

# Non-causal Effect of Circulating Vitamin D Levels on the Risk of Rheumatoid Arthritis: A Two-sample Mendelian Randomization Study

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## Research

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# Abstract

**Background:** Recently, many studies have indicated the potential roles of vitamin D in rheumatoid arthritis (RA). In the present study, the published available GWAS summary data was used to perform two-sample Mendelian randomization (MR) to infer the causal effect between circulating vitamin D levels and RA risk.

**Methods:** Single nucleotide polymorphisms (SNPs) which significantly associated with exposure were selected as instrumental variables from larger-scale genome-wide association study (GWAS). The robust analytical methods including MR Egger, inverse variance weighted (IVW), weighted median and weighted mode were conducted to infer the causal links.

**Results:** The IVW method suggested that there was no causal relationship of genetically predicted circulating vitamin D on RA (Asian: odds ratio (OR)=0.911, 95% confidence interval (CI), 0.542-1.534,  $P=0.727$ ; European: OR=0.897, 95% CI, 0.633-1.269,  $P=0.538$ ). MR Egger (Asian: OR=0.937, 95% CI, 0.373-2.352,  $P=0.895$ ; European: OR=0.853, 95% CI, 0.469-1.553,  $P=0.639$ ), weighted median (Asian: OR=0.895, 95% CI, 0.499-1.606,  $P=0.711$ ; European: OR=0.885, 95% CI, 0.620-1.264,  $P=0.503$ ) and weighted mode (Asian: OR=0.904, 95% CI, 0.515-1.588,  $P=0.738$ ; European: OR=0.898, 95% CI, 0.618-1.306,  $P=0.604$ ) demonstrated that vitamin D was not directly related to RA as well.

**Conclusions:** The MR analysis indicates that there is no evidence of causal effect of genetically predicted circulating vitamin D levels on RA risk.

## 1. Introduction

Rheumatoid arthritis (RA) is a systemic chronic autoimmune disease, mainly manifested by the proliferation of synovial lining cells and the erosion of cartilage and bone tissue. RA appears mostly in women and may occur at any age, with a peak incidence between 50 and 60 years old [1]. In general, progressive disability and shortened life expectancy are almost universal in RA patients [2], furthermore, physical pain also seriously affects the quality of life [3]. The exact pathogenesis of RA is not yet known [4], but it is believed that environmental, genetic, and infectious factors may interact in susceptible individuals and the heritability of RA is approximately 65% [5].

Vitamin D is a fat-soluble steroid that with the function of promoting the absorption of calcium and phosphorus, mainly including vitamin D2 and D3. It is generally believed that vitamin D is closely related to calcium homeostasis and bone formation. In addition, vitamin D has the potential to modulate immune cells, particularly T lymphocytes [6]. Vitamin D deficiency is common in autoimmune rheumatic diseases [7] which is accepted to be an established risk factor of numerous autoimmune diseases [8]. Vitamin D is involved in innate and adaptive immune responses and therefore insufficient vitamin D levels may be related to the loss of immune tolerance [9,10]. The inherent anti-inflammatory functions of vitamin D highlight its potential therapeutic value in autoimmune diseases [11-13]. However, no consensus is reached on whether there are causal effects between vitamin D and RA.

Two-sample Mendelian randomization (MR) is a technique which integrates large-scale genome-wide association study (GWAS) summary data, and single nucleotide polymorphisms (SNPs) significantly associated with exposure are used as instrumental variables to infer the causal links between exposure and outcome. MR method must follow the three assumptions. First, instrumental variables are independent of confounding factors. Second, instrumental variables are significantly related to exposure. Third, instrumental variables affect the outcome only through exposure [14]. The advantage of MR is that the causal inference is not interfered by common confounding factors such as environment and lifestyle.

Given the current results of the association between vitamin D and RA was inconsistent, and the causal effect between vitamin D and RA had not yet been established, the two-sample MR was performed to infer whether there were causal effects of circulating vitamin D levels on RA risk.

## 2. Methods

### 2.1 GWAS summary data

Summary data for the circulating vitamin D levels were selected from a larger-scale GWAS analysis, including 79,366 European ancestry [15]. The GWAS summary data for RA were obtained from a larger dataset with 19,234 individuals (4,873 Asian and 14,361 European ancestry) [16]. The selection of large sample GWAS was conducive to obtaining more comprehensive and reliable results. The corresponding information of SNPs including effect allele, other allele, effect sizes, standard error and effect allele frequency (EAF) was collected.

## 2.2 Instrumental variables selection

The following quality control steps were used to select the optimal instrumental variables to avoid the impact of bias on the results. First, SNPs significantly associated with exposure were served as potential instrumental variables ( $P < 5 \times 10^{-8}$ ). Second, the clumping process ( $R^2 < 0.001$ , clumping distance = 10,000 kb) was performed to avoid the underlying bias caused by strong linkage disequilibrium (LD). Third, the SNPs which with minor allele frequency (MAF) less than 0.01 were excluded from the present study. Fourthly, if the information of vitamin D related SNPs was not present in the outcome GWAS, the proxy SNPs with high LD ( $r^2 > 0.80$ ) were chosen to replace the variants of interest. Finally, to ensure that the effect of the selected SNPs on circulating vitamin D levels and the effect of the same SNPs on the outcomes corresponded to the same allele, the palindromic SNPs were excluded.

One of the assumptions of MR analysis is that the included SNPs must be highly correlated with exposure. In the present study, the  $F$  statistic ( $F = R^2(n-k-1)/(k(1-R^2))$ ) was used to explore whether there were instrumental variables that were weakly correlated with exposure. In this equation,  $R^2$  represents the cumulative explained variance of the selected instrumental variables on circulating vitamin D levels,  $k$  is the number of selected instrumental variables and  $n$  represents the sample size. When  $F > 10$ , the correlation between instrumental variables and exposure is considered to avoid the bias caused by weak instrumental variables.

## 2.3 Statistical analysis

In this study, MR methods with robust testing power including inverse variance weighted (IVW), MR Egger, weighted median and weighted mode were used to infer the causal effects of vitamin D with RA. The IVW conducts a meta-analysis approach to divide the  $\beta$  coefficient of the SNPs of RA by the  $\beta$  coefficient of the SNPs of vitamin D to obtain an overall estimate of the effect of vitamin D on RA [17]. In the absence of horizontal pleiotropy, or when the horizontal pleiotropy is balanced, IVW linear regression enable to obtain unbiased causal estimates [18]. Directional pleiotropic test, causal effect test and causal effect estimation are the three components of MR Egger [19]. Under the Instrument Strength Independent of Direct Effect (InSIDE) condition, even if all instrumental variables are invalid, MR Egger can also give a consistent causal effect estimate [20]. Weighted median is suitable for the situations where up to 50% of the information comes from invalid instrumental variables. If most of the instrumental variables in the model do not meet the requirements of using MR for causal inference, the weighted mode approach is effective [21]. Weighted mode is usually used as a supplementary analysis. MR-Egger regression was conducted to test whether the instrumental variables had potential pleiotropic effects. Cochran  $Q$  statistic was performed to quantify the heterogeneity among selected SNPs. Leave-one-out sensitivity analysis was used to test whether the overall estimates were affected by single SNP.

The TwoSampleMR package in R software (version 4.0.3) was used to conduct statistical analysis.

# 3. Results

## 3.1 Genetic variants selection

In the analysis of Asian population, after the SNPs with strong LD were excluded, 8 SNPs were selected as potential instrumental variables. After excluding a palindromic SNP (rs8018720), 7 variants of interest were selected as instrumental variables (Table 1). For European population, 5 SNPs were served as instrumental variables after excluding a palindromic SNP (rs8018720) (Table 1). The remained SNPs explained 2.2% (Asian) and 1.8% (European) of the variance of circulating vitamin D levels.  $F$  statistics were greater than 10, suggesting weak instrumental variables were less likely to exist.

## 3.2 Two-sample MR analysis

For the Asian population, IVW result indicated that there was no causal effect between circulating vitamin D levels and the risk of RA (odds ratio (OR) = 0.911, 95% confidence interval (CI), 0.542-1.534,  $P = 0.727$ ) (Table 2). Furthermore, MR Egger (OR = 0.937, 95% CI, 0.373-2.352,  $P = 0.895$ ), weighted median (OR = 0.895, 95% CI, 0.499-1.606,  $P = 0.711$ ) and weighted mode (OR = 0.904, 95% CI, 0.515-1.588,  $P = 0.738$ ) obtained consistent results (Table 2) (Fig. 1a). Leave-one-out sensitivity analysis showed that the results were reliable and stable (Fig. 2a). The results of MR-Egger regression showed that there was no horizontal pleiotropy between instrumental variables and RA ( $P = 0.946$ ) (Fig. 3a). Heterogeneity tests demonstrated that there was no significant heterogeneity exist ( $P = 0.914$ ) (Fig. 4a).

In the analysis of the European population, the results of IVW (OR = 0.897, 95% CI, 0.633-1.269,  $P = 0.538$ ), MR Egger (OR = 0.853, 95% CI, 0.469-1.553,  $P = 0.639$ ), weighted median (OR = 0.885, 95% CI, 0.620-1.264,  $P = 0.503$ ) and weighted mode (OR = 0.898, 95% CI, 0.618-1.306,  $P = 0.604$ ) indicated that no causal effect was found between circulating vitamin D levels and RA risk (Table 2) (Fig. 1b). Leave-one-out

sensitivity analysis showed that the results were reliable and stable (Fig. 2b). The results of MR-Egger regression indicated no significant evidence of horizontal pleiotropy ( $P=0.850$ ) (Fig. 3b). In addition, the results showed that there was no heterogeneity among the included instrumental variables ( $P=0.338$ ) (Fig. 4b).

## 4. Discussion

In the current study, the two-sample MR was performed to infer the potential causal links between vitamin D and RA. The results demonstrated that there was no causal effect of genetically predicted circulating vitamin D on RA risk.

In addition to its inherent functions of regulating calcium and phosphorus metabolism and promoting bone development, the immunomodulatory properties of vitamin D have also been extensively studied. However, existing evidence on the association between vitamin D and RA was contradictory. A study found that the serum 25OH vitamin D level of early RA patients was significantly lower than that of healthy controls [22]. A study focusing on serum and synovial fluid vitamin D metabolites in RA patients found no significant difference in concentrations of 25(OH)D3, 24,25(OH)2D3, 1,25(OH)2D3 and 25(OH)D2 when compared with healthy controls, except for 3-epi-25(OH)D3 [23]. Beyer *et al.* suggested that most RA patients did not suffer from hypovitaminosis D and it was not related to the differences in the severity of RA as well [24]. However, a recent study showed that vitamin D deficiency was associated with RA activity and severity, and might predict the disability and imaging progression of early RA patients within 1 year [25]. There were some researches on the vitamin D-related gene polymorphisms and RA. A study demonstrated that the serum vitamin D level of RA patients might be normal, but the polymorphisms of the *vitamin D receptor* (*VDR*) gene restricted the anti-inflammatory effect of vitamin D by changing the 1,25(OH)2 D3 binding site [26]. A meta-analysis found an association between *VDR* gene polymorphisms and RA susceptibility [27]. However, the study pointed out that some mutations would make carriers susceptible to RA, while others would reduce the susceptibility of RA.

The reasons for the inconsistent conclusions might be that the sample size was different and the studies with small sample size had a high contingency. In addition, the circulating vitamin D levels of participants were closely related to their eating habits and lifestyles, therefore, it was unreliable to estimate the association between vitamin D and RA without adjusting these confounding factors. However, some data indicated that hypovitaminosis D status was related to the progression of RA and vitamin D supplementation might alleviate the clinical symptoms of RA [28]. A study showed that treatment with vitamin D supplementation in RA patients with secondary osteoporosis could effectively increase bone mineral density [29]. Nevertheless, a study involving 1180 individuals indicated that vitamin D supplementation did not provide other benefits for anti-rheumatic therapy [30]. The specific roles of vitamin D in the pathology of RA and whether vitamin D supplementation is effective remains to be confirmed in the future.

In general, there are several limitations in the present study should be noticed. First, since the absence of clinical parameters, and disease activity information in original GWAS, further subgroup analysis was impossible. Second, our study was unable to determine whether overlapping participants were involved in the exposure and outcome GWAS used in the two sample MR analyses. Nevertheless, the deviation from participants overlap could be minimized by the *F* statistic [31].

In summary, the two-sample MR analysis suggest that there is no causal effect between circulating vitamin D levels and RA risk. However, further studies should utilize updated data from large-scale GWAS to obtain more reliable results.

## Abbreviations

CI: Confidence interval; EAF: effect allele frequency; GWAS: Genome-wide association study; InSIDE: Instrument Strength Independent of Direct Effect; IVW: Inverse variance weighted; MAF: Minor allele frequency; LD: Linkage disequilibrium; MR: Mendelian randomization; OR: Odds ratio; RA: Rheumatoid arthritis; SNP: Single nucleotide polymorphism; VDR: Vitamin D receptor.

## Declarations

### Acknowledgements

None.

### Authors' contributions

HFP conceived of the presented idea. KX performed the computations and manuscript writing. PW and SST were involved in acquisition of data. YQH, YSH, YC, YTF and XKY were involved in interpretation of data. All authors discussed the results and contributed to the final

manuscript.

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## Availability of data and materials

The dataset generated or analyzed in this study is included with this article and can be made available from the corresponding author upon reasonable request.

## Ethics approval and consent to participate

The article does not contain any studies with human participants or animals performed by any of the authors.

## Consent for publication

Not applicable.

## Competing interests

The authors declare no conflict of interest.

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## Tables

Table 1. The instrumental variants of vitamin D levels and their association with RA												
Ethnicity	SNP	Effect allele	Other allele	Vitamin D			RA			Proxy SNP	Target effect allele	Target other allele
				Beta	SE	<i>P</i> value	Beta	SE	<i>P</i> value			
Asian	rs10745742	T	C	0.017	0.002	1.88E-14	-0.020	0.026	0.38	rs1968487	T	C
	rs6839473	A	G	0.017	0.002	1.79E-15	-0.062	0.167	0.73	-	-	-
	rs2597193	A	G	0.019	0.002	6.26E-17	0.020	0.030	0.43	-	-	-
	rs17216707	C	T	-0.026	0.003	8.14E-23	0.010	0.056	0.89	-	-	-
	rs10741657	G	A	-0.031	0.002	2.05E-46	0.010	0.026	0.56	-	-	-
	rs12785878	T	G	0.036	0.002	3.81E-62	0.010	0.028	0.58	-	-	-
	rs2282679	G	T	-0.089	0.002	1.00E-200	0.010	0.028	0.73	-	-	-
European	rs10745742	T	C	0.017	0.002	1.88E-14	0.010	0.018	0.59	rs2117916	A	G
	rs6839473	A	G	0.017	0.002	1.79E-15	-0.030	0.022	0.16	-	-	-
	rs2597193	A	G	0.019	0.002	6.26E-17	0.020	0.020	0.32	-	-	-
	rs12785878	T	G	0.036	0.002	3.81E-62	-0.010	0.022	0.65	-	-	-
	rs2282679	G	T	-0.089	0.002	1.00E-200	0.010	0.017	0.56	-	-	-

Abbreviations: SNP, single nucleotide polymorphism; RA, rheumatoid arthritis

Ethnicity	Methods	Nsnp	Beta	SE	OR (95% CI)	P value	Horizontal pleiotropy			Heterogeneity		F statistics
							Egger intercept	SE	P value	Cochran's Q	P value	
Asian	MR Egger	7	-0.065	0.469	0.937 (0.373-2.352)	0.895	-0.002	0.021	0.946	1.494	0.914	255.02
	Weighted median	7	-0.111	0.298	0.895 (0.499-1.606)	0.711						
	Inverse variance weighted	7	-0.093	0.266	0.911 (0.542-1.534)	0.727						
	Weighted mode	7	-0.101	0.287	0.904 (0.515-1.588)	0.738						
European	MR Egger	5	-0.159	0.306	0.853 (0.469-1.553)	0.639	0.003	0.015	0.850	3.372	0.338	290.93
	Weighted median	5	-0.122	0.182	0.885 (0.620-1.264)	0.503						
	Inverse variance weighted	5	-0.109	0.177	0.897 (0.633-1.269)	0.538						
	Weighted mode	5	-0.107	0.191	0.898 (0.618-1.306)	0.604						

Abbreviations: SNP, single nucleotide polymorphism; RA, rheumatoid arthritis; OR, odds ratio

## Figures

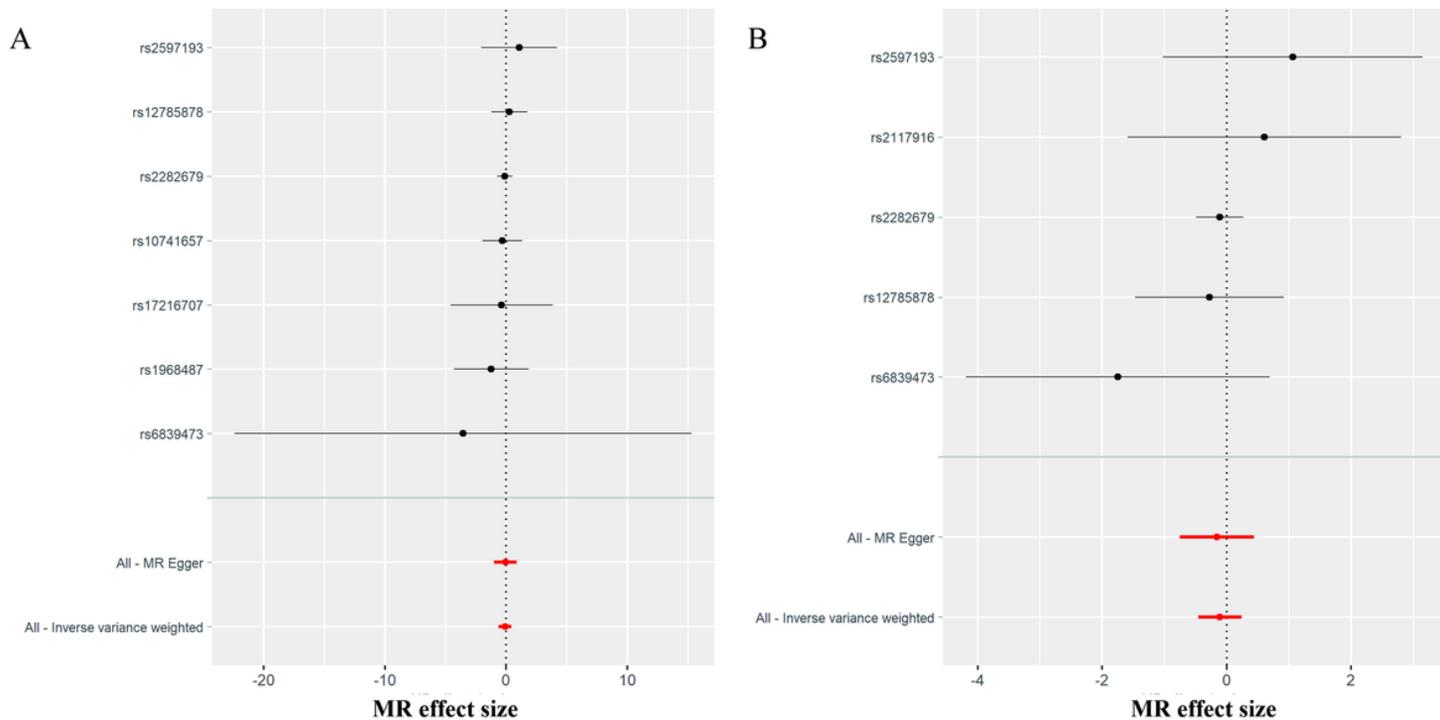


Figure 1

Forest plots of the causal effects of circulating vitamin D levels on RA risk (A: Asian; B: European)

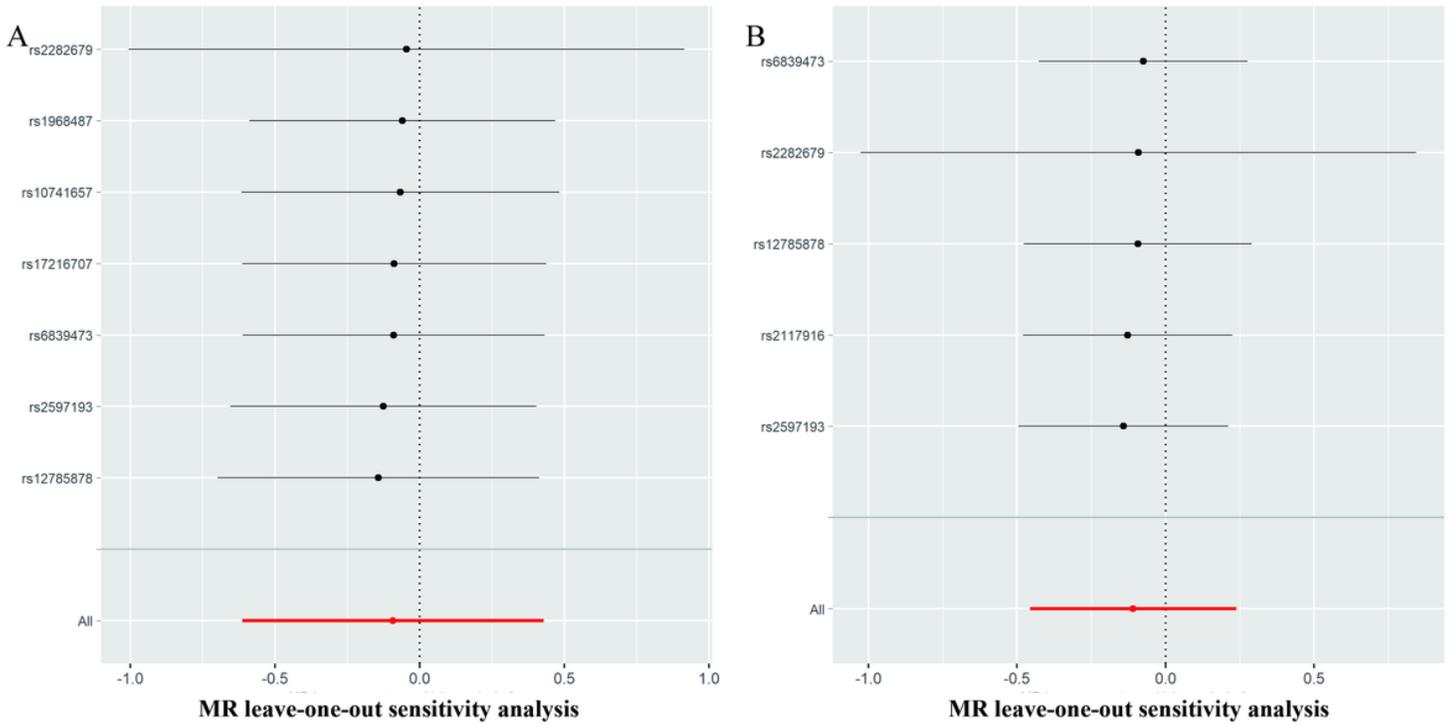


Figure 2

Sensitivity analyses of the causal effects of circulating vitamin D levels on RA risk (A: Asian; B: European)

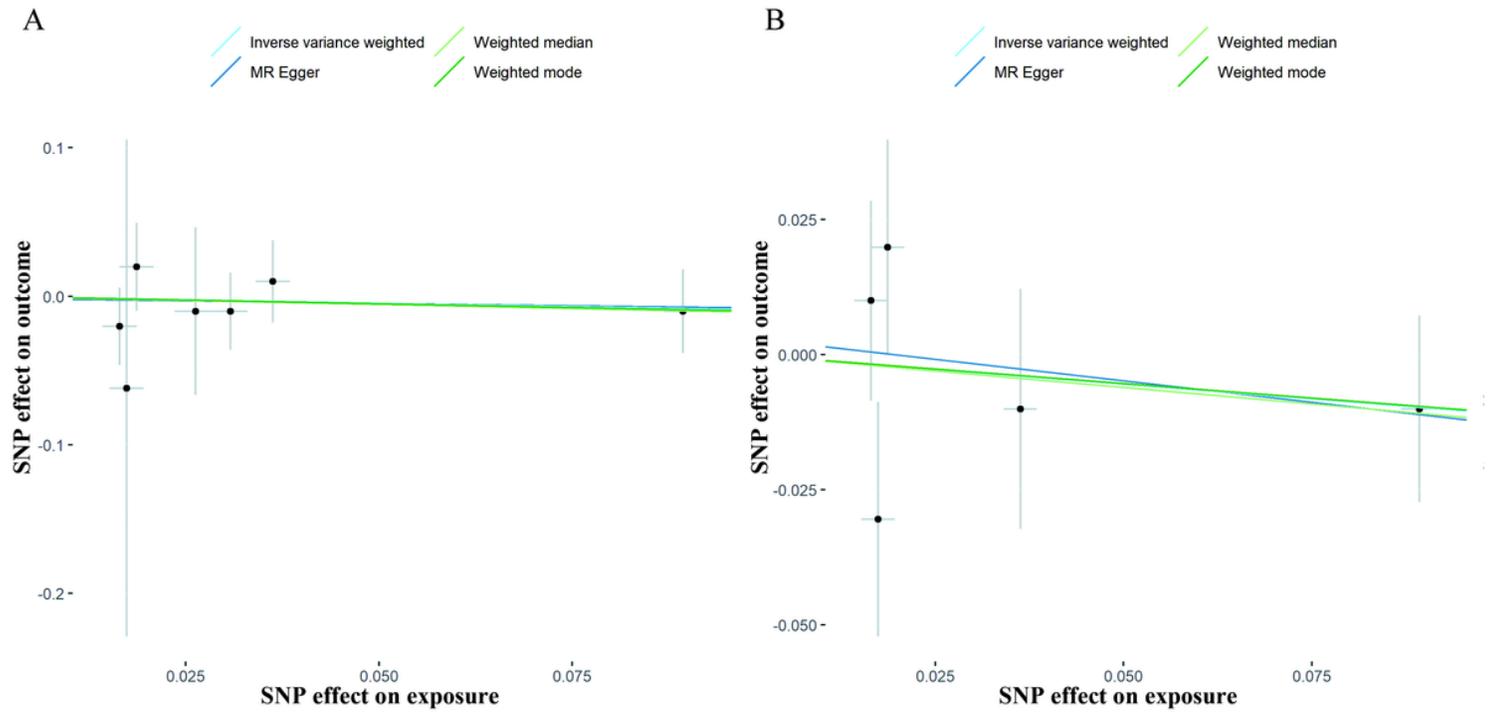
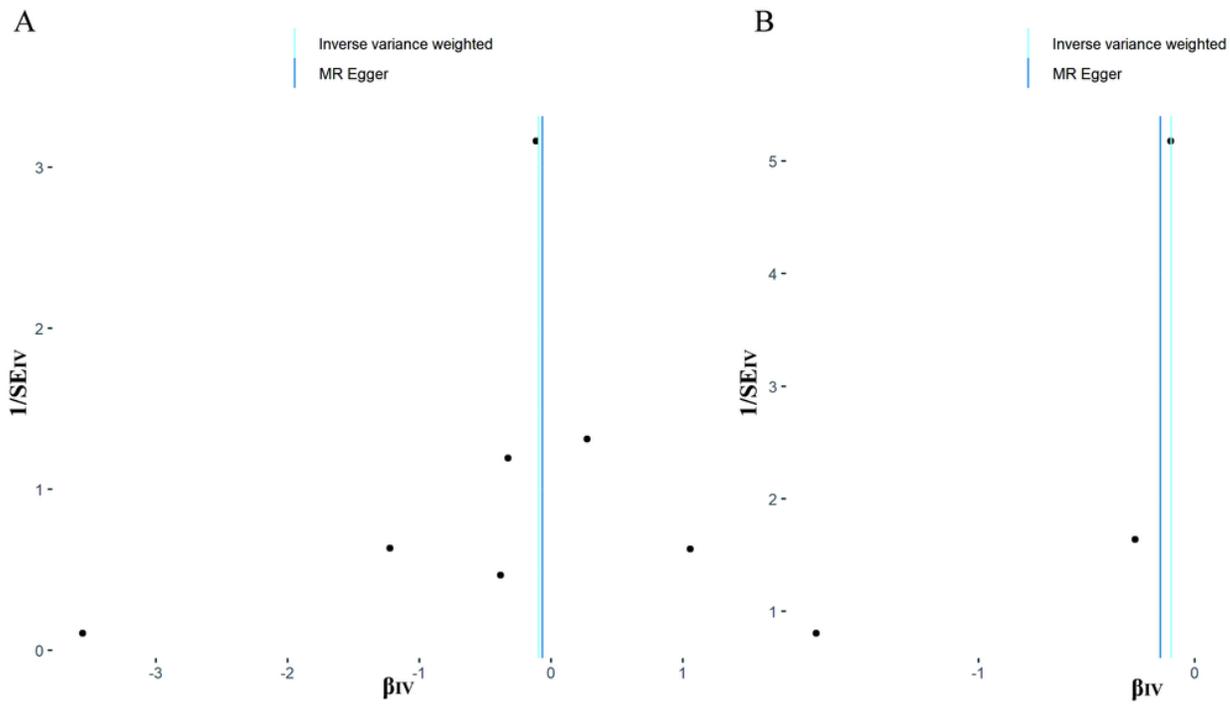


Figure 3

Scatter plots of the causal effects of circulating vitamin D levels on RA risk (A: Asian; B: European)



**Figure 4**

Funnel plots of the causal effects of circulating vitamin D levels on RA risk (A: Asian; B: European)