

METHODS AND PROTOCOLS **OPEN ACCESS**

Impact of Polymorphisms in Genes Related to Vitamin D Metabolism on Serum Response to Supplementation in Adults and Elderly: A Systematic Review and Meta-Analysis Protocol

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ABSTRACT

Background and Aims: Vitamin D deficiency is a major public health issue, with varying individual responses to supplementation. Genetic factors, especially single-nucleotide polymorphisms (SNPs) in Vitamin D metabolism genes, likely play a key role. This protocol proposes a systematic review to explore how genetic variability affects serum 25-hydroxyvitamin D [25(OH)D] levels after supplementation.

Methods: This protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P). The literature search will be conducted across MEDLINE, Scopus, Web of Science, and Embase, without restrictions on publication date or language. The study selection will be guided by Population, Exposure, Comparator, Outcomes, Study Design (PECOS) framework, focusing on randomized clinical trials that report pre- and post-supplementation serum 25(OH)D levels alongside genotype data. Inclusion criteria comprise adults and elderly individuals, from both sexes and any ethnicity, who received Vitamin D supplementation and have SNPs data, while exclusion criteria reject studies with confounding factors such as pre-existing conditions or use of medications affecting Vitamin D status. Data extraction will include study characteristics, participant demographics, intervention details, SNPs, and serum 25(OH)D data. Inter-rater reliability will be assessed using Cohen's kappa coefficient. A descriptive synthesis will summarize the findings, and if feasible, a meta-analysis will be conducted. The primary outcome will be changes in serum 25(OH)D concentrations. Heterogeneity among studies will be quantified using the I^2 statistic. The methodological quality of studies will be assessed using the Joanna Briggs Institute checklist, and the overall certainty of evidence will be evaluated using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach.

Conclusion: By identifying genetic subgroups with differential responses to vitamin D supplementation, the findings are expected to contribute to the development of personalized supplementation strategies. These insights may enhance health interventions by optimizing supplementation protocols based on genetic predispositions, ultimately improving health outcomes.

Trial Registration: This protocol has been registered with International prospective register of systematic reviews (PROSPERO) ID: CRD42023449836.

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1 | Introduction

Vitamin D (VitD) deficiency is a significant global health concern, contributing to a range of adverse health outcomes, including rickets and osteoporosis. Beyond its well-established role in bone health, Vitamin D metabolism has been implicated in the pathophysiology of cardiovascular diseases, type 1 and type 2 diabetes, autoimmune disorders, cancer, and respiratory diseases. Additionally, inadequate Vitamin D levels have been associated with a decline in both physical and cognitive function, further emphasizing its importance in overall health and well-being [1–5].

It is widely recognized that maintaining circulating 25-hydroxyvitamin D [25(OH)D] concentrations above 10 ng/mL at all ages is essential for bone health. However, growing evidence suggests that a significantly higher threshold is necessary to support not only skeletal health but also overall well-being. For example, the Institute of Medicine classifies 25(OH)D levels below 20 ng/mL as insufficient, while the US Endocrine Society recommends a minimum of 30 ng/mL to prevent adverse health effects [6–8].

Over the past decade, the global prevalence of low serum 25(OH)D concentrations has remained a significant public health concern, with levels below 20 ng/mL reported in approximately 25%–50% of the population [9–12]. Given the well-established link between Vitamin D deficiency and a wide range of chronic diseases, addressing this issue is a critical public health priority.

For most individuals, cutaneous synthesis via ultraviolet B (UVB) radiation exposure serves as the primary source of Vitamin D. However, serum Vitamin D levels are influenced by multiple factors, including age, sex, skin pigmentation, geographic location, diet, and lifestyle [3, 13]. While these determinants are extensively discussed in the literature and underscore the necessity of Vitamin D supplementation in cases of deficiency, individual responses to supplementation vary considerably. Notably, the factors traditionally associated with Vitamin D metabolism do not fully account for this variability, suggesting the presence of additional, yet-to-be fully elucidated, determinants [14, 15].

More recently, genetic variability has emerged as a crucial determinant of individual responses to Vitamin D supplementation. One of the most extensively studied aspects of this relationship is the influence of single-nucleotide polymorphisms (SNPs)—genetic variations involving the substitution of a single nucleotide at a specific position in the DNA—on serum Vitamin D concentrations [16–18]. Research has primarily focused on SNPs in genes encoding proteins involved in Vitamin D metabolism, including those regulating synthesis, transport, and receptor activity. Key genes implicated in this process include the ones on cytochrome p450 family genes (*CYP2R1*, *CYP27B1*, and *CYP24A1*), vitamin D receptor gene (*VDR*), gc-globulin gene (*GC*), and the *DHCR7/NADSYN1* region, among many others [17, 19–22].

Findings from these studies indicate that individuals carrying risk alleles associated with altered Vitamin D metabolism tend to exhibit lower serum 25OHD concentrations and may respond differently to supplementation. As a result, standardized dosing strategies may not be equally effective for all individuals,

highlighting the need for personalized Vitamin D supplementation regimens [20, 23]. This growing body of evidence reinforces the limitations of a “one-size-fits-all” approach, emphasizing the importance of precision nutrition in optimizing Vitamin D status across diverse populations.

Despite growing interest in the genetic determinants of Vitamin D metabolism, the evidence remains inconsistent, especially regarding the response to supplementation. While some research has identified specific SNPs associated with variations in serum 25OHD levels following supplementation, these findings often diverge due to differences in study design, population characteristics, and supplementation dosages [24–26]. Numerous reviews have explored the associations between SNPs, Vitamin D concentrations, and disease risk, yet relatively few have specifically examined the role of genetic polymorphisms—primarily in the *VDR* gene—in response to Vitamin D supplementation [22, 27]. Notably, no systematic review has comprehensively assessed the influence of multiple SNPs on Vitamin D supplementation outcomes, underscoring the need for a thorough synthesis of available evidence.

Therefore, a systematic evaluation of the existing literature is necessary to consolidate these findings and provide clearer guidance on how genetic variability impacts individual responses to Vitamin D supplementation. Identifying which SNPs and risk alleles contribute to variations in serum 25OHD levels is critical for public health, as it can help pinpoint individuals who may require adjusted supplementation doses to achieve optimal Vitamin D status.

In this context, Vitamin D supplementation has been shown to significantly improve Vitamin D status, and recent studies suggest that it should be more strongly integrated into preventive medicine to support health maintenance and disease treatment [5, 28]. By evaluating the relationship between SNP risk alleles and serum Vitamin D responses, this review aims to provide more precise and individualized supplementation recommendations, potentially enhancing public health outcomes and advancing the field of precision nutrition.

The objective of this paper is to outline the protocol design for conducting a systematic review to assess how SNP risk alleles influence serum 25-hydroxyvitamin D [25(OH)D] responses to Vitamin D supplementation. This review will consolidate evidence on SNPs in key Vitamin D metabolism genes (e.g., *CYP2R1*, *CYP24A1*, and *VDR*) to clarify the extent to which these genetic variants affect serum Vitamin D levels post-supplementation. Additionally, this study seeks to identify variability in supplementation responses across different population subgroups, ultimately contributing to the development of more personalized and effective supplementation strategies.

2 | Methods

2.1 | Protocol and Registration

This systematic review protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) guidelines [29, 30]. The review

has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) under protocol ID CRD42023449836. The final review will be conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [31].

2.2 | Search Strategy

The PECOS (Population, Exposure, Comparison, Outcome, Study Design) framework was employed to formulate the research question:

“Can single-nucleotide polymorphisms associated with genes related to Vitamin D deficiency contribute to a diminished response to Vitamin D supplementation in adults and elderly individuals?” (Table 1). To ensure the originality of this review and avoid redundancy with existing studies, the investigation will specifically focus on research exploring associations between genotypes for single-nucleotide polymorphisms (SNPs) in genes directly related to Vitamin D metabolism.

The search will be conducted across multiple databases, including MEDLINE (via PubMed), Scopus, Web of Science and Embase. No date or language restrictions will be applied. Synonym terms were grouped using the Boolean operator “OR” to create structured blocks, linked using the Boolean operator “AND” during the search process (Table 2).

TABLE 1 | Terms used in the article search strategies.

P	Healthy adults and elderly in use of vitamin D supplementation
E	Presence (be a carrier) of risk allele to vitamin D deficiency
C	Absence (not be a carrier) of risk allele to vitamin D deficiency
O	Serum 25-hydroxyvitamin D levels
S	Randomized clinical trial

TABLE 2 | Search strategy.

Number	Query
#1	“Dietary supplements” OR “dietary supplement” OR “supplementation” OR “administration”
#2	“Vitamin D” OR “25-hydroxyvitamin D” OR “cholecalciferol” OR “25-Hydroxyvitamin D 2” OR “25-Hydroxyergocalciferol” OR “25-Hydroxycalciferol” OR “25-Hydroxyvitamin D 3” OR “25-Hydroxycholecalciferol” OR “calcifediol” OR “ergocalciferols” OR “dihydroxycholecalciferols” OR “hypovitaminosis D” OR “vitamin D deficiency” OR “vitamin D insufficiency” OR “vitamin D sufficiency” OR “vitamin D status”
#3	“Single-nucleotide polymorphism” OR “polymorphism” OR “genetic variation” OR “gene” OR “SNP” OR “allele” OR “genetics” OR “genetic risk” OR “GRS” OR “GWAS” OR “genomic-wide association study” OR “genomics” OR “nutrigenetics” OR “DNA” OR “polygenic” OR “polygenic risk score” OR “single nucleotide variation” OR “SNV” OR “variant” OR “variants” OR “polymorphisms” OR “GWAS” OR “Vitamin D-related genes” OR “Vitamin D-related genetic variants”
#4	#1 AND #2
#5	#1 AND #2 AND #3

The search strategy will be customized to align with the specific requirements of each database. Searches will be conducted in the title, abstract, and/or keyword fields. Additional modifications may be made for each database to ensure the inclusion of relevant studies for analysis.

The search terms will be based on Medical Subject Headings (MeSH) and free-text keywords relating to vitamin D supplementation, SNPs, and serum 25-hydroxyvitamin D levels. No period, language or other restrictions will be applied to maximize the inclusion of relevant studies. The search process will be conducted between March 2025 and April 2025.

2.3 | Inclusion and Exclusion Criteria

This systematic review will include original, peer-reviewed randomized clinical trials (RCTs) that investigate adults and elderly individuals who have received Vitamin D supplementation. Eligible studies must report both pre- and post-supplementation serum 25-hydroxyvitamin D (25OHD) levels and provide genotype data for single-nucleotide polymorphisms (SNPs) related to Vitamin D metabolism, such as those found in the *CYP2R1*, *CYP27B1*, and *VDR* genes.

Studies will be excluded if they are non-RCTs, including case reports, narrative reviews, systematic reviews, or unpublished studies. Research involving medications known to interfere with Vitamin D metabolism, such as anticonvulsants and glucocorticoids, will also be excluded. Additionally, studies on populations with conditions that significantly impact Vitamin D metabolism, including malabsorption syndromes (such as cystic fibrosis, inflammatory bowel disease, Crohn's disease, or post-bariatric surgery), renal or hepatic failure, hyperparathyroidism, granulomatous diseases, and lymphomas, will not be considered. Studies evaluating pregnant or breastfeeding women will also be excluded from this review.

2.4 | Study Selection

The study selection phase will be conducted in Rayyan. Two independent reviewers will screen titles and abstracts to identify

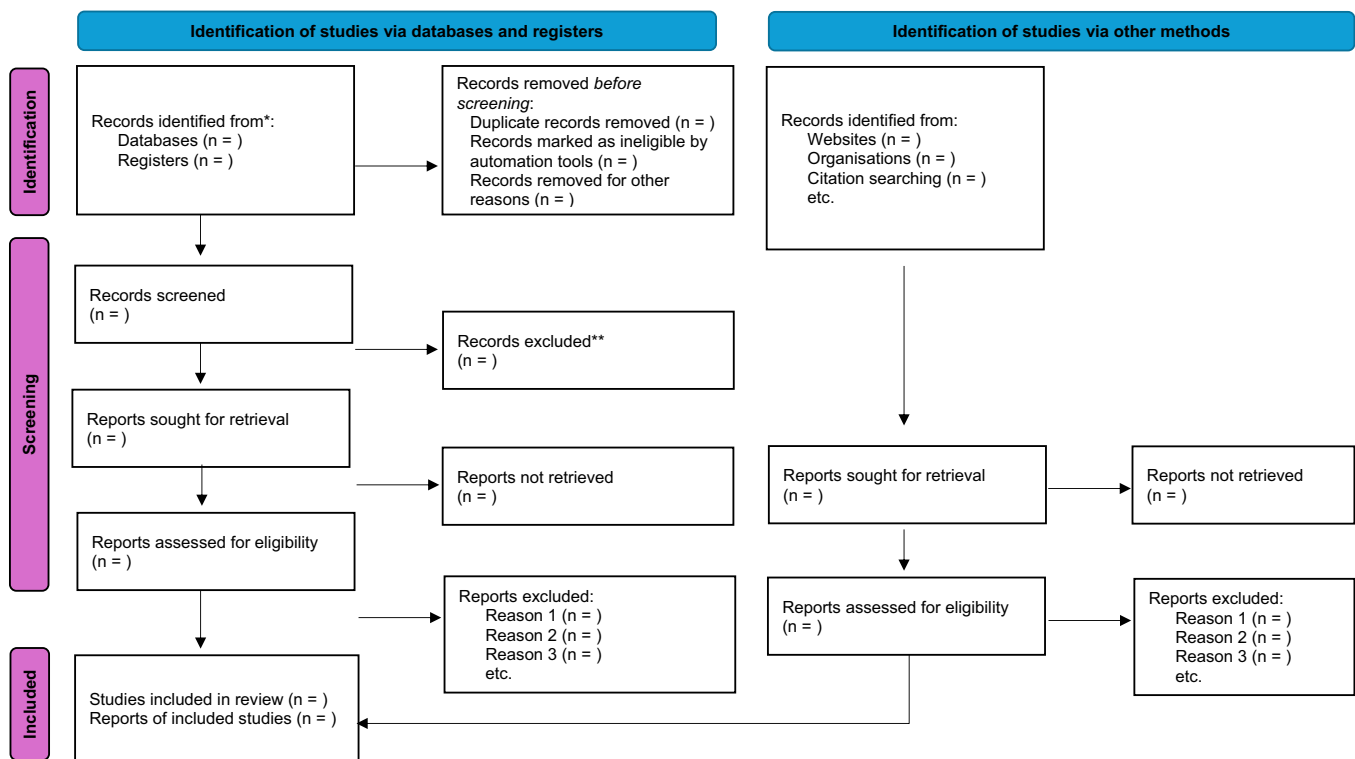


FIGURE 1 | PRISMA flowchart for article selection and inclusion [31].

studies that meet the inclusion criteria. Duplicates will be removed during this initial phase. Full-text articles of selected studies will then be independently reviewed by both reviewers to confirm eligibility. Any disagreements will be resolved by a third reviewer. The flowchart presented in Figure 1 for the search and selection process of the articles adheres to the PRISMA flowchart [31].

2.5 | Data Extraction and Synthesis of the Results

Data extraction will be conducted by two trained reviewers using a pre-defined standardized form. Key data points will include bibliographic details such as authors, title, and year of publication, as well as study duration, sample size, and population characteristics, including age, sex, ethnicity, and health status. Intervention details, such as supplement type and dose, sampling season, and dietary Vitamin D intake, will also be recorded. Information on Vitamin D measurement methods, including source and analysis technique, will be documented. Additionally, SNP data will be collected, including rs ID, genotype frequencies, and associated risk alleles. Serum 25-hydroxyvitamin D levels before and after supplementation will also be extracted.

Data extraction will be carried out independently by two trained researchers. In cases where data are missing, study authors will be contacted, with up to two follow-up attempts. Any uncertainties or discrepancies that arise during the extraction process will be resolved by a third researcher who was not involved in the initial extraction. To assess inter-rater reliability and agreement, Cohen's kappa and percentage agreement coefficients will be calculated [32].

2.6 | Data Synthesis and Analysis

A descriptive synthesis will be provided for all included studies. Where appropriate, a meta-analysis will be conducted to pool the results from studies reporting comparable outcomes. Subgroup analyses will be performed based on genotype, age, sex, study location, risk of bias, and other relevant factors. If necessary, sensitivity analyses will be conducted to assess the robustness of subgroup comparisons. Heterogeneity will be evaluated using the I^2 statistic, with thresholds of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Statistical analyses will be performed using Stata software.

To account for potential discrepancies in the Vitamin D deficiency threshold used across studies—given the lack of a universally accepted definition that may influence the interpretation of clinical outcomes—sensitivity analyses will be conducted using both 20 ng/mL and 30 ng/mL as deficiency thresholds. This approach will ensure a more comprehensive interpretation of the findings.

The general characteristics of the included studies will be summarized in Table 3. Since this systematic review focuses on serum Vitamin D concentrations before and after supplementation, as well as genetic influences, data will be analyzed in relevant subgroups. These subgroups will include overall serum Vitamin D levels before and after supplementation, stratified by risk alleles in Vitamin D-related polymorphisms. Additional subgroup analyses will consider factors such as age, sex, study location, season of sample collection, and risk of bias. The tables summarizing the results for each subgroup and study characteristic are presented in Tables 4–7.

TABLE 3 | Characteristics of the articles included in the systematic review.

Characteristics	N (%)
Publication year	
< 2010	
2010–2020	
2020–2024	
Latitude	
Above 30° N	
30° N–30° S	
Below 30° S	
Sample size	
≤ 100	
100–500	
500–1000	
> 1000	
Intervention time	
≤ 3 months	
3–6 months	
6–12 months	
> 1 year	
Season	
Spring/summer	
Winter/autumn	
Mean 25(OH)D at baseline	
Deficient (< 20 ng/mL)	
Sufficient (≥ 30 ng/mL)	
25(OH)D assessment method	
HPLC	
Other	
Food consumption evaluation	
Yes	
No	
Sun exposure evaluation	
Yes	
No	

TABLE 4 | Summary of results—general characteristics.

Authors, year	Country	Sample size	Age (mean or range)	Male/ female ratio	Ethnicity	Health status	Study location and latitude	Sample size
Study 1								
Study 2								
Study 3								
(...)								

2.7 | Methodological Quality and Risk of Bias

The Joanna Briggs Institute (JBI) checklist will be used to assess the methodological quality and risk of bias of each included study. Additionally, the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach will be applied to evaluate the overall certainty of the body of evidence, ensuring a comprehensive and rigorous analysis of the main outcomes. This dual assessment strategy will enhance the reliability of findings and strengthen the conclusions drawn from the review. Any discrepancies between reviewers will be resolved through discussion or, if necessary, by consulting a third reviewer. To further ensure the robustness of findings and the consistency of results, sensitivity analyses will be conducted.

2.8 | Publication Bias

To assess potential publication bias, a funnel plot and a scatterplot will be generated to illustrate the relationship between effect sizes and the standard errors of the included studies. The symmetry of the funnel plot will be initially evaluated visually.

Further statistical assessment of publication bias will be conducted using the Egger test, with results presented through funnel plots. All statistical tests will be two-sided, with a significance threshold of $p < 0.05$.

2.9 | Reviewer Training

Authors responsible for assessing article eligibility will undergo training on the inclusion and exclusion criteria, followed by an eligibility test on a sample of 50 titles and abstracts before proceeding with article selection [33, 34]. Rayyan software will be used to facilitate the selection process and reviewer training.

Additionally, all researchers will participate in a training session aimed at standardizing the application of the JBI checklist for risk of bias assessment and the GRADE approach for evaluating the certainty of evidence [33, 34]. This session will also cover systematic data extraction procedures to ensure uniformity, accuracy, and consistency in evaluating the included studies.

TABLE 5 | Summary of results—intervention design.

Authors, year	Season of data collection	Intervention duration	Vitamin D dose (IU)	Blinding (Y/N)	Control group (Y/N)	Form of supplementation (D2/D3)	Vitamin D assay method	Adherence to supplementation
Study 1								
Study 2								
Study 3								
(...)								

TABLE 6 | Assessment of lifestyle and environmental factors influencing Vitamin D status.

Authors, year	Dietary vitamin D intake assessed (Y/N)	Sun exposure assessed (Y/N)	Clothing habits assessed (Y/N)	Use of sunscreen assessed (Y/N)	Mean BMI in kg/m ²	Skin type/color assessed (Y/N)
Study 1						
Study 2						
Study 3						
(...)						

TABLE 7 | Summary of results—findings/outcomes by genotype.

Authors, year	SNP (rs ID)	Genotype groups	Sample size per genotype	Risk allele	Baseline 25(OH)D (ng/mL)	Post-supplementation 25(OH)D (ng/mL)	Change in 25(OH)D levels (Δ) (ng/mL)	p value	Effect size	Confidence interval (CI)	Additional notes/ findings
Study 1											
Study 2											
Study 3											
(...)											

3 | Discussion

Vitamin D deficiency is a widespread public health concern, particularly in regions with limited ultraviolet B (UVB) exposure and low dietary intake of Vitamin D-rich foods [1–5]. While Vitamin D supplementation is widely recommended as a preventive strategy, individual responses to supplementation vary significantly. Emerging evidence suggests that genetic factors, particularly single-nucleotide polymorphisms (SNPs) in genes involved in Vitamin D metabolism, play a crucial role in these differential responses. Key genes implicated in Vitamin D synthesis, transport, and receptor activity include *GC*, *CYP2R1*, *CYP27B1*, and *VDR* [19, 21, 22]. Understanding these genetic influences is essential for optimizing supplementation strategies and advancing precision nutrition approaches.

It is well established that Vitamin D levels are influenced by several factors, including diet, sunlight exposure, age, body mass index (BMI), and skin pigmentation, as well as external factors that affect sunlight exposure, such as geographical latitude, skin coverage, and seasonality. However, research indicates that these traditional factors explain only part of the variability in Vitamin D levels, and that genetic factors play a crucial role in determining individual Vitamin D status [20]. Heritable factors are estimated to influence Vitamin D levels by 20%–85% [35, 36].

The most extensively studied genes in relation to Vitamin D metabolism are those encoding proteins involved in Vitamin D synthesis, activation, transport, and degradation, including genes from the cytochrome P450 family (*CYP2R1*, *CYP27B1*, and *CYP24A1*), as well as the Vitamin D receptor gene (*VDR*) and the GC-globulin gene (*GC*). *CYP2R1* encodes the enzyme responsible for the hydroxylation of Vitamin D2 and Vitamin D3 into 25-hydroxyvitamin D [25(OH)D], the main circulating form of Vitamin D. Variants in this gene have been linked to serum 25(OH)D concentrations and an increased risk of Vitamin D deficiency. *CYP27B1* encodes 1 α -hydroxylase, the enzyme responsible for converting 25(OH)D into its active form, 1 α ,25-dihydroxyvitamin D [1 α ,25(OH)₂D]. Although the exact mechanisms remain unclear, SNPs in *CYP27B1* have been shown to influence serum 25(OH)D levels, possibly by altering the rate of conversion into the active form. *CYP24A1* encodes an enzyme involved in the inactivation of 1 α ,25(OH)₂D, playing a key role in the degradation of Vitamin D metabolites. Variants in *CYP24A1* have been associated with altered Vitamin D concentrations and may contribute to differences in Vitamin D metabolism [37].

The *GC* gene plays a crucial role in Vitamin D metabolism, as it encodes the Vitamin D-binding protein (VDBP), which is responsible for transporting 25-hydroxyvitamin D [25(OH)D] in circulation. Variants in this gene can alter the binding affinity of VDBP, thereby influencing serum 25(OH)D concentrations. Similarly, the *VDR* gene encodes the Vitamin D receptor (VDR) protein, which is essential for Vitamin D signalling and function. Single-nucleotide polymorphisms (SNPs) in *VDR* can modify both the structure and function of the receptor, ultimately affecting serum Vitamin D levels [37].

Beyond these key genes, genetic variations in *DHCR7* have also been investigated. The *DHCR7* gene encodes an enzyme involved in the conversion of 7-dehydrocholesterol into cholesterol, a process that indirectly influences Vitamin D synthesis. Genetic variants in *DHCR7* that reduce enzymatic activity may lead to lower cholesterol synthesis, resulting in a higher availability of 7-dehydrocholesterol for conversion into Vitamin D3 [38].

A recent review by Bosch et al. [35] identified associations between 43 SNPs and biochemical markers of Vitamin D, including 25(OH)D, calcitriol, and VDBP, as well as Vitamin D deficiency risk. Among these SNPs, 17 were positively associated with higher blood concentrations of these markers, 19 were negatively associated, and 7 yielded inconclusive results. The genes associated with these SNPs included *GC*, *CYP2R1*, *CYP24A1*, *NADSYN1/DHCR7*, *A2BP1*, *GPR114*, *MLL3*, and *C10orf88* [35]. Wang et al. [39], after analyzing studies investigating SNPs related to Vitamin D metabolism, suggest that genetic factors are crucial for establishing appropriate Vitamin D recommendations and may even exert a greater influence than nongenetic factors. Similarly, Bosch et al. [35] emphasize the existence of a gene–environment interaction in shaping Vitamin D status. They propose that the relationships between socio-environmental factors such as age, sex, diet, and sun exposure should be assessed alongside genetic factors to better understand their combined impact on the response to Vitamin D supplementation.

A limitation of this review is the methodological variability among the included studies, which may introduce challenges in synthesizing findings and drawing definitive conclusions. Differences in study design, sample size, genetic analysis methods, and supplementation protocols can contribute to heterogeneity in results, potentially affecting the comparability of outcomes. Additionally, variations in baseline Vitamin D status, sun exposure, dietary intake, and supplementation regimens across different populations may lead to inconsistencies in the observed associations between SNPs and Vitamin D response. Another critical gap is the lack of standardized genetic screening approaches, as many studies focus on only a subset of SNPs related to Vitamin D metabolism, potentially overlooking other genetic variants that could influence individual responses. Moreover, the underrepresentation of certain populations in genetic studies limits the generalizability of findings, as most research has been conducted in European ancestry groups, with fewer studies including diverse ethnic backgrounds. Addressing these limitations in future research will be essential to improve methodological consistency, expand genetic analyses, and enhance the applicability of findings across different demographic and environmental contexts.

This systematic review aims to synthesize existing evidence on the influence of genetic variation on serum 25-hydroxyvitamin D levels following supplementation. By integrating data from multiple studies, we expect to identify specific SNPs that are consistently associated with reduced or enhanced responses to Vitamin D supplementation, thereby elucidating the role of genetic determinants in Vitamin D metabolism. This review will also highlight how

risk alleles in genes involved in Vitamin D synthesis, transport, and receptor activity contribute to individual variability in post-supplementation Vitamin D status, ultimately advancing the understanding of personalized approaches to Vitamin D supplementation.

We also anticipate that identifying patterns of response variation across different subgroups, as certain demographic factors—such as age, sex, ethnicity, and geographic region—may influence the relationship between SNPs and Vitamin D supplementation outcomes [3, 13]. Understanding these subgroup-specific responses could provide valuable insights for developing tailored Vitamin D recommendations, ultimately enhancing the precision and effectiveness of supplementation strategies.

Despite the potential benefits of this review, certain limitations and challenges must be acknowledged. Variability in study designs, sample sizes, and methodologies across the included studies may introduce heterogeneity, complicating the synthesis of results. Differences in baseline Vitamin D status, supplementation dosage and duration, and confounding factors such as diet and sun exposure could further impact the interpretation of findings.

These confounding factors, along with population differences, contribute to the lack of consensus on the relationship between SNPs and responses to Vitamin D supplementation, potentially making it challenging to establish clear conclusions. Additionally, many studies may not provide comprehensive data on all relevant genetic variants, leading to gaps in the analysis. Addressing these limitations will be essential to ensure that the conclusions drawn are robust and meaningful, ultimately strengthening the understanding of genetic influences on Vitamin D metabolism.

Furthermore, this review is likely to identify gaps in current research, such as the limited number of studies on specific SNPs and the underrepresentation of certain populations. Highlighting these gaps will be valuable for guiding future research efforts and addressing unresolved questions about the genetic determinants of Vitamin D metabolism. Understanding the aetiology of Vitamin D deficiency and the variability in response to supplementation could have significant public health implications.

The clinical implications of this study are substantial. Identifying genetic variants that influence Vitamin D response could enable healthcare providers to personalize supplementation recommendations based on an individual's genetic profile, rather than relying on generalized guidelines. This shift toward personalized nutrition strategies could optimize Vitamin D status and improve health outcomes.

Ultimately, this systematic review aims to deepen our understanding of how genetic factors impact the efficacy of Vitamin D supplementation. By integrating genetic insights into clinical practice, this study will contribute to the growing field of nutrigenetics, demonstrating how precision-based approaches can refine and individualize health recommendations for better-targeted supplementation strategies.

Author Contributions

Lana Pacheco Franco-Gedda: methodology, data curation, writing – original draft, writing – review and editing. **Karina Rodrigues:** conceptualization, methodology, data curation, writing – review and editing. **Matias Noll:** methodology, funding acquisition, writing – review and editing. **Marcela Moraes Mendes:** conceptualization, methodology, data curation, supervision, writing – original draft, writing – review and editing. **Maria Aderuza Horst:** conceptualization, methodology, data curation, writing – review and editing, funding acquisition, and supervision.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data supporting the findings of this study will be made available from the corresponding author upon reasonable request.

Transparency Statement

The corresponding author, Maria Aderuza Horst, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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