Causal association between vitamin D levels and neonatal jaundice: results from a Mendelian randomization study

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Abstract

Introduction: Observational studies have suggested an association between vitamin D deficiency and the risk of neonatal jaundice; however, it remains unclear whether this relationship is causal. We conducted a Mendelian randomization (MR) study to evaluate whether vitamin D levels influence the risk of neonatal jaundice.

Material and methods: Single nucleotide polymorphisms (SNPs) highly associated with vitamin D levels were selected as instrumental variables from publicly available genome-wide association studies (GWAS). MR analysis was conducted using five different models, including MR-Egger regression and inverse-variance weighting (IVW). Sensitivity analysis included MR-PRESSO (MR-pleiotropy residual sum and outlier) testing, Cochran's Q heterogeneity testing, the MR-Egger method, leave-one-out analysis, and Bayesian colocalization analysis to determine whether there were shared causal loci between vitamin D levels and neonatal jaundice.

Results: A total of 160 SNPs with genome-wide significance for vitamin D levels were identified, explaining 1.4% of the genetic variance in vitamin D levels. The MR-PRESSO test did not detect any outlier values, and heterogeneity testing did not identify significant heterogeneity. However, pleiotropy testing revealed significant horizontal pleiotropy, prompting the use of the MR-Egger regression model for MR analysis. The results indicated a significant negative causal association between vitamin D levels and the risk of neonatal jaundice (OR = 0.04, 95% CI: 0.004–0.43, p = 0.0026). Sensitivity analysis and colocalization analysis further confirmed the accuracy and robustness of the results.

Conclusions: Genetically reduced vitamin D levels are causally associated with an increased risk of neonatal jaundice.

Key words: neonatal jaundice, vitamin D, Mendelian randomization, genetic epidemiology.

Introduction

Neonatal jaundice is a common physiological phenomenon observed in newborns, with a reported incidence from 60% to more than 90%. It is primarily caused by the deposition of bilirubin in the infant's skin, leading to a yellow discoloration of the skin, sclera, and mucous membranes

[1, 2]. While most cases are benign and self-limiting, severe jaundice can result in neurotoxicity and kernicterus, posing significant health risks to the infant [3, 4]. Therefore, the management and prevention of neonatal jaundice have been central concerns in clinical practice.

The etiology of neonatal jaundice is multifactorial, involving factors such as hemolysis, genetic predispositions, and liver immaturity. However, emerging research suggests that vitamin D may play a key role in its onset and progression. Vitamin D is a fat-soluble vitamin primarily obtained through dietary intake and sunlight exposure. It is crucial for the absorption and metabolism of calcium and phosphorus, as well as other physiological processes such as immune regulation and cellular differentiation [5, 6]. Previous studies have indicated that one of the main stages of vitamin D synthesis is 25-hydroxylation, which occurs in the liver. The liver not only plays a role in the synthesis of vitamin D but also is crucial in converting indirect bilirubin to direct bilirubin [7, 8]. Although the metabolism of these two compounds occurs through different pathways, they may influence each other during the liver's biosynthetic phase. Vitamin D may contribute to the regulation of bilirubin metabolism and excretion, with its deficiency potentially disrupting these processes and increasing the risk of developing neonatal jaundice.

Although observational studies have reported an association between low vitamin D levels and an increased risk of neonatal jaundice, these studies are prone to confounding factors and reverse causation. Therefore, it remains unclear whether these associations are accurate. Mendelian randomization (MR) leverages genetic variants related to vitamin D levels as instrumental variables, offering a robust framework for causal inference in observational studies. By mimicking the random allocation of alleles during meiosis, MR minimizes confounding and reverse causation bias, providing stronger evidence for causal relationships [9]. Given this context, we propose an MR study aimed at clarifying the causal effect of vitamin D deficiency on the risk of neonatal jaundice.

Material and methods

Study design and data sources

MR is a method used to identify causal relationships between exposure phenotypes and outcomes by using genetic variations associated with the exposure as instrumental variables (IVs). The IVs selected in this study were required to meet the following three assumptions: (1) the relevance assumption: the selected IVs are directly associated with the exposure; (2) the independence assumption: the selected IVs are not associated with any other factors related to both exposure and outcome; (3) the exclusion restriction assumption: the selected IVs are not related to the outcome, and affect the outcome only through the exposure [10].

The study obtained GWAS summary datasets with the largest sample sizes from the IEU OpenGWAS project. Given that population admixture could lead to biased estimates, the genetic background of the MR study population was restricted to individuals of European ancestry. The GWAS dataset for vitamin D (GWAS ID: ieu-b-4808) was sourced from a study by Manousaki *et al*., including 441,291 Europeans and 16,668,957 single nucleotide polymorphisms (SNPs). The GWAS dataset for neonatal jaundice (GWAS ID: finn-b-P16_NEONTAL_JAUND_OTH_UNSP_CAUSES) was sourced from another GWAS analysis that included 218,741 Europeans (133 neonatal jaundice cases and 218,741 healthy controls) and 16,380,466 SNPs.

Screening of instrumental variables

The criteria for selecting SNPs as instrumental variables are as follows: (1) *p*-value threshold: set at p-value $< 5 \times 10^{-8}$; (2) avoiding linkage disequilibrium (LD) bias: $R^2 < 0.001$, genetic distance = 10,000 kb. The *F*-statistic can be used to assess the strength of each instrumental variable [F-statistic = $(N - 2) \times (R^2/(1 - R^2))$, $R^2 = 2 \times (1 - MAF) \times MAF \times \beta^2$]. An *F*-statistic greater than 10 indicates that there is no weak instrumental variable bias [11, 12].

Statistical analysis

In this study, we used the TwoSampleMR package in R software (version 4.3.0) to calculate five different MR estimates for the main analysis: IVW, MR-Egger regression, weighted median, simple mode, and weighted mode, all with default parameters. As a primary MR method, the IVW method provides unbiased estimates in the absence of or balanced horizontal pleiotropy. However, when horizontal pleiotropy is present, MR-Egger regression is recommended [13]. We utilized the MR-Egger regression intercept and its 95% confidence interval (CI) to assess the degree of bias caused by pleiotropy and used the MR-PRESSO test to exclude outlier SNPs. Heterogeneity was analyzed using Cochran's Q test for IVW and MR-Egger methods; if the p-value < 0.05, it indicates significant heterogeneity, prompting the use of a random-effects model in subsequent analyses. Leave-one-out analysis was also conducted to evaluate the stability of MR results by excluding each instrument variable in turn.

Colocalization analysis is a method used to assess whether two traits are influenced by the

same or different causal variants. It involves the following hypotheses: H0, causal variants are not associated with either trait; H1, causal variants are associated with trait 1 but not with trait 2; H2, causal variants are associated with trait 2 but not with trait 1; H3, causal variants are associated with both traits but with different causal variants; H4, causal variants are associated with both traits with shared causal variants. Hypothesis H4 corresponds to colocalization. The posterior probability for each of these hypotheses can be calculated from the prior probability (which is set by the investigator) and summarized genetic association Data, which are used to compute approximate Bayes factors that represent the contribution from the likelihood [14]. We conducted Bayesian colocalization analysis using the coloc package in R software, setting the prior probability of SNPs being associated with trait 1 as 1×10^{-4}, the probability of SNPs being associated only with trait 2 as 1×10^{-4}, and the prior probability of SNPs being associated with both traits as 1×10^{-5}. A colocalization probability (PP.H4) > 80% is strong evidence of colocalization [15].

Results

Overview

Vitamin D levels served as the exposure factor, while neonatal jaundice was the outcome variable. A total of 160 SNPs were identified as instrumental variables after screening. The range of *F*-statistics for these SNPs was between 21 and 1474, all of which were above 10, indicating that they are strong instrumental variables. Moreover, these instrumental variables explained 1.4% of the variance in vitamin D levels. For further details on the SNPs, refer to Supplementary Table SI.

Mendelian randomization analysis

When instrumental variables exhibit horizontal pleiotropy, the MR-Egger regression method can provide unbiased estimates of causal relationships. The results indicate the presence of horizontal pleiotropy in the instrumental variables (Egger intercept = 0.07, $p = 0.0026$). Thus, MR-Egger was employed as the primary method for conducting the MR analysis. The MR results support a causal association between genetically decreased vitamin D levels and an increased risk of neonatal jaundice (OR = 0.04, 95% CI: 0.004–0.43, $p = 0.009$). For more details, refer to Table I, Figures 1, 2.

Heterogeneity test and sensitivity analysis

When using the MR-PRESSO method to identify outlier SNPs, it is necessary to exclude these SNPs and reanalyze the data. However, in this study, no outlier SNPs were identified (Supplementary Table SII). Heterogeneity among instrumental variables was assessed using Cochran's Q test and funnel plots. The results of the heterogeneity test based on the IVW method and MR-Egger method showed no significant heterogeneity (Supplementary Table SIII). The funnel plot also indicated no evidence of heterogeneity among the instrumental variables (Figure 3).

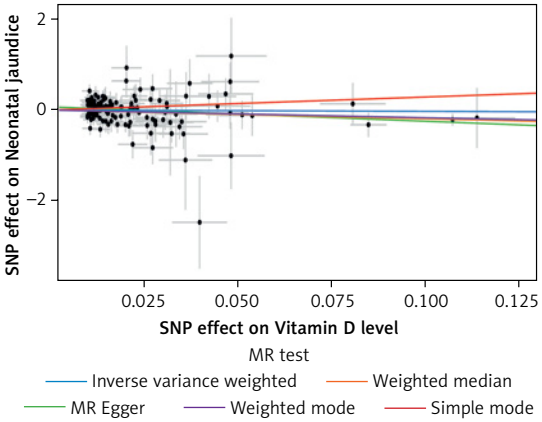

Figure 1. Scatter plot of genetic association between vitamin D levels and neonatal jaundice. The slope of the straight line indicates the magnitude of the causal association. The plot presents the effect sizes of the SNP-vitamin D levels association (*x*-axis, SD units) and the SNP-neonatal jaundice association (*y*-axis, log (OR)) with 95% confidence intervals. The different colored lines represent the fit through the different models, showing a causal association between vitamin D levels and neonatal jaundice

Table I. Mendelian randomization estimates of the association between vitamin D levels and the risk of neonatal jaundice

Methods	SNPs	β	SE	OR (95% CI)	*P*-value	Egger intercept	Intercept *P*-value
MR-Egger	160	–3.18	1.20	0.04 (0.004, 0.43)	0.009	0.07	0.0026
Weighted median	160	–1.94	1.22	0.14 (0.01, 1.56)	0.11		
IVW	160	–0.29	0.76	0.75 (0.004, 0.43)	0.70		
Simple mode	160	2.87	3.22	17.65 (0.03, 9664)	0.37		
Weighted mode	160	–1.71	1.17	0.18 (0.02, 1.81)	0.15		

All p-values < 0.05 are shown in bold.

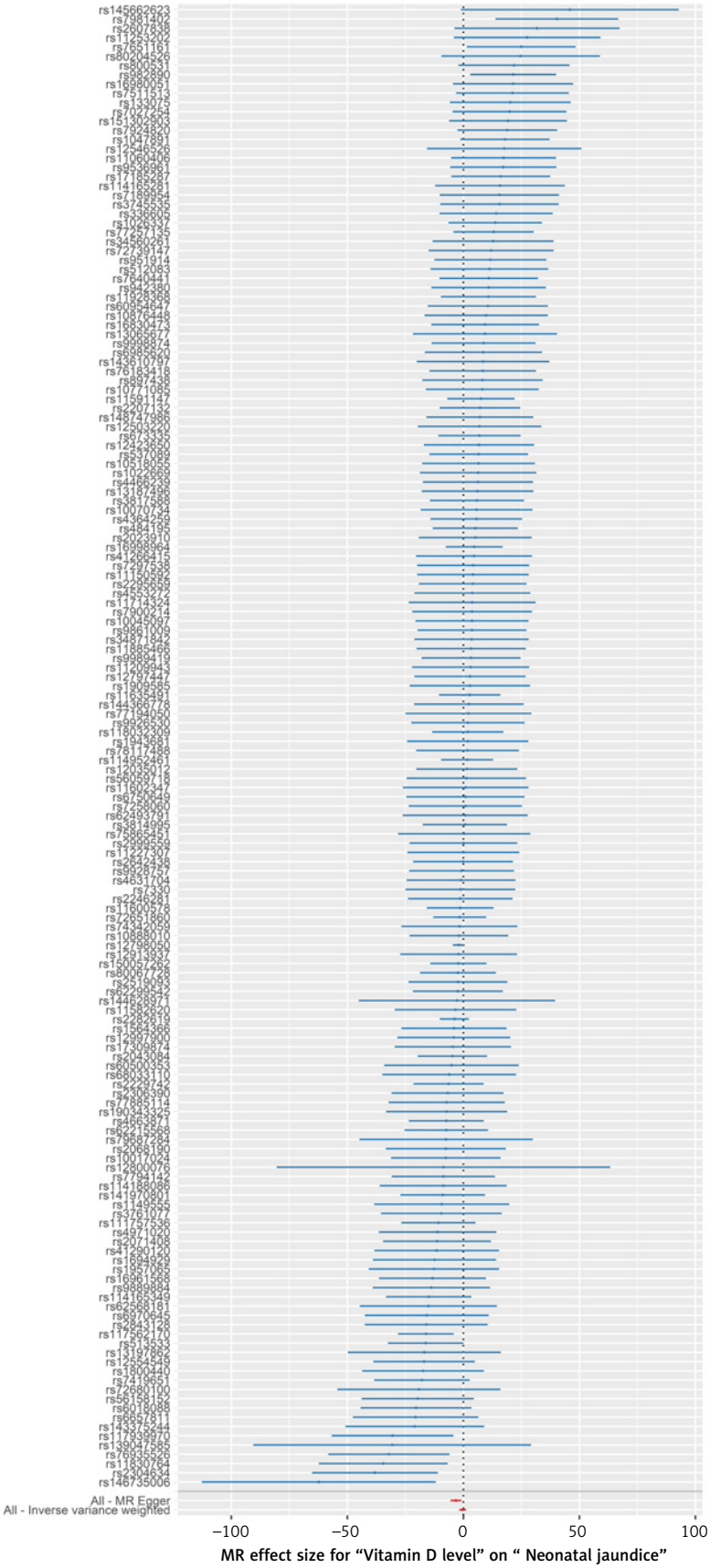

Figure 2. Forest plot of MR effect estimates for 160 SNPs. Each blue point represents the result of the MR method applied to estimate the causal effect of each SNP on neonatal jaundice. Each red point depicts the IVW and MR-Egger estimate using all SNPs

Sensitivity analysis was performed using the leave-one-out approach, where each SNP was removed individually and the causal effect of the remaining SNPs was compared with the results from MR analysis using all SNPs. Figure 4 shows that rs12798050 had a notable impact on the stability of the MR analysis results; therefore, we excluded this SNP and conducted MR analysis again. The results remained significant (OR = 0.02, 95% CI: 0.0003-0.65, *P* = 0.03), as presented in Table II.

Colocalization analysis

Colocalization analysis was performed to assess whether vitamin D levels and neonatal jaundice are influenced by the same or different causal variants. The results indicate that there is no evidence of colocalization between vitamin D levels and neonatal jaundice (PP.H4 = 8.75%), suggesting that these two traits are not driven by the same causal variants (Figure 5).

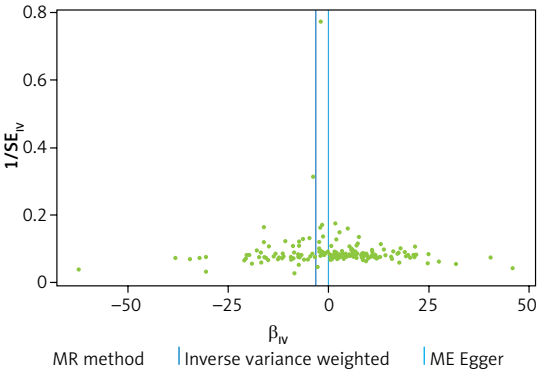

Figure 3. Funnel plot of sensitivity analysis results. Each point represents a SNP, using two methods (MR-Egger and IVW), both of which give a vertical line. If the SNPs to the left and right of the vertical line are symmetrical, there is no heterogeneity in the data

Discussion

Neonatal jaundice is one of the most common conditions in the neonatal period. If not promptly managed, it can lead to severe complications and even pose a life-threatening risk. Understanding the pathogenesis of neonatal jaundice is crucial for its prevention and treatment. This study is the first to evaluate the causal relationship between vitamin D levels and neonatal jaundice using an MR approach. The MR analysis revealed a potential causal association between vitamin D levels and the risk of neonatal jaundice, with genetically decreased vitamin D levels associated with increased risk of neonatal jaundice. This finding has significant implications for clinical practice and public health, providing a theoretical basis for future targeted prevention and treatment strategies.

First, the study used large-scale genomic data and selected 160 SNPs as instrumental variables, which demonstrated strong statistical causal inference abilities. By applying the MR-Egger regression method, we addressed potential horizontal pleiotropy issues with the instrumental variables and obtained unbiased estimates of causal relationships. The analysis results show a significant negative association between genetically lowered vitamin D levels and the occurrence of neonatal jaundice (OR = 0.04, 95% CI: 0.004–0.43, *p* = 0.009). We performed heterogeneity tests and sensitivity analyses using various methods to verify the robustness of our findings. The MR-PRESSO method did not identify any outlier SNPs, while Cochran's Q test, funnel plot analysis, and the leave-one-out method further confirmed the consistency among the instrumental variables and the stability of the study results. Moreover, the SNP rs12798050 had a substantial impact on the results, but even after excluding it and re-conducting the MR analysis, we still obtained conclusions consistent with those derived using all SNPs, further affirming the reliability of our results. Additionally, we conducted colocalization analysis to assess whether vitamin D levels and neonatal jaundice were influenced by the same or different causal variants. The results show no colocalization between the two traits (PP.H4 = 8.75%), suggesting that there is no significant evidence for co-localization between vitamin D levels and neonatal jaundice. This low probability implies that the observed association between vitamin D levels and neonatal jaundice is not confounded by shared genetic variants. This supports the hypothesis that the relationship is likely to be causal rather than Due to pleiotropy, where a single genetic variant influences multiple traits. In conclusion, the co-localization analysis strengthens our causal inference by excluding the possibility that shared genetic variants drive the association between vitamin D levels and neonatal jaundice. This adds robustness to our MR findings, suggesting that interventions aimed at modifying vitamin D levels could potentially influence the risk of neonatal jaundice through independent genetic pathways.

Epidemiological evidence suggests a correlation between vitamin D deficiency and neonatal jaundice, though most studies have only explored the difference in vitamin D levels between jaundiced and healthy newborns without establishing a clear causal relationship. For instance, several observational studies have indicated that newborns with jaundice have significantly lower vitamin D levels compared to healthy controls [16, 17]. Additionally, a meta-analysis revealed that vitamin D levels in the neonatal hyperbilirubinemia (NH) group were lower than those in the healthy newborn group [18]. Maternal nutritional status during pregnancy is also associated

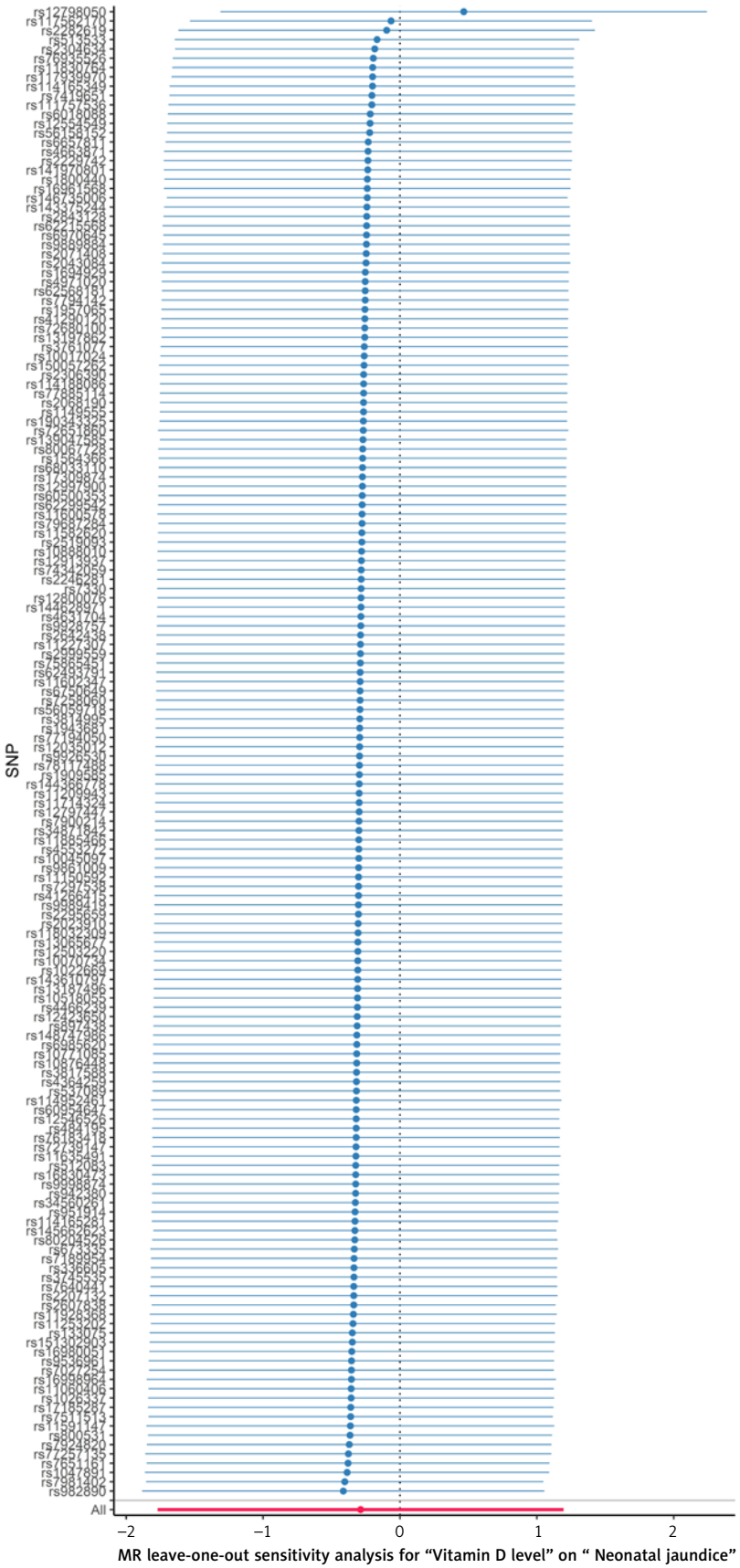

Figure 4. Leave-one-out method plot of sensitivity analysis results. Each blue point represents the result of the MR method applied to estimate the causal effect of vitamin D levels on neonatal jaundice excluding a particular SNP from the analysis

Table II. Mendelian randomization estimation of the association between vitamin D levels and the risk of neonatal jaundice (excluding rs12798050)

Methods	SNPs	β	SE	OR (95% CI)	*P*-value	Egger intercept	Intercept *P*-value
MR-Egger	159	–4.20	1.92	0.02 (0.0003, 0.65)	**0.03**	0.08	**0.007**
Weighted median	159	0.87	1.36	2.39 (0.17, 3.42)	0.52		
IVW	159	0.47	0.91	1.59 (0.27, 9.41)	0.60		
Simple mode	159	3.13	3.64	22.78 (0.02, 2.84)	0.39		
Weighted mode	159	3.33	2.38	1.39 (0.01, 1.47)	0.89		

All p-values < 0.05 are shown in bold.

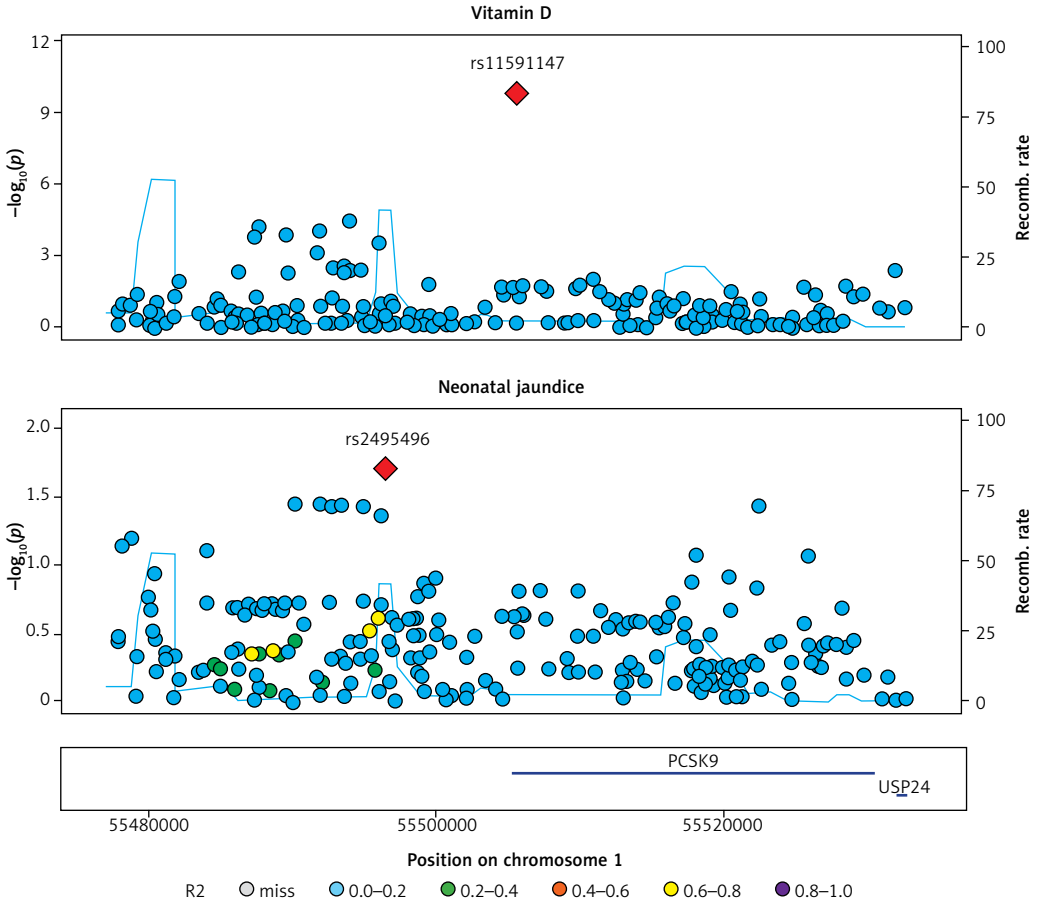

Figure 5. Manhattan plot of the colocalization analysis results. Each point in the Manhattan plot represents a SNP, and the vertical axis represents the *p*-value of each SNP (single nucleotide polymorphism), ranging from 0 to 1, where a smaller *p*-value indicates a stronger association between the SNP and a phenotypic trait or disease. The negative logarithm of the *p*-value is taken so that points with smaller *p*-values are higher on the plot and thus easier to observe. The horizontal axis represents the chromosome where the SNP is located

with adverse neonatal outcomes. A retrospective cohort study by Fernando *et al*. demonstrated that higher concentrations of maternal vitamin D and vitamin D-binding protein During pregnancy were associated with a lower likelihood of neonatal jaundice [19]. Serum vitamin D deficiency is closely associated with the risk of gestational diabetes mellitus [20]. Furthermore, vitamin D supplementation During pregnancy for patients with gestational diabetes mellitus may reduce the risk of NH in newborns [21]. Insufficient maternal vitamin D levels during pregnancy may lead to fetal vitamin D deficiency, thus increasing the risk of jaundice in newborns. Therefore, in the prevention and management of neonatal jaundice, attention should not only be given to the nutritional status of the newborn but also to the maternal nutritional health during pregnancy.

Moreover, the role of vitamin D in liver function and bilirubin metabolism is particularly noteworthy. Vitamin D is known to influence liver function through various mechanisms, including its impact on the expression of enzymes involved in bilirubin conjugation. Vitamin D may regulate the activity

of UDP-glucuronosyltransferase (UGT1A1), the key enzyme responsible for bilirubin conjugation, thereby affecting the hepatic clearance of bilirubin [22, 23]. Additionally, vitamin D possesses anti-inflammatory properties [24], which could modulate hepatic inflammation and improve bilirubin metabolism. Comparing our findings with existing literature, it is evident that the relationship between vitamin D and liver-related conditions extends beyond neonatal jaundice. Studies have shown that vitamin D deficiency is associated with various liver diseases, such as non-alcoholic fatty liver disease (NAFLD) and liver fibrosis [25, 26]. These conditions, like neonatal jaundice, are influenced by impaired bilirubin metabolism and liver function. The parallels between these conditions suggest that vitamin D plays a broader role in maintaining hepatic health, which could explain its influence on bilirubin metabolism. Moreover, studies examining the effects of vitamin D supplementation have demonstrated improvements in liver function tests and reductions in markers of liver inflammation [27], further supporting the hypothesis that adequate vitamin D levels are crucial for optimal liver function. Zhou *et al.* demonstrated an association between polymorphisms in the vitamin D metabolic pathway genes (NADSYN1/DHCR7 and CYP27B1) and NH. Specifically, the TT genotype of rs12785878 and the GT genotype of rs10877012 were found to reduce the risk of NH, while rs12785878 was significantly associated with severe NH [28]. These genetic findings reinforce the importance of vitamin D in neonatal health and suggest that genetic predispositions affecting vitamin D metabolism may influence the risk of developing neonatal jaundice. Given these connections, further research into the role of vitamin D in liver-related conditions and neonatal outcomes is warranted, particularly to explore the therapeutic potential of vitamin D supplementation During pregnancy and early infancy in preventing neonatal jaundice and improving overall neonatal health.

This study also has certain limitations. First, the only neonatal jaundice GWAS dataset we retrieved did not report specific characteristics of neonatal jaundice, such as height, weight, duration of jaundice, or type of jaundice, making it impossible to perform further stratified MR analysis based on these characteristics. Second, the genetic background of the study population is limited to individuals of European ancestry, which may restrict the generalizability of the results. Additionally, although we used methods such as MR-Egger regression and colocalization analysis to exclude potential bias from linkage disequilibrium, we were unable to minimize horizontal pleiotropy.

In conclusion, this study provides new evidence from an MR analysis supporting a causal association between vitamin D levels and neonatal jaundice. Special clinical attention should be given to newborns with vitamin D deficiency to prevent the occurrence of neonatal jaundice. Future research is needed to explore the biological mechanisms underlying this association.

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Data availability

The GWAS data were retrieved from IEU-OpenGWAS project (https://gwas.mrcieu.ac.uk/datasets/ieu-b-4808/ and https://gwas.mrcieu.ac.uk/datasets/finn-b-P16_NEONTAL_JAUND_OTH_UNSP_CAUSES/).

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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