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Causal relationship between vitamin D and stress urinary incontinence

Two-sample Mendelian randomization study

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Abstract

Observational studies have found an association between vitamin D and stress urinary incontinence (SUI); however, this conclusion remains controversial, and the causal relationship is unclear. This study aimed to investigate the causal relationship between vitamin D and SUI using a Mendelian randomization (MR) approach. We conducted an MR analysis utilizing publicly available summary data from genome-wide association studies on European ancestry for SUI, vitamin D levels, vitamin D supplementation, and vitamin D deficiency. Regression models such as the inverse variance-weighted (IVW) method, MR-Egger, weighted median, and weighted mode were used for analysis, along with heterogeneity tests, sensitivity analyses, and pleiotropy assessments.MR analysis indicated that vitamin D levels, vitamin D deficiency, and vitamin D supplementation were not causally associated with SUI (IVW OR: 0.999, 95% CI: 0.992–1.006, $P = .786$); (IVW OR: 1.000, 95% CI: 1.000–1.000, $P = .646$); (IVW OR: 1.000, 95% CI: 1.000–1.001, $P = .064$). No evidence of horizontal pleiotropy or heterogeneity was found ($P > .05$). Our findings do not support a causal relationship between vitamin D and SUI. The incidental effect of SUI and vitamin D may be mediated by other factors, warranting further observational studies and clinical trials.

Abbreviations: 25(OH)D = 25-hydroxyvitamin D, BMI = body mass index, CI = confidence interval, GWAS = genome wide association studies, IVW = inverse variance weighted, MR = Mendelian randomization, MR-Egger = Mendelian randomization based on Egger regression, MR-PRESSO = Mendelian randomization-pleiotropy residual sum and outlier, OR = odds ratio, SNPs = single nucleotide polymorphisms, SUI = stress urinary incontinence.

Keywords: 25-hydroxyvitamin D, causal relationship, Mendelian randomization, Stress urinary incontinence

1. Introduction

Stress urinary incontinence (SUI) is often caused by pelvic floor dysfunction and manifests as involuntary urine leakage during activities that increase abdominal pressure, such as coughing, laughing, or sneezing. SUI is the most common type of urinary incontinence, with a prevalence as high as 50%.[1] However, due to the low social acceptance of this condition, many patients have to pay out-of-pocket for incontinence pads, and only 25% to 40% of female patients actively seek medical help, with less than 5% undergoing surgical treatment.[2] Therefore, identifying risk factors for SUI is crucial for its treatment and prevention. Current research suggests that body mass index (BMI), pregnancy, vaginal delivery, and age are major risk factors for female SUI.[3]

Regarding the association between vitamin D and SUI, research findings are inconsistent. Vitamin D is a fat-soluble compound mainly obtained through sunlight exposure or dietary intake. In the body, vitamin D binds to vitamin D-binding protein and is converted to 25-hydroxyvitamin D [25(OH)D] by 25-hydroxylase in the liver, and its concentration is commonly used to assess an individual's vitamin D status. In primary cultures of satellite cells, 1,25-dihydroxyvitamin D3 was found to promote myogenesis differentiation and myotube formation by increasing the expression of myogenic regulatory factors such as myogenin.[4] The study by van der Meijden et al[5] showed that high levels of vitamin D promote the differentiation and maturation of skeletal muscle cells,

Informed consent was obtained from all participants in the original studies.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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increasing myotube fiber diameter and thereby improving muscle function. These findings suggest a potential new pathway for SUI treatment.

However, existing research results are inconsistent. A prospective study showed that vitamin D intake did not significantly reduce the risk of urinary incontinence,[6] while another systematic review and meta-analysis found that serum vitamin D levels in women with urinary incontinence were not lower than those in healthy controls.[7] A retrospective analysis of the Korean population also did not find a significant association between serum vitamin D levels and female urinary incontinence.[8] Conversely, some studies have reached opposite conclusions. For instance, one study found that vitamin D supplementation reduced the severity of SUI in premenopausal women,[9] but another trial in older women did not find a significant association between vitamin D levels and urinary incontinence incidence, and widespread use of moderate doses of vitamin D supplementation did not effectively reduce the occurrence of urinary incontinence.[10] Additionally, a study using the National Health and Nutrition Examination Survey database found that decreased serum 25(OH)D levels were associated with the occurrence of SUI in elderly men.[11] Current research results remain controversial; a review analyzing seven cross-sectional studies found that six studies reported a significant association between vitamin D deficiency or insufficiency and the onset and severity of urinary incontinence, whereas 2 out of three prospective studies did not find an association between vitamin D intake and urinary incontinence.[12] Given the diverse and complex risk factors for SUI, including smoking, BMI, and metabolic syndrome, caution is warranted when considering vitamin D as an independent risk factor for SUI.

Mendelian randomization (MR) is a study method that can provide causal inference, offering robust estimates between exposure factors and outcomes.[13] Unlike observational studies, MR uses single nucleotide polymorphisms (SNPs) as instrumental variables, thus avoiding confounding factors and reverse causality.[14] Therefore, this study aimed to explore the causal relationship between vitamin D and SUI through a two-sample MR analysis.

2. Materials and methods

2.1. Study design

This study used a two-sample Mendelian randomization (MR) approach to explore the causal relationship between vitamin D and stress urinary incontinence (SUI), based on publicly available summary-level data from genome-wide association studies (GWAS). The study adhered to the 3 basic assumptions of Mendelian randomization: Relevance: The selected genetic instrumental variables (SNPs) must be significantly associated with the exposure (e.g., vitamin D levels). Instrumental variables can be used to infer the causal effect of exposure on the outcome only if a sufficiently strong association exists between the instrumental variables and the exposure. Independence: The genetic instrumental variables must be independent of any potential confounders that might affect the relationship between the exposure and the outcome. This means that the instrumental variables must not be related to other external factors that could influence the outcome, as this would compromise the validity of causal inference. Exclusion restriction: The genetic instrumental variables should only affect the outcome through the exposure and not through any other pathways. This assumption ensures the accuracy of causal inference by avoiding "horizontal pleiotropy," where instrumental variables directly influence the outcome without acting through the exposure (Fig. 1).

2.2. Data sources

The SUI data in this study were obtained from the GWAS study: ukb-b-9873, which focused on primary diagnoses of SUI based on the ICD-10 diagnostic code N39.3. This dataset included 4340 European female patients and 458,670 healthy controls of European ancestry, covering 9,851,867 SNPs. The data can be accessed at https://gwas.mrcieu.ac.uk/. Genetic association data for vitamin D levels (ebi-a-GCST005367) were sourced from a large-scale GWAS, comprising 79,366 samples and 2,538,249 SNPs. Similarly, genetic association data for vitamin D deficiency (finn-b-E4_VIT_D_DEF) were based on an analysis of 16,380,466 SNPs, while data for vitamin D supplementation (ukb-a-462) covered 10,894,596 SNPs. All datasets met the import standards of the European Bioinformatics Institute (EBI) GWAS summary data.

We conducted the Mendelian randomization study using publicly available GWAS databases, all of which have obtained the necessary ethical approvals and informed consent. Therefore, no additional ethical approval or informed consent was required for this study.

2.3. Selection of genetic instruments

To assess the association between genetically predicted 25(OH)D levels and SUI while ensuring compliance with the instrumental variable assumptions, the following selection criteria were set: a P value less than 5×10^{-8}, linkage disequilibrium (LD) less than 0.001, a genetic distance of 10,000 kb, and a minor allele frequency greater than 0.01. Based on the second assumption of Mendelian randomization, which states that genetic variants should not be associated with potential confounders, we screened SNPs using the PhenoScanner V2 database and excluded those related to BMI,[15] metabolic syndrome (MS),[16] and smoking history (ever smoked) to avoid confounding effects.[17] Furthermore, we validated the relevance assumption of the instrumental variables by calculating the F-statistic to assess potential weak instrument bias. An F-statistic greater than 10 indicates no weak instrument bias. The F statistic was calculated using the formula: $F = R^2 (N - K - 1)/[K (1 - R^2)]$, where N represents the sample size of the exposure, K is the number of instrumental variables, and R^2 indicates the proportion of variance in the exposure explained by the instrumental variables.

2.4. Mendelian randomization statistical analysis

The inverse variance-weighted (IVW) method was used as the primary approach for MR analysis in this study.[18] In

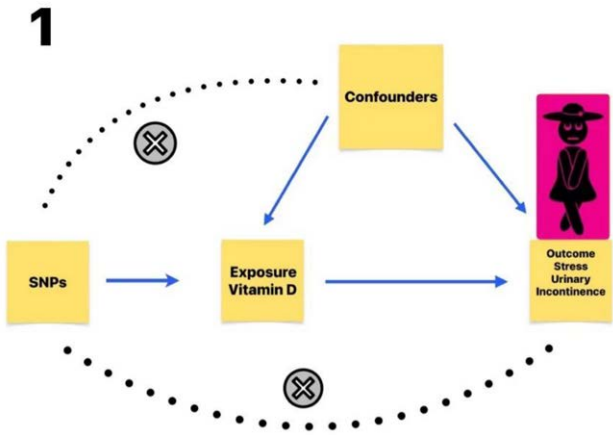

Figure 1. Diagram illustrating the assumptions underlying Mendelian randomization.

the IVW model, the association between each SNP and vitamin D levels, vitamin D deficiency, and vitamin D supplementation with the risk of SUI was independently estimated. By calculating the weighted average of the effect sizes of each SNP, IVW provided an overall causal estimate of the effect of vitamin D levels, vitamin D deficiency, and vitamin D supplementation on the risk of SUI, with weights assigned according to the precision of each SNP's effect estimate. A *P* value of less than .05 in the IVW analysis indicated a significant causal association between vitamin D and SUI.

To ensure the robustness of the findings, additional methods such as the weighted median (WM), MR-Egger, and weighted mode were also applied. Sensitivity analyses included heterogeneity and pleiotropy assessments. Cochran's Q test was used to evaluate consistency across different SNP effects, with a *P* value of less than .05 indicating significant heterogeneity. Funnel plots were also used to visually inspect heterogeneity, where symmetric SNP distribution suggested low heterogeneity. Pleiotropy was assessed using MR-Egger regression, and a non-zero intercept indicated potential pleiotropy issues.[19–22] Furthermore, a "leave-one-out" analysis was conducted, where each SNP was sequentially excluded to re-estimate the causal effect, allowing assessment of whether any single SNP had a significant impact on the overall effect estimate. All data analyses were performed using the TwoSampleMR package (R version 4.3.1). A *P* value of < .05 was considered statistically significant.

3. Results

Genetic Instruments: In the analysis exploring the association between vitamin D levels, vitamin D deficiency, and vitamin D supplementation with SUI, SNPs were selected as potential instrumental variables ($P < 5 \times 10^{-8}$, $R^2 < 0.001$). After removing those in linkage disequilibrium and excluding retrospective SNPs and confounders, 6, 6, and 9 SNPs associated with SUI were ultimately included, respectively, with all F-statistics greater than 10.

3.1. Mendelian randomization causal analysis

The IVW analysis showed no significant causal effect of vitamin D levels on the risk of SUI [OR = 0.999, 95% CI (0.992, 1.006), *P* = .786]. Similarly, no significant association was found between vitamin D deficiency and the risk of SUI [OR = 1.000, 95% CI (1.000, 1.000), *P* = .646]. Vitamin D supplementation also did not show a statistically significant effect on the risk of SUI [OR = 0.943, 95% CI (0.886, 1.003), *P* = .064]. The results from other supplementary methods also indicated no causal association with SUI (Fig. 2).

3.2. Heterogeneity and pleiotropy analysis

The MR-PRESSO Global test indicated no evidence of horizontal pleiotropy, with all *P* > .05 (vitamin D levels *P* = .789; vitamin D deficiency *P* = .801; vitamin D supplementation *P* = .521), suggesting no outliers among the instrumental variables. Cochran's Q test (vitamin D levels, MR-Egger: *P* = .595; vitamin D deficiency, MR-Egger: *P* = .719; vitamin D supplementation, MR-Egger: *P* = .446) showed no evidence of heterogeneity. The MR-Egger intercept test also showed no statistical significance (vitamin D levels: intercept = –0.00009, *P* = .777; vitamin D deficiency: intercept = –0.0002, *P* = .661; vitamin D supplementation: intercept = 0.0003, *P* = .516), indicating no observed pleiotropy (Fig. 2).

3.3. Visualization of causal relationships

Scatter Plot: The scatter plot visualized the effect estimates of SNPs related to vitamin D (including vitamin D levels, vitamin D deficiency, and vitamin D supplementation) on SUI. In the absence of significant associations, data points were scattered without a clear trend, indicating no significant relationship between changes in vitamin D and SUI. Funnel Plot: The funnel plot showed symmetrical and concentrated data points around the null effect, suggesting no significant bias or small-study effects in the analysis of the relationship between vitamin D and SUI, supporting the null results. Leave-One-Out Analysis: The leave-one-out analysis indicated that removing any SNP related to vitamin D did not significantly alter the overall effect estimate, and the effect remained close to zero. This suggests that no single SNP overly influenced the analysis results, indicating the robustness of the study conclusion that there is no significant causal relationship between vitamin D and SUI. Forest Plot: The forest plot showed that the confidence intervals of most SNP effect estimates crossed the null line, indicating no significant causal association. This further supported the conclusion that vitamin D levels, vitamin D deficiency, and vitamin D supplementation are not significantly causally associated with SUI (Figs. 3–5).

4. Discussion

In this Mendelian randomization (MR) analysis, we utilized GWAS summary data on vitamin D levels, vitamin D deficiency, vitamin D supplementation, and stress urinary incontinence (SUI) from a European population and constructed robust instrumental variables using SNPs. Multiple MR methods were applied to investigate the relationship between vitamin D levels, vitamin D deficiency, or vitamin D supplementation and SUI. However, these analyses did not provide evidence for a causal relationship between vitamin D levels, vitamin D deficiency, or vitamin D supplementation and SUI.

Vitamin D is a steroid hormone that plays a key role in regulating calcium and phosphorus balance in bones and muscles.

Exposure	Outcome	Method	N.SNP	P.value	OR(95%CI)	Heterogeneity.Test.P	MR.Egger.Intercept.P	MR.PRESSO.Global.Test.P
Vitamin D levels	Stress urinary incontinence	Inverse variance weighted	6	0.786	1.00(0.99 to 1.01)			
		MR Egger	6	0.845	1.00(0.98 to 1.03)	0.595	0.777	0.789(raw,0 outliers)
		Weighted median	6	0.809	1.00(0.99 to 1.01)			
		Weighted mode	6	0.907	1.00(0.99 to 1.01)			
Vitamin D deficiency	Stress urinary incontinence	Inverse variance weighted	6	0.646	1.00(1.00 to 1.00)			
		MR Egger	6	0.596	1.00(1.00 to 1.00)	0.719	0.661	0.8016667(raw,0 outliers)
		Weighted median	6	0.452	1.00(1.00 to 1.00)			
		Weighted mode	6	0.554	1.00(1.00 to 1.00)			
Vitamin supplements: Vitamin D	Stress urinary incontinence	Inverse variance weighted	9	0.064	0.94(0.89 to 1.00)			
		MR Egger	9	0.348	0.84(0.59 to 1.18)	0.446	0.516	0.521(raw,0 outliers)
		Weighted median	9	0.291	0.95(0.88 to 1.04)			
		Weighted mode	9	0.490	0.95(0.84 to 1.08)			

p<0.05 was considered statistically significant

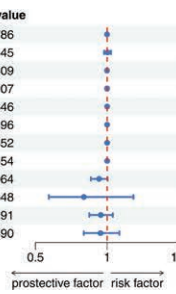

Figure 2. Associations of vitamin D levels, vitamin D deficiency, and vitamin D supplementation with Stress urinary incontinence. CI = confidence interval, OR = odds ratio, SNP = single nucleotide polymorphism.

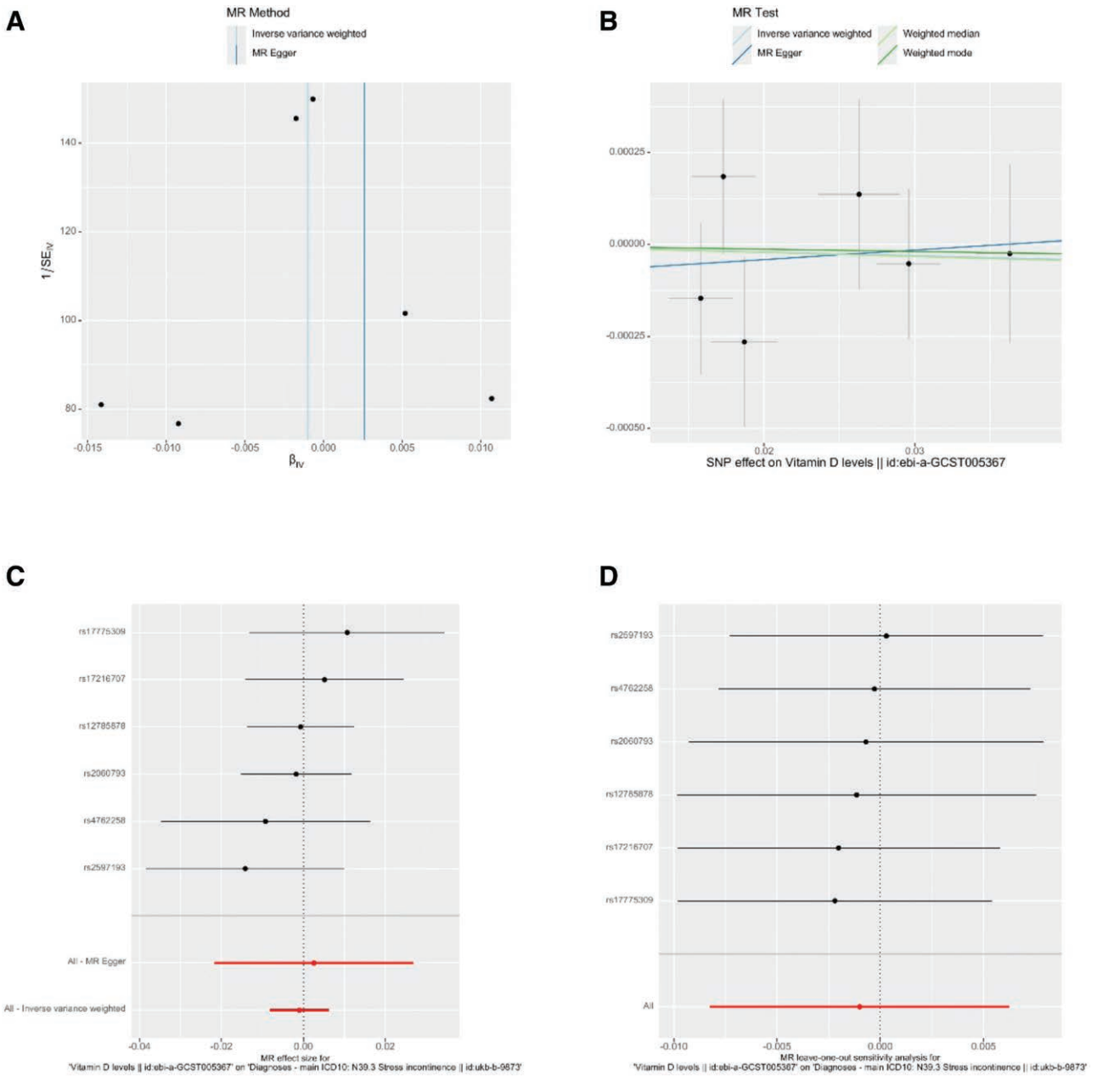

Figure 3. Mendelian randomization analysis of vitamin d levels and stress urinary incontinence (SUI). A: Funnel plot of SNPs associated with vitamin D levels and SUI-related SNPs. B: Scatter plot showing the relationship between SNPs related to vitamin D levels and the risk of SUI. C: Forest plot of the relationship between SNPs associated with vitamin D levels and the risk of SUI. D: "Leave-one-out" analysis plot for the relationship between SNPs related to vitamin D levels and SUI risk. SNP = single nucleotide polymorphism.

Stress urinary incontinence is caused by a decline in pelvic floor muscle function, which may play an important role in the development of SUI.[23] Vitamin D has an important role in muscle regulation, and its receptor (VDR) is widely expressed in human muscle tissues.[24] Studies have shown that VDR expression increases in skeletal muscle of animals with sufficient vitamin D or a vitamin D-rich diet,[25] while vitamin D deficiency reduces VDR expression in muscle and the VDR gene.[26] This indicates that the effect of vitamin D depends on its receptor; activation of VDR promotes protein synthesis in muscles, increases muscle cell volume and muscle mass, thereby enhancing muscle strength and function.

Additionally, vitamin D deficiency, accompanied by the production of reactive oxygen species, adversely affects mitochondrial function, leading to muscle atrophy.[27] Studies have also shown that even with calcium and phosphorus supplementation, VDR gene knockout mice exhibit muscle weakness and atrophy from a young age.[28] Furthermore, observational clinical studies have found that low vitamin D levels are associated with muscle weakness, decreased postural stability, and an increased risk of falls.[29] Interventional studies have also found that vitamin D supplements can improve muscle strength in those with vitamin D deficiency. One study reported that vitamin D supplementation increased muscle strength in athletes deficient in vitamin D.[30] In summary, it is theoretically plausible that vitamin D levels can regulate pelvic floor muscle function. However, current clinical results regarding the effect of vitamin D on SUI remain inconsistent. Further experimental studies are needed to verify the effect of vitamin D on SUI, particularly its effect on urethral sphincter strength.

This study has the advantage of being based on a large population sample and, for the first time, systematically explores

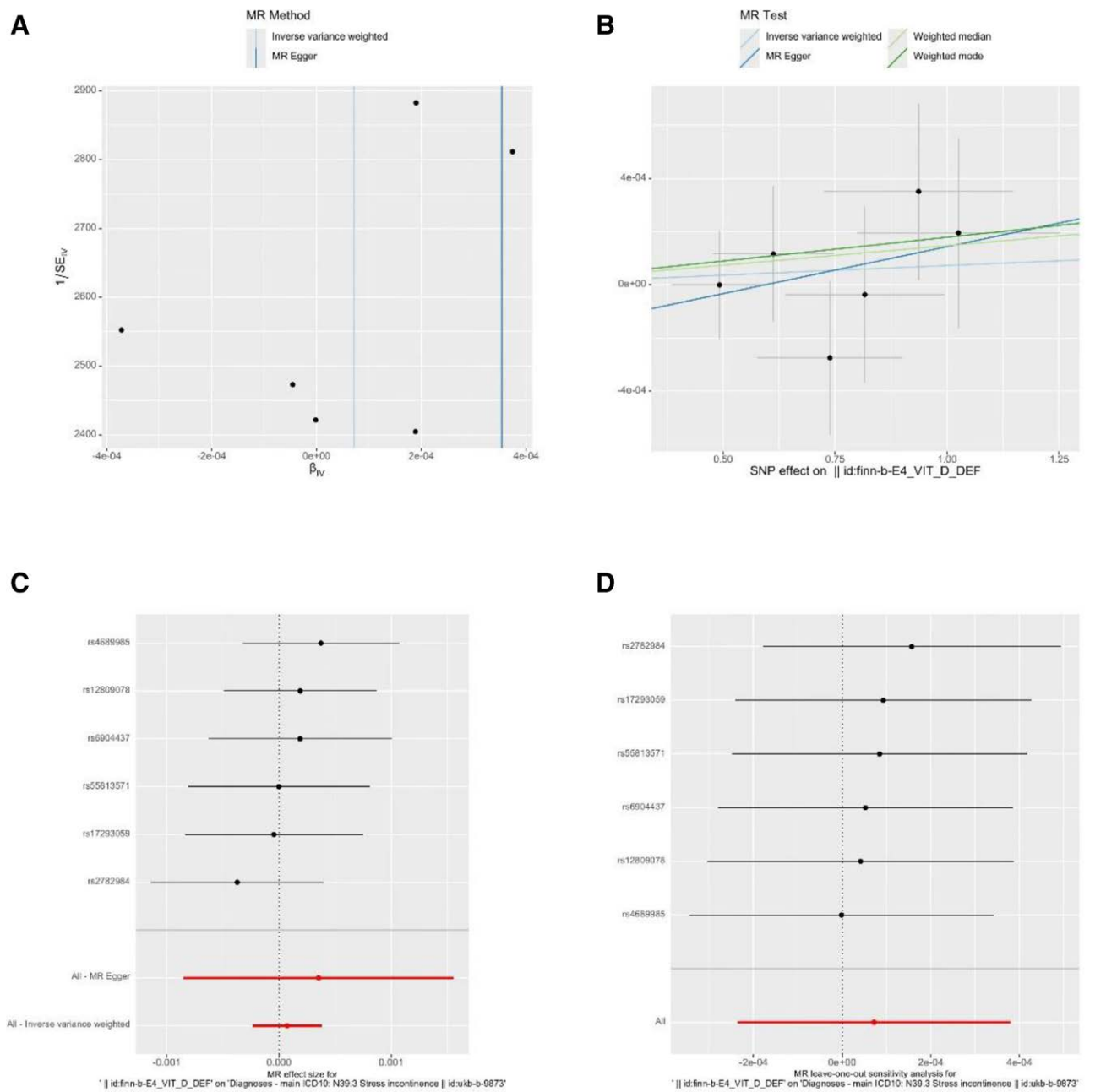

Figure 4. Mendelian randomization analysis of vitamin D deficiency and stress urinary incontinence (SUI). A: Funnel plot of SNPs related to vitamin D deficiency and SUI-associated SNPs. B: Scatter plot displaying the relationship between SNPs associated with vitamin D deficiency and the risk of SUI. C: Forest plot for the relationship between SNPs linked to vitamin D deficiency and the risk of SUI. D: "Leave-one-out" analysis plot for the relationship between SNPs related to vitamin D deficiency and SUI risk. SNP = single nucleotide polymorphism.

the potential causal relationship between vitamin D levels, vitamin D deficiency, or vitamin D supplementation and SUI from a genetic perspective. By using genetic variations as instrumental variables, we effectively minimized confounding factors and reverse causality that are common in traditional observational studies. In addition, the exposure and outcome data in this study were independent of each other, which further improved the accuracy of the results. To validate the robustness of the results, various statistical methods, including IVW, WMM, MR-Egger regression, and MR-PRESSO, were used.

It is important to note that MR is based on three core assumptions and seeks to approximate a randomized controlled trial through specific methods to assess the robustness of results and draw relatively accurate conclusions. However, MR itself has certain limitations, such as the association between genetic factors and exposure or outcomes (whether the selected instrumental variables fully meet the requirements: linkage disequilibrium, *P* value, consideration of confounding factors, inclusion criteria for populations, race, gender, age group, etc.), and the fact that not all diseases follow Mendelian inheritance. Therefore, the results of MR should be interpreted with caution and supported by "evidence synthesis," meaning that the more consistent the results, the more reliable the conclusion. When genetic factors are not significantly associated with exposure or outcomes, negative MR results do not rule out a causal relationship between exposure and outcomes, as conclusions may vary by ethnicity, age, gender, and the selection of instrumental variables, necessitating validation through multiple approaches.

Although observational studies suggest that vitamin D levels may be associated with the development of SUI, our MR results did

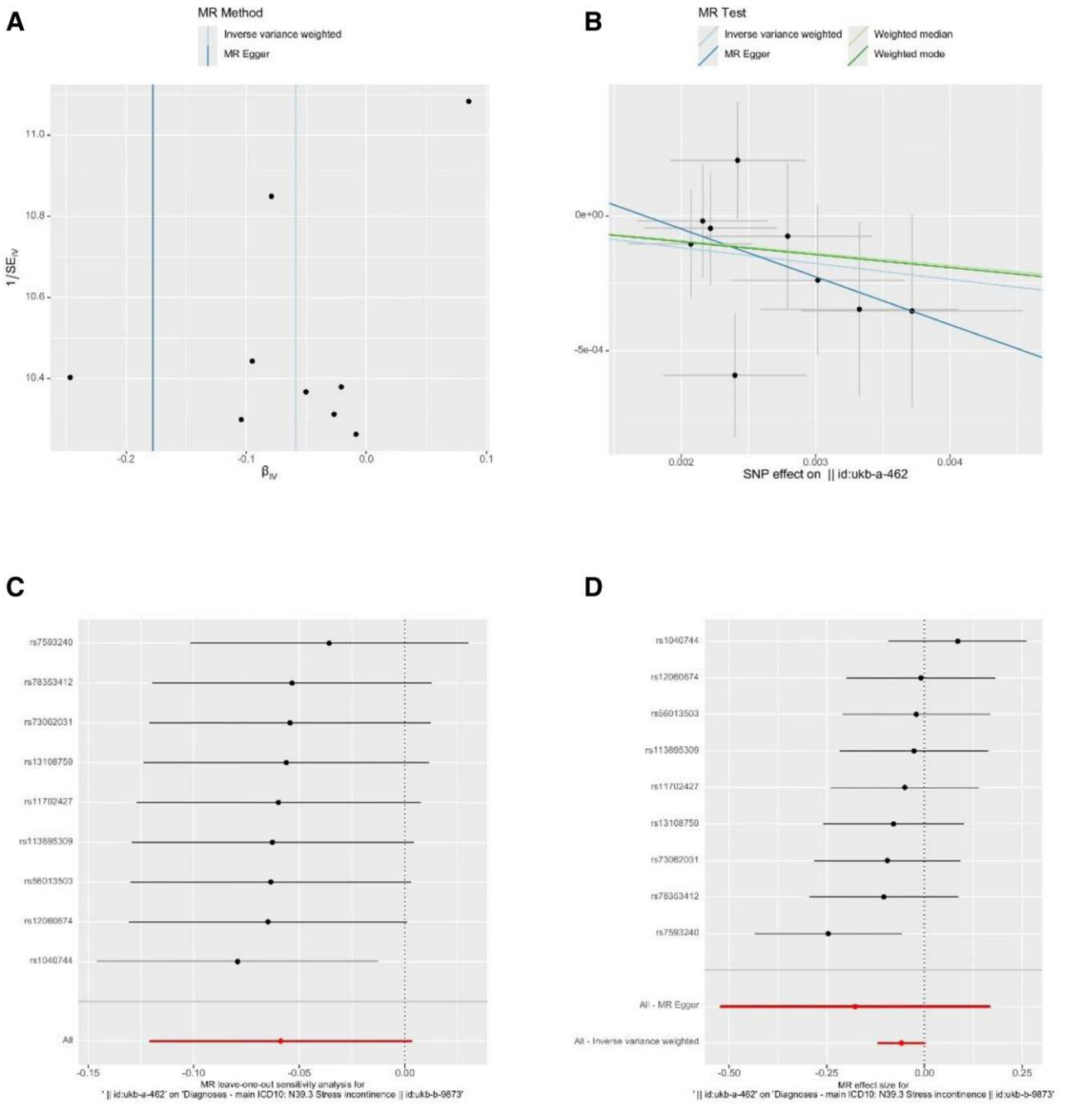

Figure 5. Mendelian randomization analysis of vitamin D supplementation and stress urinary incontinence (SUI). A: Funnel plot of SNPs related to vitamin D supplementation and SUI-associated SNPs. B: Scatter plot showing the relationship between SNPs associated with vitamin D supplementation and the risk of SUI. C: Forest plot for the relationship between SNPs related to vitamin D supplementation and the risk of SUI. D: "Leave-one-out" analysis plot for the relationship between SNPs associated with vitamin D supplementation and SUI risk. SNP = single nucleotide polymorphism.

not find evidence of a genetic-mediated relationship between vitamin D levels, vitamin D deficiency, or vitamin D supplementation and SUI. Existing cross-sectional and observational studies may be influenced by environmental confounders. Mendelian randomization, by excluding confounding factors, provides clearer evidence that there is no causal relationship between vitamin D levels, vitamin D deficiency, or vitamin D supplementation and SUI.

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Author contributions

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Supervision: Hui Wang.
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