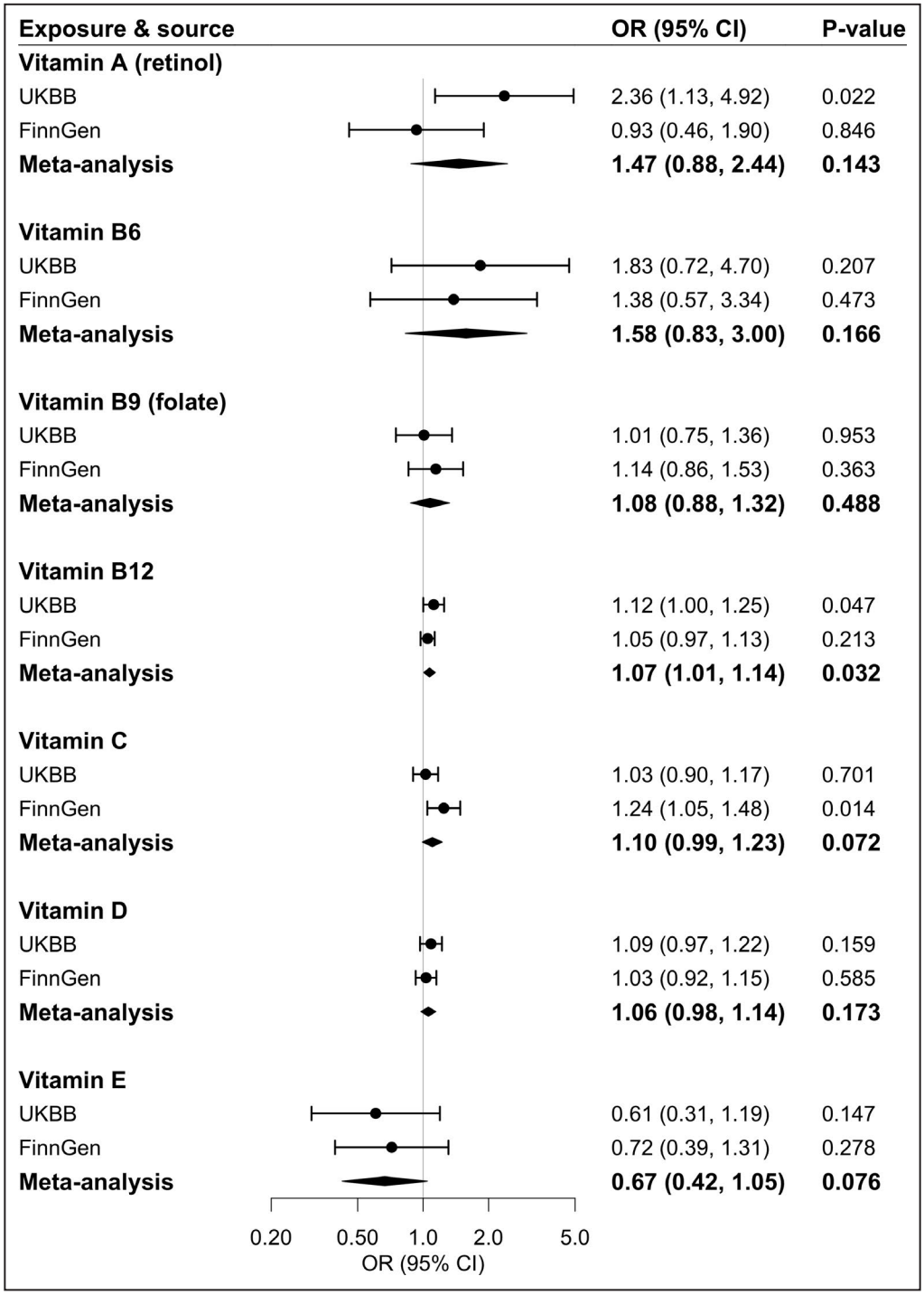

Figure 3. Associations of genetically predicted circulating vitamins with risk of varicose veins. Estimates were obtained from the inverse-variance–weighted method. ORs were scaled to a 1-unit increase in natural logarithm (ln)-transformed levels of genetically predicted vitamin A in micrograms per liter, 1-SD increase in genetically predicted vitamin B6, folate, B12, C and D levels, and 1-unit increase in ln–transformed levels of genetically predicted vitamin E in milligrams per liter. Circles represent the study-specific OR, and horizontal lines represent the 95% CI of the OR. Diamonds represent the meta-analysis OR estimate with it 95% CI. OR indicates odds ratio; and UKBB, UK Biobank.

alcohol consumption (Table S4). Horizontal pleiotropy indicated by the intercept in MR-Egger regression (P<0.05) was observed in the analyses of blood pressure and smoking initiation, and the associations of these exposures with varicose veins became stronger after adjustment for this horizontal pleiotropy

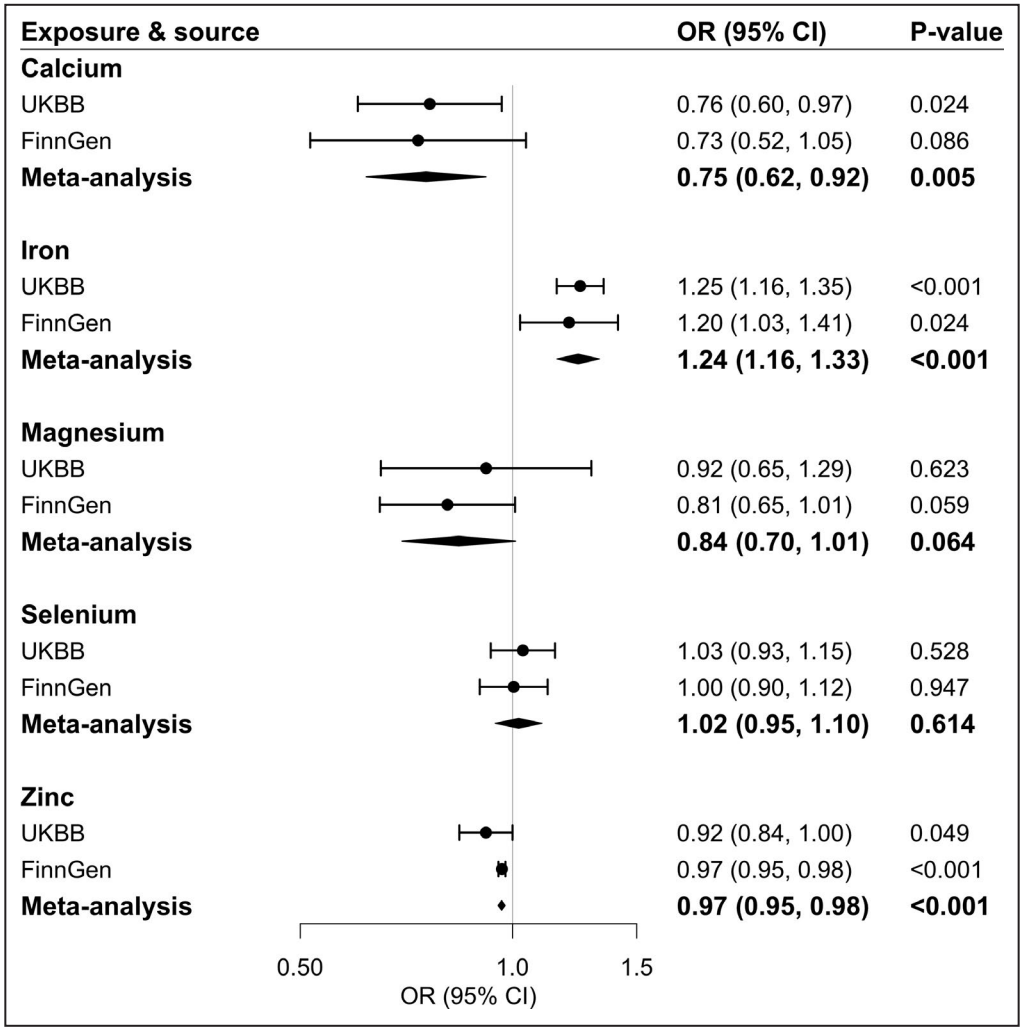

Figure 4. Associations of genetically predicted circulating minerals with risk of varicose veins. Estimates were obtained from the inverse-variance–weighted method. ORs were scaled to a 1-SD increase in genetically predicted calcium, iron, and magnesium levels and 1-unit increase in log-transformed levels of genetically predicted toenail selenium in micrograms per gram. The unit for zinc is unknown. Circles represent the study-specific OR, and horizontal lines represent the 95% CI of the OR. Diamonds represent the meta-analysis OR estimate with it 95% CI. OR indicates odds ratio; and UKBB, UK Biobank.

(Table S4). A few outliers were detected in the MR-PRESSO analysis (Table S4).

DISCUSSION

The present study found that genetically predicted higher height (positive control), body mass index, smoking, and higher circulating iron levels were associated with an increased risk of varicose veins, whereas genetically predicted systolic blood pressure and circulating calcium and zinc levels were inversely associated with the disease. However, the association for genetically predicted systolic blood pressure did not remain after adjustment for genetically predicted height. There was suggestive evidence in support of associations of genetically predicted coffee consumption and circulating vitamin B12 and magnesium levels with varicose veins. There was limited evidence in support of associations for genetically predicted type 2 diabetes, alcohol consumption, circulating vitamin A, vitamin B6, folate, vitamin C, 25-hydroxyvitamin D, vitamin E, and selenium, whereas power for these analyses might be inadequate.

We validated our outcome data using genetically predicted height as the positive control.[9] A positive association between body mass index and risk of varicose veins is a consistent finding in previous traditional observational studies[7–9,50] and supported the present MR study. In the largest of previous studies, including 493 519 British adults followed up for a median of 6.2 years, the risk of incident varicose veins increased

by 11% per 1-kg/m^2 increase in body mass index.[9] The same study also found an inverse association between systolic blood pressure and risk of varicose veins,[9] a finding confirmed by another previous study[51] and our MR study, but not all studies.[7,8] The association for systolic blood pressure did not remain after adjusting for genetically predicted height, which indicated that the observed association for systolic blood pressure was caused by pleiotropy from height.

Evidence on the association between smoking and varicose veins is inconsistent. Some studies observed an elevated risk of varicose veins in smokers compared with nonsmokers,[7,52] whereas other studies failed to replicate this positive association.[53–55] A large cohort study reported a suggestive positive association between current smoking and varicose veins after adjustment for traditional risk factors and genetic ancestry.[9] The present study using 2 sets of genetic instruments for smoking and 2 data sources for varicose veins found a strong causal association of smoking initiation and lifetime smoking index with an increased risk of varicose veins.

Studies on alcohol and coffee consumption in relation to varicose veins are limited. An MR phenome-wide association study showed that certain coffee-consumption–associated SNPs in *ABCG2* and *BDNF* gene regions were associated with varicose veins in the UK Biobank study.[56] We also observed an inverse association between coffee consumption instrumented by 12 SNPs and varicose veins in the UK Biobank study. However, the association was not replicated in Finnish adults, a population with the highest per capita consumption of coffee. Genetically predicted coffee consumption is also associated with standard tea consumption in UK Biobank,[57] and it is possible that the observed association in the UK population is related to consumption of tea, which contains thousands of biological compounds with potential cholesterol-lowering and antioxidative effects.[58] In addition, we noticed a sample overlap for the analysis of coffee consumption in UK Biobank, which might bias the causal estimation in MR analysis. The discrepancy in the association for coffee consumption with varicose veins between 2 populations might be explained by this sample overlap. Although we observed no association between genetically predicted alcohol consumption and varicose veins, the association was in the positive direction in both populations. Considering the low variance explained by the genetic instrument for alcohol, we cannot rule out that a weak association was overlooked.[59]

Data on the associations of vitamins and minerals with varicose veins are scarce. A small case-control study found that patients with varicose veins had more hyperhomocysteinemia, which was caused by the *MTHFR C677T* homozygous genotype or vitamin B12 deficiency, compared with the controls.[60] Nevertheless, another small case-control study found no difference in circulating ferritin, vitamin B12, folate, or homocysteine level in patients with varicose veins compared with the controls.[61] We observed a possibly elevated risk of varicose veins with higher circulating levels of vitamin B12 with validated genetic instruments.[62,63] A previous MR study observed a positive association between blood iron levels instrumented by 3 SNPs and risk of varicose veins in 310 999 unrelated UK Biobank participants,[15] with a robust association in both sexes.[14] We replicated the association with more SNPs and confirmed the association in a Finnish population, therefore strengthening the evidence of a causal detrimental role of high circulating iron levels in the development of varicose veins. The observed protective associations of high levels of calcium and zinc and possibly magnesium with risk of varicose veins in 2 independent populations. The association for calcium was observed in the analysis based on the SNP located in the *CASR* gene (encoding calcium-sensing receptor) but not in the colocalization analysis. These findings were novel and need confirmation.

Although the mechanisms linking the studied exposures to risk of varicose veins are not fully understood, several explanations are proposed, such as venous endothelial injury caused by cigarette smoking, systemic inflammation activated by smoking, obesity, and high iron status.[12] In addition, the beneficial effects of calcium and zinc may be a consequence of moisturizing vein cells, relaxing veins and thus preventing and deferring structural changes in the vein wall.[12,64]

There are several strengths of the present study, of which the main one is the MR design. This study design diminished residual confounding and reverse causality and strengthened the causal inference in the observed exposure–varicose vein associations. We examined associations in 2 independent populations, and the high consistency of results reduces the likelihood that the observed associations are chance findings. The meta-analysis of 2 sources also increases the number of cases and the statistical power of the analyses. Despite this, we might have overlooked weak associations, in particular in analyses based on instruments explaining a small proportion of the phenotypic variance. In addition, we confined the analysis to individuals of European descent, which reduced potential bias introduced by population structure but limited the generalizability of our findings to other populations.

Limitations deserve consideration when interpreting our findings. An important limitation in MR studies is horizontal pleiotropy. However, we did not detect any horizontal pleiotropy in MR-Egger analyses of the studied exposures with the exception for blood pressure. The associations for systolic blood pressure

persisted in the MR-Egger regression with adjustment for pleiotropic effects and MR-PRESSO analysis with the removal of outliers. Associations across sensitivity analyses were consistent, which reinforced our results and minimized the possibility that our findings were biased by horizontal pleiotropy, whereas sensitivity analyses were unavailable with regard to several exposures proxied by few SNPs. In addition, results of the weighted median analysis for the exposure with a few SNPs might be driven by the estimate of a single SNP that explains the majority of phenotypic variance. For certain traits proxied by SNPs that explained limited phenotypic variance, this study might have had inadequate power to detect associations with varicose veins (false negative findings). We detected moderate to high sample overlap for certain exposures in the analyses based on data from UK Biobank, which would bias the causal estimates toward observational estimates. However, the corresponding *F* statistics for these associations were >10, which means a good strength of used genetic instruments and a minimal bias caused by sample overlap.[44] SNPs for vitamin B6 and zinc were identified from genome-wide association studies with a small sample size, which might introduce imprecision in SNP selection for these traits. Furthermore, genetic instruments that we used might not be strongly associated with the exposure in the outcome population given that no replication was conducted for these associations in UK Biobank or FinnGen. In addition, the summary-level data for these associations in the genome-wide association studies on the exposure could be inflated because of winner's curse and thus bias the MR results in the direction away from the null. Future study is needed to confirm our findings. Circulating levels of vitamins and minerals do not necessarily equate to dietary intake, whereas endogenous levels of nutrients increase with exogenous dietary consumption over a certain range of intake.[10,11] For certain factors, such as alcohol and coffee consumption and circulating biomarkers, nonlinear associations could not be explored in this study based on summary-level data.

In conclusion, this MR study provides results in support of causal associations between several metabolic, lifestyle, and nutritional factors and risk of varicose veins. Strategies targeting these modifiable factors, such as lowering body mass index, reducing smoking initiation and encouraging smoking cessation, and avoiding excessive iron intake may prevent varicose veins and reduce corresponding disease burden. The associations of coffee consumption, vitamin B12, calcium, zinc, and magnesium with varicose veins need more study.

ARTICLE INFORMATION

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Author contributions: S. Yuan and Drs Damrauer and Larsson designed the study. S. Yuan analyzed the data, made the figures, and drafted the article. S. Yuan and Drs Bruzelius, Damrauer, and Larsson contributed with critical review of the interpretation and the article, and approved the final version of the article.

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Disclosures

S. Yuan and Drs Bruzelius and Larsson declare no competing interests. Dr Damrauer receives research support from RenalytixAI and personal consulting fees from Calico Labs, outside the scope of the current research.

Supplementary Material

Tables S1–S7

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SUPPLEMENTARY MATERIAL

Table S1. Characteristics of used studies and consortia

Table S2. Sample overlap, F-statistic, and power estimation

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Table S4. Associations of metabolic, lifestyle and nutritional factors with varicose veins in sensitivity analyses

Table S5. Associations of nutritional factors with varicose veins in the leave-one-out analysis

Table S6. Associations of genetically predicted vitamin B12, calcium and iron with varicose veins in the analysis based on SNPs in protein encoding genes

Table S7. Colocalization analysis results for genetic associations with calcium and varicose veins in UK Biobank

Table S1. Characteristics of used studies and consortia

Exposure or outcome	Unit	Instruments	Participants	Adjustments	PubMed ID or URL
Height (positive control)	SD	236	253 288 individuals of European ancestry	The first 20 principal components	25282103
Body mass index	SD	312	806 834 individuals of European ancestry	Age, sex and genetic 1-5 principal components	30239722
Type 2 diabetes	One-unit in log-transformed odds ratio of type 2 diabetes	497	228 499 type 2 diabetes cases and 1 178 783 non-cases of multi-ancestries	Age, sex, and the first 10 genetic principal components	32541925
Systolic blood pressure	10 mmHg	231	Up to 1 006 863 individuals of European ancestry	Age, sex, BMI, genotyping chips	30224653
Diastolic blood pressure	10 mmHg	278	Up to 1 006 863 individuals of European ancestry	Age, sex, BMI, genotyping chips	30224653
Smoking initiation	SD increase of log-transformed odds ratio of smoking initiation	314	1 232 091 European-descent individuals	Age, sex, and the first 10 genetic principal components	30643251
Lifetime smoking index	SD	126	462 690 European-descent individuals	Sex, assay batch, population stratification and relatedness	31689377
Alcohol consumption	SD increase of log-transformed alcoholic drinks/week	84	941 280 European-descent individuals	Age, sex, and the first 10 genetic principal components	30643251
Coffee consumption	50% change	12	375 833 European-descent individuals	Age, sex, BMI, total energy, proportion of typical food intake, and 20 genetic principal components	31046077
Vitamin A (retinol)	ln(ug/L)	2	5006 European-descent individuals	Age, case status, BMI, serum cholesterol, population structure	21878437
Vitamin B6	SD	1	1864 European-descent individuals	Not reported	19303062
Folate (vitamin B9)	SD	2	37 341 European-descent individuals	Age, sex and year of birth	23754956
Vitamin B12	SD	12	45 576 European-descent individuals	Age, sex and year of birth	23754956

Vitamin C	SD	10	52 018 individuals of European descent	Age, sex, the first 10 genetic principal components and study center	33203707
Vitamin D	SD	6	79 366 European-descent individuals	Age, sex, BMI, month of sample collection, principal components, geographical location and assay batch	29343764
Vitamin E	ln(mg/L)	3	7781 European-descent individuals	Age, BMI, cholesterol and cancer status	21729881
Calcium	SD	7	39 400 European-descent individuals	Age, sex, principal components and study center	24068962
Iron	SD	5	48 972 European-descent individuals	Age, sex and principal components	25352340
Zinc	SD	3	2603 European-descent individuals	Age and sex,	23720494
Selenium	log(µg/g)	2	9639 European-descent individuals	Age sex, smoking status, geographical location, principal components and study center	25343990
Magnesium	SD	6	15 366 European-descent individuals	Age, sex and study center	20700443
Varicose veins	One-unit in log-transformed odds ratio of varicose veins	-	8763 cases and 352 431 non-cases of European ancestry	Age, sex, and up to 20 genetic principal components	UK Biobank (http://www.nealelab.is/uk-biobank)
Varicose veins	One-unit in log-transformed odds ratio of varicose veins	-	13 928 cases and 153 951 non-cases of European ancestry	Age, sex, 10 genetic principal components, and genotyping batch	FinnGen consortium (https://www.finngen.fi/fi)

SD = standard deviation; SNPs = single nucleotide polymorphisms.
Cases of varicose veins in UK Biobank and FinnGen include both incident and prevalent cases.

Table S2. Sample overlap, F-statistic, and power estimation

Exposure	Overlap with UK Biobank	Variance explained by instruments	F-statistic	OR with 80% power in UK Biobank	OR with 80% power in FinnGen
Height (positive control)	0%	14%-16%	175-204	<0.92 or >1.08	<0.93 or >1.07
Body mass index	60%	7.7%	216	<0.89 or >1.11	<0.91 or >1.09
Type 2 diabetes	31%	NA	NA	NA	NA
Systolic blood pressure	46%	4.8%	220	<0.86 or >1.14	<0.89 or >1.12
Diastolic blood pressure	46%	4.5%	171	<0.85 or >1.15	<0.88 or >1.12
Smoking initiation	61%	2.3%	92	<0.80 or >1.20	<0.84 or >1.17
Lifetime smoking index	100%	NA	NA	NA	NA
Alcohol consumption	61%	0.3%	34	<0.45 or >1.56	<0.56 or >1.47
Coffee consumption	89%	0.5%	157	<0.58 or >1.43	<0.66 or >1.36
Vitamin A (retinol)	0%	2.3%	59	<0.80 or >1.20	<0.84 or >1.17
Vitamin B6	0%	1.4%	26	<0.75 or >1.26	<0.79 or >1.22
Folate (vitamin B9)	0%	1.0%	189	<0.70 or >1.31	<0.75 or >1.26
Vitamin B12	0%	6.3%	219	<0.80 or >1.12	<0.90 or >1.10
Vitamin C	0%	1.9%	101	<0.78 or >1.22	<0.82 or >1.18
Vitamin D (25-hydroxyvitamin D)	0%	2.8%	381	<0.82 or >1.19	<0.85 or >1.15
Vitamin E	0%	1.7%	45	<0.77 or >1.24	<0.81 or >1.20
Calcium	0%	NA	NA	NA	NA
Iron	0%	3.3%	334	<0.83 or >1.17	<0.86 or >1.14
Zinc	0%	8.0%	75	<0.89 or >1.11	<0.91 or >1.09
Selenium	0%	2.3%	113	<0.80 or >1.20	<0.83 or >1.17
Magnesium	0%	1.6%	42	<0.76 or >1.24	<0.80 or >1.20

NA, not available; OR, odds ratio.
OR in power calculation was based on per standard deviation of the exposure variable. Power estimation was using the online tool: https://shiny.cnsgenomics.com/mRnd/

Table S3. Results of False Discovery Rate correction

Exposure	Original P value	Critical Value	Benjamini-Hochberg adjusted P value	Significant after correction
Height	0.000	0.002	0.000	Yes
Body mass index	0.000	0.005	0.000	Yes
Iron	0.000	0.007	0.000	Yes
Zinc	0.000	0.010	0.000	Yes
Coffee consumption	0.002	0.012	0.008	Yes
Smoking index	0.003	0.014	0.011	Yes
Smoking initiation	0.004	0.017	0.012	Yes
Calcium	0.005	0.019	0.013	Yes
Systolic blood pressure	0.007	0.021	0.016	Yes
Vitamin B12	0.032	0.024	0.067	No
Magnesium	0.064	0.026	0.122	No
Vitamin C	0.072	0.029	0.126	No
Vitamin E	0.076	0.031	0.123	No
Alcohol consumption	0.089	0.033	0.134	No
Vitamin A	0.143	0.036	0.200	No
Vitamin B6	0.166	0.038	0.218	No
25-hydroxyvitamin D	0.173	0.040	0.214	No
Diastolic blood pressure	0.315	0.043	0.368	No
Vitamin B9	0.488	0.045	0.539	No
Type 2 diabetes	0.614	0.048	0.645	No
Selenium	0.614	0.050	0.614	No

Table S4. Associations of metabolic, lifestyle and nutritional factors with varicose veins in sensitivity analyses

Source	Exposures	SNPs	Cochrane's Q	Weighted median		MR-Egger			MR-PRESSO		
				OR (95% CI)	P	OR (95% CI)	P	$P_{intercept}$	Outlier	OR (95% CI)	p
UKBB	Height	235	476	1.32 (1.17, 1.47)	<0.001	1.54 (1.19, 1.98)	0.001	0.192	8	1.30 (1.20, 1.41)	<0.001
FinnGen	Height	234	444	1.33 (1.20, 1.48)	<0.001	1.30 (1.03, 1.65)	0.029	0.686	5	1.38 (1.27, 1.50)	<0.001
Meta-analysis	Height			1.32 (1.23, 1.43)	<0.001	1.41 (1.18, 1.67)	<0.001			1.34 (1.27, 1.42)	<0.001
UKBB	Body mass index	311	466	1.34 (1.11, 1.61)	0.003	1.54 (1.11, 2.14)	0.010	0.251	2	1.24 (1.09, 1.41)	0.001
FinnGen	Body mass index	305	438	1.67 (1.37, 2.05)	<0.001	1.68 (1.24, 2.28)	0.001	0.385	1	1.50 (1.33, 1.70)	<0.001
Meta-analysis	Body mass index			1.49 (1.29, 1.70)	<0.001	1.62 (1.29, 2.02)	<0.001			1.37 (1.25, 1.50)	<0.001
UKBB	Type 2 diabetes	491	767	0.95 (0.88, 1.02)	0.180	0.94 (0.85, 1.04)	0.233	0.185	3	1.00 (0.95, 1.04)	0.847
FinnGen	Type 2 diabetes	472	718	0.99 (0.92, 1.06)	0.737	0.95 (0.86, 1.03)	0.223	0.294	2	0.99 (0.95, 1.04)	0.805
Meta-analysis	Type 2 diabetes			0.97 (0.92, 1.02)	0.229	0.94 (0.88, 1.01)	0.087			1.00 (0.96, 1.03)	0.755
UKBB	Systolic BP	229	360	0.90 (0.75, 1.07)	0.235	0.50 (0.29, 0.86)	0.014	0.066	2	0.82 (0.71, 0.94)	0.004
FinnGen	Systolic BP	217	354	0.93 (0.78, 1.10)	0.391	0.53 (0.32, 0.90)	0.018	0.034	3	0.93 (0.82, 1.06)	0.265
Meta-analysis	Systolic BP			0.91 (0.81, 1.03)	0.149	0.52 (0.36, 0.76)	0.001			0.87 (0.80, 0.96)	0.005
UKBB	Diastolic BP	278	568	1.27 (0.97, 1.67)	0.087	0.66 (0.28, 1.55)	0.342	0.333	4	1.13 (0.90, 1.41)	0.288
FinnGen	Diastolic BP	258	481	0.81 (0.62, 1.06)	0.118	0.21 (0.10, 0.43)	<0.001	<0.001	4	0.89 (0.73, 1.09)	0.251
Meta-analysis	Diastolic BP			1.01 (0.83, 1.22)	0.937	0.34 (0.20, 0.60)	<0.001			0.99 (0.85, 1.15)	0.887
UKBB	Smoking initiation	312	438	1.14 (0.98, 1.33)	0.087	1.82 (1.12, 2.95)	0.017	0.057	2	1.12 (1.00, 1.25)	0.054
FinnGen	Smoking initiation	297	372	1.15 (0.99, 1.34)	0.065	1.74 (1.10, 2.73)	0.018	0.046	1	1.12 (1.00, 1.24)	0.045
Meta-analysis	Smoking initiation			1.15 (1.03, 1.28)	0.012	1.77 (1.27, 2.47)	0.001			1.12 (1.03, 1.21)	0.005
UKBB	Smoking index	126	226	1.26 (0.91, 1.75)	0.162	2.27 (0.77, 6.69)	0.140	0.456	2	1.40 (1.09, 1.79)	0.009
FinnGen	Smoking index	124	188	1.17 (0.86, 1.59)	0.326	0.90 (0.33, 2.48)	0.839	0.610	1	1.20 (0.95, 1.52)	0.130
Meta-analysis	Smoking index			1.21 (0.97, 1.52)	0.094	1.39 (0.66, 2.91)	0.385			1.29 (1.09, 1.53)	0.003
UKBB	Alcohol consumption	84	142	1.37 (0.82, 2.30)	0.235	1.83 (0.87, 3.87)	0.118	0.303	2	1.31 (0.94, 1.81)	0.113
FinnGen	Alcohol consumption	80	103	1.45 (0.89, 2.36)	0.133	1.66 (0.69, 4.01)	0.260	0.446	0	NA	NA
Meta-analysis	Alcohol consumption			1.41 (0.99, 2.01)	0.056	1.76 (0.99, 3.11)	0.052			NA	NA
UKBB	Coffee consumption	12	8	0.67 (0.49, 0.90)	0.008	0.48 (0.31, 0.73)	0.007	0.069	0	NA	NA
FinnGen	Coffee consumption	12	20	0.88 (0.66, 1.18)	0.395	0.79 (0.45, 1.38)	0.427	0.308	1	0.98 (0.81, 1.18)	0.814
Meta-analysis	Coffee consumption			0.77 (0.63, 0.95)	0.014	0.57 (0.41, 0.81)	0.001			NA	NA
UKBB	Vitamin B12	12	25	1.04 (0.93, 1.16)	0.514	1.10 (0.92, 1.31)	0.322	0.807	1	1.05 (0.96, 1.15)	0.281
FinnGen	Vitamin B12	12	13	0.99 (0.91, 1.08)	0.787	0.96 (0.86, 1.07)	0.464	0.061	0	NA	NA
Meta-analysis	Vitamin B12			1.01 (0.94, 1.08)	0.863	0.99 (0.91, 1.09)	0.904			NA	NA
UKBB	Vitamin C	10	7	0.96 (0.78, 1.17)	0.666	0.87 (0.68, 1.11)	0.283	0.115	0	NA	NA
FinnGen	Vitamin C	10	10	1.15 (0.93, 1.43)	0.194	1.20 (0.87, 1.64)	0.300	0.765	0	NA	NA
Meta-analysis	Vitamin C			1.05 (0.90, 1.21)	0.560	0.98 (0.81, 1.19)	0.825			NA	NA
UKBB	Vitamin D	6	7	1.09 (0.97, 1.23)	0.150	1.10 (0.90, 1.36)	0.409	0.873	0	NA	NA
FinnGen	Vitamin D	6	6	1.02 (0.90, 1.14)	0.779	1.09 (0.90, 1.31)	0.441	0.533	0	NA	NA
Meta-analysis	Vitamin D			1.05 (0.97, 1.14)	0.223	1.09 (0.95, 1.26)	0.210			NA	NA
UKBB	Vitamin E	3	2	0.74 (0.28, 1.91)	0.528	12.97 (0.07, 2315)	0.510	0.450	NA	NA	NA
FinnGen	Vitamin E	3	2	0.71 (0.31, 1.60)	0.404	14.5 (0.11, 1848)	0.475	0.435	NA	NA	NA
Meta-analysis	Vitamin E			0.72 (0.39, 1.34)	0.297	13.77 (0.40, 475)	0.147			NA	NA

UKBB	Calcium	7	6	0.76 (0.57, 1.01)	0.057	0.82 (0.51, 1.31)	0.439	0.745	0	NA	NA
FinnGen	Calcium	7	14	0.83 (0.64, 1.09)	0.184	0.78 (0.38, 1.59)	0.519	0.861	0	NA	NA
Meta-analysis	Calcium			0.80 (0.66, 0.97)	0.023	0.81 (0.54, 1.19)	0.279			NA	NA
UKBB	Iron	5	2	1.27 (1.13, 1.44)	0.000	1.31 (1.08, 1.60)	0.075	0.606	0	NA	NA
FinnGen	Iron	5	8	1.20 (1.04, 1.39)	0.013	1.27 (0.89, 1.82)	0.279	0.743	0	NA	NA
Meta-analysis	Iron			1.25 (1.13, 1.37)	<0.001	1.30 (1.10, 1.55)	0.003			NA	NA
UKBB	Magnesium	6	16	0.87 (0.65, 1.16)	0.345	0.39 (0.18, 0.85)	0.077	0.086	1	1.17 (0.85, 1.61)	0.395
FinnGen	Magnesium	6	7	0.79 (0.63, 0.99)	0.043	0.43 (0.25, 0.75)	0.042	0.081	0	NA	NA
Meta-analysis	Magnesium			0.82 (0.69, 0.98)	0.030	0.42 (0.27, 0.66)	<0.001			NA	NA
UKBB	Zinc	3	2	0.92 (0.82, 1.02)	0.114	0.74 (0.46, 1.20)	0.438	0.541	0	NA	NA
FinnGen	Zinc	3	0	0.96 (0.88, 1.06)	0.457	1.00 (0.66, 1.52)	0.999	0.895	NA	NA	NA
Meta-analysis	Zinc			0.94 (0.88, 1.01)	0.110	0.88 (0.64, 1.21)	0.425			NA	NA

BP = blood pressure; CI = confidence interval; NA = not available; OR = odds ratio; SNP = single nucleotide polymorphism.

Table S5. Associations of nutritional factors with varicose veins in the leave-one-out analysis

B12 (UKB)

SNP_exclude	OR	P value
rs1131603	1.13 (1.01, 1.27)	0.030
rs1141321	1.12 (0.99, 1.25)	0.065
rs117456053	1.12 (0.99, 1.25)	0.061
rs12272669	1.19 (1.03, 1.38)	0.018
rs2270655	1.12 (1.00, 1.25)	0.060
rs2336573	1.13 (1.00, 1.27)	0.053
rs34324219	1.09 (0.97, 1.22)	0.136
rs34528912	1.13 (1.02, 1.26)	0.025
rs3742801	1.12 (1.00, 1.26)	0.049
rs41281112	1.12 (1.00, 1.26)	0.060
rs56077122	1.13 (1.01, 1.27)	0.039
rs602662	1.05 (0.96, 1.15)	0.257
Meta-analysis	1.12 (1.00, 1.25)	0.047

B12 (FinnGen)

SNP_exclude	OR	P value
rs1131603	1.05 (0.97, 1.14)	0.239
rs1141321	1.04 (0.97, 1.12)	0.275
rs117456053	1.05 (0.97, 1.13)	0.243
rs7131243	1.12 (1.01, 1.23)	0.028
rs2270655	1.05 (0.98, 1.13)	0.185
rs2336573	1.05 (0.97, 1.14)	0.221
rs34324219	1.06 (0.97, 1.14)	0.190
rs34528912	1.04 (0.97, 1.11)	0.310
rs3742801	1.04 (0.97, 1.13)	0.255
rs41281112	1.05 (0.97, 1.14)	0.236
rs56077122	1.05 (0.97, 1.14)	0.223
rs602662	1.02 (0.95, 1.10)	0.570
Meta-analysis	1.05 (0.97, 1.13)	0.213

Calcium

SNP_exclude	OR	P value
rs10491003	0.78 (0.61, 1.01)	0.056
rs1550532	0.78 (0.61, 1.01)	0.059
rs1570669	0.79 (0.61, 1.02)	0.070
rs1801725	0.69 (0.47, 1.02)	0.060
rs7336933	0.79 (0.61, 1.02)	0.065
rs7481584	0.73 (0.57, 0.94)	0.014
rs780094	0.74 (0.58, 0.95)	0.020
Meta-analysis	0.76 (0.60, 0.97)	0.030

Calcium

SNP	OR	P value
rs10491003	0.72 (0.48, 1.06)	0.096
rs1550532	0.82 (0.65, 1.04)	0.110
rs1570669	0.72 (0.48, 1.07)	0.100
rs1801725	0.73 (0.40, 1.33)	0.304
rs7336933	0.72 (0.48, 1.06)	0.093
rs7481584	0.72 (0.49, 1.07)	0.104
rs780094	0.72 (0.49, 1.07)	0.101
Meta-analysis	0.73 (0.52, 1.05)	0.086

Iron

SNP_exclude	OR	P value
rs1799945	1.22 (1.09, 1.37)	0.001
rs1800562	1.21 (1.07, 1.38)	0.002
rs7385804	1.24 (1.12, 1.38)	0.000
rs8177240	1.26 (1.13, 1.39)	0.000
rs855791	1.30 (1.15, 1.48)	0.000
Meta-analysis	1.25 (1.13, 1.38)	0.000

Iron

SNP_exclude	OR	P value
rs1799945	1.14 (0.97, 1.34)	0.108
rs1800562	1.25 (1.03, 1.51)	0.023
rs7385804	1.24 (1.08, 1.42)	0.002
rs8177240	1.19 (0.99, 1.43)	0.062
rs855791	1.20 (0.93, 1.53)	0.156
Meta-analysis	1.20 (1.03, 1.41)	0.024

Zinc

SNP_exclude	OR	P value
rs1532423	0.92 (0.79, 1.06)	0.223
rs2120019	0.96 (0.86, 1.07)	0.480
rs5914779	0.88 (0.79, 0.98)	0.019
Meta-analysis	0.92 (0.84, 1.00)	0.050

Zinc

SNP_exclude	OR	P value
rs1532423	0.97 (0.88, 1.07)	0.509
rs2120019	0.96 (0.85, 1.08)	0.477
rs4826508	0.97 (0.88, 1.07)	0.539
Meta-analysis	0.97 (0.89, 1.05)	0.421

CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism; UKB, UK Biobank.

Table S6. Associations of genetically predicted vitamin B12, calcium and iron with varicose veins in the analysis based on SNPs in protein encoding genes

Source	Exposure	SNP	Gene	OR	*P*
UKB	Vitamin B12	rs602662	*FUT2*[a]	1.54 (1.28, 1.87)	<0.001
FinnGen	Vitamin B12	rs602662	*FUT2*[a]	1.23 (1.03, 1.47)	0.023
Meta-analysis	Vitamin B12			1.37 (1.20, 1.56)	<0.001
UKB	Calcium	rs1801725	*CASR*[b]	0.82 (0.60, 1.12)	0.215
FinnGen	Calcium	rs1801725	*CASR*[b]	0.74 (0.55, 0.99)	0.046
Meta-analysis	Calcium			0.77 (0.62, 0.96)	0.021
UKB	Iron	rs1799945	*HFE*[c]	1.35 (1.08, 1.69)	0.008
UKB	Iron	rs1800562	*HFE*[c]	1.31 (1.11, 1.56)	0.002
UKB	Iron	rs855791	*TMPRSS6*[d]	1.15 (0.97, 1.36)	0.104
FinnGen	Iron	rs1799945	*HFE*[c]	1.47 (1.16, 1.87)	0.002
FinnGen	Iron	rs1800562	*HFE*[c]	1.06 (0.84, 1.34)	0.617
FinnGen	Iron	rs855791	*TMPRSS6*[d]	1.21 (1.03, 1.43)	0.023
Meta-analysis	Iron			1.24 (1.15, 1.34)	<0.001

CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism; UKB, UK Biobank.

[a] Hazra A, Kraft P, Selhub J, Giovannucci EL, Thomas G, Hoover RN, Chanock SJ, Hunter DJ. Common variants of FUT2 are associated with plasma vitamin B12 levels. Nat Genet. 2008;40(10):1160-2.

[b] Egbuna OI, Brown EM. Hypercalcaemic and hypocalcaemic conditions due to calcium-sensing receptor mutations. Best Pract Res Clin Rheumatol. 2008;22(1):129-48.

[c] Townsend A, Drakesmith H. Role of HFE in iron metabolism, hereditary haemochromatosis, anaemia of chronic disease, and secondary iron overload. Lancet. 2002;359(9308):786-90.

[d] Finberg KE, Heeney MM, Campagna DR, Aydinok Y, Pearson HA, Hartman KR, Mayo MM, Samuel SM, Strouse JJ, Markianos K, Andrews NC, Fleming MD. Mutations in TMPRSS6 cause iron-refractory iron deficiency anemia (IRIDA). Nat Genet. 2008;40(5):569-71.

Table S7. Colocalization analysis results for genetic associations with calcium and varicose veins in UK Biobank

Results by setting region ± 500 kb

SNP	Chr	Position_hg19	Gene	N_SNPs	PP.H0	PP.H1	PP.H2	PP.H3	PP.H4
rs1550532	2	234264848	*DGKD*	4212	0.000	0.715	0.000	0.214	0.071
rs780094	2	27741237	*GCKR*	2792	0.000	0.760	0.000	0.163	0.077
rs1801725	3	122003757	*CASR*	3814	0.000	0.733	0.000	0.194	0.073
rs10491003	10	9328651	*LINC00709*	3995	0.000	0.728	0.000	0.205	0.067
rs7481584	11	3029089	*CARS*	4274	0.000	0.715	0.000	0.214	0.072
rs7336933	13	42559076	*VWA8-AS1*	4134	0.000	0.715	0.000	0.214	0.071
rs1570669	20	52774427	*CYP24A1*	4527	0.000	0.705	0.000	0.225	0.071

Results by setting region ± 50 kb

SNP	Chr	Position_hg19	Gene	N_SNPs	PP.H0	PP.H1	PP.H2	PP.H3	PP.H4
rs1550532	2	234264848	*DGKD*	386	0.000	0.886	0.000	0.025	0.089
rs780094	2	27741237	*GCKR*	296	0.000	0.891	0.000	0.020	0.089
rs1801725	3	122003757	*CASR*	426	0.000	0.885	0.000	0.026	0.089
rs10491003	10	9328651	*LINC00709*	449	0.000	0.888	0.000	0.027	0.084
rs7481584	11	3029089	*CARS*	504	0.000	0.880	0.000	0.032	0.088
rs7336933	13	42559076	*VWA8-AS1*	339	0.000	0.895	0.000	0.022	0.083
rs1570669	20	52774427	*CYP24A1*	621	0.000	0.880	0.000	0.037	0.083

SNP, single nucleotide polymorphism.
N_SNPs, the number of SNPs included in the colocalization analysis; PP.H0 to PP.H4 are the posterior probability (PP) of each colocalization hypothesis tested: H0 (neither trait associated), H1 (calcium associated only), H2 (varicose veins associated only), H3 (both calcium and varicose veins associated, but with different causal variants), H4 (colocalization, both traits associated with the same causal variant).