Association of vitamin D status with arterial blood pressure and hypertension risk: a mendelian randomisation study


Summary

Background Low plasma 25-hydroxyvitamin D (25(OH)D) concentration is associated with high arterial blood pressure and hypertension risk, but whether this association is causal is unknown. We used a mendelian randomisation approach to test whether 25(OH)D concentration is causally associated with blood pressure and hypertension risk.

Methods In this mendelian randomisation study, we generated an allele score (25(OH)D synthesis score) based on variants of genes that affect 25(OH)D synthesis or substrate availability (CYP2R1 and DHCR7), which we used as a proxy for 25(OH)D concentration. We meta-analysed data for up to 108 173 individuals from 35 studies in the D-CarDia collaboration to investigate associations between the allele score and blood pressure measurements. We complemented these analyses with previously published summary statistics from the International Consortium on Blood Pressure (ICBP), the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium, and the Global Blood Pressure Genetics (Global BPGen) consortium.

Findings In phenotypic analyses (up to n=49 363), increased 25(OH)D concentration was associated with decreased systolic blood pressure (β per 10% increase, –0·12 mm Hg, 95% CI –0·20 to –0·04; p=0·003) and reduced odds of hypertension (odds ratio [OR] 0·98, 95% CI 0·97–0·99; p=0·0003), but not with decreased diastolic blood pressure (β per 10% increase, –0·02 mm Hg, –0·08 to 0·03; p=0·37). In meta-analyses in which we combined data from D-CarDia and the ICBP (n=146 581, after exclusion of overlapping studies), each 25(OH)D-increasing allele of the synthesis score was associated with a change of –0·10 mm Hg in systolic blood pressure (–0·21 to –0·001; p=0·0498) and a change of –0·08 mm Hg in diastolic blood pressure (–0·15 to –0·02; p=0·01). When D-CarDia and consortia data for hypertension were meta-analysed together (n=142 255), the synthesis score was associated with a reduced odds of hypertension (OR per allele, 0·98; 95% CI 0·96–0·99; p=0·001). In instrumental variable analysis, each 10% increase in genetically instrumented 25(OH)D concentration was associated with a change of –0·29 mm Hg in diastolic blood pressure (–0·52 to –0·07; p=0·01), a change of –0·37 mm Hg in systolic blood pressure (–0·73 to 0·003; p=0·052), and an 8·1% decreased odds of hypertension (OR 0·92, 0·87–0·97; p=0·0002).

Interpretation Increased plasma concentrations of 25(OH)D might reduce the risk of hypertension. This finding warrants further investigation in an independent, similarly powered study.

Funding British Heart Foundation, UK Medical Research Council, and Academy of Finland.

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Introduction Low vitamin D status has been associated with an increased risk of cardiovascular disease and all-cause mortality, and the possible benefits of vitamin D supplementation are being actively investigated and debated.1,2 In observational studies, low plasma 25-hydroxyvitamin D (calcidiol, 25(OH)D) concentration is associated with an increased risk of hypertension.3
However, few large randomised controlled trials of vitamin D supplementation with primary cardiovascular outcomes have been done, and secondary analyses from other trials have provided little evidence to support an effect of vitamin D supplementation on cardiovascular outcomes.1,4 The largest of the randomised controlled studies was the Women’s Health Initiative trial (n=36,282), the results of which did not show any changes in blood pressure or hypertension after 7 years of follow-up.4 However, the vitamin D dose used in that trial was quite small (400 IU per day), and women in both treatment and placebo groups were allowed to take up to 1000 IU per day of additional open-label vitamin D supplementation. Some evidence for possible effects of vitamin D supplementation on blood pressure has been obtained from randomised controlled trials with higher doses5 and those investigating individuals with cardio-metabolic risk; however, as Elamin and colleagues have previously noted,7 the quality of the available evidence is “low to moderate at best.”

In this study, we explored the possible causal relation between vitamin D status and blood pressure and hypertension using a genetic approach. Mendelian randomness exploits the fact that individual genotypes are assigned randomly at meiosis, so the effect of genetics randomisation exploits the fact that individual genotypes are assigned randomly at meiosis, so the effect of genetics reverse causality.8 Recent genome-wide association studies (GWAS) have identified several variants that affect circulating concentrations of 25(OH)D9. If 25(OH)D concentrations are causally involved in determining blood pressure or the risk of hypertension, then the genetic variants that affect circulating concentrations of 25(OH)D could be expected to affect blood pressure and hypertension risk. This assumption seems to be valid for at least two of the genes that affect 25(OH)D, namely CYP2R1 (encoding 7-dehydrocholesterol reductase). These genes function upstream of 25(OH)D production and affect vitamin D synthesis or substrate availability.10 Two further downstream variants affect 25(OH)D, GC (encoding group-specific component [vitamin D binding protein]) and CYP24A1 (encoding cytochrome P450, family 2, subfamily A, polypeptide 1) and DHCR7 (encoding 7-dehydrocholesterol reductase). These genes function downstream of 25(OH)D production and affect vitamin D synthesis or substrate availability.11

To further increase the statistical power of our study, we meta-analysed our results in adults with data from the International Consortium for Blood Pressure (ICBP)14 when examining systolic or diastolic blood pressure as the outcome (n=146,581, after exclusion of overlapping studies; figure 1). At the time of the study, hypertension had not been formally examined as an outcome in the ICBP consortium, and related coefficients were not available. Therefore, we used summary data from Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE; n=29,136)16 and Global Blood Pressure Genetics (Global BPGen) (n=34,433)15 consortia when examining hypertension as the outcome (n=142,255 after exclusion of overlapping studies; figure 1).

**Phenotypic measures**

Hypertension was defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or current use of antihypertensive drugs. For participants taking antihypertensive drugs, we added 15 mm Hg to systolic and 10 mm Hg to diastolic blood pressure to correct for the effect of the treatment.14

25(OH)D concentrations were available for 19 of the 35 studies in the D-CarDia collaboration (n=51,122), with values expressed in nmol/L for all studies. The appendix (pp 2–19) includes details about the methods used to measure 25(OH)D concentration in each study.

**Selection of SNPs and allele scores**

To create vitamin D allele scores, we selected four vitamin D-related SNPs (DHCR7 rs12785878, CYP2R1 rs12794714, GC rs2282679, and CYP24A1 rs6013897) based on the results of the GWAS by the SUNLIGHT Consortium,17 with two SNPs in genes located upstream (DHCR7 and CYP2R1) and two downstream (GC and CYP24A1) of the 25(OH)D metabolite.17 All but one (CYP2R1) were selected as the top hit; for CYP2R1 we used an alternative SNP also identified by the GWAS by the SUNLIGHT Consortium (r²=0.41) with the first-stage GWAS top hit rs10741657. The appendix (pp 2–25) includes a detailed description of the genotyping and imputation methods and effect allele frequencies for all studies included in the meta-analysis.

**Methods**

**Study design and population**

We used a mendelian randomisation approach to investigate the association between genetic variants that affect concentrations of circulating 25(OH)D and blood pressure measurements. We meta-analysed data from 35 studies in the D-CarDia collaboration, with results complemented by previously published summary statistics from other large-scale consortium efforts.9,16

D-CarDia is a collaboration of studies, consisting of cohorts of European ancestry from Europe and North America, that investigates the association of vitamin D and the risk of cardiovascular disease and related traits.11 We meta-analysed directly genotyped and imputed single-nucleotide polymorphisms (SNPs) from 31 adult (aged 31–92 years, n=99,582) and four adolescent (aged 10–20 years, n=8591) cohorts in the D-CarDia collaboration (table 1, figure 1). All participants provided written informed consent, and all participating studies received approval from local research ethics committees. The appendix (pp 2–19) includes descriptions of all the studies included in the analysis.

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### Sample size

<table>
<thead>
<tr>
<th>Study</th>
<th>Total (men, women)</th>
<th>Men</th>
<th>Women</th>
<th>All participants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies in adults</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NFBC 1966</td>
<td>4488 (2270, 2218)</td>
<td>312</td>
<td>657</td>
<td>312 (0.3)</td>
</tr>
<tr>
<td>Young Finns</td>
<td>2443 (1123, 1320)</td>
<td>376</td>
<td>239</td>
<td>376 (0.3)</td>
</tr>
<tr>
<td>NESDA</td>
<td>1712 (551, 1166)</td>
<td>437</td>
<td>317</td>
<td>437 (0.3)</td>
</tr>
<tr>
<td>1958BC</td>
<td>7152 (3525, 3627)</td>
<td>450</td>
<td>329</td>
<td>450 (0.3)</td>
</tr>
<tr>
<td>GOYA</td>
<td>1466 (1465, 1 women)</td>
<td>456</td>
<td>986</td>
<td>456 (0.3)</td>
</tr>
<tr>
<td>FHS</td>
<td>5654 (267, 2977)</td>
<td>467</td>
<td>582</td>
<td>467 (0.3)</td>
</tr>
<tr>
<td>LifeLines</td>
<td>1323 (552, 770)</td>
<td>490</td>
<td>2186</td>
<td>490 (0.3)</td>
</tr>
<tr>
<td>SPLIT</td>
<td>498 (213, 285)</td>
<td>479</td>
<td>809</td>
<td>479 (0.3)</td>
</tr>
<tr>
<td>Twins UK</td>
<td>2392 (189, 220)</td>
<td>486</td>
<td>732</td>
<td>486 (0.3)</td>
</tr>
<tr>
<td>PREVEND</td>
<td>3649 (1880, 1769)</td>
<td>510</td>
<td>732</td>
<td>510 (0.3)</td>
</tr>
<tr>
<td>DOPS</td>
<td>1684 (10, 1684)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GENMETS</td>
<td>868 (421, 447)</td>
<td>492</td>
<td>157</td>
<td>492 (0.3)</td>
</tr>
<tr>
<td>DPP</td>
<td>1398 (601, 1307)</td>
<td>551</td>
<td>264</td>
<td>551 (0.3)</td>
</tr>
<tr>
<td>MRC NSHD</td>
<td>2634 (1340, 1294)</td>
<td>530</td>
<td>767</td>
<td>530 (0.3)</td>
</tr>
<tr>
<td>ORCADES</td>
<td>718 (334, 384)</td>
<td>543</td>
<td>145</td>
<td>543 (0.3)</td>
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<tr>
<td>NPHSIL</td>
<td>2771 (2771, 0)</td>
<td>561</td>
<td>1460</td>
<td>561 (0.3)</td>
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<tr>
<td>KORCULA</td>
<td>901 (332, 569)</td>
<td>575</td>
<td>190</td>
<td>575 (0.3)</td>
</tr>
<tr>
<td>VIS</td>
<td>782 (332, 450)</td>
<td>560</td>
<td>824</td>
<td>560 (0.3)</td>
</tr>
<tr>
<td>Tromsø</td>
<td>9467 (4482, 4985)</td>
<td>587</td>
<td>2819</td>
<td>587 (0.3)</td>
</tr>
</tbody>
</table>

*Age (years), Systolic blood pressure (mm Hg), Diastolic blood pressure (mm Hg), Participants with hypertension.*

(Table 1 continues on next page)
### Characteristics of the D-CarDia study cohorts, stratified by sex

**Table 1:**

- **Studies in adults**
  - **GOOD 941**
  - **TRAILS 1289**
  - **NFBC 1986 5460**
  - **PIVUS 995**
  - **EAS 907**
  - **ULSAM 1129**
  - **Health ABC 1554**
  - **MrOS Sweden 2911**

- **Studies in adolescents**
  - **LISA plus and GIMPaLus 901**
  - **NFBC 1986 5460**
  - **TRAILS 1289**
  - **GOOD 941**

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Men (years)</th>
<th>Women (years)</th>
<th>All participants (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Syntolic blood pressure (mm Hg)</td>
<td>Diastolic blood pressure (mm Hg)</td>
<td>Participants with hyper-tension</td>
</tr>
<tr>
<td>Whitehall II</td>
<td>5146 (2097 men, 1349 women)</td>
<td>60.8 (5.9)</td>
<td>132.6 (22.2)</td>
</tr>
<tr>
<td>HBCS</td>
<td>1278 (737 men, 991 women)</td>
<td>61.6 (4.2)</td>
<td>149.6 (21.9)</td>
</tr>
<tr>
<td>ESTHER</td>
<td>8199 (4598 men, 3601 women)</td>
<td>62.2 (6.5)</td>
<td>140.9 (18.7)</td>
</tr>
<tr>
<td>LURIC</td>
<td>3287 (2293 men, 994 women)</td>
<td>64.8 (10.2)</td>
<td>154.0 (25.9)</td>
</tr>
<tr>
<td>EAS</td>
<td>907 (448 men, 459 women)</td>
<td>64.2 (5.7)</td>
<td>144.5 (24.4)</td>
</tr>
<tr>
<td>HCS</td>
<td>2906 (1536 men, 1370 women)</td>
<td>66.7 (2.7)</td>
<td>137.8 (22.7)</td>
</tr>
<tr>
<td>ELSA</td>
<td>5054 (2399 men, 2755 women)</td>
<td>66.3 (9.8)</td>
<td>136.6 (20.9)</td>
</tr>
<tr>
<td>InCHIANTI</td>
<td>1210 (540 men, 670 women)</td>
<td>70.2 (0.2)</td>
<td>157.7 (26.1)</td>
</tr>
<tr>
<td>PIVUS</td>
<td>995 (498 men, 497 women)</td>
<td>69.1 (15.6)</td>
<td>153.2 (26.6)</td>
</tr>
<tr>
<td>ULSAM</td>
<td>1129 (1129 men, 0 women)</td>
<td>71.0 (0.6)</td>
<td>150.8 (21.9)</td>
</tr>
<tr>
<td>Health ABC</td>
<td>1554 (826 men, 728 women)</td>
<td>74.9 (2.9)</td>
<td>137.6 (21.3)</td>
</tr>
<tr>
<td>MoS Sweden</td>
<td>2911 (2911 men, 0 women)</td>
<td>75.4 (3.2)</td>
<td>155.2 (23.9)</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th><strong>Age</strong></th>
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</tr>
</thead>
</table>

Data are n, mean (SD), or n (%).

Table 1: Characteristics of the D-CarDia study cohorts, stratified by sex

We created two separate vitamin D allele scores: a synthesis allele score, created by summing the vitamin D-increasing alleles in the genes located upstream (**DHCR7** and **CYP2R1**; score range 0–4), and a metabolism allele score, created by summing the vitamin D-increasing alleles in the genes located downstream (**GC** and **DHRS5**; score range 0–10).
CYP24A1; score range 0–4) of the 25(OH)D metabolite. The synthesis allele score can be regarded as an instrument for 25(OH)D concentration when testing for causal association in mendelian randomisation analyses because it consists of variants that directly affect substrate availability or synthesis of 25(OH)D. Components included in the metabolism score are relevant for the transfer and clearance of 25(OH)D and could provide insights into the effect of vitamin D metabolism on blood pressure. However, the use of the metabolism score as a formal instrument in mendelian randomisation analyses is not possible because of problems with quantification of expected associations, pleiotropic effects, and the metabolic feedback loops associated with the clearance of vitamin D-related metabolites by CYP24A1. Investigations with the vitamin D metabolism score were therefore exploratory only.

**Statistical analysis**

Statistical analyses in each of the D-CarDia studies were done in accordance with a standard analysis plan. We used the natural-log transformation for 25(OH)D concentrations to achieve a closer approximation of the normal distribution, and to remove non-linearity in the association with the outcomes. Additive models with systolic blood pressure, diastolic blood pressure, and metabolic feedback loops associated with the clearance of vitamin D-related metabolites by CYP24A1. Investigations with the vitamin D metabolism score were therefore exploratory only.

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hypertension as outcomes were adjusted for age, age
squared, BMI, sex, geographical region, or principal
components (as relevant for the study); models with
25(OH)D concentration as the outcome were additionally
adjusted for month of blood sample collection and
laboratory batch, as relevant.

With respect to the phenotypic analyses, confounding
factors that affect 25(OH)D concentrations were assessed
previously with the 1958 British birth cohort and
in selected D-CarDia studies with individual-level data
(appendix pp 26–28). To assess the association of
25(OH)D concentration with systolic blood pressure,
diastolic blood pressure, and hypertension, the
investigators of each of the D-CarDia studies did linear
regression analyses, adjusting for the key covariates as
adjusted for in the additive models, and the models
were repeated stratified by sex (appendix p 39).

With respect to genetic effects on 25(OH)D con-
centration, the effect allele was the 25(OH)D-increasing
allele, as established by the SUNLIGHT Consortium.9
We tested the association of the four individual
vitamin D-related genetic markers, and the two vitamin D
allele scores, with 25(OH)D concentrations using linear
regression models, adjusting for the same covariates as
adjusted for in the additive models. We tested for
associations of the synthesis score, and its components,
with several confounders: age, sex, season, BMI, total
cholesterol, and triglycerides (appendix pp 29–32). To
examine variations that could affect the validity of the
instruments, we used meta-regression to assess hetero-
genesis in the associations between the SNPs and
25(OH)D concentration by study-level factors: sex, age,
method of blood pressure measurement (manual,
or automated, or random-zero manometer), proportion
of hypertensive participants, geographical region (UK,
central and southern Europe, North America,
Scandinavia, or Finland), and BMI. Models were repeated
with adjustment for serum triglycerides and total
cholesterol [to exclude pleiotropic effects through lipid
metabolism, since 25(OH)D is a cholesterol derivative] in
addition to the covariates as adjusted for in the
additive models when examining systolic blood
pressure, diastolic blood pressure, and hypertension as
outcomes.

To examine the strength of the synthesis allele score as an
instrument, we calculated the F-statistic from the
proportion of variation in the respective phenotype (R²)
explained by the allelic score (F-statistic=([R²×(n–2)]/(1–R²))) as
we used the inverse of the F-statistic to calculate the relative bias
of the instrumental variable ratio compared with ordinary
least-squares linear regression.16 Because external weights
were not available and the use of internal weights could bias
the instrumental variable results, we did an unweighted
meta-analysis of study-specific instrumental variable
ratios (appendix p 37). All meta-analyses were done at the
UCL Institute of Child Health (University College London, London, UK)
with Stata version 12.

Role of the funding source
The funders of the study had no role in study design, data
collection, data analysis, data interpretation, or writing of
the report. The corresponding author had full access to
summary data from all studies and had final responsibility
for the decision to submit for publication.

Results
All four vitamin D-related SNPs were strongly associated
with 25(OH)D concentrations (p<2.22×10⁻¹² for all
comparisons; appendix p 33). As previously reported,17,18
the synthesis and metabolism allele scores were strongly
associated with 25(OH)D concentrations (synthesis score
β 2.83%, 95% CI 2.48–3.18, p=2.70×10⁻⁵⁵, R²=0.5%
metabolism score β 5.38%, 4.67–6.08, p=5.93×10⁻⁵⁰,
R²=1.4%; appendix p 33). There was no evidence for
heterogeneity in the association between the synthesis
instrumental variable ratio method.20 To estimate the
instrumental variable ratio for the effect of 25(OH)D
concentration on systolic blood pressure, diastolic blood
pressure, and hypertension, we divided the meta-analysed
association of the vitamin D synthesis allele score with
systolic blood pressure, diastolic blood pressure, and
hypertension by the association of vitamin D synthesis
allele score with 25(OH)D concentration. We estimated
the variance for the instrumental variable ratio using a
Taylor expansion.21

We used summary statistics for the four vitamin D SNPs
from the ICBP, Global BPGen and CHARGE
consortia to increase the statistical power of our analyses
of the association between the vitamin D allele scores
and blood pressure outcomes. We used an approximation
method that has previously described21 to combine
SNPs into the synthesis and metabolism allele scores.

In the presence of heterogeneity of association between
the studies, we used random-effects meta-analyses;
otherwise, we tested fixed-effects models. We investigated
sources of heterogeneity with univariate meta-regression
models.

Four studies in the D-CarDia collaboration are in
adolescents (aged 10–20 years, n=8591). The main
meta-analyses were restricted to adult populations (aged
31–92 years, n=99,582), and only exploratory analyses
were done in adolescents because of insufficient sample
sizes (appendix pp 20, 33, and 39).

We did additional sensitivity analyses to examine the
effect of adjusting for lipids (appendix p 34) of the quality
of genetic information (appendix p 35), and of the
adjustment applied for the use of antihypertensive drugs
(appendix p 36), as well as to compare the two-stage
instrumental variable ratio method with the meta-
analyses of study-specific instrumental variable
ratios (appendix p 37).

All meta-analyses were done at the UCL Institute of
Child Health (University College London, London, UK)
with Stata version 12.

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6
score and 25(OH)D concentration ($P=0\%$, $p=0.48$).

Heterogeneity was seen for the metabolism score ($P=57\%$, $p=0.003$), with evidence of variation in the association between metabolism score and 25(OH)D concentration by mean study BMI ($p=0.02$). The $I^2$-statistic for the synthesis allele score was $219.7$, which suggests a strong composite instrument. The relative bias of the instrumental variable ratio compared with ordinary least-square linear regression was small ($0.5\%$).

Increased 25(OH)D concentrations were associated with reduced systolic blood pressure ($\beta$ per 10 change, $-0.12$ mm Hg, $95\%$ CI $-0.20$ to $-0.04$; $p=0.003$) and reduced odds of hypertension (odds ratio [OR] $0.98$, $95\%$ CI $0.97$–$0.99$; $p=0.0003$); however, we did not see an association between 25(OH)D concentration and diastolic blood pressure ($-0.02$ mm Hg, $-0.08$ to $0.03$; $p=0.37$; appendix p 40). Despite evidence for heterogeneity in the phenotypic association between 25(OH)D concentration and the outcomes within the studies done in adults (systolic blood pressure, $P=73\%$, $p=0.19$ $10^{-97}$; diastolic blood pressure, $P=78\%$, $p=5.00 \times 10^{-9}$; hypertension, $P=62\%$, $p=0.001$), the observed association between 25(OH)D concentration and systolic blood pressure, diastolic blood pressure, or hypertension between studies did not vary by age (meta-regression $p=0.09$ for all comparisons), sex (meta-regression $p=0.65$), method of blood pressure measurement (meta-regression $p=0.14$), geographical region (meta-regression $p=0.39$), or BMI (meta-regression $p=0.10$). However, for the association between 25(OH)D concentration and diastolic blood pressure, there was variation across the proportion of hypertensive participants (meta-regression $p=0.01$).

In the meta-analyses of the D-CarDia studies ($n=108173$), there was no association of the synthesis allele score with systolic blood pressure ($\beta$ per 25(OH)D-increasing allele, $-0.10$ mm Hg, $95\%$ CI $-0.15$ to $0.0001$; $p=0.11$), diastolic blood pressure ($-0.07$ mm Hg, $-0.15$ to $0.01$; $p=0.07$), or hypertension (OR $0.99$, $95\%$ CI $0.97$–$1.00$; $p=0.08$). After increasing the sample size by meta-analysing the D-CarDia results with the summary data from the ICBP consortium (total $n=146581$, after exclusion of overlapping studies), the precision of estimation was improved, but the estimated strengths of these associations remained unchanged. The synthesis score was associated with both systolic blood pressure ($-0.10$ mm Hg, $-0.21$ to $-0.0001$; $p=0.0498$) and diastolic blood pressure ($-0.08$ mm Hg, $-0.27$ to $0.15$; $p=0.0003$).

### Figure 2: Meta-analysis of D-CarDia studies with summary data from the ICBP, CHARGE, and Global BPGen consortia

<table>
<thead>
<tr>
<th>Study Name</th>
<th>β (95% CI)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIHUS</td>
<td>-1.27 (-3.01 to 0.48)</td>
<td>0.85 (0.72 to 1.00)</td>
</tr>
<tr>
<td>DOPPS</td>
<td>-1.00 (-2.05 to 0.05)</td>
<td>0.90 (0.82 to 0.99)</td>
</tr>
<tr>
<td>Young Finns</td>
<td>-0.84 (-1.43 to -0.25)</td>
<td>0.91 (0.85 to 0.97)</td>
</tr>
<tr>
<td>Goya</td>
<td>-0.73 (-1.68 to 0.23)</td>
<td>0.92 (0.83 to 1.03)</td>
</tr>
<tr>
<td>Whitehall II</td>
<td>-0.60 (-1.27 to -0.02)</td>
<td>0.92 (0.79 to 1.08)</td>
</tr>
<tr>
<td>NPHSII</td>
<td>-0.55 (-1.42 to 0.32)</td>
<td>0.94 (0.83 to 1.05)</td>
</tr>
<tr>
<td>Tromso</td>
<td>-0.16 (-0.63 to 0.32)</td>
<td>0.95 (0.79 to 1.12)</td>
</tr>
<tr>
<td>ICBP</td>
<td>-0.11 (-0.25 to 0.03)</td>
<td>0.96 (0.80 to 1.15)</td>
</tr>
<tr>
<td>EAS</td>
<td>-0.10 (-0.85 to 0.66)</td>
<td>0.97 (0.93 to 1.01)</td>
</tr>
<tr>
<td>LifeLines</td>
<td>-0.10 (-0.54 to 0.36)</td>
<td>0.97 (0.93 to 1.01)</td>
</tr>
<tr>
<td>PREVEND</td>
<td>0.00000 (-0.63 to 0.63)</td>
<td>0.98 (0.90 to 1.07)</td>
</tr>
<tr>
<td>LURIC</td>
<td>0.02 (-0.92 to 0.95)</td>
<td>0.98 (0.94 to 1.04)</td>
</tr>
<tr>
<td>CROATIA-Korcula</td>
<td>0.11 (-1.41 to 0.64)</td>
<td>0.99 (0.89 to 1.11)</td>
</tr>
<tr>
<td>CROATIA-Split</td>
<td>0.17 (-0.17 to 0.52)</td>
<td>0.99 (0.90 to 1.11)</td>
</tr>
<tr>
<td>HBCS</td>
<td>0.19 (-0.18 to 0.46)</td>
<td>0.99 (0.88 to 1.13)</td>
</tr>
<tr>
<td>GENMETS</td>
<td>0.28 (-0.96 to 1.52)</td>
<td>0.99 (0.89 to 1.11)</td>
</tr>
<tr>
<td>ELSA</td>
<td>0.40 (-0.21 to 1.01)</td>
<td>1.01 (0.86 to 1.19)</td>
</tr>
<tr>
<td>ULSAM</td>
<td>0.52 (-0.85 to 1.89)</td>
<td>1.01 (0.88 to 1.17)</td>
</tr>
<tr>
<td>MRCSNHID</td>
<td>0.52 (-0.40 to 1.45)</td>
<td>1.02 (0.95 to 1.09)</td>
</tr>
<tr>
<td>NESDA</td>
<td>0.61 (-0.26 to 1.49)</td>
<td>1.03 (0.87 to 1.22)</td>
</tr>
<tr>
<td>MROS Sweden</td>
<td>0.72 (-0.99 to 2.43)</td>
<td>1.05 (0.92 to 1.19)</td>
</tr>
<tr>
<td>Health ABC</td>
<td>0.86 (-0.29 to 2.00)</td>
<td>1.06 (0.89 to 1.25)</td>
</tr>
<tr>
<td>Overall</td>
<td>-0.10 (-0.21 to -0.0001)</td>
<td>0.98 (0.96 to 0.99)</td>
</tr>
</tbody>
</table>

Association of the synthesis score with systolic blood pressure, diastolic blood pressure, and hypertension. Includes data for 146581 individuals, after exclusion of overlapping studies. The area of the grey boxes around a point estimate is proportional to the study’s weight in the meta-analysis. ICBP=International Consortium for Blood Pressure. CHARGE=Cohorts for Heart and Aging Research in Genomic Epidemiology. Global BPGen=Global Blood Pressure Genetics.

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Figure 3: Mendelian randomisation triangulation for hypertension

Exposure (X) 25(OH)D concentration

\[ \beta_{X=0.2-0.3} \] (95% CI 0.2-0.3) Observed association of the synthesis score (per allele) with 25(OH)D concentration

Instrument (Z) Synthesis score

\[ \beta_{Z=0.98} \] (95% CI 0.96-0.99) Estimated 8% reduction in odds of hypertension for a 10% increase in 25(OH)D using synthesis score as an instrumental variable

Outcome (Y) Hypertension

\[ \text{OR}_{X=0.98} \] (95% CI 0.97-0.99) OR for observed association of 25(OH)D (per 10% increase) with hypertension

\[ \text{OR}_{Z=0.98} \] (95% CI 0.96-0.99) OR for observed association of synthesis score (per allele) with hypertension

25(OH)D concentration was associated with 0.29 mm Hg lower diastolic blood pressure (95% CI 0.07 to 0.52; \( p=0.01 \)) and a 0.37 mm Hg lower systolic blood pressure (\(-0.003 \text{ to } 0.73; \ p=0.052 \)). Every 10% increment in 25(OH)D concentration was associated with an 8.1% reduced odds of hypertension (OR 0.92, 95% CI 0.87–0.97; \( p=0.002 \)) in the instrumental variable ratio analyses (table 2, figure 3).

The CYP2RI SNP was individually associated with reduced diastolic blood pressure (per allele, \( \beta=0.09 \text{ mm Hg, } 95\% \text{ CI } -0.21 \text{ to } 0.00; \ p=0.03 \)) and reduced odds of hypertension (OR for increase per allele, 0.98, 0.96–1.00; \( p=0.02 \)), but no individual associations were seen for the DHCRI genotype, or either of the downstream metabolism SNPs (GC and CYP24A1), with any of the blood pressure outcomes (appendix pp 41–43).

Discussion

The results of our mendelian randomisation analysis provide evidence for a causal effect of low vitamin D status on increasing blood pressure and risk of hypertension. This finding lends support to continued efforts to prevent vitamin D deficiency. In view of the costs and side-effects associated with antihypertensive drugs, the potential to reduce hypertension by vitamin D is very attractive. However, because we cannot exclude the possibility that our findings were caused by chance, they need to be replicated in an independent, similarly powered study.

Evidence from randomised controlled trials to assess the effectiveness of vitamin D supplementation in reducing blood pressure have not provided consistent evidence of a benefit.\(^1\) In subgroup analyses done within meta-analyses of these trials, \(^2\) some reductions in diastolic blood pressure were reported for participants with hypertension or cardiometabolic disease, and when studies that used higher doses were compared with those that used lower doses of vitamin D.\(^3\) Although the investigators of one study\(^4\) reported dose-dependent reductions in systolic blood pressure after 3 months of supplementation with 1000 IU, 2000 IU, and 4000 IU of vitamin D per day (0·66, 3·4, and 4·0 mm Hg, respectively), no effect was seen in another trial\(^5\) in which participants were given a bolus supplement of 100 000 IU every 3 months. These inconsistencies could be attributed to differences in the mode of administration, dose, and duration of supplementation, or to baseline differences in 25(OH)D concentrations or blood pressure, or other sources of heterogeneity between the studies. Thus, the evidence remains inconclusive. Nevertheless, these exploratory randomised controlled trials have paved the way for large trials (with upwards of 18 000 participants) that are being undertaken to examine the benefits of vitamin D for the prevention of cardiovascular disease outcomes.\(^6\)

Our findings are biologically plausible. Inappropriate activation of the renin-angiotensin system increases blood pressure and the risk of cardiovascular disease.\(^7\)
Studies in animals have shown that 1,25-dihydroxyvitamin D (calcitriol, 1,25(OH)\textsubscript{2}D) suppresses the expression of the renin gene by a vitamin D receptor-dependent mechanism, thereby lowering blood pressure.\textsuperscript{7} In an open-label, blinded-endpoint trial\textsuperscript{30} in 101 patients with chronic heart failure who were randomly assigned to receive 2000 IU of oral vitamin D3 per day for 6 weeks or control (no treatment), treatment led to a significant decrease in plasma renin activity (p=0.002) and concentration (p=0.02). However, some findings have raised concerns about whether activation of the renin-angiotensin system has a role in the vitamin D-deficient state in human beings.\textsuperscript{29} Vitamin D metabolites could also exert antihypertensive effects through various other molecular mechanisms. Vitamin D is indirectly related to blood pressure through its regulation of calcium absorption from the gut and its interaction with parathyroid hormone in the maintenance of calcium homeostasis. The renoprotective and anti-inflammatory actions of vitamin D metabolites and their analogues suggest a possible role for vitamin D deficiency in cardiovascular morbidity and mortality in patients with chronic kidney disease.\textsuperscript{31} Furthermore, adipocyte inflammation has a crucial role in hypertension: in an in-vitro study,\textsuperscript{32} 1,25(OH)\textsubscript{2}D inhibited lipopolysaccharide-stimulated cytokine secretion in two human adipocyte models through direct inhibition of nuclear factor-κB. On the basis of our effect size estimates, the genetic associations of the synthesis allele score with systolic or diastolic blood pressure were less pronounced than that seen for hypertension (represented as a binary trait). This finding might suggest that adequate 25(OH)D concentrations are particularly important for the prevention of hypertension as a clinical outcome. This interpretation is also supported by the results of sensitivity analyses in normotensive individuals, which showed that both the phenotypic association and the genetically indexed association between 25(OH)D concentrations and blood pressure were substantially weaker in this subgroup than in the full sample (data not shown). Although the mendelian randomisation approach is helpful in testing for underlying causality,\textsuperscript{33} an imbalance in the possible overestimation or underestimation of the genetic associations for the outcome and exposure could affect the interpretation of the effect.\textsuperscript{34} The weaker association with blood pressure than with hypertension could also reflect a greater measurement error or heterogeneity in the assessment of gradual increases across the range of the blood pressure distribution, compared with the classification of hypertension by raised blood pressure or use of antihypertensive drugs. Such noise or heterogeneity in the blood pressure measurements in our meta-analyses could also account for the estimated strength of the associations between 25(OH)D concentrations and blood pressure outcomes were weaker than we would have expected on the basis of previous observational analyses or of power calculations that were done with data from one of the D-CarDia studies (1958 British birth cohort, n=6877).\textsuperscript{18}

The main strength of our study is in the large sample size (up to n=146 581), which allowed us to study the consistency of associations across several studies and to gain sufficient power for conclusive analyses. This study shows the benefits of the mendelian randomisation approach: although the phenotypic associations between 25(OH)D concentrations and blood pressure or hypertension were very heterogeneous across the studies, notably less heterogeneity was seen for the genetic associations. Age and adiposity are issues that would be expected to affect 25(OH)D concentrations and bias the phenotypic association it might have with blood pressure; but participating studies included both young and old cohorts, and both lean and obese participants. By contrast, genetic variants used in mendelian randomisation would be expected to reflect lifelong differences in 25(OH)D concentrations and would therefore be less affected by temporal variations in individual characteristics.

Potential limitations with the mendelian randomisation approach include the requirement of large sample sizes, the possibility of population stratification, canalisation, pleiotropy, and an inability to generalise findings to people in other ethnic groups. A limitation of our study was that we only looked at associations with blood pressure and hypertension, and whether these associations are related to differences in the risks of rarer disease outcomes remains uncertain. Population stratification is unlikely to have had a major effect on our main findings, since participants were all of European descent, and we adjusted for geographical region and principal components from the population stratification analysis in the statistical models.

The synthesis or metabolism SNPs might have led to biological adaptations during development (ie, canalisation),\textsuperscript{4} although this possibility seems unlikely in view of the similar associations with 25(OH)D seen in the analyses done in adolescents and adults. Pleiotropic effects, wherein the genetic instruments might affect other metabolic pathways independent of their influence on 25(OH)D concentrations, are more likely. Our main instrument was a composite score consisting of two independent SNPs. Although differential associations between the components included in the score can suggest a possible pleiotropic effect, in our case the associations for CYP2R1 and DHCR7 were similar for all three outcomes (appendix p 38). Furthermore, because 25(OH)D is a secosteroid, we explicitly sought to exclude pleiotropic effects through lipid metabolism by adjusting for serum triglycerides and total cholesterol in addition to other covariates, and noted no differences in our findings (appendix p 34). However, pleiotropy is an issue with the metabolism variants included in our secondary analyses.
Panel: Research in context

Systematic review

Investigators of several systematic reviews have summarised evidence for the phenotypic association between 25-hydroxyvitamin D (25(OH)D) and blood pressure and assessed the cardiovascular effects of vitamin D supplementation in randomised controlled trials. A prospective phenotypic association is well established, but few large randomised controlled trials of vitamin D with primary cardiovascular outcomes have been done. Evidence is largely restricted to secondary analyses of mostly small trials that were initially established to assess the effects of vitamin D supplementation on bone health. Some effects have been reported from subgroup analyses of trials focused on individuals with cardiometabolic disease, but the quality of the available evidence has been criticised. Previous studies that have used mendelian randomisation analyses to examine the association of 25(OH)D and cardiovascular outcomes have been underpowered and evidence for causality of association is inconclusive.

Interpretation

Our results suggest that people who have genetic variants associated with low endogenous production of 25(OH)D have an increased risk of hypertension, emphasising the need for further, well-designed randomised controlled trials to assess causality and the potential clinical benefits of vitamin D supplementation. In view of the costs and side-effects associated with antihypertensive drugs, the possibility of preventing or reducing hypertension with vitamin D supplementation is very attractive. However, because we cannot exclude the possibility that the findings from this study were caused by chance, they need to be replicated in an independent, similarly powered study.

The GC allele that is associated with increased 25(OH)D concentrations also leads to reduced bioavailability of active 1,25(OH)D, hence increased serum concentrations of the 25(OH)D substrate are a possible consequence of reduced uptake by the cells. CYP24A1 in turn acts as a hydroxylase for other vitamin D metabolites in addition to reduced uptake by the cells.

Contributors

KSV, AC, DJB, CL, ACA, ETI, AW, MM, KAJ, IMN, TSA, DP, LZ, JD, LP, and EHy took part in data analysis. KSV, AC, DJB, ADH, JCW, and EHy contributed to study design. RJ, AKD, HJLH, JE, DKH, PJDM, ETHi, VV, RMF, JEH, RADB, BS, K-US, MIM, SS, AP, JLaI, MEK, GN, ML, KJ, NA, JC, JA, RH, SR, LKB, JLaI, CoS, BWP, LR, KK, RPS, DGHi, LB, EHy, HM, EI, DM, OL, IT, SM, EThi, CMTT, AJ, PN, AFW, OP, CH, JFW, IR, VS, JFHi, JG, JFP, MK, LL, KM, SB, TMF, CAH, TIAS, SBR, BL, IGE, JCF, TDS, TL, DKL, SEHi, CC, CoH, WM, MHDiB, MK, MKn, TJW, CP, HB, GG, PViDH, HS, SP, M-RJ, and EHy contributed to data collection. KSV, AC, DJB, ADH, JCW, and EHy interpreted results. The writing group consisted of KSV, AC, SP, and EHy. All the authors have read the report critically and approved the submitted version. A full list of study and consortia investigators is provided in the appendix (pp 45–48).

Declaration of interests

TJW is on the scientific advisory board for DiaSorin and has received research support from the company. JCW is employed by GlaxoSmithKline and holds shares in the company. JCF has received honoraria from Lilly for consulting. All other authors declare no competing interests.

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