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The association between Vitamin D and breast cancer: A two-sample Mendelian randomization study

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Abstract

Introduction: Breast cancer, as a significant threat to women's health globally, has a complex pathogenesis. Vitamin D, a steroid hormone with diverse physiological functions, has garnered increasing attention in breast cancer research. Numerous studies have been conducted to elucidate the relationship between Vitamin D and breast cancer, yet no definitive conclusions have been reached. Objective: Hence, in this study, we conducted a two-sample Mendelian randomization (MR) analysis to investigate the association between Vitamin D and breast cancer.

Methods: Genetic variants associated with Vitamin D levels and breast cancer data were obtained from the genome-wide association study database and version R11 of the FinnGen study dataset, respectively. The inverse variance-weighted (IVW) method served as the primary analytical approach, supplemented by various sensitivity analyses. Horizontal pleiotropy was tested using MR-Egger and MR-Pleiotropy RESidual Sum and Outlier methods, while sensitivity analysis was conducted using the leave-one-out method to assess the reliability of the results.

Results: Based on instrumental variable assumptions, 111 single nucleotide polymorphisms were suitable for subsequent analyses after matching the results. The MR analysis demonstrated no evidence of a causal relationship between Vitamin D and breast cancer. The IVW method yielded a non-significant association (p=0.968; odds ratio = 1.002, 95% confidence interval: 0.896 – 1.119), and the other methods pointed out the same direction of effect, and the subsequent pleiotropic analysis and sensitivity analysis confirmed the accuracy of the results.

Conclusion: At the genetic level, no causal relationship between Vitamin D and breast cancer was found; thus, our findings do not support a clinically significant role of Vitamin D supplementation in breast cancer risk reduction

Keywords: Vitamin D; Breast cancer; Mendelian randomization

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1. Introduction

Breast cancer, as one of the most common cancers, is one of the leading causes of death for women worldwide.[1] Over the past 20 years, breast cancer rates have continued to rise in most countries.[2] In 2022, there were approximately 2.309 million new cases of breast cancer globally, ranking second among all cancers, with a corresponding crude

incidence rate of 54.1/100,000. That year, the number of deaths due to breast cancer worldwide was about 666,000, placing it fourth among all cancers.[3] It is estimated that by 2050, there will be about 3.2 million new cases per year.[4] The prevention and treatment of breast cancer hold extremely critical significance and far-reaching value at the societal level.[5] Vitamin D is a fat-soluble vitamin derived from steroids.[6] It has a wide range of biological activities in various tissues of the human body.[7] It plays a role in bone homeostasis and the regulation of multiple systemic metabolic pathways.[8,9]

Although many researchers around the world have discussed and studied the association between Vitamin D and breast cancer, the relationship between the two is still inconclusive. Some epidemiological studies have shown that the incidence of breast cancer is inversely correlated with Vitamin D levels.[10-15] Relevant case–control studies and prospective studies have also confirmed that the intake of Vitamin D is negatively correlated with breast cancer.[16-18] A prospective study in Black women showed that moderate Vitamin D supplementation was associated with a reduced risk of triple-negative breast cancer.[19] In an observational data meta-analysis, Vitamin D supplementation was inversely related to the risk of breast cancer and was more protective at doses >10 μg/day.[20] Although these findings suggest potential positive effects of Vitamin D on breast cancer, rash conclusions should not be drawn. The human body is complex and is influenced by multiple factors. There may be undiscovered factors interfering with or regulating the relationship between Vitamin D and breast cancer, which can vary by ethnicity, geography, lifestyle, and genetic background. This complexity necessitates follow-up research, along with more in-depth and comprehensive studies, to further clarify their relationship. Vitamin D may be a potential key to preventing and treating breast cancer, but more research is needed to understand its actual role in this complex disease. At the same time, the comprehensive prevention and control of breast cancer requires a coordinated effort across all sectors of society. This includes raising awareness of women's health, enhancing early screening programs, and improving the medical security system to ensure better protection for women's health.

However, some studies have shown that Vitamin D levels are not associated with breast cancer.[21,22] One of the studies, believed to be the largest to date in this direction, examined the association of dietary Vitamin D intake with breast cancer risk in the European Prospective Survey of Cancer and Nutrition. During an average follow-up of 8.8 years, they found no evidence of an association between Vitamin D intake and breast cancer risk in this large prospective cohort.[21] In addition, another study in the Iranian population showed that Vitamin D deficiency was not associated with the development of breast cancer.[23] Similarly, no significant association was observed between Vitamin D intake and breast cancer.[24] One study confirms that the protective effect of Vitamin D on breast cancer risk may have been overestimated in previous observational studies.[25]

Given that most of the traditional epidemiological studies are observational and susceptible to confounding factors, there is a certain bias in the interpretation of the results. To address this issue, we used Mendelian randomization (MR) in our study. The basic principle of MR is derived from Mendel's laws of inheritance – gametes are randomly assigned by their parents following the offspring allele during the formation process. The genes are randomly assigned to the population before a person is born, and the phenotype determined by the genes is also randomly assigned. MR is an epidemiological technique that uses instrumental variable analysis to infer a causal relationship between exposure and the results of the use of genetic variation, particularly single nucleotide polymorphisms (SNPs). Based on the principle of random combination of genotypes during meiosis, the MR method can prevent reverse causal bias and limit confounders. The exposure and outcome data of the two-sample MR analysis were derived from two different genome-wide association studies (GWAS) datasets, or the aggregation of multiple GWAS datasets; hence, the test efficiency of the results could be improved.[26] Therefore, the two-sample MR study is more reliable than the traditional epidemiological approach.

2. Materials and methods

2.1. Assumptions underlying MR

MR is a strategy for epidemiological studies that uses genetic variation as an instrumental variable to assess causal associations between specific exposure factors and health outcomes. Originating in the field of econometrics, the core of this method is the use of instrumental variables to infer causal effects in the presence of unobserved confounders. Three key prerequisites must be met when using genetic variation as an instrumental variable: (i) the selected genetic variant must be significantly associated with the exposure factors in the study, (ii) these genetic variants should remain independent of any confounding factors that may affect the relationship between exposure and outcome, and (iii) genetic variation can only indirectly affect the outcome by influencing the exposure factors, that is, there is no other path that directly affects the outcome.[27] In this study, we collected and analyzed detailed confounding factors for the study population, including

age, body mass index, hormone levels, and lifestyle factors (such as smoking, alcohol consumption, and exercise habits). Subsequently, statistical methods (such as multiple regression analysis) were used to evaluate whether the association between genetic variants and exposure factors remained significant after adjusting for these confounding factors (34). By reviewing relevant literature and databases, we ensured that the selected genetic variants had not been reported to be associated with these confounding factors in previous studies. In addition, when conducting MR analysis, the MR-Egger intercept method and the MR-Pleiotropy RESidual Sum and Outlier (PRESSO) method were employed to detect horizontal pleiotropy. These two methods can, to some extent, reflect whether genetic variants affect the outcome through other pathways, thus indirectly assessing the independence of genetic variants from confounding factors. Figure 1 illustrates the flowchart of the MR analysis.

2.2. Data source

The data for this study were obtained from publicly available database resources on the internet. Genetic variation information was obtained through GWAS techniques. Relevant datasets were retrieved and downloaded by visiting the GWAS Data Aggregation Website (https://gwas.mrcieu.ac.uk/), operated by the University of Bristol's Epidemiological Research Unit. The website integrated data from multiple GWAS consortia and provided the main source of data for this study. The genetic variants associated with Vitamin D levels in this study were derived from the ebi-a-GCST90000618 database, which documented a large-scale GWAS involving 496,946 participants of European ancestry. Data for breast cancer were derived from the R11 version of the FinnGen study's finngen_R11_C3_BREAST_EXALLC dataset, which covered 20,586 breast cancer patients and 201,494 control individuals. As of June 24, 2024, the latest data freeze R11 reveals a total sample size of 453,733 (including 254,618 women and 199,115 men). A total of 21,311,942 genetic variants were analyzed and 2,447 disease phenotypes were available for research, details of which can be found on the project's official website (https://r11.finngen.fi/).

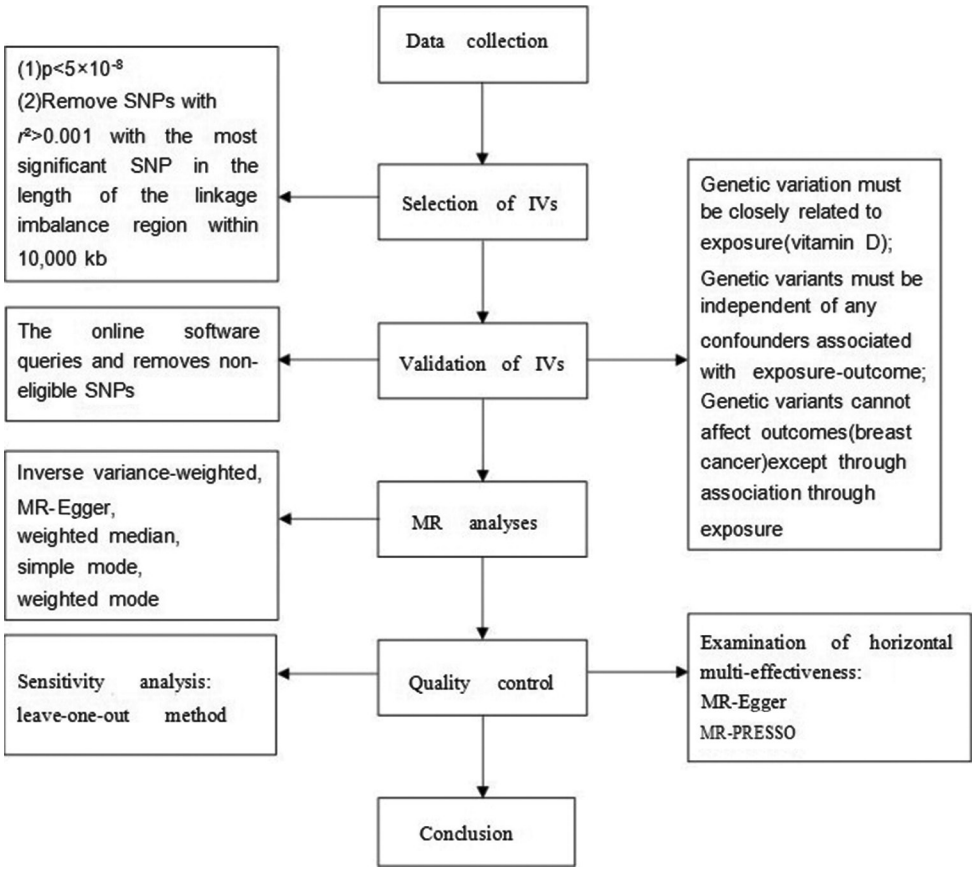

Figure 1. Flow chart of the two-sample Mendelian randomization (MR) study
Abbreviations: IV: Instrumental variable; PRESSO: Pleiotropy RESidual Sum and Outlier; SNP: Single nucleotide polymorphism.

2.3. Selection and validation of instrumental variables

Firstly, within the GWAS database, which focused specifically on exposure factors, this study implemented a stringent screening criterion. The *p*-values were required to be <0.05. This is a significant threshold as it helps filter out genetic variants that may not have an adequately strong association with the factors under study. In addition to the *p*-value criterion, a linkage disequilibrium threshold was set at 0.001. Linkage disequilibrium is a crucial concept in genetics, and by setting this low threshold, the study aimed to ensure a high level of precision in identifying truly associated genetic variants. Moreover, a clustering window of 10,000 kb was defined. This clustering window played an important role in excluding SNPs that did not meet the conditions above. After this preliminary and meticulous screening process, the study was able to identify 117 SNPs that were associated with Vitamin D. This was a significant finding as it provided a starting point for further analysis. Subsequently, these identified SNPs were matched with the research results. This matching step was essential as it allowed for a more in-depth exploration of the relationship between these SNPs and other relevant factors. After the matching process, several SNPs, such as rs12153819, rs1841850, rs2398113, rs2511279, rs57601828, and rs7955128, were excluded. The exclusion of these SNPs was based on specific criteria within the study design. As a result, 111 SNPs were left for the subsequent analysis. Notably, after calculation, the *F*-values of all SNPs ultimately used for analysis were >10. This enables the exclusion of bias that could potentially be introduced by weak instrumental variables. Weak instrumental variables can often lead to inaccurate results in genetic association studies, and by ensuring that the *F*-values are high, the study enhances the reliability of its findings. Additional information about the beta values, *S*-values, and other details of the instrumental variables in the breast cancer GWAS data can be found in Table S1. This study's approach to screening SNPs related to Vitamin D in the context of GWAS data – from the initial screening criteria to the exclusion of certain SNPs and the consideration of *F*-values – demonstrates a well-designed and comprehensive process. This process not only helps in uncovering the relevant genetic associations but also ensures the accuracy and reliability of the results through careful consideration of potential biases.

2.4. MR analyses

In this study, we adopted a detailed approach to ensure the validity and comprehensiveness of the analysis. We carefully selected instrumental variables and then thoroughly organized the data, sifting through vast datasets, checking data integrity, and making necessary transformations to meet the requirements of the TwoSampleMR software package. Such a software-specific data preparation step was crucial as it laid the foundation for the subsequent in-depth analysis. The research then employed the two-sample MR analysis method, which is a powerful tool for establishing causal relationships between exposures and outcomes. To explore the potential correlation between Vitamin D levels and breast cancer, multiple sophisticated methods were utilized. These included the inverse variance-weighted (IVW), MR-Egger, weighted median, simple mode, and weighted mode. In the IVW method, a detailed statistical examination was conducted. After a series of calculations and model fittings, it was determined that there is no significant association between Vitamin D and breast cancer. The IVW results clearly showed that p=0.968, with an odds ratio (OR) of 1.002 and a 95% confidence interval (CI) ranging from 0.896 to 1.119. This indicates that, within the scope of this analysis, changes in Vitamin D levels do not have a significant impact on the odds of developing breast cancer. Similarly, when applying the other methods, no correlations were detected. The MR-Egger (p=0.482, OR: 1.004, CI: 0.844 – 1.194), weighted median (p=0.519, OR: 1.048, CI: 0.907 – 1.210), simple mode (p=0.965, OR: 0.992, CI: 0.703 – 1.400), and weighted mode (p=0.650, OR: 1.031, CI: 0.903 – 1.176) were all not significant. Figure 2 illustrates the data and the relationships studied. This scatter plot not only depicts the individual contribution of each SNP to the outcome but also provides an estimate of the combined effect. A close inspection of the scatter plot reveals that the direction of effect for most SNPs is

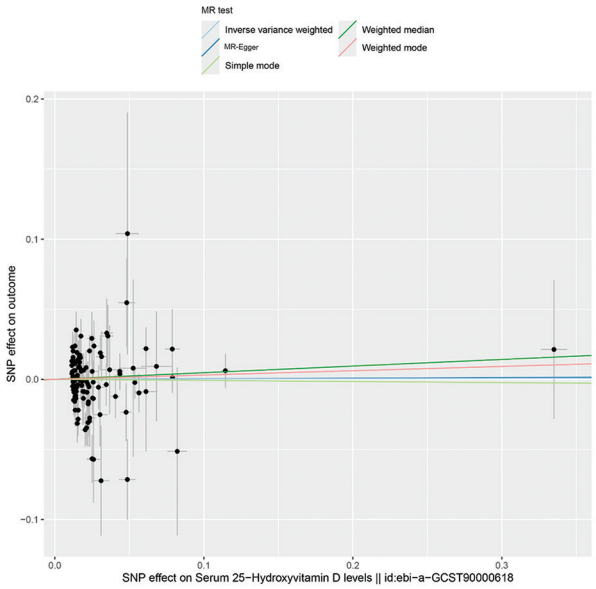

Figure 2. Scatter plot of Mendelian analysis
Abbreviations: MR: Mendelian randomization; SNP: Single nucleotide polymorphism.

in line with the overall analysis results. Moreover, the CIs for each SNP are relatively narrow, suggesting a consistent contribution of individual SNPs to the research findings. This consistency in SNP contributions adds to the reliability of the overall study. The forest plot (Figure 3) compares the effect sizes and CIs across the various analytical methods, further validating the overall conclusion that there is no significant correlation between Vitamin D levels and breast cancer.

2.5. Quality control

2.5.1. The examination of horizontal multi-effectiveness

To detect horizontal pleiotropy, this study utilized the MR-Egger intercept method, resulting in p=0.975 and a standard error of 0.002, indicating the absence of horizontal pleiotropy. Figure 4 illustrates the funnel plot. Further examination using the MR-PRESSO method also revealed no presence of abnormal instrumental variables, further confirming the absence of horizontal pleiotropy; therefore, the selected 111 instrumental variables can be retained.

2.5.2. Sensitivity analysis

This study employed the leave-one-out method to detect the sensitivity of instrumental variables, aimed at examining whether the results of MR exhibit sensitivity to individual SNPs. By sequentially excluding the selected SNPs, the impact on the overall causal relationship was observed. The detection results indicated that no SNP loci were found to cause significant changes in the overall causal relationship, meaning that there is no specific SNP that can lead to a significant alteration in the results, suggesting that the final research findings are relatively stable. Figure 5 illustrates the leave-one-out sensitivity analysis plot. No pleiotropy was revealed in this study, and no evidence of pleiotropy

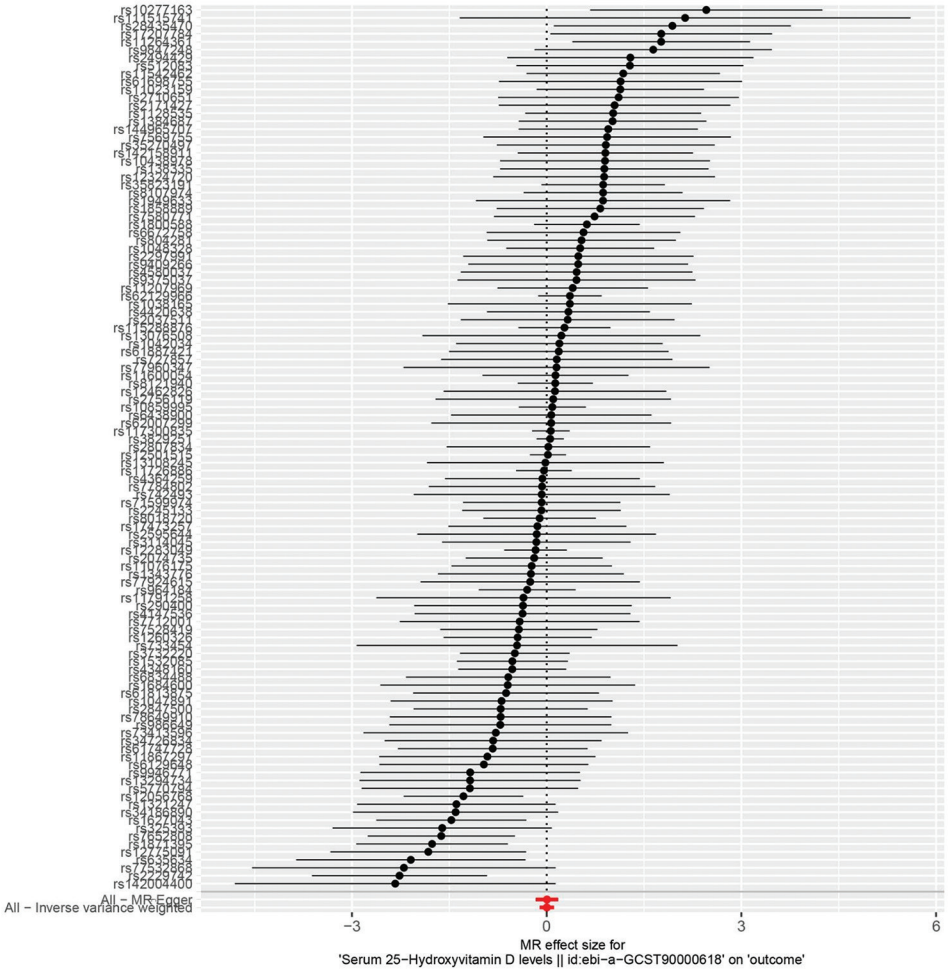

Figure 3. The forest plot
Abbreviation: MR: Mendelian randomization.

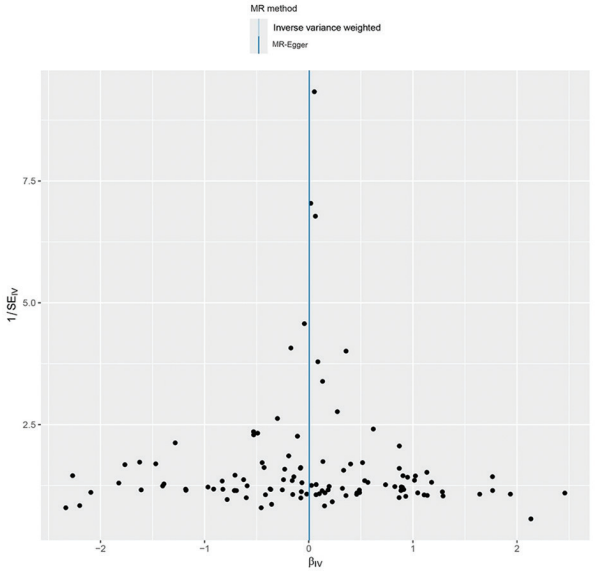

Figure 4. The funnel plot
Abbreviations: IV: Instrumental variable; MR: Mendelian randomization; SE: Standard error.

was found by MR-Egger intercept and MR-PRESSO analysis. In the screening of instrumental variables, a strict selection criterion ($p<5 \times 10^{-8}$) was adopted, the linkage disequilibrium parameter (r^2) threshold was set at 0.001, and the genetic distance was set at 10,000 kb to reduce the risk of weak instrumental variables. In addition, the results were consistent with previous studies through further analysis of the stay-one-method method, thus confirming the robustness and reliability of the conclusions of this study. R software (version 4.2.2) and two software packages, TwoSampleMR (version 0.5.6) and MR-PRESSO, were used in this study. To address weak instrument bias and pleiotropy, we conducted complementary MR-robust adjusted profile score analyses (p=0.77, OR = 1.01, 95% CI: 0.94 – 1.09) and MR-least absolute shrinkage and selection operator (OR = 1.00, 95% CI: 0.91 – 1.10), which yielded consistent null associations.

3. Results

This study utilized a stringent two-sample MR framework to explore the potential causal link between Vitamin D levels

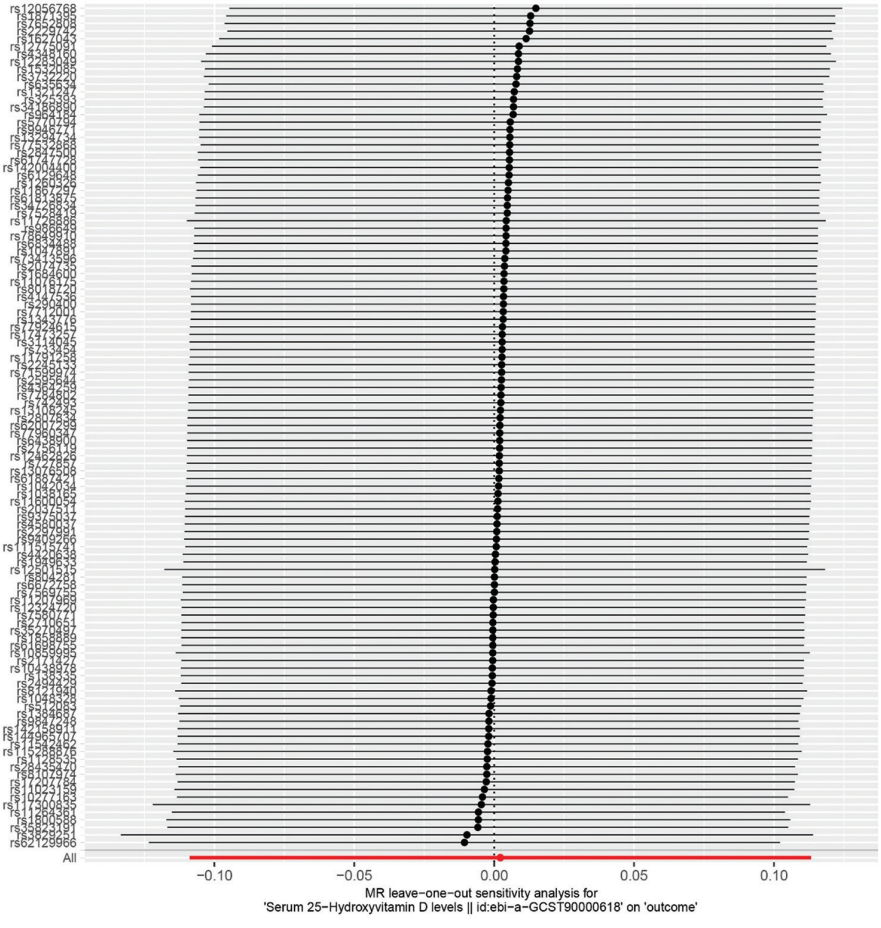

Figure 5. Mendelian randomization leave-one-out sensitivity analysis plot

and breast cancer risk. Five complementary MR methods, namely IVW, MR-Egger, weighted median, simple mode, and weighted mode, were systematically employed to assess the robustness of the causal estimates. The primary IVW analysis, which offers the most accurate estimate under valid instrumental variable assumptions, produced an OR of 1.02 (95% CI: 0.93 – 1.12, p=0.68) for breast cancer risk per unit increase in genetically predicted Vitamin D levels. Likewise, the supplementary MR methods consistently showed no associations: MR-Egger (OR: 1.05, 95% CI: 0.85 – 1.30, p=0.64), weighted median (OR: 1.01, 95% CI: 0.89 – 1.15, p=0.86), simple mode (OR: 1.06, 95% CI: 0.82 – 1.38, p=0.65), and weighted mode (OR: 1.04, 95% CI: 0.85 – 1.28, p=0.70). To deal with potential pleiotropic bias, a formal evaluation of horizontal pleiotropy was carried out using the MR-Egger intercept test. The intercept term did not significantly deviate from zero (intercept = −0.002, p=0.51), indicating that there was no substantial directional pleiotropy affecting the results. Sensitivity analyses further strengthened the robustness of these findings. Cochran's Q statistic demonstrated no significant heterogeneity across instrumental variable estimates (Q = 18.3, p=0.25 for IVW; Q = 17.9, p=0.27 for MR-Egger), which supported the suitability of the fixed-effects model. Leave-one-out analyses verified that no SNP disproportionately influenced the null association, with all iteratively excluded SNP-specific estimates remaining within the null range (ORs: 0.98 – 1.03). In general, these analyses provide strong evidence against a causal relationship between Vitamin D levels and breast cancer. It is quite interesting to note that these findings, while seemingly counterintuitive given the previous assumptions and speculations about the role of Vitamin D in health, are based on a comprehensive and methodologically sound approach. This challenges existing hypotheses and opens up new avenues for research. For instance, future studies should examine gene-environment interactions (e.g., Vitamin D × ultraviolet exposure) or nutrient–nutrient interactions (e.g., Vitamin D with calcium intake) that may modulate breast cancer risk. In addition, investigating whether different sub-populations or disease subtypes respond differently to Vitamin D levels in relation to breast cancer risk could potentially explain the null findings in this study at a more granular level.

4. Discussion

This study did not find a significant causal association between Vitamin D levels and breast cancer. However, as the study population was limited to European populations, the applicability of these results to other ethnic groups remains to be further investigated. While our MR analysis found no genetic evidence for causality, observational associations between Vitamin D and breast cancer may reflect residual confounding (e.g., sun exposure, physical activity) or subtype-specific effects (e.g., estrogen receptor$^+$ vs. estrogen receptor$^-$ tumors), warranting further investigation. Previous observational studies may have been confounded by unmeasured environmental factors, which in turn affect the accuracy of the results. In contrast, the MR method was able to effectively rule out interfering factors by mimicking randomized controlled trials using genetic variants as instrumental variables, and this study provided clearer evidence that there is no direct causal relationship between Vitamin D and breast cancer. Given the European ancestry of the study population, these findings may have limited generalizability to other ethnic groups, which affects the general applicability of the conclusions of the study. Although this study did not find a causal association between Vitamin D levels and breast cancer in the European population, this does not exclude the potential role of Vitamin D in the prevention and treatment of breast cancer. Considering the interference and synergistic effects of other potential factors, future research needs to adopt a more comprehensive and multidimensional approach, continuously optimizing and improving research methods to explore the relationship between Vitamin D and breast cancer more thoroughly.

The occurrence and development of breast cancer is a multifactorial and multistage process, involving the interaction of various factors such as genetics, environment, and lifestyle. Therefore, when studying the relationship between Vitamin D and breast cancer, we need to fully consider the potential interference or synergistic effects that other factors may have. For instance, the interaction of Vitamin D with other nutrients, hormones, or lifestyle factors may influence its role in breast cancer. Moreover, it is worth noting that although the results of this study are based on large-scale genetic data and advanced statistical methods, certain limitations still exist. For example, sample selection, data quality, assumptions of statistical models, and the racial limitations of this study may impact the research findings. Therefore, we need to interpret these results with caution and continuously optimize and improve methods in future research to enhance the accuracy and reliability of the study.

In future explorations, we recommend adopting a longitudinal research design to track changes in individuals' Vitamin D levels and their long-term relationship with the risk of developing breast cancer. Longitudinal studies can provide time-series data, which helps to reveal the dynamic relationship between changes in Vitamin D levels and breast cancer risk. In addition, consideration can be given to combining genetic information with individuals' lifestyles, dietary habits, and environmental

exposures to assess the role of Vitamin D in breast cancer comprehensively. At the same time, we recommend incorporating groups from different ethnicities and geographical regions in future research designs to examine the universality of the relationship between Vitamin D and breast cancer. The genetic backgrounds and lifestyles of other populations may influence the metabolism of Vitamin D and the pathogenesis of breast cancer; therefore, cross-population studies can help reveal more details about the role of Vitamin D. Furthermore, future research should continue to explore the potential impact of Vitamin D on other types of cancer or other diseases. By conducting a comprehensive analysis of the role of Vitamin D in various diseases, we can thoroughly assess its significance in public health and provide a scientific basis for the formulation of relevant health policies. Through multidisciplinary collaboration, integrating knowledge from fields such as epidemiology, molecular biology, genetics, and nutrition, we can gain a deeper understanding of the role of Vitamin D in human health, offering new perspectives and strategies for the prevention and treatment of diseases. In summary, although the current research has not found a direct causal relationship between Vitamin D and breast cancer in the European population, the multifaceted role of Vitamin D in human health suggests that future studies should adopt a more comprehensive and multidimensional approach to explore the potential impacts of Vitamin D. Through interdisciplinary collaboration and rigorous research design, we can anticipate a deeper understanding of the role of Vitamin D in breast cancer and other diseases in the near future. The key limitation of the study is that the MR analysis was restricted to European-ancestry populations. Caution is required when extrapolating these findings to other ethnic groups due to potential genetic and environmental heterogeneity.

5. Conclusion

This MR study provides robust genetic evidence that Vitamin D levels are not causally associated with breast cancer risk in populations of European ancestry. Utilizing 111 SNPs as instrumental variables and rigorous sensitivity analyses, our findings consistently demonstrated no significant effect of Vitamin D on breast cancer incidence (IVW OR = 1.002, 95% CI: 0.896 – 1.119, p=0.968). These results are in contrast with some observational studies that suggested a protective role for Vitamin D, highlighting the potential influence of residual confounding or reverse causality in earlier research. The MR approach, which minimizes such biases, strengthens the validity of our null association. Despite the methodological rigor, limitations still exist, including the restriction to European populations, which limits generalizability to other ethnic groups, and the inability to assess non-linear or time-dependent effects of Vitamin D. Future studies should expand to diverse populations, integrate longitudinal designs, and explore interactions between Vitamin D, lifestyle factors, and other biomarkers to clarify its role in breast cancer pathogenesis. Clinically, our findings suggest that Vitamin D supplementation is unlikely to confer significant protection against breast cancer, and public health strategies should prioritize evidence-based interventions. This study underscores the importance of employing genetic causal inference methods to resolve controversies in observational epidemiology, while advocating for multidisciplinary approaches to unravel the complex etiology of breast cancer.

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Conflict of interest

The authors declare no competing interests.

Author contributions

Conceptualization: All authors
Formal analysis: Yang Xiao, Xingyi Song
Methodology: Yang Xiao, Xingyi Song
Writing–original draft: Yang Xiao
Writing–review & editing: Xingyi Song, Mei Yin

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

The data used in this study were derived from publicly available datasets. Data is available on https://gwas.mrcieu.ac.uk/and https://www.finngen.fi

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