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Research article

Exploring the Missing link between vitamin D and autism spectrum disorder: Scientific evidence and new perspectives

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ABSTRACT

Aim: This study aims to address the key question of the causal relationship between serum levels of 25-hydroxyvitamin D (vitamin D) and autism spectrum disorders (ASD).
Methods: Publicly available Genome-Wide Association Study (GWAS) datasets were used to conduct the bidirectional Two-sample MR analyses using methods including inverse-variance weighted (IVW), weighted median, MR-Egger regression, simple mode, MR-PRESSO test, Steiger filtering, and weighted mode, followed by BWMR for validation.
Results: The MR analysis indicated that there was no causal relationship between Vitamin D as the exposure and ASD as the outcome in the positive direction of the MR analysis (IVW: OR = 0.984, 95 % CI: 0.821–1.18, $P = 0.866$). The subsequent BWMR validation stage yielded consistent results (OR = 0.984, 95 % CI 0.829–1.20, $P = 0.994$). Notably, in the reverse MR analysis with ASD as the exposure and Vitamin D as the outcome, the results suggested that the occurrence of ASD could lead to decreased Vitamin D levels (IVW: OR = 0.976, 95 % CI: 0.961–0.990, $P = 0.000855$), with BWMR findings in the validation stage confirming the discovery phase (OR = 0.975, 95 % CI: 0.958–0.991, $P = 0.00297$). For the positive MR analysis, no pleiotropy was detected in the instrumental variables. Similarly, no pleiotropy or heterogeneity was detected in the instrumental variables for the reverse MR analysis. Sensitivity analysis using the leave-one-out approach for both positive and reverse instrumental variables suggested that the MR analysis results were robust.
Conclusion: Through the discovery and validation analysis process, we can confidently assert that there is no causative link between Vitamin D and ASD, and that supplementing Vitamin D is not expected to provide effective improvement for patients with ASD. Our study significantly advances a new perspective in ASD research and has a positive impact on medication guidance for patients with ASD.

1. Introduction

ASD is a neurodevelopmental disorder intricately linked to atypical brain development. Impairments in regions of the brain

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governing social interaction, communication, and cognitive behavior could contribute to the multifaceted features of ASD [1]. Symptoms vary widely among individuals and typically encompass repetitive behaviors, stereotypical movements, challenges in social engagement, language deficits, narrow interest scopes, and an acute sensitivity to environmental changes [2]. ASD is found worldwide, yet its prevalence differs across regions and countries. The Centers for Disease Control and Prevention (CDC) reported in 2018 that one in 59 children (one in 37 boys and one in 151 girls) is diagnosed with ASD, with an increasing trend observed year by year [3]. Vitamin D, a crucial nutrient, is widely recognized for its significant connection to various mental health disorders. Recent observational studies have revealed lower levels of vitamin D in individuals with ASD compared to the baseline of the general population [4]. Moreover, meta-analyses investigating the link between vitamin D and ASD have reported consistently low levels of vitamin D in those with ASD [5]. Importantly, a prospective study involving pregnant women showed that supplementation of vitamin D during pregnancy does not substantially reduce the risk of developing ASD in offspring [6]. Likewise, another meta-analysis and systematic review suggested that using vitamin D as a treatment does not significantly alleviate the core symptoms of ASD [7].Due to the prevailing uncertainty about the effects of vitamin D supplementation on patients with ASD, a thorough investigation and clearer understanding of the association between vitamin D and ASD is warranted.MR analysis [8] assesses the causality between observed changes in exposure or clinical risk factors and clinical outcomes. When random controlled trials do not provide clear causal relationships, and observational studies suffer from biases due to a multitude of potential confounders or reverse causality, genetic approaches can serve as an effective alternative for assessing causation [9]. This study aims to investigate the relationship between vitamin D and ASD. The findings suggest that vitamin D supplementation does not confer benefits to ASD patients and that ASD may, in fact, contribute to lower levels of vitamin D, providing novel insights for advancing medical treatment strategies for ASD patients.

2. Materials and methods

2.1. Data source

Relevant GWAS datasets were collected via the website (https://gwas.mrcieu.ac.uk). The vitamin D GWAS dataset (ID: ebi-a-GCST90000615) originates from a GWAS meta-analysis, which includes 417,580 participants of European ancestry [10]. The ASD GWAS dataset (ID: ieu-a-1185) comes from another study from the iPSYCH consortium [11], downloaded from the iPSYCH-PGC ASD portal (http://www.med.unc.edu/pgc), comprising 46,351 individuals of European ancestry and more than 8,643,988 single nucleotide polymorphisms (SNPs). All of the above data come from publicly available databases.

2.2. Instrumental variable selection

Using SNPs as instrumental variables, to avoid bias caused by linkage disequilibrium (LD) [12], we conducted LD clumping analysis with PLINK2, utilizing an r2 of 0.001 and a 10,000 kb window threshold on the relevant SNPs [13]. It is noteworthy that these thresholds are consistent with the widely accepted standards in MR analysis. To minimize the bias due to weak instrumental variables, we used the following formulas to calculate the R2 and F-statistic: R2 = (2 *βˆ2 * EAF * (1 - EAF))/(2 *βˆ2 * EAF * (1 - EAF) + 2 * (seˆ2 * N * EAF * (1 - EAF))); F = (N - K - 1) *R2/(K * (1 - R2)) [14]. In these formulas, β is the effect size of the selected SNP, EAF is the effect allele frequency of the selected SNP, SE is the standard error of the effect size of the selected SNP, R2 is the exposure level of the selected SNP, N is the total number of participants exposed, and K is the number of SNPs filtered out [15]. To ensure the robustness of our analysis, we removed any instrumental variables with an F-value lower than 10. Additionally, we excluded SNPs associated with outcomes with $p < 5.0 * 10ˆ-8$ and SNPs with $p < 5.0 * 10ˆ-6$ [16]. Significant SNPs associated with the exposure factor were extracted from the outcome GWAS dataset, and the final instrumental variables were documented, together with information such as effect allele, allele effect size (β), standard error (SE), and *p-value*.

2.3. Study design

2.3.1. Statistical methods

Data statistical analysis was performed using R version 4.3.2 and packages such as BWMR, TwoSampleMR, MR-PRESSO, Mendelian Randomization, and others. Summary statistics for the coordinated adjustment of related exposure factors and clinical outcome datasets were processed to align the effects of SNPs on the exposure factors with their effects on clinical outcomes in relation to the same alleles.

For the bidirectional Two-sample MR analysis to infer causal relationships, methods including IVW, weighted median, MR-Egger, simple mode, and weighted mode were employed, with IVW as the primary MR analytical method [17]. IVW combines the MR effect estimates of each SNP to produce an overall weighted estimate of the potential causal effect; the results of IVW are most reliable when the instrumental variables do not have horizontal pleiotropy [18]. Even when up to 50 % of the information from the exposure or outcome instrumental variables comes from genetic variants of invalid tools, the weighted median method can still achieve a consistent estimate of causal effects [19]. Potential pleiotropy associated with the selected instrumental variables was assessed using the MR-Egger intercept and MR-PRESSO global test. If pleiotropy was detected, SNPs with values less than 1.00 were excluded as outliers [20], and the Steiger test was used to determine the direction of the causal inference. For accuracy, Leave-One-Out analysis was conducted to identify outlier SNPs that may affect the precision of the results. Heterogeneity was quantified with Cochran's Q [21] test, with $P < 0.05$ indicating heterogeneity, though negligible heterogeneity can be ignored. If heterogeneity exists among the instrumental variables, the IVW random effects model was used to estimate the causal effect. The level of significance α was set at 0.05,

with $P < 0.05$ considered statistically significant [22].(see Fig. 1)

The basic steps of BWMR.Eq (1) [23].

$$\begin{aligned}&\mathbf{p}\left(\widehat{\gamma},\widehat{\Gamma},\beta,\pi_1,\gamma,\mathbf{w}\middle|\sigma_X^2,\sigma_Y^2,\tau^2,\sigma^2,\sigma_0^2,\mathbf{a_0}\right)\\&=\frac{\mathbf{1}}{\mathbf{A}}\mathcal{N}\left(\beta\middle|\mathbf{0},\sigma_0^2\right)\mathbf{Pr}(\pi_1|\mathbf{a_0})\prod_{j=1}^{N}\mathcal{N}\left(\gamma_j\middle|\mathbf{0},\sigma^2\right)\prod_{j=1}^{N}\mathbf{Pr}\left(\mathbf{w_j}\middle|\pi_1\right)\\&\prod_{j=1}^{N}\mathcal{N}\left(\widehat{\gamma}_j\middle|\gamma_j,\sigma_{X_j}^2\right)\prod_{j=1}^{N}\mathcal{N}\left(\widehat{\Gamma}_j\middle|\beta\gamma_j,\sigma_{Y_j}^2+\tau^2\right)^{w_j}\end{aligned}\qquad \text{Eq(1)}$$

include: utilizing the principles of MR to estimate the causal association between exposure and outcome using instrumental variables. By establishing a Bayesian model, causal inference is enhanced. Bayesian inference techniques, such as Markov chain Monte Carlo (MCMC) methods, are employed to obtain point estimates and confidence intervals of parameters from the posterior distribution. The advantages of BWMR methods include the ability to handle issues such as genetic correlation, measurement error, and confounding factors, while providing a probability distribution for causal inference. It can further enhance the reliability and accuracy of causal inference. Refer to https://github.com/jiazhao97/BWMR for detailed code examples and instructions on using the R package.

3. Results

3.1. Forward MR analysis (causal effect of vitamin D on ASD)

For the causal effect of vitamin D as the exposure and ASD as the outcome, with the significance threshold set at P < 5.0 × 10ˆ-8, 79 SNPs were ultimately selected as instrumental variables, all with F-values >10. The MR-Egger regression intercept was near zero (Egger's intercept = −0.00751, P = 0.0843), indicating no horizontal pleiotropy in the instrumental variables and no significant impact on the MR analysis results. Directionality was confirmed correct by the Steiger test (P = 3.14 × 10ˆ-109). As there was no horizontal pleiotropy in the instrumental variables, the IVW random effects model was used as the main analytical method for the MR analysis, with IVW: OR = 0.984, 95 % CI: 0.82–1.18, P = 0.866, suggesting no causal relationship between vitamin D and ASD. The BWMR results in the validation stage also indicated no causal link (OR = 0.984, 95 % CI: 0.829–1.20, P = 0.994) with Cochran's Q = 149, Cochran's Q degrees of freedom (Qdf) = 78, (P = 2.34 × 10ˆ-6), indicating only weak heterogeneity between the instrumental variables. Sensitivity analysis was performed using leave-one-out, where each SNP was removed in turn, comparing the causal effect of the remaining SNPs with the MR analysis results for all SNPs, indicating a reliable MR analysis outcome. The detailed analysis results are shown in (Fig. 2a and b, and Table).

3.2. Reverse MR analysis (causal effect of ASD on vitamin D)

Considering ASD as the exposure and vitamin D as the outcome, the study adopted a more liberal significance threshold (P < 5.0 ×

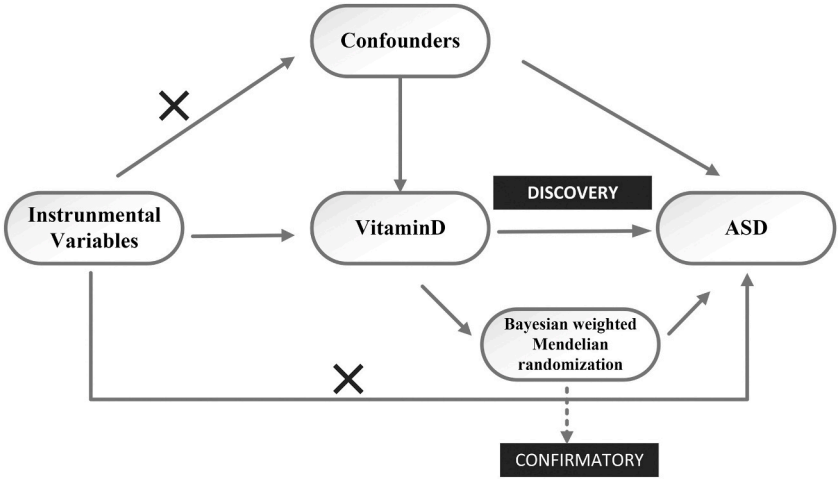
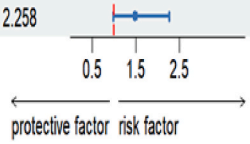
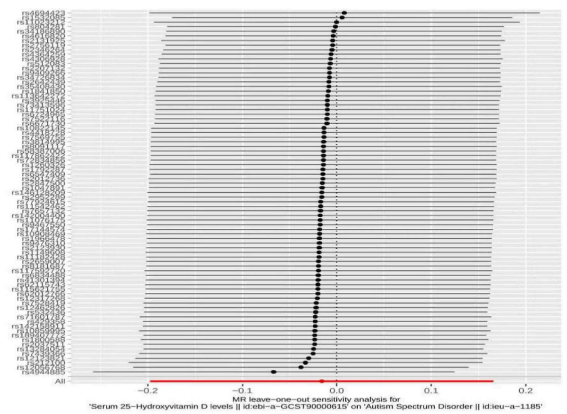


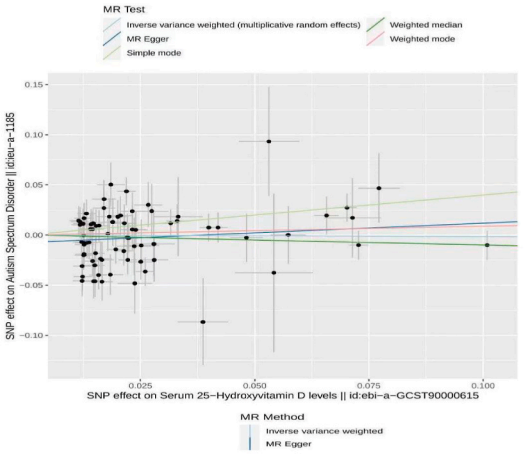
Fig. 1. The flowchart is designed to highlight the selection of instrumental variables, labeled "instrumental variables," which must remain unaffected by any confounders that influence the outcome (ASD). Additionally, these instrumental variables cannot have a direct effect on ASD, thereby ensuring compliance with Mendelian randomization requirements. They may only influence the outcome (ASD) through the exposure factor (Vitamin D). The aforementioned phase of result discovery is based on the verification of a non-causal relationship between Vitamin D and ASD using BWMR.

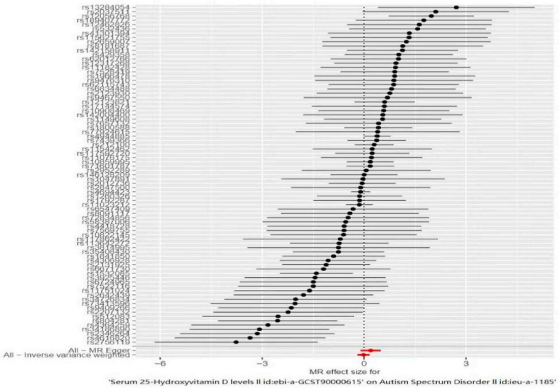
method	b	se	pval	or	or_lci95	or_uci95	OR(95%CI)
MR Egger	0.193	0.150	0.203	1.213	0.903	1.630	1.213(0.903 to 1.630)
Weighted median	-0.099	0.112	0.375	0.905	0.727	1.128	0.905(0.727 to 1.128)
Inverse variance weighted	-0.016	0.093	0.866	0.984	0.821	1.180	0.984(0.821 to 1.180)
Weighted mode	0.088	0.092	0.344	1.092	0.912	1.307	1.092(0.912 to 1.307)
Simple mode	0.400	0.212	0.062	1.491	0.985	2.258	1.491(0.985 to 2.258)

P<0.05 was considered statistically significant









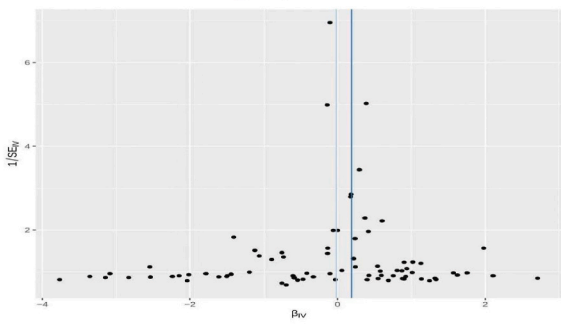


Fig. 2. Fig. 2a Forest plots from five methods show that a p-value less than 0.05 denotes statistical significance. An odds ratio (OR) greater than 1 indicates a risk factor, while an OR less than 1 suggests a protective factor.
Fig. 2b Leave-one-out method, forest plots, and funnel plot scatter diagrams are used to assess the robustness of the results.

10^-6) [23] to include more SNPs. Ultimately, 14 SNPs were selected as instrumental variables, all with F-values >10. Cochran's Q = 14.2, Q degrees of freedom (Qdf) = 13, (P = 0.359) indicated no heterogeneity among the instrumental variables. The MR-PRESSO test showed no outliers (P = 0.398), and the MR-Egger regression intercept was near zero (Egger's intercept = −0.000688, P = 0.748), which indicates no pleiotropy. The directionality was confirmed by the Steiger test (P = 5.46 × 10^-63). Therefore, the IVW random effects method was used, and the IVW results (IVW: OR = 0.976, 95 % CI: 0.96–0.99, P = 0.000855) indicated that the occurrence of ASD could lead to a reduction in vitamin D levels. The BWMR validation phase (OR = 0.975, 95 % CI: 0.958–0.991, P = 0.00297) also supported the presence of the above-mentioned causal relationship. Sensitivity analysis using leave-one-out was performed; SNPs were removed individually, and the causal effect of the remaining SNPs was compared with the MR analysis results for all SNPs, showing the MR analysis to be reliable. Detailed analysis results are provided in (Fig. 3a and b, and Table).

4. Discussion

ASD is a complex neurodevelopmental disorder with a multifaceted etiology, involving various genetic and environmental factors

Table 1
He results indicate that the number of SNPs (single nucleotide polymorphisms) and their directional p-values being less than 0.005 signify statistical significance. A Steiger p-value of less than 0.005 also holds statistical meaning, suggesting the correct causal direction is indicated by correct_causal_direction.
Table Results. Table. The results show that the number of SNPs and their directional p-values less than 0.005 indicate statistical significance.

TwoSampleMR							
id.exposure	**id.outcome**	**outcome**	**exposure**	**steiger *p***	**correct_causal_direction**	**nsnp**	**AVERAGE F**
ebi-a-GCST90000615	**ieu-a-1185**	**ASD**	**VitaminD**	**3.13 × 10*-109**	**TURE**	**79**	**142.452**
id.exposure	**id.outcome**	**outcome**	**exposure**	**steiger *p***	**correct_causal_direction**	**nsnp**	**AVERAGE F**
ieu-a-1185	**ebi-a-GCST90000615**	**VitaminD**	**ASD**	**5.46 × 10*-63**	**TURE**	**14**	**26.572**
BWMR							
id.exposure	**id.outcome**	**outcome**	**exposure**	**steiger *p***	**correct_causal_direction**	**nsnp**	**AVERAGE F**
ebi-a-GCST90000615	**ieu-a-1185**	**ASD**	**VitaminD**	**3.13 × 10*-109**	**TURE**	**79**	**142.452**
id.exposure	**id.outcome**	**outcome**	**exposure**	**steiger *p***	**correct_causal_direction**	**nsnp**	**AVERAGE F**
ieu-a-1185	**ebi-a-GCST90000615**	**VitaminD**	**ASD**	**5.46 × 10*-63**	**TURE**	**14**	**26.572**

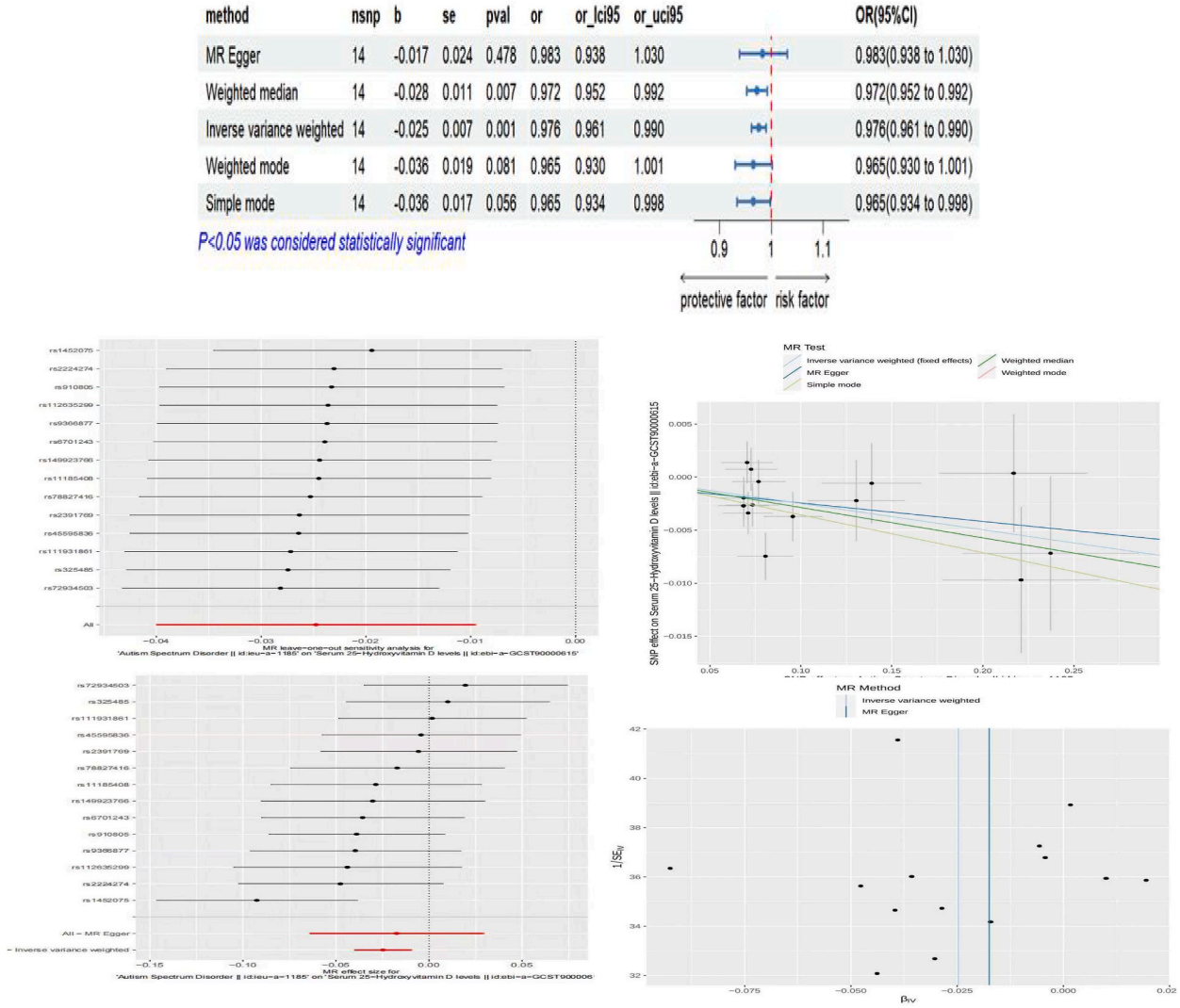


Fig. 3. Fig. 3a Forest plots from five methods show that a p-value less than 0.05 denotes statistical significance. An odds ratio (OR) greater than 1 indicates a risk factor, while an OR less than 1 suggests a protective factor. Fig. 3b Leave-one-out method, forest plots, and funnel plot scatter diagrams are used to assess the robustness of the results.

[24] Although current research has not yet determined the specific mechanisms that cause ASD, our study has meticulously confirmed that there is no direct link between vitamin D and ASD. However, in a reverse analysis where ASD leads to a decrease in vitamin D levels, our findings lend some support to the rationale for choosing vitamin D as an intervention for ASD. This significantly bolsters our confidence in our procedural design and conclusions.

From the molecular perspective, ASD may be a highly complex brain neurosystem disorder where the causes may involve multiple interactions between genetic regulation and environmental factors [25]. Vitamin D is widely considered to play a crucial role in the development and maintenance of the nervous system. Its main roles may include regulation of gene expression, immune response, inflammation, and its impact on the development of the nervous system (vitamin D's involvement in the brain's neural construction may affect early-stage ASD) [26–28].However, to date, the role and regulatory mechanisms between vitamin D and ASD remain contested.

Our focus will be on the potential impacts of vitamin D on neurodevelopment, immune responses, and inflammatory processes, as well as gene expression regulation, aiming to delve deeply into whether there are substantive connections between these biological processes.

First, the limitations of neuroprotection: Although vitamin D has some neuroprotective effects [29], what might be needed for treating ASD patients is a more complex and precise neural system regulation, including neurotransmitter levels, synaptic function, and neural circuitry shaping [30], where potential neural system regulation likely does not wholly depend on the biological role played by vitamin D [31]. Secondly, the dosage and timing: Vitamin D is indeed more capable of crossing the blood-brain barrier (BBB) compared to water-soluble substances [32]. This is because the BBB has a certain permeability to lipid-soluble molecules, which can pass through the lipid bilayer of cell membranes. Vitamin D [33], as a fat-soluble hormone, can pass into the brain relatively freely through the BBB. However, even if vitamin D can relatively easily cross the BBB, this does not mean that it can freely participate in regulatory mechanisms or exert biological effects in the brain [34]. Overall levels of vitamin D in the body, the state of the BBB, the residual amount of vitamin D after crossing the BBB, and its metabolism and utilization in the brain will all affect whether vitamin D can exert real effects on brain cells [35–37].

The limitations of immunity and inflammation: Firstly, the impact of neuroinflammatory pathways [38]: Some studies have found signs of neuroinflammation in ASD patients [39]. Although vitamin D can reduce inflammatory responses by lowering the production of pro-inflammatory cytokines [40], the root cause of neuroinflammation in ASD may not be merely due to immune system abnormalities but could involve other contributory factors [41,42]. Secondly, the contribution of glial cells: Functions of microglia and astrocytes, which regulate the integration of brain neuronal signals and participate in maintaining the neuronal environment in the brain, may be impaired in ASD [43]. However, these changes are not merely related to the singular immune response involving vitamin D but may also involve broader regulation of the brain's internal environment homeostasis [44–46].

The complexity of gene expression and regulation: Firstly, vitamin D can affect gene expression through its receptor (Vitamin D receptor, VDR) [47] within the cell nucleus. However, ASD may involve a vast number of genes with extremely complex mechanisms of interaction, and a singular vitamin D intervention is unlikely to broadly change this complex gene regulatory network. Secondly, the temporality of neurodevelopment: The neurodevelopmental abnormalities in ASD likely take place early in life, which is a precisely regulated process involving temporal gene expression changes [48,49]. Vitamin D's gene regulatory behavior may not precisely match the specific timing requirements associated with neurodevelopment [50]. Lastly, it is worth noting the limitations of epigenetic regulation: Besides changes in the genes themselves, the development of ASD may also relate to epigenetic factors, such as DNA methylation and histone modification. These modifications do not alter the DNA sequence but affect the regulation of gene expression, and vitamin D's role is likely limited here [51–53].

In our reverse analysis, we accidently discovered that the occurrence of ASD might lead to a decrease in vitamin D levels in the body, a finding that caught our high attention. Therefore, we explored its causes from both biological and environmental perspectives. First, at the genetic level, ASD may influence the gene regulation of the VDR and associated enzymes, such as the 1-α-hydroxylase which is responsible for vitamin D activation. Variations or abnormal expressions of these genes might interfere with the normal metabolism of vitamin D [54], leading to a decreased level in the bloodstream.Next is the regulation of Vitamin D Binding Protein (VDBP) [55]. Since VDBP is a crucial protein that transports vitamin D, if VDBP expression or function is affected in patients with ASD, the level of available vitamin D in the blood may be reduced correspondingly.

Furthermore, the inflammatory pathway is also a factor to consider. Studies have shown that ASD may be related to the body's state of inflammation [56]. Considering that vitamin D plays an essential role in modulating the immune response, it may be consumed during the inflammatory process, which might mean that higher levels of inflammation could reduce the levels of vitamin D in the blood [41].

Lastly, environmental factors were considered. For example, children and adults with ASD might spend less time engaging in outdoor activities [57]. Since vitamin D is primarily produced in the skin through exposure to sunlight [58], the reduction in sunlight exposure can directly lead to decreased production of vitamin D in the body [59]. Additionally, problematic behaviors based on restrictive and repetitive actions, such as particular dietary preferences and aversions, could lead to an imbalance in nutritional intake, including insufficient vitamin D [60,61].

Our research methodology offers several distinctive advantages. This study represents the inaugural application of the bidirectional MR framework for investigative purposes, with the BWMR technique providing subsequent validation. The latter is acclaimed for its exceptional adaptability in addressing numerous interrelated genetic variations, outcomes, or the potency of genetic instrumental variables [62]. In instances of genetic pleiotropy or when the instrumental variables demonstrate weak associations, BWMR delivers estimations of enhanced robustness by amalgamating diverse information sources and types [63]. BWMR also effectively ameliorates the minor heterogeneity detected in our investigation. The Bayesian framework furnishes a more solid evaluation in the face of result

heterogeneity [63]. Moreover, the utilization of GWAS data sourced from an extensive sample size and recent collection substantially corroborates the credibility of our findings.

Our investigation reveals certain limitations. The GWAS dataset employed originates from a European cohort and may reflect ethnic biases, rendering the extrapolation of the positive findings to other ethnicities uncertain. Furthermore, the precision of the instrumental variables is contingent upon the sample size of the GWAS; consequently, an expanded GWAS is imperative to uncover a broader array of genetic variations pertinent to MR analysis. Collectively, our findings indicate no causal link between vitamin D levels and the incidence of ASD. It may be essential to consider reverse causality; for instance, the development of ASD could precipitate diminished vitamin D concentrations. These insights confer an elevated tier of evidence in clinical research, markedly diminishing expenditures and human resource investments. They also introduce an innovative angle to ASD research, inform the development of therapeutic strategies by clinicians for ASD, and alleviate the necessity for redundant trials by clinical investigators.

5. Conclusion

In summary, our research found that the levels of Vitamin D did not have a causal intervention effect on autism, but surprisingly, the occurrence of autism actually led to a decrease in the levels of Vitamin D in the body.

Ethics approval and consent to participate

I would like to confirm that the data used in this study is publicly available and can be reused without restrictions under an open license. All datasets in this research have been downloaded from public databases. These public databases permit researchers to download and analyze public datasets for scientific purposes, thereby negating the need for ethical approval.

Code availability

The codes used in this study can be found at:
TwoSampleMR:https://github.com/MRCIEU/TwoSampleMR.
MR-PRESSO:https://github.com/rondolab/MR-PRESSO.
BWMR:https://github.com/jiazhao97/BWMR.

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CRediT authorship contribution statement

Tianci Gao: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Wenjun Dang:** Writing – review & editing, Writing – original draft, Validation, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Zhimei Jiang:** Visualization, Supervision, Software, Project administration, Funding acquisition, Formal analysis. **Yuwei Jiang:** Writing – original draft, Visualization, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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