Observational Study

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Application of Mendelian randomized analysis method in Vitamin D research

A 10-year bibliometric analysis

Tai-Long Lv, MM[a], Wen-Wen Li, MD[a], Zhen-Hai Sun, MD[a], Meng-He Zhang, MD[b], Yao-Yao Zuo, MM[b], Shu-Di Li, MM[a], Yun-Xiao Zhang, MM[a], Hui-Dan Xie, MM[a], Shou-Qiang Chen, PD[b,*]

Abstract

Vitamin D is an open-cyclic steroidal trace organic compound that plays a crucial role in human metabolism and nutritional health. In recent years, Mendelian randomization (MR) has emerged as a widely adopted method for analyzing causal relationships, particularly in studying the association between Vitamin D and related diseases. However, no bibliometric analyses have been conducted to explore the research hotspots and trends regarding Vitamin D status in MR studies. This study utilized the Web of Science Core Collection as a source database and retrieved articles on Vitamin D status in MR published from 2014 to 2024. Bibliometric and visualization analyses utilized VOSviewer, Microsoft Excel 2021, and Scimago Graphica. An in-depth analysis of country or region, authors, journals, keywords, and references were performed to provide insights into the content related to the field. A total of 186 documents authored by 1122 contributors across 30 countries were identified. China and the University of Bristol had the highest publication counts, with 94 and 19 articles, respectively. The nutrients published the largest number of articles, and J Brent Richards was the largest contributors. The most frequently used keywords included "Mendelian randomization," "Vitamin D," "25-hydroxyVitamin D," "obesity," and "Type 2 Diabetes." The current research focuses on using MR methods to explore the associations between Vitamin D status and metabolic, cardiovascular, immune skin, psychiatric and neurological diseases. The related research in this field will continue to increase in the next few years, which is a promising research prospect in this field. This study systematically reviews the literature from the past decade, revealing research hotspots and trends in the field of Vitamin D status within MR studies. This information will provide a strong reference for readers and researchers.

Abbreviations: 25 (OH)D = 25-hydroxyVitamin D, BMI = body mass index, MR = Mendelian randomization, VDR = Vitamin D receptor, WOS = web of science.

Keywords: bibliometric analysis, Mendelian randomization, visualization analysis, Vitamin D, VOSviewer

1. Introduction

Vitamin D is a fat-soluble, open-ring steroidal vitamin that exists in the form of Vitamin D2 (ergosterol) from plant sources and Vitamin D3 (cholecalciferol) from animal sources. Vitamin D is first synthesized in the liver through the catalytic synthesis of 25-hydroxyVitamin D (25 (OH)D) by the enzyme 25-hydroxylase (CYP2R1),[1] which is the major storage form and circulating metabolite of Vitamin D in the body. Notably, 25(OH)D is now recognized as an indicator of Vitamin D status due to its long half-life.[2] Subsequently, 25(OH)D is rehydroxylated in the kidney by 1-alpha-hydroxylase (CYP27B1) to produce 1,25(OH)2D,[3] the major active metabolite of Vitamin D in vivo. 1,25(OH)2D not only binds to the Vitamin D receptor (VDR), which is widely present in the tissues and exerts a hormone-like effect, but also binds to the Retinoid X receptor. It also binds to the Retinoid X receptor and acts as a nuclear transcription factor, altering gene expression and inducing protein synthesis.[4] With the discovery that the VDR is expressed in several cell types that are not involved in bone and mineral metabolism,[5] there has been a shift in the viewpoints of how Vitamin D affects human health. In general, the main physiological role of Vitamin D and its metabolites is to promote calcium and phosphorus absorption in the gut and to inhibit parathyroid hormone release, maintaining normal blood calcium and phosphorus levels and thus ensuring bone health.[6] In addition, it acts as an immunomodulatory hormone that acts on the VDR to exert a variety of extraskeletal

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Ethical approval is not required, since no original clinical data was used in this study.

[a] Shandong University of Traditional Chinese Medicine, Jinan, China, [b] The Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, China.

** Correspondence: Shou-Qiang Chen, The Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan 250000, China (e-mail: csq23800@163.com).*

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effects,[7] including regulation of muscle, cardiovascular, metabolism, immunity, tumorigenesis, pregnancy, fetal development, and so on.[8]

Mendelian randomization (MR) is a well-established method in genetic epidemiology that has garnered increasing attention in observational epidemiology in recent years. Randomized controlled trials, despite being the gold standard for conducting causal analyses, are known to be challenging to implement due to factors such as practicality, cost, and ethical considerations.[9] In contrast, MR, as a method for determining causality through genetic variation screening, has become increasingly prominent due to its timely and cost-effective nature. The MR method utilizes single nucleotide polymorphisms linked to 25(OH)D levels in Genome-Wide Association Studies to estimate 25(OH)D levels, enabling examination of whether genetically determined decreases or increases in 25(OH)D levels correlate with heightened risk of diverse diseases. It is noteworthy that this approach effectively mitigates confounding factors and reverse causality,[10] complementing findings from both observational studies and randomized controlled trials,[11] thereby enhancing the robustness of conclusions drawn. Given the global prevalence of Vitamin D deficiency, comprehensive studies in this domain are highly valuable. Furthermore, the MR method: a relatively novel approach to causal inference, has garnered considerable interest in its application to investigating the Vitamin D-disease relationship in recent years.

MR analyses have been increasingly used to explore the correlation between Vitamin D and disease, coinciding with a rapid increase in research papers in this area. Several studies have shown that Vitamin D levels are associated with various diseases, including heart failure,[12] polycystic ovary syndrome,[13] chronic obstructive pulmonary disease,[14] systemic lupus erythematosus,[15] Alzheimer disease,[16] and multiple sclerosis.[17] However, to the best of our knowledge, there has been no systematic analysis and intuitive summary in this area. To systematically study the trends and hotspots of Vitamin D in MR, a bibliometric analysis was conducted in this study. Bibliometric techniques are used for assessing and characterizing research results and trends. Bibliometric studies yield more objective and less biased results when comparing contributions of publications from various countries, units, or individuals.[18] This study employed bibliometric methods to investigate trends and hotspots in research on Vitamin D in MR over the past decade. This study aims to reveal new insights into academic trends, drug development, and disease treatment, while also supporting evidence-based practices in clinical education.

2. Materials and methods

2.1. Data sources and search strategies

The search strategy outlined in Table 1 was employed to retrieve relevant publications from the Web of Science Core Collection (WoSCC). Data were searched and exported up to June 30, 2024, to mitigate conflicts related to database updates. The retrieved information was analyzed and visually presented using VOSviewer (version 1.6.20), Microsoft Excel 2021, and Scimago Graphica (version 1.0.42). Countries, journals, keywords, year of publication, institutions, and authors in the field were examined using VOSviewer. Long-term publication trends were visualized using Microsoft Excel 2021. Additionally, Scimago Graphica generated a world map depicting the distribution of publications by country.

2.2. Inclusion and exclusion criteria

It was necessary to screen the retrieved literature to ensure the reliability of the data used for the analysis. Two authors independently reviewed the documents in accordance with the following criteria, and any differences were resolved through consultation with third parties.

Inclusion criteria: (1) the research topic of the article involves MR study and Vitamin D. (2) The document type is "article." (3) The document language is limited to "English." (4) The publication time is from January 1, 2014, to June 30, 2024.

Exclusion criteria: (1) the topic of the study is not MR and Vitamin D. (2) The document type is "review articles." (3) Withdrawn or duplicate publications. (4) Documents that cannot provide the basic information required for bibliometric analysis such as title, author, keywords, abstract, time, journal information, references, and country.

3. Results

3.1. General information

Based on the established search strategy, we identified 186 publications authored by 1122 individuals from 413 institutions across 30 countries, published in 99 journals between January 2014 and June 2024. These publications are depicted in Figure 1, illustrating an increasing trend in the number of publications in this field over time. Specifically, from 2014 to 2017, there was a gradual increase in publications on Vitamin D status and disease correlation in MR. The number of publications remained stable from 2018 to 2020 but has significantly increased since 2020. Additionally, Figure 2 displays a world map depicting the distribution of papers across various countries. The publication of papers in the field of "Vitamin D status and disease correlation in Mendelian randomization" is notably active in Europe, particularly with the United Kingdom leading in the number of publications. China leads in the Asian region, while the United States and Canada in North America, and Australia in Oceania, also contribute significantly.

3.2. Analysis of countries

Papers on the relationship between Vitamin D status and disease in MR were published across 30 countries. Table 2 summarizes the 6 countries with the highest number of research articles in this field. China contributed the most articles at 50.5% (94/186), followed by the United Kingdom (30.6%; 57/186), the United States (21.0%; 39/186), Sweden (10.8%; 20/186), Australia (10.2%; 19/186), and Canada (9.7%; 18/186). This can also be seen in the graphical representation of the literature density visualization in Figure 3. Notably, Canada, despite publishing fewer papers (18) compared to other top 6 countries, had the highest average number of citations (53.9), highlighting its significant impact in the field. Additionally, China has the lowest

Table 1

Summary of the literature search strategy in this study.

Content	
Research database	Web of Science Core Collection
Citation indexes	SCI-EXPANDED
Searching period	January 2014 to June 2024
Language	"English"
Searching keywords	TS=("Mendelian randomization" OR "Mendelian randomization") AND TS=("Vitamin D" OR "25-hydroxyVitamin D" OR "25(OH) D")
Document types	"Articles" and "Review Articles"
Data extraction	Export with full records and cited references in plain text format
Sample size	186

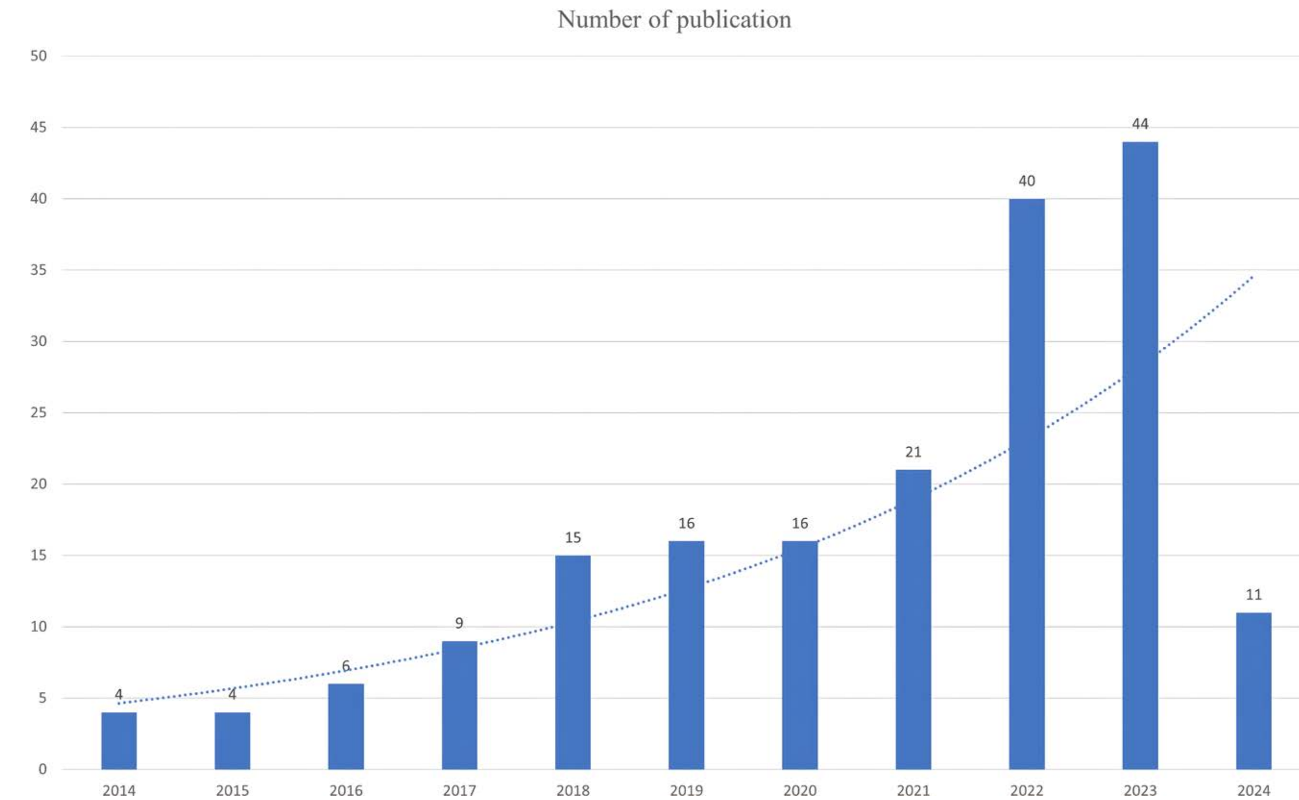

Figure 1. The annual trends of publications.

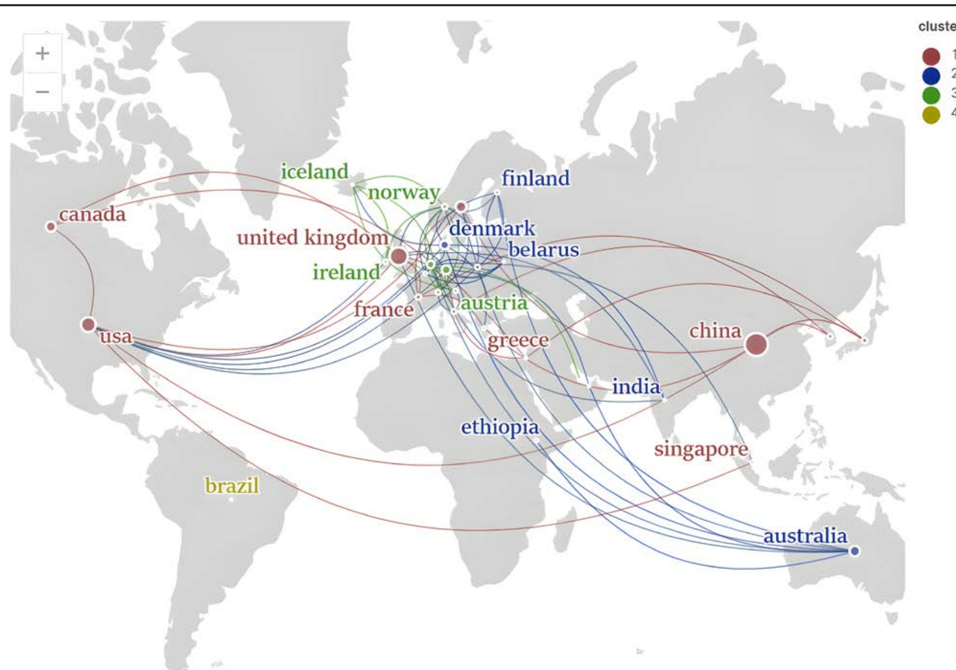

Figure 2. A world map of publications delivered in different countries. (The size of the node is an indication of the number of publications).

average number of citations despite its high publication count, indicating a need to enhance the depth of related research. Regarding international collaboration in this field, Figure 4 provides insightful data: the UK demonstrates extensive and frequent collaboration with other countries, particularly with the US and Canada.

3.3. Analysis of institutions

One hundred eighty-six papers on the relationship between Vitamin D status and disease in MR were published by 413 institutions. Table 3 reveals that the University of Bristol had the highest number of publications (19 papers, 10.2%), followed by the Karolinska Institute (17 papers, 9.1%), King's College

London (14 papers, 7.6%), McGill University (11 papers, 6.0%), University of Cambridge (10 papers, 5.4%), and University of Copenhagen (10 papers, 5.4%). All of these institutions, except McGill University, are located in Europe. The overlay visualization of institutions indicates that most papers were published after 2020 (Fig. 5). Additionally, the average number of citations per institution helps assess its impact in the field. McGill University had the highest average number of citations at 73.5, followed by King's College London (62.0), the University of Bristol (39.3), the University of Cambridge (29.0), Karolinska Institute (24.8), and the University of Copenhagen (24.2).

3.4. Analysis of keywords

Investigating co-occurring keywords helps researchers understand current research trends and future directions. Figure 6 illustrates high-frequency keywords in the field of Vitamin D status-disease relationships in MR, such as "Mendelian randomization," "Vitamin D," "25-hydroxyVitamin D," "genome-wide association study," "genetics," "parathyroid hormone," "Vitamin D deficiency," "multiple sclerosis," "obesity," and "Type 2 Diabetes," among others. Temporal mapping of keywords indicates that in recent years, the focus has been on exploring the relationship between various Vitamin D levels and cardiovascular diseases, nonalcoholic fatty liver disease, and polycystic ovary syndrome using the MR method. Additionally, cluster analysis categorized these high-frequency keywords into 4 clusters (Fig. 7): Cluster 1 (red nodes, 15 items) focuses on Vitamin D status in various diseases, including keywords such as Vitamin D, heart failure, cancer, Alzheimer disease, COVID-19, depression, and periodontitis. Cluster 2 (green nodes, 12 items) centers on the correlation between Vitamin D and cardiovascular and metabolic diseases in MR, with keywords such as 25-hydroxyVitamin D, myocardial infarction, hypertension, stroke, Type 2 Diabetes, and metabolic syndrome. Cluster 3 (blue nodes, 10 items) examines the association of Vitamin D with inherited diseases in MR, featuring keywords like polycystic ovary syndrome, obesity, psoriasis, osteoporosis, inflammation, and causality. Cluster 4 (yellow node, 8 items) focuses on genetic and epidemiological analyses involving Vitamin D-related genes in MR, including keywords such as genetics, calcium, genetic variants, and epidemiology.

3.5. Analysis of journals

Articles in the field of the relationship between Vitamin D status and disease in MR were published in 99 journals. Figure 8 illustrates the network of journals, where node size indicates the number of published articles. Table 4 lists the top 6 most productive journals: nutrients published the most articles (15 articles, 8.1%), followed by Frontiers in Nutrition (13 articles, 7.0%), International Journal of Epidemiology (7 articles, 3.8%), Scientific Reports (7 articles, 3.8%), Journal of Clinical Endocrinology & Metabolism (6 articles, 3.2%), and PLoS Medicine (5 articles, 2.7%). It is notable that all the aforementioned high-yield journals, except Frontiers in Nutrition (Q2), were classified as Q1 (JCR Partition). Frontiers in Nutrition has the lowest average citation rate for published literature at 3.5. Interestingly, PLoS Medicine, despite publishing the fewest articles, has the highest average citation rate at 110.2.

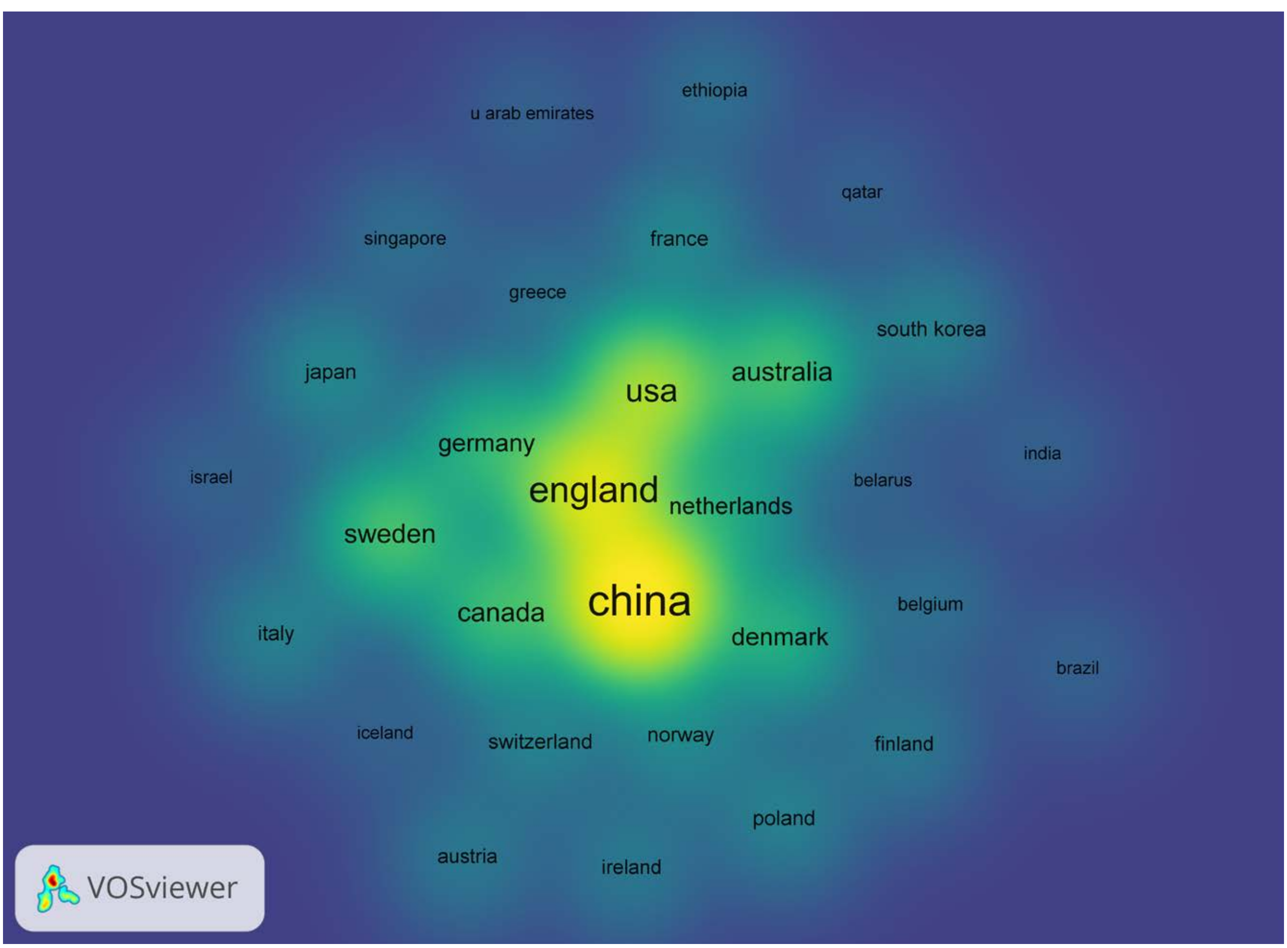

Figure 3. Density visualization of the distribution of all documents across countries. (Larger and brighter regions indicate the greatest number of publications in the field of Mendelian randomization of Vitamin D status in relation to disease from a specific country).

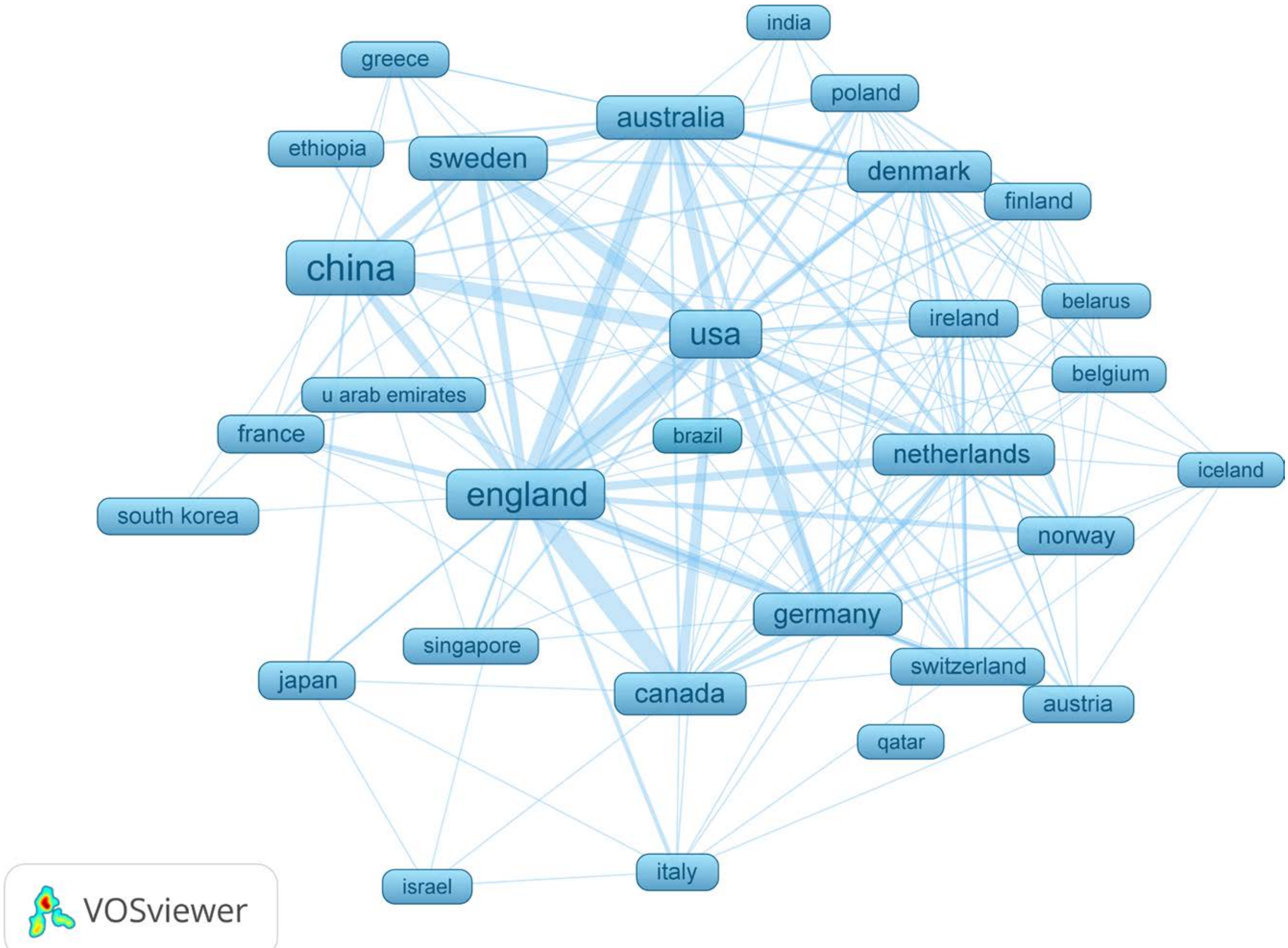

Figure 4. Visualization of Cooperation between countries. (The map square represents countries, and the lines connecting the squares represent collaborative relationships. The thicker the line width, the more the national collaborations).

Table 2

The top 6 countries contributed to research publications in the field of Mendelian randomization of Vitamin D status in relation to disease.

Rank	Country	Publications	Percentage	Average citation
1	China	94	50.5	7.16
2	England	57	30.6	31
3	United States	39	21.0	28.8
4	Sweden	20	10.8	22.2
5	Australia	19	10.2	32.4
6	Canada	18	9.7	53.9

3.6. Analysis of authors

A total of 1122 authors contributed to the 186 selected papers. Table 5 lists the 6 most productive authors: J Brent Richards (n = 12), Susanna C Larsson (n = 10), Elina Hyppönen (n = 8), Despoina Manousaki (n = 8), Shoaib Afzal (n = 6), and Karl Michaëlsson (n = 6). Furthermore, in conjunction with the total link strengths shown in Table 5, Figure 9 shows a closer collaboration between J Brent Richards and Despoina Manousaki, which is shown in an article entitled "Vitamin D levels and risk of Type 1 Diabetes: A Mendelian randomization study" can be observed. Similarly, Susanna C Larsson and Karl Michaëlsson have shown a productive collaboration, exemplified by their joint work titled "Serum 25-hydroxyVitamin D Concentrations and Major Depression: A Mendelian Randomization Study."

Table 3

The top 6 most productive institutions in the field of Mendelian randomization of Vitamin D status in relation to disease.

Rank	Institutions	Country	Publications	Percentage	Average citation
1	University of Bristol	England	19	10.2	39.3
2	Karolinska Institute	Sweden	17	9.1	24.8
3	King's College London	England	14	7.6	62.0
4	McGill University	Canada	11	6.0	73.5
5	University of Cambridge	England	10	5.4	29.0
6	University of Copenhagen	Denmark	10	5.4	24.2

3.7. Analysis of co-cited references

Figure 10 displays a visualization of the network of co-cited references generated with VOSviewer. Out of 5109 cited references, those with a minimum of 25 citations were included in this analysis, totaling 21 references. Additionally, the network visualization of the co-occurrence analysis reveals that these references are primarily divided into 3 clusters: the blue cluster focuses on literature about the theoretical tools of MR, the green cluster centers on literature related to the genomic analysis of Vitamin

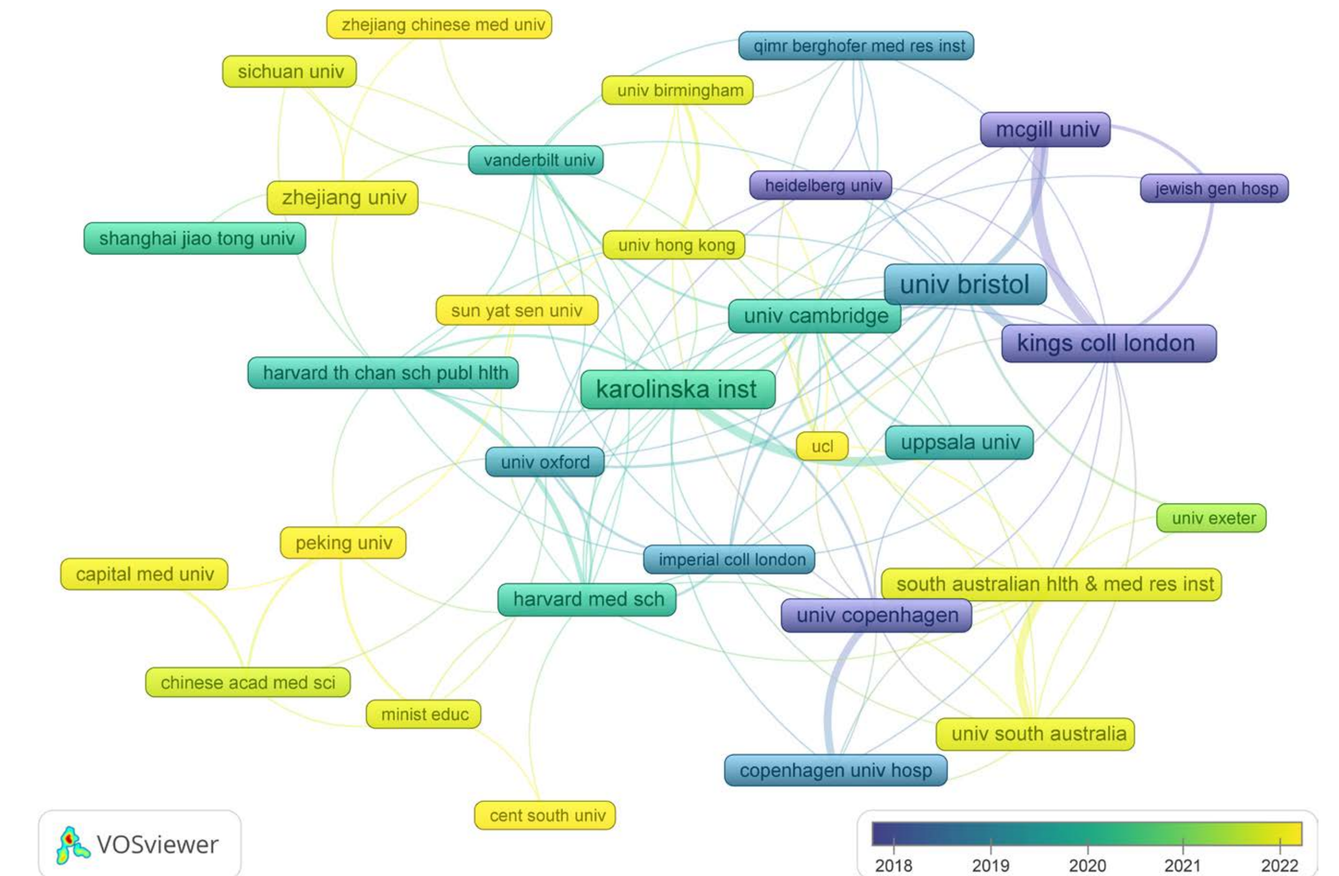

Figure 5. Overly visualization of institutions with different publication periods. (The larger the bubbles are, the greater the number of publications of the institution appearing. In terms of time, the brighter the bubble is, the closer the publications issued by specific institutions are to the present time).

D correlation in MR, and the red cluster's literature primarily examines the role of Vitamin D in various diseases through MR. Table 6 presents the top 6 co-cited references in the field of Vitamin D status and its correlation with disease in MR.

4. Discussion

4.1. Current research situation

4.1.1. Basic information. This study conducted a bibliometric analysis of 186 publications on Vitamin D status in MR concerning disease from January 2014 to June 2024, utilizing the WoSCC database, VOSviewer software, Microsoft Excel 2021, and Scimago Graphica. To the best of our knowledge, this represents the inaugural bibliometric analysis of MR studies on Vitamin D status in disease contexts. Coupled with the trend in publication output, research on Vitamin D in MR has notably advanced since 2021. It is expected that the number of papers published in this area will continue to increase in the coming years, which may provide more popular research ideas for researchers investigating the role of Vitamin D status in related diseases.

4.1.2. Geographical distribution and collaborative patterns. The country with the most publications is China, followed by the United Kingdom and the United States, which have contributed a lot to this field. Regarding the average number of citations of articles, the best performer is Canada, whereas China leaves much to be desired in this respect. Regarding national collaborations, according to the visualization of the VOSviewer software, there are more frequent collaborations between the United Kingdom and the United States. For example, a study by Luke C Pilling (UK) and George A Kuchel (USA) found that genetically down-regulated serum 25(OH)D levels were associated with an increased risk of incident hospital-diagnosed delirium in older adults.[19] The neuroprotective effects of Vitamin D, which shield neurons from oxidative stress and are essential for their growth and survival, are considered to be the potential underlying mechanisms.[20] Furthermore, Adil Harroud (USA) and George Davey Smith (UK) coauthored an article entitled "The relative contributions of obesity, Vitamin D, leptin, and adiponectin to multiple sclerosis risk: A Mendelian randomization mediation analysis."[21] They found that Vitamin D supplementation could only provide a moderate alleviation of the impact of obesity on multiple sclerosis. This is because, although a genetic predisposition to a higher body mass index (BMI) was associated with an increased risk of multiple sclerosis, only a small fraction of this risk was mediated by reduced Vitamin D levels. Therefore, for the prevention of multiple sclerosis, the focus should be on controlling BMI rather than on Vitamin D supplementation. It is worth noting that 5 of the top 6 highly productive institutions are from Europe, suggesting that the contribution of relevant European institutions is important in this area.

4.1.3. Journal and author landscape. Academic journals serve as significant sources of cutting-edge knowledge in specific disciplines and as platforms for researchers to publish their findings. Based on our co-occurrence analysis of published journals, a total of 99 journals have published articles on Vitamin D status and disease in MR. It is worth noting that the top 6 most productive journals with the highest number of articles were Nutrients, followed by Frontiers in Nutrition, 2 journals that deal with human nutritional health and

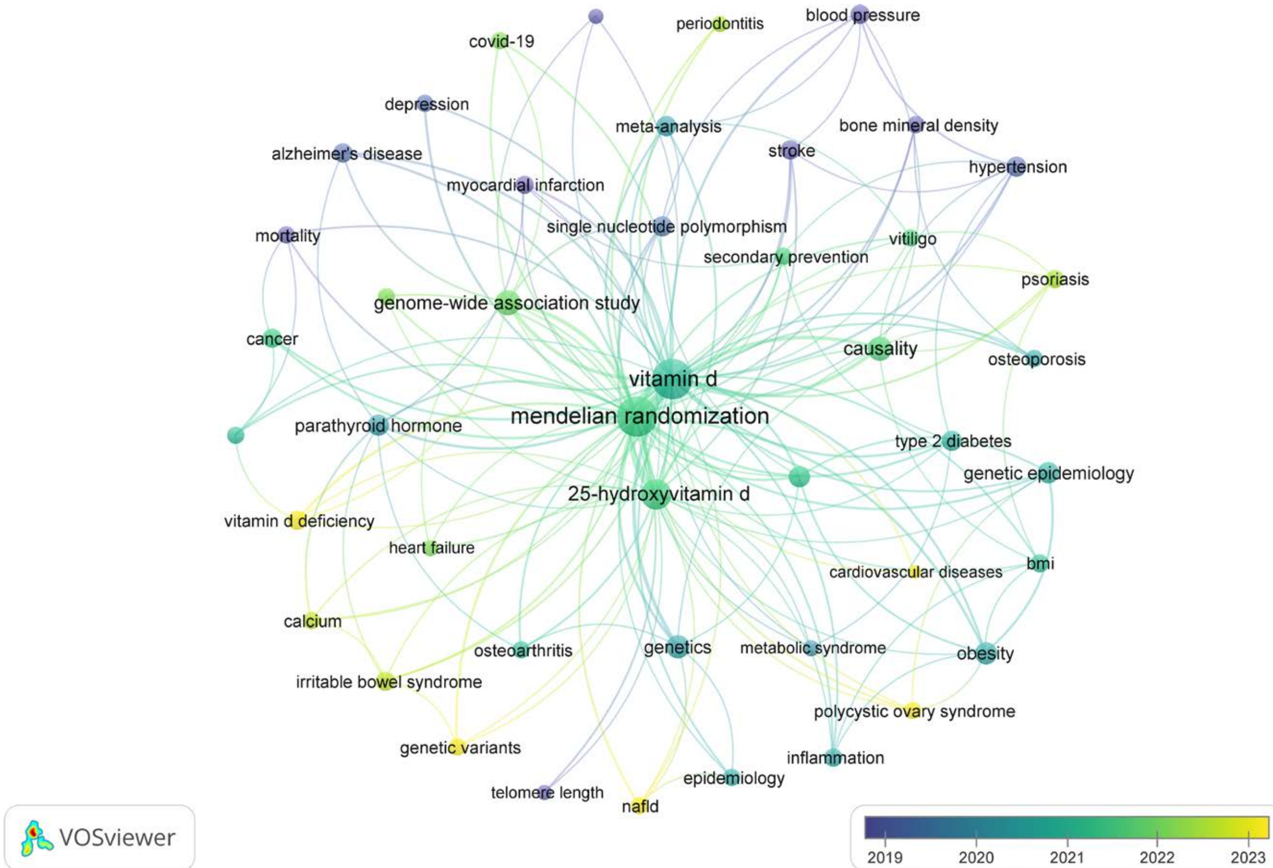

Figure 6. Overly visualization of co-occurrence keywords with different publication periods. (The larger the bubbles are, the greater the number of publications of the institution appearing. In terms of time, the brighter the bubble is, the closer the publications issued related to that keyword are to the present time).

nutrition-related diseases, which fit the theme of Vitamin D. Three other journals (International Journal of Epidemiology, Scientific Reports, and PLoS Medicine) are generalist journals that cover the medical field and research in multiple disease categories, and journal articles demonstrate the diversity of research related to Vitamin D in humans, encompassing topics such as C-reactive protein,[22] ovarian cancer,[23] COVID-19,[24,25] schizophrenia,[26] and others. Furthermore, the Journal of Clinical Endocrinology & Metabolism focuses on endocrine and metabolic diseases, indicating a significant research interest in the correlation between Vitamin D and metabolic diseases in MR.[27–29] Regarding authors, J Brent Richards is the author with the highest number of publications, and surprisingly, most of her articles are dedicated to the neurological field of the brain, investigating the relationship between Vitamin D concentration levels and neurological disorders such as Alzheimer disease,[30] multiple sclerosis,[31] and Parkinson disease.[32] Susanna C Larsson, the second-highest published author, has focused her research on the association between Vitamin D and metabolic diseases.[33–35]

4.2. Research hotspots and trends

4.2.1. Association between metabolic diseases and Vitamin D. Keyword co-occurrence analysis assists researchers in identifying current research hotspots and future trends more effectively. Among frequently co-occurring keywords, "obesity" and "Type 2 Diabetes" emerge as significant themes, which are research hotspots in the study of Vitamin D using MR. Previous MR studies have demonstrated that there is minimal association between genetically determined 25(OH)D levels and weight gain.[36] However, Vitamin D supplementation may still be necessary for individuals with overweight or obesity. Karani S Vimaleswaran and colleagues, by employing a bidirectional MR approach to analyze the large-sample size and the individual level population-based data from North America and Europe, found that a higher BMI could lead to Vitamin D deficiency.[37] Subsequently, the research team of Ying Yue Huang, through MR analysis of data from the Guangzhou Biobank Cohort Study, further corroborated this conclusion and provided additional evidence from the Asian region.[38] The reasons for the lower Vitamin D levels among people with a high BMI are still a matter of debate. Several hypotheses have been proposed to elucidate the underlying mechanisms. For instance, fat-soluble Vitamin D can be sequestered in adipose tissue, reducing its availability in circulation. The larger body volume in obesity may lead to a dilution effect, which lowers the concentration of Vitamin D in the blood.[39] In addition, reductions in hepatic 25-hydroxylase enzyme activity and changes in parathyroid hormone metabolism caused by obesity can also affect Vitamin D levels.[40] Further investigation is warranted in future studies to verify these assumptions. Utilizing MR to explore the association between Vitamin D and Type 2 Diabetes has emerged as a popular research direction. Previous epidemiological studies have found inverse associations between Vitamin D and Type 2 Diabetes.[41] The MR study conducted by Jing Xiao et al corroborated this view, as they identified a risk effect of lower serum 25(OH)D concentrations on the development of Type 2 Diabetes.[42] Additionally, Costan G Magnussen et al demonstrated that increasing and maintaining serum 25(OH)D levels during childhood and adolescence reduces the risk of developing Type 2 Diabetes mellitus in adulthood.[43] Previous studies have demonstrated the presence

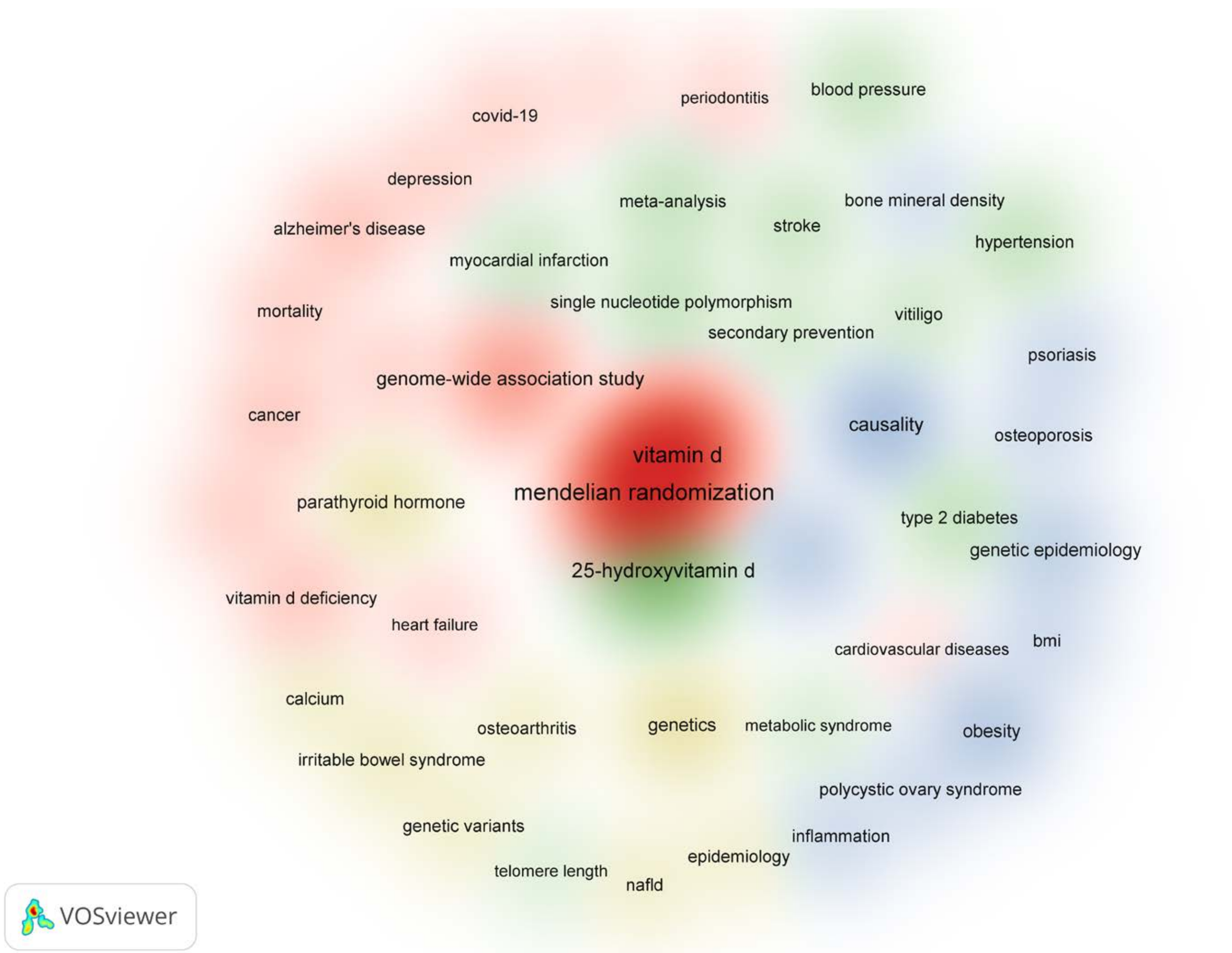

Figure 7. Visualization of co-occurrence keywords. (The larger the bubbles are, the higher the probability of the keyword appearing. The different colors of the bubbles represent different clusters, implying that the keyword represented by the same color of the bubble has a stronger correlation).

of Vitamin D-related receptors in pancreatic β-cells. Vitamin D deficiency not only leads to the closure of calcium channels and subsequent reductions in insulin synthesis and secretion but also impairs the phosphorylation of insulin receptor substrates, thereby increasing insulin resistance.[44–47] Moreover, high concentrations of 25(OH)D may reduce the risk of Type 2 Diabetes by modulating immune function and attenuating inflammatory processes.[48] These integrated mechanisms may collectively contribute to the inverse associations between Vitamin D and Type 2 Diabetes.

4.2.2. Association between cardiovascular diseases and Vitamin D.

Cardiovascular-related diseases were prominent in the keyword clustering analysis, representing another research hotspot in Vitamin D studies using MR. Zhishuai Zhang team conducted a MR study to explore the causal relationship between Vitamin D levels and various cardiovascular diseases.[49] Their findings revealed that Vitamin D levels are causally associated with a reduced risk of angina pectoris and coronary heart disease. This is attributed to Vitamin D's ability to enhance endothelial function and counteract inflammation and oxidative stress, thereby preventing the development of coronary atherosclerosis.[50,51] Furthermore, Vitamin D can lower tissue factor levels, downregulate the pro-thrombotic plasminogen activator inhibitor-1 and thrombospondin-1 mRNA expression, and upregulate thrombomodulin, thus exerting an antithrombotic effect.[52] A large cohort study involving over 1400 patients undergoing coronary angiography also arrived at a similar conclusion, showing that lower circulating 25(OH) D levels were independently associated with the prevalence and severity of coronary artery disease.[53] Notably, there are 2 MR studies that have both demonstrated a potential inverse association between elevated 25(OH)D levels and the risk of heart failure,[12,54] which is consistent with the findings of a previous study.[55] Several potential mechanisms could explain this process. Vitamin D can disrupt calcium ion handling in cardiomyocytes, leading to calcium overload and impaired cardiac contraction and relaxation. Moreover, it may cause inflammation, activate the renin-angiotensin system, and lead to endothelial dysfunction. These factors can contribute to fibrosis, cardiomyocyte hypertrophy, and ultimately heart failure.[56] In addition, hypertension has long been a subject of concern. Karani S Vimaleswaran and colleagues utilized MR to elucidate the relationship between hypertension and Vitamin D status. Their study provides evidence for a causal effect of low Vitamin D status on increasing blood pressure and risk of hypertension.[57] Vitamin D deficiency may lead to increased renin production, activating the renin–angiotensin system and causing vasoconstriction and sodium retention, which in turn raises blood pressure. Additionally, Vitamin D plays a role in maintaining endothelial function and reducing inflammation, and its deficiency may impair these processes, further contributing to the development of hypertension.[58,59] However, the MR study conducted by Lin Jiang et al failed to establish a causal relationship between serum

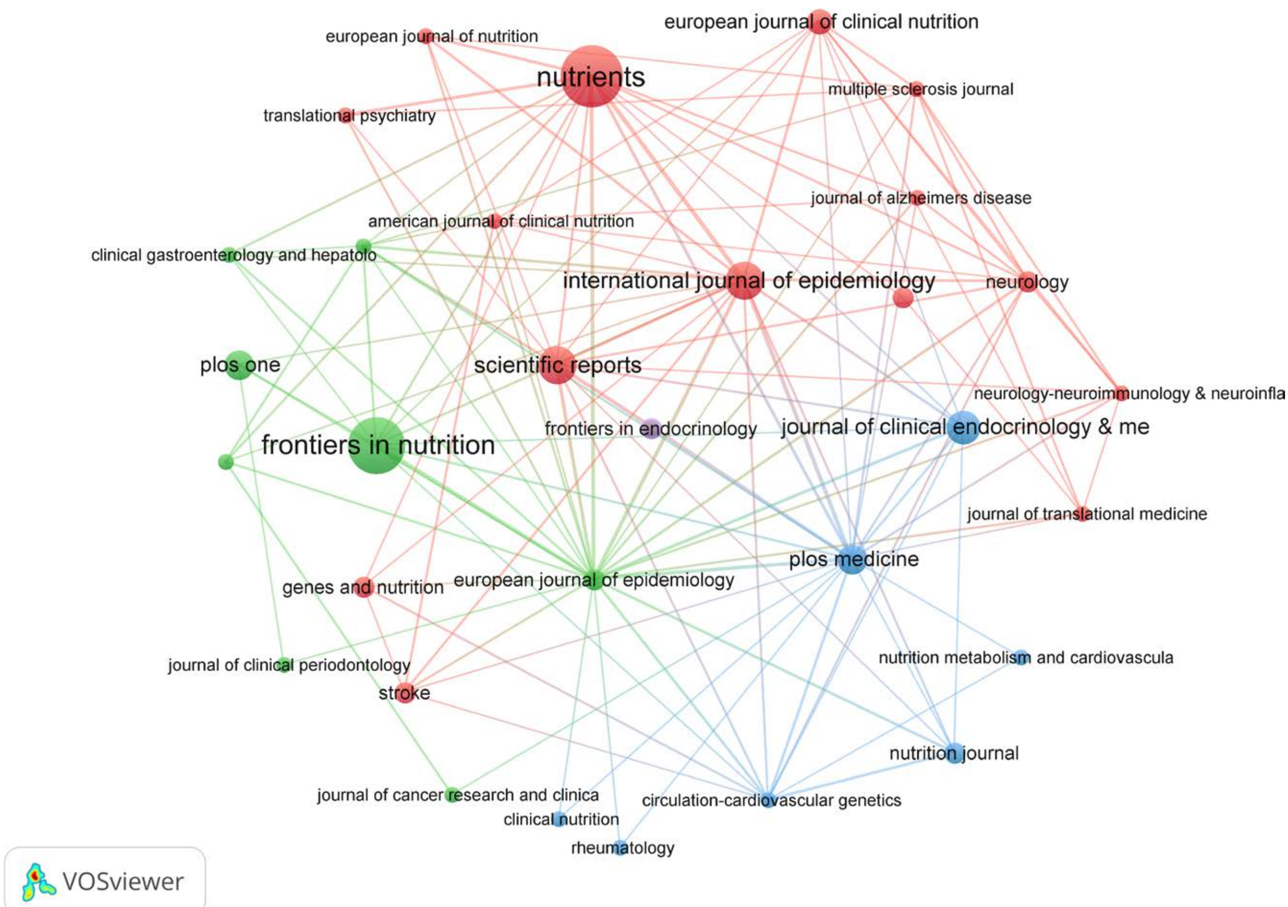

Figure 8. Visualization of published journals. (A larger square frame indicates that the greatest number of publications were published by this journal).

Table 4

The top 6 productive journals in the field of Mendelian randomization of Vitamin D status in relation to disease.

Rank	Journal	Documents	Percentage	Average citation	IF (2024)	JCR (2024)
1	Nutrients	15	8.1	12.5	4.8	Q1
2	Frontiers in Nutrition	13	7.0	3.5	4.0	Q2
3	International Journal of Epidemiology	7	3.8	47.6	6.4	Q1
4	Scientific Reports	7	3.8	17.9	3.8	Q1
5	Journal of Clinical Endocrinology & Metabolism	6	3.2	13.2	5.0	Q1
6	PLoS Medicine	5	2.7	110.2	10.5	Q1

Vitamin D levels and blood pressure or hypertension risk in the general population.[60] The discrepancy between these 2 MR studies on hypertension could be due to a combination of factors such as sample size, confounding factors and study population characteristics. Further research is needed to clarify the reasons for the inconsistent findings and to better understand the causal relationship between the genetic variants and hypertension. It is worth noting that several MR studies have reported null findings when exploring the relationship between Vitamin D levels and cardiovascular disease, such as heart attack, atrial fibrillation, and the right ventricular structure.[49,61,62] Further investigation through larger-sample MR analysis is needed in the future to verify whether Vitamin D supplementation can bring clinical benefits to cardiovascular-related diseases, or large-scale randomized controlled studies should be conducted to establish this.

4.2.3. Association between other diseases and Vitamin D. Based on the temporal mapping of keywords, in recent years, there has been a growing number of MR studies investigating the associations between Vitamin D and a more diverse range of diseases. For instance, the MR study conducted by Bingrui Gao et al indicated that genetically determined lower serum Vitamin D levels are associated with an increased risk of developing polycystic ovary syndrome.[13] This process may be related to Vitamin D's regulation of testosterone levels. According to previous research findings, serum Vitamin D can enhance the activity of aromatase in the ovaries, thereby promoting the conversion of androgens to estrogens. This ultimately leads to a reduction in testosterone production and inhibits the occurrence and progression of polycystic ovary syndrome.[63] Yunqing Ren and colleagues investigated the relationship between Vitamin D and psoriasis, revealing that elevated levels of Vitamin D could confer protection against the development of psoriasis.[64] This is attributed to the widespread presence of Vitamin D receptors in keratinocytes, dendritic cells, macrophages, and T cells. The active form of Vitamin D interacts with these receptors within the immune cells, thereby promoting antimicrobial or antiviral innate responses and attenuating adaptive immunity.[65] Furthermore, psychiatric diseases are also one of the hot topics of research at present. Anwar Mulugeta et al found that depression leads to a decrease in the concentration of 25(OH)D,[66] a finding that is consistent with the results of a previous clinical trial.[67] Depression is often associated with fatigue, isolation, and a sedentary lifestyle, which may lead to increased indoor time and reduced sunlight exposure. Poor dietary choices or decreased appetite can decrease Vitamin D intake from food, which has a causal impact on lowering the concentration of 25(OH)D. Vitamin D levels, of course, have also been associated with other diseases, such as glioma,[68] nonalcoholic fatty liver disease,[35] irritable bowel syndrome,[69] systemic lupus erythematosus,[70] and so on. Table 7 shows the correlation between Vitamin D and hotspot diseases and the literature information. In summary, current research focuses on using MR methods to explore the associations between Vitamin D status and metabolic, cardiovascular, immune skin, psychiatric and neurological diseases. Furthermore, future trends in the field involve using MR methods to investigate additional forms of Vitamin D associations in newly identified diseases related to the aforementioned categories.

Table 5

The 6 high-yield authors in the field of Mendelian randomization of Vitamin D status in relation to disease.

Rank	Author	Publications	Average citation	Total link strength	Country
1	J Brent Richards	12	69.8	35	Canada
2	Susanna C Larsson	10	21.0	18	Sweden
3	Elina Hyppönen	8	32.3	14	Australia
4	Despoina Manousaki	8	37.5	22	Canada
5	Shoaib Afzal	6	30.3	9	Denmark
6	Karl Michaëls-son	6	26.1	15	Sweden

5. Strengths and limitations

Overall, this study has several unique advantages. First, this study employs bibliometric and visual analysis methods to comprehensively summarize the knowledge structure and research frontiers regarding the relationship between Vitamin D status and disease in MR. Second, the results of the present study convey that the application of MR methods to explore the genetic correlations that exist between Vitamin D and a number of human-related disorders has developed into a current research interest. Furthermore, in the future, large-sample, multicenter research will contribute to highlighting the significance of MR, and help shape the design of effective diseases intervention strategies in line with those findings.

This study also has several limitations. Firstly, like previous bibliometric analyses, some relevant literature was unavoidably omitted because the data were exclusively

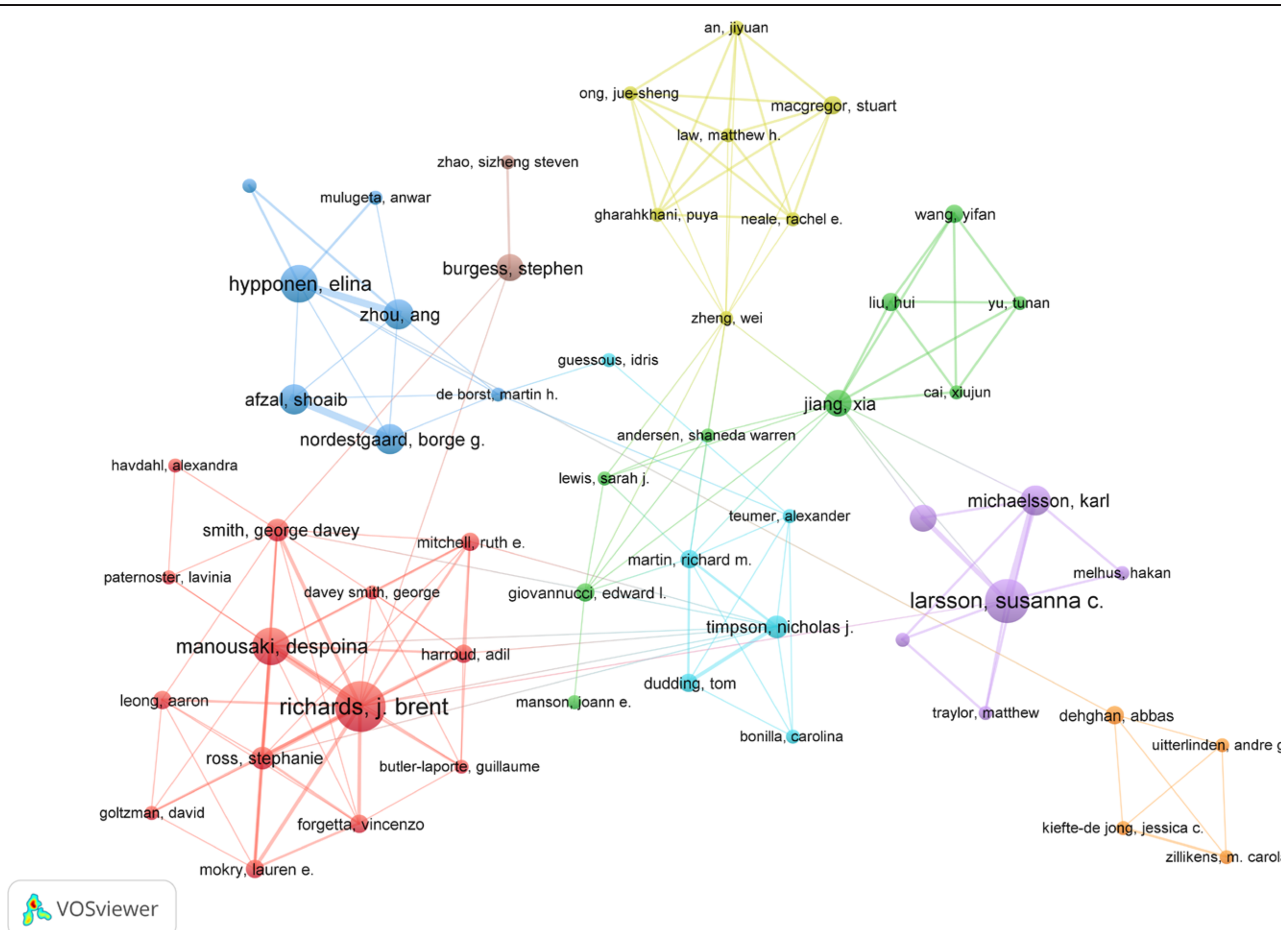

Figure 9. Cooperation network of productive authors. (The map bubbles represent authors, and the lines connecting the bubbles represent collaborative relationships. The larger the bubble area, the greater the number of publications).

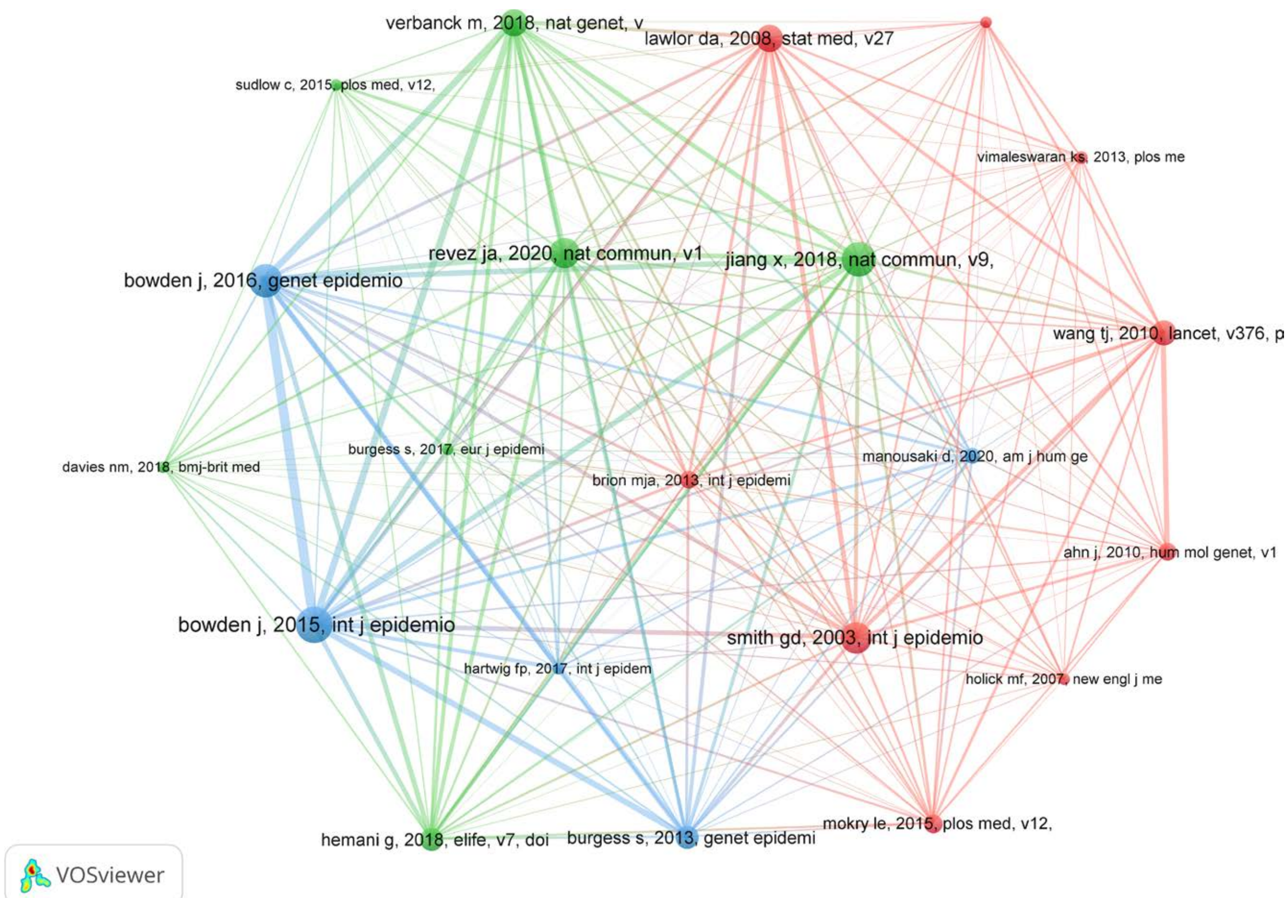

Figure 10. Visualization of co-cited references. (The larger the bubble, the more the literature is likely to be co-cited. The different colors of the bubbles represent different clusters. Differences in the topics covered by these co-cited references are indicated by different clusters).

sourced from the WoSCC database. Secondly, the inclusion criteria were limited to English-language papers, potentially overlooking contributions in other languages. Nevertheless, we maintain that despite these limitations, the findings of this scientific study accurately reflect the general state of research and trends in the field, given the authority of the WoSCC database.

6. Conclusion

We systematically analyzed studies of Vitamin D in MR through bibliometrics analysis, which can provide a comprehensive guide for scholars concerned with relevant research. The number of publications in this field has notably increased since 2020, underscoring the growing interest in research related to Vitamin D status and disease. China and the UK are the most active countries involved, with particularly close collaboration observed between the UK and the US. The current research focuses on using MR methods to explore the associations between Vitamin D status and metabolic, cardiovascular, immune skin, psychiatric and neurological diseases. The related research in this field will continue to increase in the next few years, which is a promising research prospect in this field.

Author contributions

Conceptualization: Tai-Long Lv, Zhen-Hai Sun.
Data curation: Tai-Long Lv.
Formal analysis: Wen-Wen Li.
Funding acquisition: Shu-Di Li, Yun-Xiao Zhang.
Investigation: Hui-Dan Xie.
Methodology: Meng-He Zhang.
Project administration: Yao-Yao Zuo, Shou-Qiang Chen.
Supervision: Zhen-Hai Sun.
Writing – original draft: Tai-Long Lv.
Writing – review & editing: Tai-Long Lv.

Table 6

The top 6 co-cited references in the field of Mendelian randomization of Vitamin D status in relation to disease.

Rank	Author	Title	Year	Journal	Citations
1	Jack Bowden	Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression	2015	International Journal of Epidemiology	80
2	Xia Jiang	Genome-wide association study in 79,366 European-ancestry individuals informs the genetic architecture of 25-hydroxyVitamin D levels	2018	Nature Communications	75
3	Jack Bowden	Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator	2016	Genetic Epidemiology	73
4	George Davey Smith	"Mendelian randomization": can genetic epidemiology contribute to understanding environmental determinants of disease?	2003	International Journal of Epidemiology	68
5	Joana A Revez	Genome-wide association study identifies 143 loci associated with 25-hydroxyVitamin D concentration	2020	Nature Communications	67
6	Marie Verbanck	Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases	2018	Nature Genetics	60

Table 7

The correlation between Vitamin D and hotspot diseases in Mendelian randomization and the literature information.

Disease	Year	Authors	Journal	Conclusion	Reference number
Delirium	2020	Luke C Pilling et al.	Journal of the American Geriatrics Society	The Vitamin D deficiency and insufficient levels predicted increased risks of incident hospital-diagnosed delirium.	19
Multiple sclerosis	2021	Adil Harroud et al.	Multiple Sclerosis Journal	The higher 25(OH)D levels reduced odds of multiple sclerosis.	21
Weight change	2022	Pollyanna Patriota et al.	International Journal of Molecular Sciences	There is little association between genetically determined Vitamin D levels and weight or waist gain.	36
Obesity	2013	Karani S Vimaleswaran et al.	PLoS Medicine	The higher BMI leads to lower 25(OH)D, while any effects of lower 25(OH)D increasing body mass index are likely to be small.	37
Obesity	2023	Ying Yue Huang et al.	European Journal of Clinical Nutrition	The higher body mass index causes Vitamin D deficiency.	38
Type 2 Diabetes	2021	Jing Xiao et al.	BMC Geriatrics	The serum 25(OH) D concentration was inversely associated with Type 2 Diabetes risk in middle-aged and elderly participants.	42
Coronary heart disease	2023	Zhishuai Zhang et al.	Heliyon	The higher Vitamin D level cause a lower risk of coronary heart disease.	49
Angina pectoris	2023	Zhishuai Zhang et al.	Heliyon	The higher Vitamin D level cause a lower risk of angina pectoris.	49
Heart failure	2022	Ning Gao et al.	Frontiers in Nutrition	There is inverse association between elevated 25(OH)D levels and the risk of heart failure.	54
Heart failure	2022	Qiang Luo et al.	Nutrition Metabolism and Cardiovascular Diseases	There is inverse association between elevated 25(OH)D levels and the risk of heart failure.	12
Hypertension	2014	Karani S Vimaleswaran et al.	Lancet Diabetes & Endocrinology	There is a causal effect of low Vitamin D status on increasing blood pressure and risk of hypertension.	57
Hypertension	2024	Lin Jiang et al.	Scientific Reports	There is no causal relationship between serum Vitamin D levels and blood pressure or hypertension risk in the general population.	60
Atrial fibrillation	2022	Nan Zhang et al.	Frontiers in Nutrition	There is no causal relationship between Vitamin D levels and atrial fibrillation.	61
Heart attacks	2023	Zhishuai Zhang et al.	Heliyon	There is no causal relationship between Vitamin D levels and heart attacks.	49
Right ventricular structure	2024	Limeng Ning et al.	Nutrition Metabolism and Cardiovascular diseases	There is no causal association between Vitamin D levels and the structure and function of the right ventricle.	62
Polycystic ovary syndrome	2024	Bingrui Gao et al.	Journal of Ovarian Research	The lower serum Vitamin D level cause a higher risk of developing polycystic ovary syndrome.	13
Psoriasis	2023	Yunqing Ren et al.	Nutrients	The higher serum Vitamin D level protected individuals from developing psoriasis.	64
Depression	2020	Anwar Mulugeta et al.	Nutrients	Depression leads to lower 25(OH)D concentrations.	66
Glioma	2018	Hannah Takahashi et al.	Scientific Reports	There is no causal relationship between 25(OH)D levels and all forms of glioma risk.	68
Nonalcoholic fatty liver disease	2023	Shuai Yuan et al.	Clinical Gastroenterology and Hepatology	The serum 25(OH) D concentration was inversely associated with nonalcoholic fatty liver disease risk.	35
Irritable bowel syndrome	2023	Senbao Xu et al.	Genes and Nutrition	There is negative causal relationship between 25(OH) D and irritable bowel syndrome.	69
Systemic lupus erythematosus	2023	Sizheng Steven Zhao et al.	Seminars in Arthritis and Rheumatism	There is negative causal relationship between 25(OH) D and Systemic lupus erythematosus.	70

BMI = body mass index, 25(OH)D = 25-hydroxyVitamin D.

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