Original Article

Circulating vitamin D concentrations and the risk of urticaria: A bidirectional two-sample Mendelian randomization study

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Background and Objectives: Vitamin D deficiency has been linked to urticaria, but causality remains uncertain. We used Mendelian randomization (MR) to investigate potential causal effects of vitamin D and its metabolites on urticaria risk. **Methods and Study Design:** Summary statistics from genome-wide association studies (GWAS) of total 25-hydroxyvitamin D [25(OH)D] (n=120,618), 25-hydroxyvitamin D3 [25(OH)D3] (n=40,562), and C3-epimer-25-hydroxyvitamin D3 [C3-epi-25(OH)D3] (n=40,562) in Europeans were used, along with data on urticaria and its subtypes from FinnGen consortium (R10 release). For validation, we performed additional MR analyses using a larger dataset that meta-analyzed data from the UK Biobank and GWAS results from the SUNLIGHT consortium (n=496,946) as exposure variables. We performed comprehensive sensitivity analyses, including heterogeneity tests, pleiotropy assessments, and leave-one-out analyses to evaluate result robustness. Statistical power calculations were conducted to validate the reliability of our findings. **Results:** MR analysis revealed a causal protective effect of higher total 25(OH)D levels on urticaria risk [odds ratio (OR) = 0.81, 95% confidence interval (CI):0.69-0.95, p =0.008, statistical power = 81.1%]. Similar causal effects were observed for 25(OH)D3 levels (OR = 0.85, 95% CI: 0.74-0.98, p = 0.023, statistical power = 67.4%).These findings were validated in the replication cohort using serum 25(OH)D measurements (OR = 0.69, 95%CI: 0.56-0.85, p = 0.001, statistical power = 96.1%). Sensitivity analyses showed no significant heterogeneity or pleiotropy. Reverse MR analysis found no evidence that genetic risk of urticaria affects vitamin D levels, suggesting a potentially unidirectional causal relationship. **Conclusions:** This study provides the first genetic evidence that higher vitamin D levels may reduce urticaria risk, offering a new theoretical basis for urticaria prevention and treatment strategies.

Key Words: vitamin D, urticaria, mendelian randomization, 25-hydroxyvitamin D, 25-hydroxyvitamin D3

INTRODUCTION

Urticaria is a common worldwide disease caused by mast cells, resulting in pruritic wheals (hives) and/or angioedema. Predictions suggest a lifetime prevalence rate ranging from 15.7% to 23.6%.[1] Urticaria can be categorized as acute (less than six weeks) or chronic (greater than six weeks).[2] According to research, prevalence rates of acute and chronic urticaria are around 20% and 4.4%,[3,4] respectively. There are variations between different countries and regions, with lower rates in Europe and America, and higher rates in Latin America and Asia.[4] Females commonly experience all kinds of urticaria, with the exception of cholinergic urticaria, which affects mostly adult males.[5] Urticaria has a high global incidence, with 160 million new cases recorded each year.[6] The prevalence of chronic urticaria has increased two to ten times in the last ten years,[5] and it has had a substantial impact on people's quality of life worldwide.[7]

Vitamin D is a fat-soluble vitamin that plays a critical role in regulating calcium-phosphate balance, immunity, inflammation, and many other biological activities.[8] The liver converts vitamin D3 and vitamin D2 into 25-hydroxyvitamin D3 [25(OH)D3] and 25-hydroxyvitamin D2 [25(OH)D2], respectively. Together, these two forms of 25-hydroxyvitamin D [25(OH)D] represent the overall vitamin D levels in the human body.[9] C3-epi-25(OH)D3 is the epimer of 25(OH)D3. The enzyme C3-epimerase

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alters the structure of a molecule from 3β to 3α.[10] C3-epi-25(OH)D3 could serve as a biomarker for pathological conditions associated with various disorders.[11]

The relationship between vitamin D and urticaria remains a topic of debate. Previous research has linked vitamin D deficiency to both acute and chronic urticaria.[12,13] Serum 25(OH)D levels were significantly lower in patients with chronic urticaria than in healthy people, and the levels decreased as the urticaria worsened.[14,15] However, some research holds the opposing view, asserting that low levels of 25(OH)D do not correlate with chronic spontaneous urticaria.[16] As a result, we have not established a definitive link between vitamin D and urticaria.

Mendelian randomization (MR) study designs are an effective method of exploiting genetic diversity in order to infer the causal relationships between exposures and outcomes. MR studies provide an advantage over standard observational studies in that they reduce the possibility of confounding and reverse causality.[17,18] Generally, well-designed MR analyses with excellent experimental designs and appropriate assumptions outperform standard observational analyses.[19] As a result, MR is particularly useful for determining the cause-and-effect link between vitamin D levels and urticaria.

METHODS

Study design

This study followed the STROBE-MR reporting guideline to reach high professional and academic quality standards.[20] The basic design and important measures taken in the MR investigation were presented in Figure 1. We applied a two-sample MR design with ten simple criteria.[21] For an instrumental variable to be considered valid, three things must be true: it must be connected to the chosen exposure, not have any complicated links to the outcome, and it must be incapable of altering the outcome other than through exposure.[20,22]

Data sources

We selected genome-wide association study (GWAS) data from European populations as exposure variables, including total 25(OH)D (n = 120,618), 25(OH)D3 (n = 40,562), and C3-epi-25(OH)D3 (n = 40,562).[23] Outcome data were obtained from the FinnGen consortium (R10 release), comprising 409,391 cases of urticaria and its seven subtypes: other and unspecified urticaria (URTICA_NAS) (n = 405,190), dermatographic urticaria (n = 400,282), contact urticaria (n = 398,292), idiopathic urticaria (n = 398,763), urticaria due to cold and heat (COLDHEATU) (n = 398,438), allergic urticaria (n = 400,823), and cholinergic urticaria (n = 398,351). Supplementary Table 1 provides detailed information about the GWAS data sources. We obtained all the GWAS datasets for this analysis from publicly available and ethically authorized publications. Independent ethics approval was not needed for this investigation. To verify the robustness of our research findings, we conducted additional MR analysis using a larger dataset that meta-analyzed UK Biobank data and GWAS results of 25(OH)D from the SUNLIGHT consortium, including a total of 496,946 participants (Supplementary Table 1). We selected genetic variants strongly associated with 25(OH)D levels as instrumental variables (IVs) to reassess the causal relationships with urticaria and its subtypes.[24]

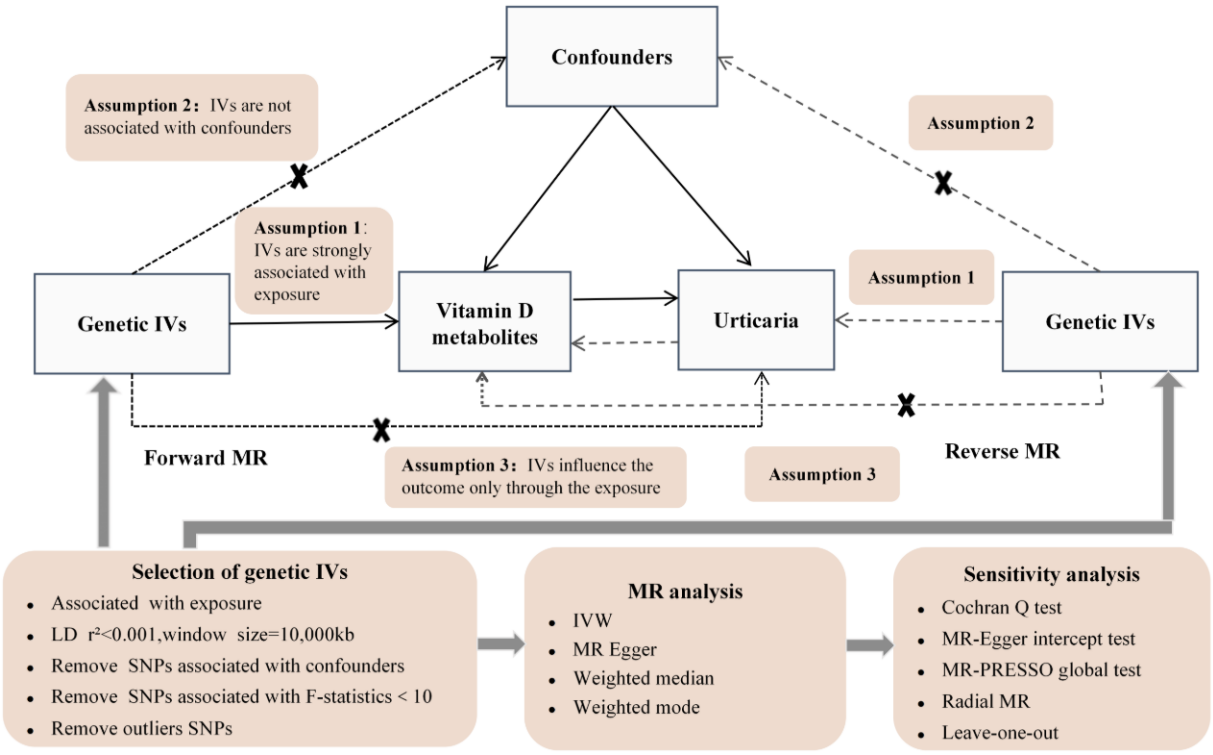

Figure 1. Overview of study design. IVs, instrumental variables; MR, mendelian randomization; LD, Linkage disequilibrium; SNPs, single-nucleotide polymorphisms; IVW, inverse variance weighting; Radial MR, Radial Mendelian Randomization; MR-PRESSO, Mendelian Randomization Pleiotropy Residual Sum and Outlier.

Selection of IVs

Total 25(OH)D (n = 120,618), 25(OH)D3 and C3-epi-25(OH)D3 (n = 40,562)

To identify eligible IVs for MR analysis, we followed the methods below: First, we screened those single nucleotide polymorphisms (SNPs) that were closely linked with exposure at genome-wide statistical significance ($p < 5 \times 10^{-8}$). We used a lower significance level ($p < 5 \times 10^{-6}$) for the MR analysis with C3-epi-25(OH)D3 as the exposure variable because only a few SNPs met stricter criteria. We next used R's TwoSampleMR package to perform LD clumping using an r^2 threshold of 0.001 and a genomic window of 10,000 kb.[25] We then examined the remaining SNPs in LDlink using the LDtrait link (https://ldlink.nci.nih.gov/tab=ldtrait) and removed those identified as confounders or potentially biased.[26] Previous studies have identified allergic disorders,[27] dehydroepiandrosterone,[28] and the action of eosinophils[29] as the primary causes of urticaria. Height, BMI, and bone mineral density primarily determine vitamin D levels. Subsequently, we calculated F-statistics for each SNP and removed those with F-statistics < 10 from further analysis.[30,31] Lastly, we used the MR-PRESSO test[32] and the MR-radial method[33] to find any possible outliers and exclude them.

Serum 25(OH)D (n = 496,946)

In our MR study examining the causal relationship between serum 25(OH)D levels (n = 496,946) and urticaria risk, we selected genetic variants from regions directly involved in vitamin D metabolism pathways as IVs. These gene regions include DHCR7/NADSYN1, CYP2R1, CYP24A1, GC, SEC23A, AMDHD1, SLCO1B1, UGT family, SULT2A1 and SDR42E1, which play crucial roles in vitamin D synthesis, transport, metabolism, and degradation pathways.[24, 34-37]

DHCR7 encodes 7-dehydrocholesterol reductase, which regulates the conversion of vitamin D precursors in the skin;[38] CYP2R1 serves as a key 25-hydroxylase in the liver responsible for converting vitamin D to 25(OH)D, while CYP24A1 catalyzes hydroxylation reactions that inactivate active vitamin D metabolites;[39] The GC gene encodes vitamin D binding protein, a highly polymorphic protein that transports 25(OH)D and its metabolites in the bloodstream, extending their functional half-life;[40] SLCO1B1 encodes a transmembrane receptor that mediates sodium-independent uptake of various endogenous compounds, including sulfated steroid molecules;[24] SEC23A, as a component of the COPII complex, participates in vesicle formation in the endoplasmic reticulum, potentially facilitating intracellular transport of vitamin D metabolites;[41] UGT family enzymes (particularly UGT1A3 and UGT1A4) catalyze the glucuronidation of 25(OH)D3, influencing its metabolism and excretion;[42] Additionally, SULT2A1 is the major enzyme catalyzing the formation of 25(OH)D3-3-O-sulfate from 25(OH)D3, while SDR42E1, a short-chain dehydrogenase/reductase, plays a role in steroid metabolism.[24]

Through systematic screening of variant sites significantly associated with 25(OH)D levels in each gene region, we ultimately identified seven SNPs as genetic IVs: rs117913124 (CYP2R1), rs1871395 (SLCO1B1), rs8018720 (SEC23A), rs8121940 (CYP24A1), rs3732220 (UGT family), rs296381 (SULT2A1) and rs11542462 (SDR42E1).

Statistical analysis

We used the "TwoSampleMR" and "MR-PRESSO" packages in R software (version 4.4.0) to perform a two-sample MR analysis to investigate the link between serum vitamin D levels and urticaria. MR-Egger regression, weighted median (WM), inverse variance weighted (IVW), simple mode, and weighted mode were applied in five MR approaches.[43] Indeed, we conducted the main analysis using the IVW method, which employs a meta-analysis approach to amalgamate the available Wald estimates from each individual instrumental variable, thereby yielding a robust and precise result on causal estimation findings.[44] This ideal situation necessitates validation from other approaches. IVW analysis revealed a causal effect ($p < 0.05$). This indicates that if the OR exceeds one, the exposure is a risk factor for the outcome; otherwise, it is a protective factor.[19] We also utilized the "ggplot2" package to generate plots for MR analyses. We used the online tool MR Power Calculator (https://sb452.shinyapps.io/power/) to evaluate the statistical power of our binary outcome MR study.[31]

Sensitivity and reverse analysis

We used the MR-PRESSO method to identify outliers and horizontal pleiotropy and MR-radial analysis to find genetic instruments that were inconsistent with the overall dataset.[32,33] We reanalyzed the MR data after removing the outliers. We applied Cochran's Q statistic to detect heterogeneity, with $p > 0.05$ indicating no significant heterogeneity.[45] We also employed funnel plots and leave-one-out analyses to further evaluate heterogeneity. Additionally, we performed the MR-Egger intercept test to assess directional pleiotropy, with $p > 0.05$ indicating no evidence of directional pleiotropy.[46] Finally, we conducted a reverse causation analysis to determine reverse causality.

RESULTS

Characteristics of selected SNPs

After intensive screening of SNPs, we ultimately selected 6-10 SNPs representing the concentrations of vitamin D and its metabolites. (Supplementary Table 2 and Table 3). The F-statistic ranged from 11.6 to 3428, indicating that all selected instruments were sufficiently strong (F > 10) and unlikely to introduce weak instrument bias (Supplementary Table 3).Supplementary Table 6 presents SNPs associated with urticaria in the reverse MR analysis.

Main analysis

This study employed five MR methods to systematically evaluate associations between various exposures and outcomes (Supplementary Table 4). IVW-MR analysis (Figure 2) provided evidence of a significant causal effect between genetically predicted total 25(OH)D levels and urticaria risk. Higher genetically predicted total 25(OH)D levels had a significant causal effect on reduced urticaria risk (odds ratio [OR] = 0.81, 95% confidence interval [CI]: 0.69-0.95, $p = 0.008$), with robust statistical power

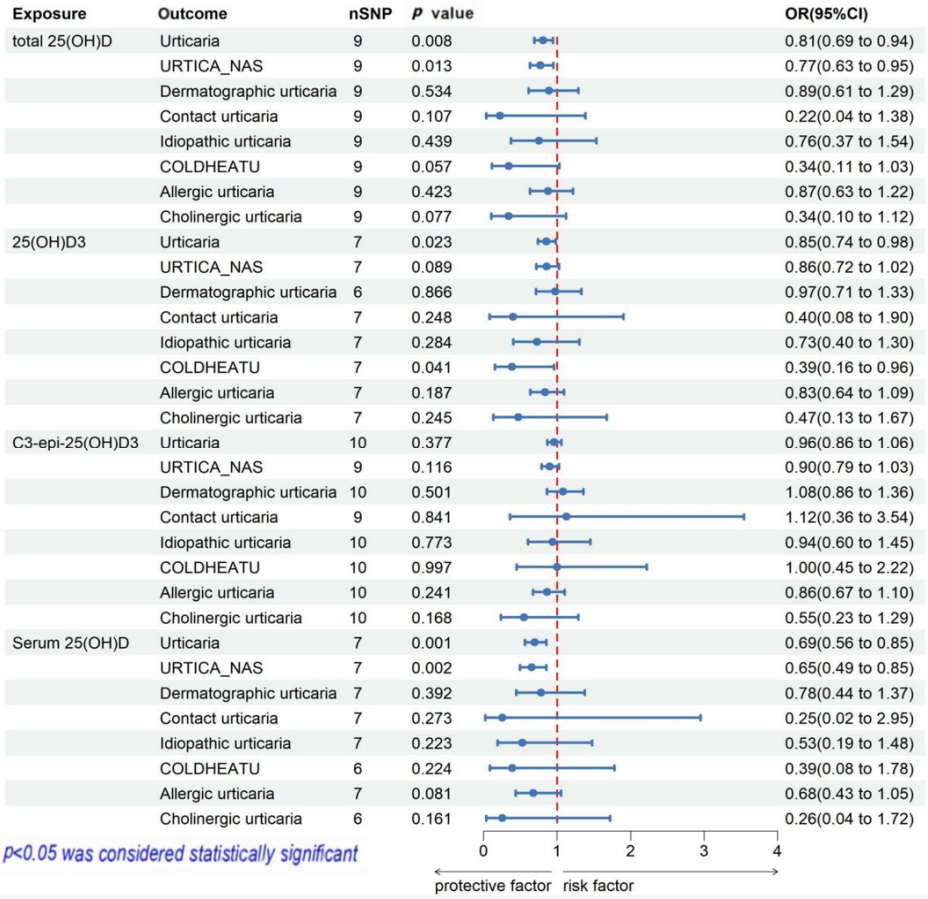

Figure 2. Forest plot showing genetic associations between vitamin D and its metabolites with urticaria risk. CI, confidence interval; nSNP, number of single-nucleotide polymorphisms; OR, odds ratio; 25(OH)D,25-hydroxyvitamin-D; 25(OH)D3, 25-hydroxyvitamin D3; C3-epi-25(OH)D3, C3-epimer of 25-hydroxyvitamin D3; URTICA_NAS, other and unspecified urticaria; COLDHEATU, urticaria due to cold and heat

(81.1%) (Supplementary Table 4 and 5). This finding was further confirmed by weighted median analysis (OR = 0.76, 95%CI: 0.62-0.93, p = 0.007). Additionally, when serum 25(OH)D was used as the exposure in the MR analysis, the IVW estimate similarly suggested a causal effect on reduced risk of urticaria (OR = 0.69, 95%CI: 0.56-0.85, p=0.01), with similarly high statistical power (96.1%). In the urticaria subtype analyses, the IVW estimate suggested a causal effect of genetically predicted total 25(OH)D levels on reduced risk of URTICA_NAS (OR = 0.77, 95%CI: 0.63-0.95, p=0.001), with statistical power (77.4%). This was consistent with the results when serum 25(OH)D was used as the exposure in the IVW analysis (OR = 0.65, 95%CI: 0.50-0.85, p = 0.002), with statistical power = 93.2%.While other subtype analyses did not reach statistical significance, all causal effect estimates showed consistent directionality (OR<1). This consistent causal trend suggests a potential causal relationship between vitamin D levels and urticaria risk, indicating that higher 25(OH)D levels may play a role in reducing urticaria risk.

In analyses using 25(OH)D3 as the exposure, MR results revealed a significant causal relationship between genetically instrumented 25(OH)D3 levels and urticaria risk (OR = 0.85, 95%CI: 0.74-0.98,p = 0.023), with a statistical power of 67.4%. For the COLDHEATU subtype, MR analysis also identified a statistically significant causal relationship (OR = 0.39, 95%CI: 0.16-0.96, p = 0.041), although this analysis had relatively lower statistical power (54.9%). While MR analyses for other subtypes did not reach statistical significance and had limited statistical power, most causal effect estimates yielded ORs below 1, suggesting a potential causal relationship wherein genetically determined higher 25(OH)D3 levels may reduce urticaria risk.

However, future studies are needed to further validate these preliminary findings. Notably, MR analyses did not detect statistically significant causal relationships between genetically determined circulating C3-epi-25(OH)D3 levels and urticaria or any of its subtypes (statistical power ranging from 2.5% to 35.5%). These non-significant results may be partially attributed to insufficient statistical power in these analyses.

MR sensitivity analysis

Table 1 summarizes the results of our comprehensive sensitivity analyses. All p-values for heterogeneity and pleiotropy tests were higher than 0.05, indicating the absence of significant heterogeneity or pleiotropy across studies. The lowest p-value observed was 0.053 in the analysis of C3-epi-25(OH)D3 and urticaria, which still remains above the conventional significance threshold (α = 0.05), supporting the robustness of our findings. To ensure the validity and consistency of our research findings, we conducted multiple tests, including the MR-Egger intercept test, Cochran's Q test, and MR-PRESSO

Table 1. Sensitivity analysis results

Exposure and outcome	Heterogeneity test		Pleiotropy test		MR-PRESSO
	Cochran's Q statistic	*p* values	Intercept	*p* values	Global Test_*p* values
Total 25(OH)D					
Urticaria	4.17	0.84	0.00	0.79	0.77
URTICA_NAS	5.46	0.71	0.01	0.58	0.72
Dermatographic urticaria	3.40	0.91	0.00	0.94	0.94
Contact urticaria	4.09	0.85	0.00	1.00	0.83
Idiopathic urticaria	7.89	0.44	-0.01	0.75	0.44
COLDHEATU	5.03	0.75	0.03	0.60	0.73
Allergic urticaria	5.92	0.66	0.01	0.53	0.54
Cholinergic urticaria	5.92	0.66	0.05	0.48	0.52
25(OH)D3					
Urticaria	6.84	0.34	0.01	0.69	0.35
URTICA_NAS	6.91	0.33	0.02	0.31	0.42
Dermatographic urticaria	3.08	0.69	-0.01	0.77	0.58
Contact urticaria	6.69	0.35	0.10	0.57	0.42
Idiopathic urticaria	4.93	0.55	-0.03	0.65	0.53
COLDHEATU	3.96	0.68	0.02	0.81	0.68
Allergic urticaria	2.51	0.87	0.02	0.53	0.83
Cholinergic urticaria	9.14	0.17	0.22	0.09	0.21
C3-epi-25(OH)D3					
Urticaria	7.23	0.61	0.00	0.88	0.63
URTICA_NAS	6.27	0.62	-0.03	0.22	0.65
Dermatographic urticaria	7.76	0.56	0.06	0.10	0.58
Contact urticaria	5.72	0.68	0.12	0.58	0.73
Idiopathic urticaria	5.23	0.81	0.02	0.83	0.84
COLDHEATU	12.5	0.19	0.04	0.75	0.24
Allergic urticaria	13.4	0.15	0.07	0.05*	0.18
Cholinergic urticaria	5.83	0.76	0.19	0.18	0.78
Serum 25(OH)D					
Urticaria	3.59	0.73	-0.01	0.41	0.79
URTICA_NAS	3.53	0.74	-0.01	0.47	0.85
Dermatographic urticaria	7.72	0.26	-0.03	0.34	0.45
Contact urticaria	3.94	0.68	0.14	0.29	0.56
Idiopathic urticaria	7.02	0.32	0.02	0.72	0.47
COLDHEATU	3.22	0.67	0.02	0.81	0.62
Allergic urticaria	1.20	0.98	0.00	0.95	0.99
Cholinergic urticaria	8.35	0.14	0.14	0.24	0.35

25(OH)D, 25-hydroxyvitamin-D; 25(OH)D3,25-hydroxyvitamin D3; C3-epi-25(OH)D3, C3-epimer of 25-hydroxyvitamin D3; URTICA_NAS, other and unspecified urticaria; COLDHEATU, urticaria due to cold and heat.The asterisk (*) represents an actual value of 0.053.All *p*-values > 0.05 indicate no significant heterogeneity or pleiotropy.

global test. In all analyses, the *p*-values of the MR-Egger intercept test were >0.05, indicating no directional pleiotropy bias. Similarly, the p-values of Cochran's Q test were also above 0.05, further confirming no significant heterogeneity among the genetic variants used as IVs. Additionally, the MR-PRESSO global test showed no horizontal pleiotropy bias, and its outlier test indicated no outliers were present.

Although several outlier IVs were identified by the MR-radial method (Supplementary Table 2, Figures 10, 17, 19, 29, 31), further MR analyses excluding those outliers showed the robustness and consistency of our results. Notably, further analyses using MR-PRESSO and MR-radial methods did not detect more outliers. The multiple testing approaches that we applied indicated a lack of pleiotropy bias, heterogeneity, and outlier effects, further strengthening the validity of our findings. Leave-one-out analyses, scatter plots, funnel plots, forest plots, and MR-radial plots are presented in Supplementary Figures 1-31. Figure 3 display the visualization results of the effects of total 25(OH)D on urticaria.

Reverse MR analysis

We performed reverse two-sample MR analysis to investigate the bidirectional causal relationship between vitamin D metabolites and urticaria. This comprehensive analysis examined total 25(OH)D, 25(OH)D3, and C3-epi-25(OH)D3 levels in relation to urticaria and its various subtypes, allowing us to assess potential causal relationships in both directions. Given the limited number of available SNPs, we relaxed the significance threshold to 5×10^{-6} when analyzing urticaria and its seven subtypes as exposure factors. We identified IVs associated with various urticaria subtypes, but we were unable to find valid instruments for contact urticaria, COLDHEATU, or cholinergic urticaria (Supplementary Table 6). Our analyses revealed no significant association between the genetic risk of urticaria and blood vitamin D levels (Supplementary Table 7 and Table 8). These findings suggest a potential unidirectional relationship whereby vitamin D levels influence urticaria risk, but not vice versa.

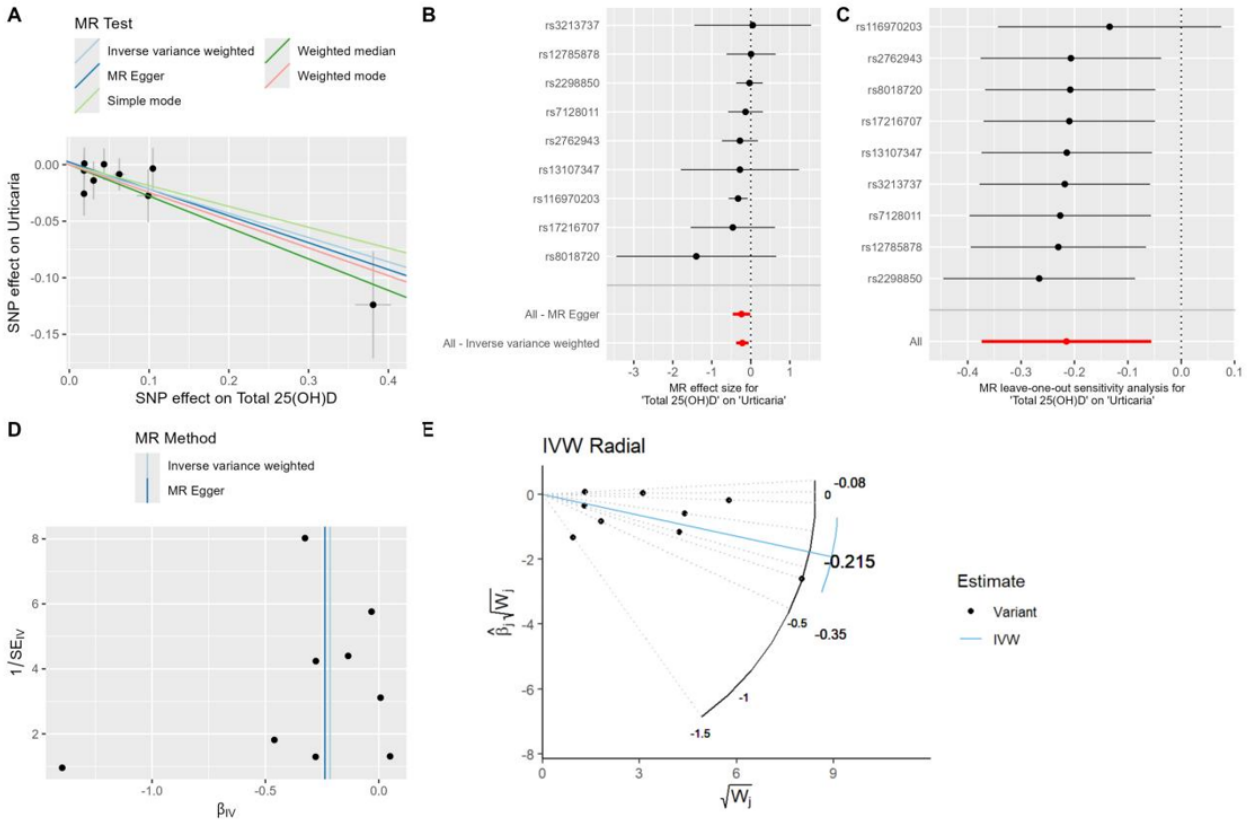

Figure 3. Visualization of Mendelian randomization (MR) estimates showing the causal effects of genetically predicted 'Total 25(OH)D' on 'Urticaria'.(A) Scatter plot. (B) Forest plot. (C) Leave-one-out plot. (D) Funnel plot. (E) Radial plot

DISCUSSION

In this study, we identified a significant causal relationship between vitamin D metabolites [25(OH)D and 25(OH)D3] and urticaria, providing the first genetic evidence suggesting that low vitamin D levels may increase the risk of urticaria. This finding is supported by a meta-analysis by Li et al.,[13] which confirmed that serum 25(OH)D deficiency is associated with increased incidence of chronic urticaria, indicating that reduced serum 25(OH)D levels may constitute a risk factor for urticaria development. Collectively, these results suggest that vitamin D levels may play a key role in the pathogenesis of urticaria.

Previous studies have shown that the skin of patients with chronic urticaria contains significantly more mast cells and higher levels of released chemical mediators compared to the skin of healthy individuals.[29,47] The IgE/FcεRI pathway plays a key role in the pathogenesis of urticaria.[48] When specific allergen IgE binds to FcεRI on the mast cell surface, it can trigger degranulation and the release of pro-inflammatory mediators, leading to the characteristic wheal and flare response. This IgE-dependent mast cell activation constitutes an important link between allergen sensitization and clinical manifestation of urticaria.[49,50] Research has also found that the serum of patients with chronic urticaria contains components capable of activating mast cells via the IgG receptor pathway.[51]

Recent studies suggest that vitamin D may improve clinical symptoms of chronic spontaneous urticaria by modulating the PI3K/Akt/p38 MAPK/HIF-1α signaling pathway and inhibiting mast cell release of vascular endothelial growth factor.[52] Research by Liu et al.[53] indicates that vitamin D deficiency may lead to abnormal mast cell activation, while supplementation with calcitriol (1α,25-dihydroxyvitamin D3, the biologically active form of vitamin D) can upregulate vitamin D receptor (VDR) expression on mast cells, highlighting the potential role of vitamin D in maintaining mast cell homeostasis. These findings emphasize the importance of vitamin D signaling in regulating mast cell function.

Notably, Yip described a potential bidirectional regulatory network between mast cells and vitamin D metabolism. Mast cells express the vitamin D-activating enzyme CYP27B1, which can convert 25(OH)D3 to the more potent 1α,25(OH)2D3, suggesting their role in tissue vitamin D homeostasis.[54] By binding to VDR on mast cells, 1α,25(OH)2D3 may inhibit the production and release of inflammatory mediators and initiate signaling cascades that suppress IgE-mediated mast cell degranulation, forming a negative feedback regulatory loop. This bidirectional control system may help maintain mast cell functional homeostasis and prevent tissue damage while ensuring appropriate local vitamin D concentrations, avoiding mast cell dysfunction caused by deficient or excessive levels. Additionally, vitamin D may influence the progression of urticaria through its immunomodulatory properties, such as inducing increased production of interleukin-10 (IL-10), promoting CD4+ T regulatory cell differentiation, and potentially inhibiting mast cell differentiation—mechanisms that may contribute to alleviating urticaria symptoms.[55,56] It is noteworthy that vitamin D deficiency is prevalent in various autoimmune conditions[57] such as systemic lupus erythematosus,[58] rheumatoid arthritis,[59]

and autoimmune thyroid diseases,[60] which have been associated with chronic urticaria.[61] The immunomodulatory effects of vitamin D—including regulation of T cell differentiation, modulating of B cell and dendritic cell function—are crucial for maintaining immune tolerance and preventing autoimmunity.[62,63] Our research provides genetic evidence for a potential causal relationship between vitamin D and urticaria, but certain genetic variants related to vitamin D metabolism may influence urticaria risk through other immunoregulatory pathways not entirely dependent on circulating vitamin D levels. These potential mediating mechanisms still require further in-depth investigation through appropriate mediation analyses.

Regarding C3-epi-25(OH)D3, despite its structural similarity to 25(OH)D3, its biological function in humans has not been fully elucidated.[64] Our study did not identify a clear causal association between C3-epi-25(OH)D3 and any type of urticaria. Research indicates that C3-epi-25(OH)D3 has approximately 2-3% binding affinity for the vitamin D receptor (VDR) compared to 25(OH)D3, and approximately 1/200 to 1/400 that of 1,25(OH)2D3.[65] Other studies have shown that the binding capacity of C3-epi-25(OH)D3 to VDR is approximately 35 to 120 times lower than that of 1,25(OH)2D3,[66,67] resulting in significantly reduced VDR binding.[68] This suggests that C3-epi-25(OH)D3 may have lower biological activity compared to 25(OH)D3 and 1α,25(OH)2D3, thus potentially limiting its ability to activate VDR-mediated signaling pathways. Additionally, C3-epi-25(OH)D may have a shorter half-life and potentially a faster metabolic clearance rate *in vivo*,[69] characteristics that may limit its role in regulating mast cell activity and the development and progression of urticaria.

In our study, we did not observe a reverse causal effect of urticaria on vitamin D levels. Although urticaria itself can lead to reduced vitamin D levels through certain behaviors: for example, increased photosensitivity during acute urticaria flares may reduce outdoor activities and sun exposure;[70] patients with chronic urticaria may decrease outdoor activities to avoid environmental triggers (such as temperature changes, physical stimuli),[71] thereby reducing vitamin D synthesis. Additionally, certain medications used to treat urticaria (e.g., corticosteroids) may also influence vitamin D metabolism.[72] Although these non-genetic factors might influence causal inference, our reverse MR analysis found no significant effect of urticaria genetic risk on vitamin D levels, suggesting a potentially unidirectional causal effect of vitamin D levels on urticaria risk. This interpretation is consistent with findings from a prospective, double-blind, randomized controlled trial showing that high-dose vitamin D supplementation (4000 IU/day) significantly improved chronic urticaria symptoms compared to low-dose supplementation (600 IU/day).[73]

The main advantage of this study is the use of MR to evaluate the causal relationship between exposure factors and outcomes. Compared to observational studies, MR can reduce or exclude confounding factors and reverse causality. Our study used large-sample GWAS data from European populations, giving us sufficient statistical power and allowing us to enhance the reliability of the results by using larger sample sizes in the validation phase. However, our results could be confounded because vitamin D levels are associated with multiple factors [body mass index (BMI), sun exposure, diet, skin pigmentation, season and geographical location, etc.], which may also influence the risk of urticaria. Vitamin D levels are negatively associated with BMI,[74] which is also associated with an increased risk of chronic urticaria.[75] Sun exposure is associated with vitamin D synthesis and may also independently influence the occurrence and progression of urticaria.[63] Foods containing vitamin D are often also rich in other nutrients and bioactive substances[76] that may have synergistic effects on skin barrier function and immune regulatory processes; however, it is unclear whether these factors simultaneously affect vitamin D levels and the risk of urticaria. Our study was limited to European populations, so our results may not be applicable to other racial or population backgrounds. Our analysis of the association between C3-epi-25(OH)D3 and urticaria subtypes was limited due to the lack of statistical power.

Conclusion

In summary, this study employed MR to demonstrate a significant correlation between genetically determined higher levels of vitamin D and reduced risk of urticaria. This finding not only enhances our comprehension of the potential role of vitamin D in preventing urticaria but also provides robust theoretical evidence for using vitamin D supplements as a promising therapeutic strategy. However, further rigorous and large-scale randomized controlled trials are still necessary to validate the specific effects and safety of vitamin D supplementation in preventing urticaria. This will enable us to comprehensively evaluate the feasibility and effectiveness of vitamin D supplementation as a preventive measure for urticaria.

SUPPLEMENTARY MATERIALS

All supplementary figures and tables are available upon request to the editorial office.

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DISCLOSURE ON THE USE OF AI AND AI-ASSISTED TECHNOLOGIES

Manuscript preparation was performed while using the services of Claude Pro, an AI language model developed by Anthropic, for professional editing to enhance the linguistic clarity and readability of the text.

CONFLICT OF INTEREST AND FUNDING DISCLOSURES

We hereby affirm that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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