SCIENTIFIC Publishing Limited

**Trends in Immunotherapy**

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*Review*

# The Umbrella Review of VDR Gene Polymorphism and the Risk of Diabetes and Possible Implications in Immunotherapy

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**Received:** 18 March 2025; **Revised:** 6 May 2025; **Accepted:** 5 June 2025; **Published:** 26 January 2026

**Abstract:** Systematic reviews and meta-analyses investigated VDR gene polymorphism correlations with T1D and T2D outcomes. We reviewed and meta-analyzed all VDR gene polymorphism research, including clinical outcome case-control studies. We conducted a comprehensive review using systematic data analysis to evaluate the association between VDR gene polymorphism and the risk of diabetes. According to the predefined search strategy and selection criteria, the article reporting the correlations of *FokI* polymorphisms and the risk of T1D included 40 papers (5,406 cases and 7,507 controls). Forty-three papers (10,252 cases and 9466 controls) focused on the associations between the *FokI* polymorphisms and T2D risk. The articles evaluated 10,252 cases and 9466 controls. Six meta-analyses linked the *FokI* gene polymorphism to T1D and T2D. Summaries were nominally significant in 50% of observational meta-analyses. We demonstrated no association between VDR gene polymorphism and T1D risk across different ethnicities. T2D risk was also highly connected to the *FokI* polymorphism in Asian ethnicity. Gene-environment interactions must be investigated to understand these associations. The *FokI* polymorphism in the VDR gene has been extensively investigated, but more research is needed to know how VDR SNPs cause DM. Diabetes risk is linked to VDR gene polymorphism in this study. Diabetes risk is linked to the VDR gene polymorphism in this study. More research and well-planned studies are necessary for certainty.

**Keywords:** Diabetes; Vitamin D Receptor; Polymorphism; Umbrella Review

## 1. Introduction

Diabetes mellitus (DM), a prevalent chronic condition, can develop serious vascular complications that cause significant injury and death. Type 1 diabetes (T1D) is characterized by the immune system attacking and destroying the pancreatic beta cells. The primary source of this illness is T cells, which account for just 5% to 10% of diabetes cases worldwide [1]. Type 2 diabetes (T2D), which affects 90–95% of diabetics, is caused by inadequate insulin production in response to insulin resistance [2]. Geographic location, body mass index, dietary habits, and physical activity are among environmental factors that can influence both types of diabetes [3–5]. However, genetic

predispositions significantly impact both forms of DM [6,7].

Shreds of evidence, using vitamin D (VD) supplements during early childhood, especially at high dosages, may be associated with a diminished risk of T1D or T2D [8,9]. Any hereditary mutation may affect VD diffusion across the membrane or VD receptor (VDR) functional ability, which leads to impacts on the development of T2D directly [10,11]. This is due to VD's possible crucial role in the regulation of insulin secretion through the management of calcium concentration and other activities. VD might also activate PPAR-ά, a transcriptional factor, which expands muscle and adipose tissues' insulin sensitivity and regulates the insulin receptor gene [12].

VDR, the steroid hormone receptor superfamily member, is a hormone receptor within a cell that binds to the active form of vitamin D and ultimately leads to its function. Hereafter, the gene responsible for VDR may contribute to the onset and DM progression. The active form of VD binds to the VDR. Thus, the VDR gene may play a part in the onset and development of DM, whether T1D or T2D. So far, *FokI* is one of the four most studied single-nucleotide polymorphisms (SNPs) in the gene responsible for VDR [13].

The *FokI* polymorphism is placed at the start codon of the gene responsible for VDR. The presence of the polymorphic form (f) leads to the production of a variation of the protein that consists of 427 amino acids. According to some laboratory studies, a more extended VDR gene, encoded by the F allele, can potentially be less functional [14–16]. Since this variation has not been detected in other *in vitro* experiments, our knowledge of this single-nucleotide polymorphism's (SNPs) available activity is limited [17]. The variant in VDR *FokI* found in exon 2 causes a shift in the starting point of transcription [18]. The VDR protein gains three more amino acids as a result of this. The available information suggests that this VDR polymorphism influences the immunological response. Scientists found that cells without the VDR *FokI* mutation increased rapidly and had a more robust immunological response [19,20].

VD plays an important role in bone health. Since the VDR and its activating enzymes are present on the surface of all white blood cells (B cells, T cells, and antigen-presenting cells), and these immunological cells can synthesize the active metabolite of VD, this vitamin has beneficial effects on improving the mechanisms of the immune system in the body [21]. VD not only modulates immune responses but also plays a role in maintaining the health of the immune system, which is very complex. Generally, suppose the immune system is overstimulated or deviates from its normal function, it may develop a wide range of diseases, from autoimmune diseases such as lupus and multiple sclerosis (MS), to rheumatoid arthritis (RA) [22].

Additionally, the absence of the variant was associated with increased production of IL-12 of p70 protein by triggered monocytes and dendritic cells [23]. In the presence of stimulation, this rise was noted. Previous evidence from research looked into the *FokI* VDR gene polymorphism and T1D, but found no evidence of a link to β-cell autoimmunity [24]. In contrast, individuals with T1D who carried this particular genetic variation had lower levels of residual pancreatic β-cell activity than those without the variant with the same length of disease.

An umbrella assessment of the data through current systematic reviews and meta-analyses (SRMA) was performed to provide an overview of the breadth and validity of the stated correlations of gene polymorphism of VDR with varied outcomes in different types of DM. Our primary objective was to systematically analyse and meta-analyse all available research on VDR gene polymorphism, including case-control studies that looked at the correlations between VDR gene polymorphism and other clinical outcomes.

### 1.1. Immunotherapy and Reversing T1D

Scientists have successfully reversed T1D in genetically susceptible mice by injecting them with an antibody. Just two injections improved the disease without any damage to the immune system [25]. For the first time, a short course of immunotherapy has been shown to improve the symptoms of T1D in people newly diagnosed with the disease. This type of diabetes, also known as insulin-dependent diabetes, is an autoimmune disease in which the body's own immune system's T cells destroy insulin-producing cells (beta cells in the pancreas). The body's immune cells include T cells that maintain immunity against various pathogenic bacteria and viruses. In people with T1D, autoreactive T cells become over-activated and destroy beta cells. Of course, there are methods called depleting antibodies for patients who have recently been diagnosed with T1D, but this method is only useful for a short time. These antibodies are unable to recognize and differentiate normal T cells and autoreactive T cells. Therefore, normal T cells are also eliminated by this method, and the person is exposed to other diseases. With existing methods, the disease can be temporarily affected, but it cannot be cured, the complications caused by the removal of T cells can

be dangerous for the patient. Recent studies used non-depleting antibodies, which specifically bind to CD4 and CD8 that are produced by all T cells, but do not cause T cell destruction and have no effect on the total number of T cells. Scientists are also studying other immunotherapies that they hope will follow the path of teplizumab, giving us a range of different treatments that target different parts of the immune attack in T1D [26]. This includes a drug called Abatacept, which is currently used to treat people with autoimmune diseases such as rheumatoid arthritis [27]. Scientists have previously shown that Abatacept can help people newly diagnosed with T1D preserve their beta cells for longer and reduce the activity of NK immune cells that are responsible for destroying healthy beta cells. However, Abatacept can also reduce levels of helper immune cells, called regulatory T cells, or Tregs. Regulatory T cells patrol the body and give immune signals, or orders, to killer immune cells. If Tregs are too numerous, killer immune cells can go rogue and mistakenly attack self-cells. So Abatacept cannot be as effective as it could be.

### 1.2. Immunotherapy in the Treatment of Diabetic Ulcers

Diabetic ulcers (DUs) are a complex and common problem among people with diabetes. These ulcers, especially in the leg area, are difficult to heal due to reduced blood flow, frequent infections, and the body's inability to repair itself promptly [28]. DUs can lead to serious complications such as amputation and even death. Therefore, the search for more effective and efficient solutions for the treatment of diabetic ulcers is essential. One of these new methods is the use of immunotherapy, which speeds up wound healing by strengthening the body's immune system. Immunotherapy uses substances that boost or regulate the body's immune system and help wounds heal [29]. These substances can include monoclonal antibodies, immune cells such as lymphocytes, and immunotherapy vaccines. By boosting the immune system, the body can better fight infections and heal wounds. The immune system plays a vital role in the wound-healing process. By activating immune cells, inflammation is reduced, and the repair of damaged tissue is accelerated. Consequently, by enhancing these responses, immunotherapy helps diabetic wounds heal faster and more efficiently [30]. Several clinical trials have been conducted on the use of immunotherapy to treat DUs. These trials have shown that immunotherapy can significantly reduce wound healing time and reduce infection rates [31]. For example, one study showed that using monoclonal antibodies in diabetic patients significantly reduced wound size and healing time. Case studies have also shown positive results for immunotherapy in the treatment of diabetic ulcers. For example, a case study conducted on a diabetic patient showed that the use of immune cells by injection led to the complete healing of chronic leg ulcers in a short period [32]. These results indicate the high potential of immunotherapy in the treatment of diabetic ulcers.

### 1.3. Vitamin D and Diabetes

Researchers examined the effects of VD supplementation on the risk of DM. The study included adults with prediabetes and compared the effects of VD on this group. The results showed that over a three-year follow-up period, early diabetes occurred in 22.7% of adults who received VD and 25% of those who received a placebo. These data indicate a 15% reduction in the relative risk of developing diabetes in the group taking VD [33]. There is growing evidence that VD deficiency may be a contributing factor in the development of DM [34]. This evidence suggests that VD treatment can improve glucose tolerance and insulin resistance. Insulin secretion is also affected by VD. Studies have shown that VD supplementation can restore insulin secretion in animals [35]. Researchers have also found an indirect effect of VD on insulin secretion, potentially through the effect of calcium on insulin secretion. VD helps normalize extracellular calcium and ensures the normal flow of calcium across cell membranes. Therefore, low VD may reduce the ability of calcium to affect insulin secretion [36]. These mechanisms suggest that VD may help prevent and manage diabetes by modulating various metabolic and biochemical processes. However, the exact effect of VD on DM requires further research, and it is recommended that this vitamin be taken under the supervision of a physician and at an appropriate dosage.

## 2. Materials and Methods

Umbrella reviews are a comprehensive evaluation that gathers and assesses data from several reviews, covering all outcomes, either clinical or observational, that studied [37]. To gather data about the association between gene polymorphism in VDR and health-related consequences in T1D and T2D, we aimed to gather data from published reviews, regardless of whether they were quantitative syntheses. Due to the significant heterogeneity in

observational research, meta-analysis is frequently not conducted in systematic reviews of such studies [38]. If accessible, we also thoroughly examined the meta-analyses and their potential indications of bias [39,40].

## 2.1. Search Strategy

Two reviewers (FR, TK) independently conducted duplicate searches of selected databases from 1990 to 11 Jan 2025 (last update). We searched major indexing databases, including PubMed, Scopus, ISI Web of Science, Cochrane Library, and CNKI, for relevant systematic reviews and meta-analyses. The searches were limited to studies conducted on humans and published in English. We discussed and settled any differences. Before retrieving papers for full-text review, we reviewed all titles and abstracts of potentially selected articles.

## 2.2. Eligibility Criteria and Critical Appraisal

The umbrella study encompassed clinical outcomes in T1D and T2D, as investigated through reviews. Additionally, it incorporated observational associations between circulating VDR and *FokI* gene polymorphism. We excluded studies that assessed VD condition as a consequence, articles that report the occurrence of deficiency in the VD levels in the population of interest, reviews including observational studies that evaluated nutritional or supplemental VD consumption, and articles that examined genetic variations associated with VD metabolism, such as the other VDR gene polymorphisms. We only included meta-analyses that did not use age or clinical setting as criteria for selecting the populations. Each publication that included meta-analyses of numerous eligible outcomes or types of clinical contexts was evaluated individually. The objective of this extensive evaluation did not encompass assessing individual component research. The original purpose of the meta-analyses and systematic reviews was to incorporate assessments of study quality. To evaluate the quality of the evidence in the selected studies, we employed methodologies thoroughly explained in the data analysis section.

## 2.3. Data Collection

Two investigators (FR and TK) individually retrieved and collected the data. The subsequent data were derived from all potentially pertinent meta-analyses and systematic reviews. The requested information includes the first author's details, publication date, VD biomarker, population, and study result. We derived a concise statement encapsulating the authors' primary findings from each selected study. We obtained additional data from each selected study, including study-detailed estimates, such as risk ratio (RR) as indicated in the published papers, confidence intervals, and the total number of participants from each study.

## 2.4. Risk of Bias Assessment

We used the Newcastle-Ottawa scale to assess the quality of selected studies according to the rules for enhancing the clarity of SRMA of observational studies [41].

## 2.5. Statistical Analysis

We performed an inclusive assessment of the selected reviews. Each systematic review examining the association of *FokI* polymorphism with the risk of both types of DM was categorized into four groups according to the robustness of the evidence: strong correlation, weak correlation, no correlation, or inadequate evidence. We evaluated the agreement of the primary reported findings when multiple systematic reviews were performed on the identical outcome. We have chosen those reviews that fulfill the selection criteria for further analysis. We specifically selected outcomes that fulfilled the following criteria: they displayed the associations in selected and included studies, had minimal variability across the studies, and did not exhibit any signs of low study effects or excessive significance. In addition, we recorded the count of cases that met the identical criteria but had a $p$-value of $\leq 0.001$. This threshold is widely accepted as a more appropriate level of statistical significance to minimise the chances of obtaining false positive results [42,43]. In the end, we employed a specific set of criteria to assess the degree of confidence in the evidence supporting a specific outcome, classifying it as either conclusive, likely, indicative, inconclusive, or unlikely.

## 3. Results

All of the steps in our literature search procedure are illustrated in **Figure 1**.

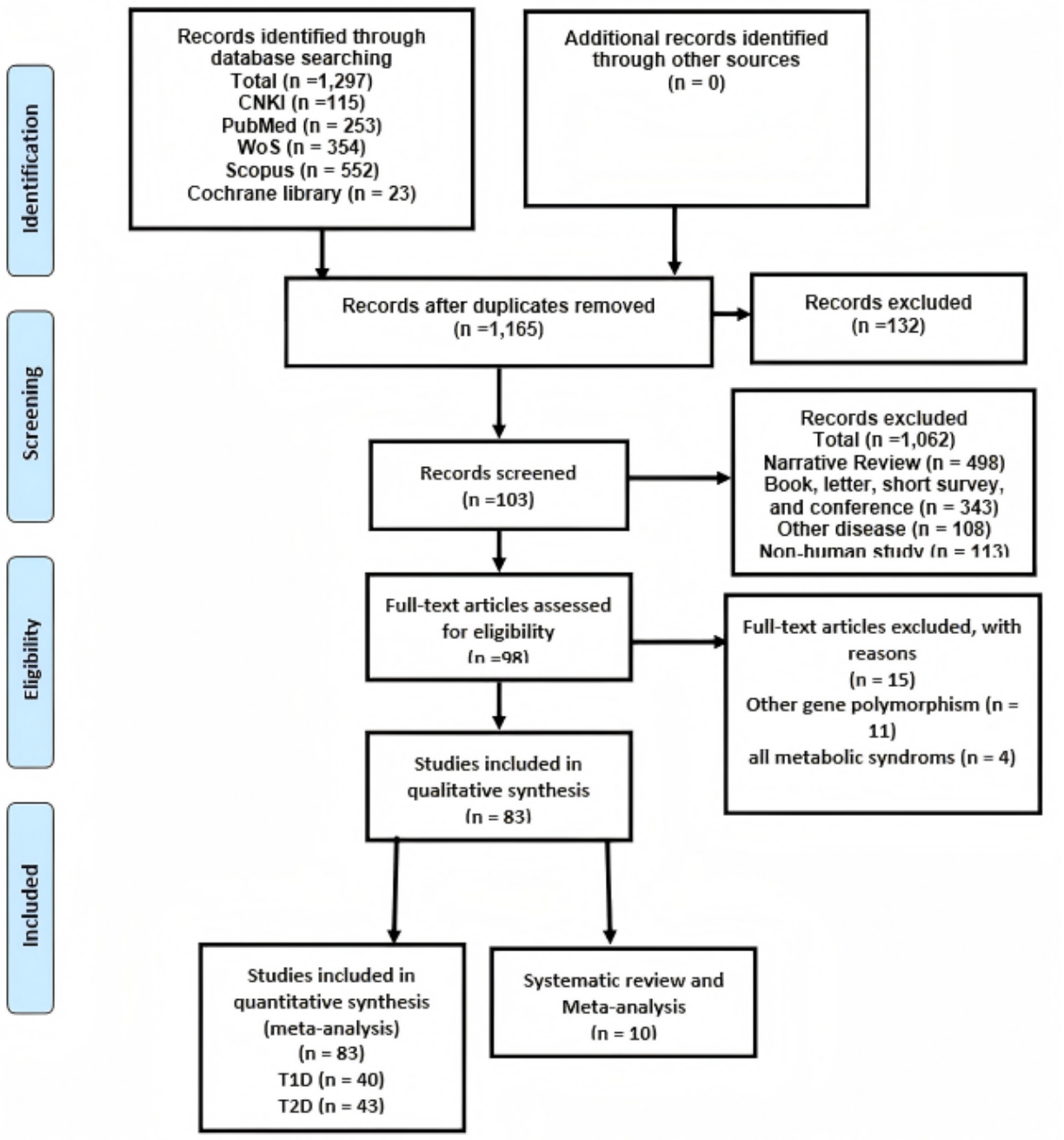


**Figure 1.** Flow-diagram of study selection.

According to the predefined search strategy and selection criteria, the article reporting the correlations of *FokI* polymorphisms and the risk of T1D included 40 papers (5406 cases and 7507 controls) (**Table 1**). Forty-three papers (10,252 cases and 9466 controls) focused on the associations between the *FokI* polymorphisms and T2D risk (**Table 1**). A case-control study design was used in all the included investigations. Every single study was rated as "Low", "Medium," or "High" quality level. The study characteristics are presented in **Table 1**.

**Table 1.** Summary of selected studies related to *FokI* polymorphisms in Type 1 diabetes (T1D) and Type 2 diabetes (T2D).

| Study ID, Country | Ethnicity | Population Case/Control | Age (Case/Control) | Genotyping Method | Findings | Quality Score |
|---|---|---|---|---|---|---|
| | | | T2D | | | |
| Malecki et al. 2003, Poland | European | 308/239 | 59.8 ± 9.2/54.0 ± 15.1 | RFLP-PCR | No association | 7 |
| Shen et al. 2004, China | Asian | 96/52 | 36.0 ± 4.9/ 65.6 ± 10.5 | RFLP-PCR | Significant association | 8 |
| Bid et al. 2009, India | Asian | 100/160 | 49.32 ± 10.97/NR | RFLP-PCR | Significant association | 6 |
| Al-Daghri et al. 2012, Saudi Arebia | Asian | 368/259 | 59.7 ± 8.7/57.9 ± 8.1 | Taq-Man | Significant association | 7 |
| Vedralová et al. 2012, Czech | European | 116/113 | 51.5 ± 8.6/44.1 ± 9.9 | RFLP-PCR | No association | 6 |
| Xia et al. 2014, China | Asian | 97/231 | 67.2 ± 12.44/45.0 ± 7.31 | RFLP-PCR | Significant association | 6 |
| Mackawy et al. 2014, Egypt | African | 130/60 | 47.96 ± 5.61/47.90 ± 7.1 | RFLP-PCR | Significant association | 5 |
| Zhao et al. 2014, China | Asian | 391/400 | 53.37 ± 10.99/46.65 ± 10.78 | Mini-sequencing | Significant association | 7 |
| Abdeltif et al. 2014, Moroco | African | 176/177 | 57.01 ± 11.46/56.94 ± 11.47 | RFLP-PCR | No association | 7 |
| Angel et al. 2015, Chile | American | 160/160 | 69.4 ± 6.9/45.6 ± 7.6 | RFLP-PCR | Significant association | 6 |
| Zhong et al. 2014, China | Asian | 204/116 | 45.6 ± 7.6/58.11 ± 10.7 | RFLP-PCR | Significant association | 6 |
| Sentinelli et al. 2012, Italy | European | 839/949 | 48.1 ± 14.8/47.6 ± 15 | RFLP-PCR | Significant association | 7 |
| Shab-Bidar et al. 2016, Iran | Asian | 358/372 | 45.61 ± 7.60/50.27 ± 7.98 | RFLP-PCR | No association | 7 |
| Mahjoubi et al. 2016, Tunisia | African | 439/302 | 55.96 ± 9.6/49.3 ± 9.63 | RFLP-PCR | No association | 6 |
| Yu et al. 2016, China | Asian | 397/775 | 59.53 ± 11.9 /59.54 ± 11.9 | Mini-sequencing | Significant association | 8 |
| Rahmannezhad et al. 2016, Iran | Asian | 157/157 | 50.27 ± 7.98/49.65 ± 9.78 | RFLP-PC | Significant association | 7 |
| Maia et al. 2016, Brazil | American | 100/100 | 65.7 ± 7.8/65.1 ± 9.8 | Taq-Man | Significant association | 6 |
| Soroush et al. 2017, Iran | Asian | 107/105 | 55.96 ± 7.80/59.7 ± 8.50 | RFLP-PCR | Significant association | 6 |
| Bertoccini et al. 2017, Italy | European | 883/830 | 48.1 ± 14.8/47.6 ± 15 | Taq-Man | No association | 8 |
| Rasheed et al. 2017, Egypt | African | 180/150 | 43.2 ± 6.5/44.3 ± 4.1 | Taq-Man | No association | 6 |
| Xia et al. 2017, China | Asian | 242/100 | 76.8 ± 11.8/75.8 ± 11.2 | RFLP-PCR | Significant association | 6 |
| Angel et al. 2018, Chile | American | 138/172 | 69.4 ± 6.9/65.6 ± 7.6 | RFLP-PCR | Significant association | 6 |
| Dong et al. 2018, China | Asian | 180/96 | 47.59 ± 10.8/45.4 ± 13.6 | Taq-Man | Significant association | 5 |
| Sarma et al. 2018, India | Asian | 40/20 | 51.0 ± 8.2/52.4 ± 6.55 | Taq-Man | Significant association | 7 |
| Saxena et al. 2018, Saudi Arebia | Asian | 440/440 | 48.10 ± 8.2/45.68 ± 9.1 | RFLP-PCR | Significant association | 7 |
| Safar et al. 2018, UAE | Asian | 261/90 | 60.5 ± 11.59/48.21 ± 12.1 | Taq-Man | Significant association | 6 |
| Gnanaprakash et al. 2018, India | Asian | 162/147 | 50.9 ± 8.1/48.8 ± 8.2 | RFLP-PCR | Significant association | 6 |
| Hadi et al. 2018, Iraq | Asian | 94/101 | 47.59 ± 10.8/45.4 ± 13.6 | ARMS-PCR | Significant association | 5 |
| Rodrigues et al. 2019, Brazil | American | 115/69 | 58.2 ± 9.7/49.6 ± 10.7 | Taq-Man | No association | 5 |
| F. ALI and AL-TIMIMI et al. 2019, Iraq | Asian | 96/66 | 45.52 ± 7.61/49.17 ± 6.98 | RFLP-PCR | Significant association | 5 |
| Pinho et al. 2019, Brazil | American | 115/69 | 58.2 ± 9.7/49.6 ± 10.7 | Taq-Man | No association | 5 |
| Ma et al. 2020, China | Asian | 674/521 | 61.9 ± 6.9/62.4 ± 3.3 | RFLP-PCR | Significant association | 8 |
| Gendy et al. 2021, Egypt | African | 50/50 | 51.0 ± 8.2/52.4 ± 6.55 | RFLP-PCR | Significant association | 5 |
| Gusemi et al. 2021, Tunisia | African | 95/153 | 36.49 + 10.87/34.99 + 12.99 | RFLP-PCR | Significant association | 6 |
| Alharbi et al. 2021, Saudi Arebia | Asian | 100/100 | 54.92 ± 6.29/54.48 ± 6.85 | RFLP-PCR | Significant association | 6 |
| Sattar et al. 2021, UK | European | 500/200 | 45.49 ± 8.63/47.16 ± 6.73 | RFLP-PCR | No association | 7 |
| Selvarajan et al. 2021, India | Asian | 200/300 | 45.61 ± 7.60/50.27 ± 7.95 | Taq-Man | Significant association | 6 |
| Memon et al. 2022, Pakistan | Asian | 100/100 | 52.3 ± 9.6/50.11 ± 10.8 | RFLP-PCR | Significant association | 6 |
| Yavuz et al. 2022, Turkey | European | 141/100 | 55.6 ± 8.1/53.5 ± 7.2 | RFLP-PCR | No association | 7 |
| Shafie et al. 2022, Saudi Arebia | Asian | 100/50 | 42.74 ± 6.49/44.44 ± 5.78 | RFLP-PCR | No association | 6 |
| Mohammed et al. 2023a, Egypt | African | 156/145 | 44.5 ± 5.97/49 ± 9.2 | Taq-Man | Significant association | 8 |
| Tarfeen et al. 2023, India | Asian | 100/100 | 51.20 ± 8.79/45.02 ± 11.01 | Taq-Man | Significant association | 7 |
| Mohammed et al. 2023b, Iraq | Asian | 181/181 | 44.51 ± 8.60/46.27 ± 7.93 | RFLP-PCR | No association | 6 |

**Table 1.** *Cont.*

| Study ID, Country | Ethnicity | Population Case/Control | Age (Case/Control) | Genotyping Method | Findings | Quality Score |
|---|---|---|---|---|---|---|
| | | | T1D | | | |
| Hauache et al. 1998, Brazil | American | 78/94 | 23.5 ± 5.5/32.4 ± 6.5 | RFLP-PCR | No association | 5 |
| Ban et al. 2001, Japan | Asian | 78/250 | 26.0 ± 3.7/34.5 ± 6.5 | RFLP-PCR | Significant association | 6 |
| Yokota et al. 2002, Japan | Asian | 108/120 | NR/NR | RFLP-PCR | No association | 5 |
| Guja et al. 2002, Romania | European | 212/544 | 31.6 ± 9.6/32.5 ± 8.7 | SSP-PCR | Significant association | 6 |
| Fassbender et al. 2002, Germany | European | 75/55 | 33.5 ± 10.7/33.5 ± 10.9 | RFLP-PCR | No association | 7 |
| Györffy et al. 2002, Hungary | European | 107/103 | 5.8 ± 3.2/7.9 ± 5.63 | RFLP-PCR | No association | 6 |
| Turpeinen et al. 2003, Finland | European | 1064/2683 | 7.8 ± 4.1/8.9 ± 3.62 | Mini-sequencing | No association | 8 |
| Martí et al. 2004a, Spanish | European | 155/280 | NR/NR | Taq-Man | Significant association | 6 |
| Martí et al. 2004b, Spanish | European | 89/116 | NR/NR | Taq-Man | Significant association | 6 |
| San-Pedro et al. 2004, Spanish | European | 71/116 | 14.5 ± 9.9/NR | RFLP-PCR | No association | 7 |
| Zemunik et al. 2005, Croatia | European | 134/132 | 8.6 ± 4.3/8.2 ± 4.9 | RFLP-PCR | Significant association | 7 |
| Capoluongo et al. 2006, Italy | European | 246/246 | 39.3 ± 11.1/39.6 ± 9.1 | RFLP-PCR | Significant association | 7 |
| Mimbacas et al. 2007, Uruguay | American | 100/45 | NR/NR | RFLP-PCR | No association | 6 |
| Boraska et al. 2008, Croatia | European | 132/120 | 8.86 ± 5.36/8.7 ± 3.62 | RFLP-PCR | Significant association | 5 |
| López et al. 2008, Chile | American | 151/182 | 8.02 ± 4.0/9.20 ± 3.01 | RFLP-PCR | Significant association | 7 |
| Lemos et al. 2008, Portugal | European | 207/249 | 27.5 ± 10.2/36.8 ± 13.8 | RFLP-PCR | No association | 6 |
| Mory et al. 2009, Brazil | American | 189/194 | 17.2 ± 5.4/12.2 ± 1.8 | RFLP-PCR | Significant association | 7 |
| Panierakis et al. 2009, Greece | European | 100/96 | 14.4 ± 10.1/11.01 ± 3.69 | RFLP-PCR | Significant association | 6 |
| Israni et al. 2009, India | Asian | 233/191 | 14.74 ± 7.57/16.89 ± 7.25 | RFLP-PCR | Significant association | 7 |
| Kocabaş et al. 2010, Turkey | European | 90/86 | 11.7 ± 3.82/28.9 ± 5.9 | RFLP-PCR | Significant association | 6 |
| Gogas Yavuz et al. 2011, Turkey | European | 170/134 | 27.6 ± 7.3/26.2 ± 5.3 | RFLP-PCR | No association | 7 |
| Mohammadnejad et al. 2012, Iran | Asian | 87/100 | 27.93 ± 10.86/ 28.58 ± 7.40 | RFLP-PCR | Significant association | 7 |
| Bonakdaran et al. 2012, Iran | Asian | 69/45 | NR/NR | RFLP-PCR | No association | 6 |
| Greer et al. 2012, Australia | Asian | 56/46 | 12.9 ± 4.86/9.1 ± 6.40 | RFLP-PCR | No association | 7 |
| Sahin et al. 2012, Turkey | European | 55/80 | 35.3 ± 10.2/37 ± 13.8 | RFLP-PCR | Significant association | 6 |
| Hamed et al. 2013, Egypt | African | 132/40 | 8.5 ± 3.3/9 ± 1.5 | RFLP-PCR | No association | 6 |
| Abd-Allah et al. 2014, Egypt | African | 120/120 | 11.7 ± 2.8/11.1 ± 2.6 | RFLP-PCR | Significant association | 7 |
| Morán-Auth et al. 2015, Germany | European | 20/23 | 44/35 | Taq-Man | Significant association | 6 |
| Nasreen et al. 2016, Pakistan | Asian | 44/44 | 17.92 ± 2.8/14.81 ± 2.7 | RFLP-PCR | No association | 6 |
| Mory et al. 2009, Brazil | American | 25/155 | 16.8 ± 7.1/17.1 ± 5.0 | RFLP-PCR | Significant association | 7 |
| Mukhtar et al. 2017, Pakistan | Asian | 102/100 | 13.27/13.74 | RFLP-PCR | Significant association | 7 |
| Ali et al. 2018, Saudi Arabia | Asian | 100/102 | 10.33 ± 3.15/35 ± 5.8 | RFLP-PCR | Significant association | 6 |
| Kirac et al. 2018, Turkey | European | 55/40 | 29.8 ± 7.75/28.9 ± 5.29 | RT-PCR | Significant association | 7 |
| Rasoul et al. 2019, Kuwait | Asian | 235/214 | 8.5 ± 5.5/8.9 ± 5.2 | RFLP-PCR | Significant association | 7 |
| Tangjittipokin et al. 2021, Thailand | Asian | 100/100 | 14.5 ± 2.7/14.3 ± 2.7 | RFLP-PCR | Significant association | 7 |
| Khadir et al. 2021, Jordan | Asian | 50/50 | 20 ± 9.4/24.7 ± 6.4 | RFLP-PCR | No association | 7 |
| Eissa et al. 2021, Egypt | African | 180/120 | 12.7/13.1 | RFLP-PCR | Significant association | 6 |
| Ferraz et al. 2022, Brazil | American | 65/83 | 27.28 ± 10.38/38.49 ± 13.55 | Mini-sequencing | Significant association | 6 |
| Thirunavukkarasu et al. 2023, India | Asian | 120/214 | 24.10 ± 10.07/20.55 ± 12.33 | RFLP-PCR | Significant association | 6 |
| Mostafa et al. 2024, Egypt | African | 85/37 | 12.28 ± 3.32/10.86 ± 3.32 | RT-PCR | Significant association | 7 |

Note: RT-PCR, real-time polymerase chain reaction; RFLP -PCR, Restricted fragment length polymorphism- polymerase chain reaction.

Then, we searched all published meta-analyses and compared the ten final selected reviews with our study (**Table 2**).

**Table 2.** Characteristics and details of included studies.

| Study Year (Reference) | Target Gene | Polymorphisms | Total Included Studies /Major Ethnicity | Participants Case/Control | Study Design | Disease T1D | Disease T2D | Outcomes |
|---|---|---|---|---|---|---|---|---|
| Present study | *FokI* | rs10735810 | T1D (40)<br>T2D (43) | 5,406/7,507<br>10,252/9,466 | SR and MA | X | X | Significant associations |
| Zeng et al., 2022 [43] | *FokI* | rs739837 | 9/Asian | 3,423/5,381 | SR and MA | - | X | Significant associations |
| Yu et al., 2022 [44] | *ApaI*<br>*BsmI*<br>*TaqI*<br>*FokI* | rs7975232<br>rs1544410<br>rs731236<br>rs10735810 | 50/ Mix | - | SR | X | - | Significant associations |
| Najjar et al., 2021 [45] | *CYP2R1*<br>*CYP2R1*<br>*DHCR7/NADSYN1*<br>*GC*<br>*CYP24A1*<br>*AMDHD1*<br>*SEC23A* | rs10741657<br>rs117913124<br>rs12785878<br>rs3755967<br>rs17216707<br>rs10745742<br>rs8018720 | 10/European | 20,858/941,736 | SR and MA | X | - | No association |
| Liu et al., 2021 [46] | *ApaI*<br>*BsmI*<br>*TaqI*<br>*FokI* | rs7975232<br>rs1544410<br>rs731236<br>rs10735810 | *ApaI* (19),<br>*BsmI* (37),<br>*TaqI* (24),<br>*FokI* (31), | *ApaI* (2593/3557),<br>*BsmI* (5586/6484),<br>*TaqI* (3221/4027),<br>*FokI* (6525/7464) | SR and MA | - | X | All notable correlations exhibited diminished credibility in terms of favorable outcomes |
| Ran et al., 2021 [47] | *ApaI*<br>*BsmI*<br>*TaqI*<br>*FokI* | rs7975232<br>rs1544410<br>rs731236<br>rs10735810 | - | - | SR and MA | X | - | Protocol, no results |
| Zhai et al., 2020 [48] | *ApaI*<br>*BsmI*<br>*TaqI*<br>*FokI* | rs7975232<br>rs1544410<br>rs731236<br>rs10735810 | 29/15 European<br>9 Asian | 3723/5578 | SR and MA | X | - | Significant associations |
| Yu et al., 2016 [49] | *BsmI*<br>*FokI* | rs1544410<br>rs10735810 | *BsmI* (18),<br>*FokI* (12) | *BsmI* (2,757/3,517),<br>*FokI* (2,218/1,859) | SR and MA | - | X | Significant associations |
| Wang et al., 2014 [50] | Vitamin D binding ptotein | *DBP* | 6/3 European<br>3 Asian | 1191/882 | SR and MA | - | X | Asians were marginally related with T2D susceptibility, but Caucasians were not |
| Tizaoui et al., 2014 [51] | *ApaI*<br>*BsmI*<br>*TaqI*<br>*FokI* | rs7975232<br>rs1544410<br>rs731236<br>rs10735810 | 23/Mixed | - | SR and MA | X | - | Significant associations |
| Wang et al., 2012 [52] | *ApaI*<br>*BsmI*<br>*TaqI*<br>*FokI* | rs7975232<br>rs1544410<br>rs731236<br>rs10735810 | T1D (29)<br>T2D (24) | 22 studies<br>(2,940/4,942<br>for FokI<br>polymorphis) | SR and MA | X | X | In Asians, BsmI polymorphism can raise T1D risk while FokI polymorphism may increase T2D risk |

Note: TID, Type 1 diabetes; SR, Systematic Review; MA, Meta-analysis; T2D, Type 2 diabetes.

## 3.1. *FokI* Polymorphism of the VDR Gene and the Risk of T2D

Our SRMA indicates a substantial relationship between the *FokI* polymorphism of the VDR gene and the T2D risk, particularly among individuals of Asian descent. Nevertheless, no substantial relationship was found between selected genetic polymorphisms and the T1D risk. Using five genetic models, Zeng et al. [43] conducted a thorough SRMA and the analysis of the study subgroup to evaluate the correlation between the rs739837 polymorphism in the gene responsible for VDR and T2D. The analysis included a total of 9 papers. The comprehensive study revealed that the VDR gene variant was linked to a heightened susceptibility to T2D.

## 3.2. *FokI* Polymorphism in the VDR Gene and the T1D Risk

Najjar et al. [45] performed an SRMA to evaluate the connections between specific genetic variations that impact the 25-hydroxyvitamin D [25(OH)D] levels and the risk of developing T1D. No correlation was found between polymorphism in the gene responsible for T1D in a subgroup of Caucasian individuals.

## 3.3. Meta-Analyses Metrics

Six SRMA observed the relationship between the *FokI* gene polymorphism with T1D and T2D (**Table 3**). Five (50%) of 10 SRMA reported a considerable statistically significant finding (**Table 3**).

## 3.4. Risk of Bias Assessment

We assessed the possible risk of bias (RoB) in all selected studies. The results of the RoB evaluation are displayed in **Table 4**. Upon deeper inspection, we found RoB in all the included SRMA. Common concerns revolved around the reliance on primary investigations that studied all participants using a single standard nutritional intervention test. This method prompted inquiries regarding possible bias.

**Table 3.** Characteristics and main findings of meta-analyses of observational studies reporting risk of diabetes associated with the *FokI* gene polymorphism.

| ID | Metric | Main Group | Comparator | NoS | Estimate (95% CI) | *p* | $I^2$ (%) | *p* for Heterogeneity |
|---|---|---|---|---|---|---|---|---|
| Zeng et al., 2022 [43]/Fokl gene | OR | 3,423 | 5,381 | 9 | 1.088 (1.018–1.163) | 0.012 | 0.0% | 0.787 |
| Liu et al., 2021 [46]/ApaI, BsmI, TaqI, Fokl genes | OR | 6,525 | 7,464 | 31 | 0.99 (0.96–1.02) | 0.002 | 22.9% | 0.127 |
| Zhai et al., 2020 [48]/ApaI, BsmI, TaqI, Fokl genes | OR | 3,723 | 5,578 | 29 | 0.96 (0.69–1.35) | 0.83 | 25.5% | <0.001 |
| Yu et al., 2016 [49]/BsmI, FokI | OR | 2,218 | 1,859 | 12 | 1.57 (1.28–1.93) | <0.001 | 4.1% | 0.408 |
| Tizaoui et al., 2014 [51]/ApaI, BsmI,TaqI, Fokl genes | OR | - | - | 18 | 0.968 (0.743–1.263) | 0.813 | 57.7% | 0.101 |
| Wang et al., 2012 [52]/ApaI, BsmI, TaqI, Fokl genes | OR | 2,940 | 4,942 | 22 | 1.30 (1.10–1.55) | 0.002 | 74.4% | < 0.001 |
| Present MA | OR | 5,975 | 7,044 | 27 | 1.41 (1.11–1.79) | 0.004 | 88% | <0.00001 |

Note: Odds Ratio (OR); 95% confidence interval (95%CI); NoS, Number of studies.

**Table 4.** Methodological quality assessment and appraisal of the included studies.

| Study ID | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 | Q11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Zeng 2022 [43] | YES | YES | YES | No | YES | YES | YES | YES | No | N/A | YES |
| Yu 2022 [44] | YES | No | YES | No | YES | YES | YES | YES | No | YES | No |
| Najjar 2021 [45] | YES | U | YES | No | YES | YES | YES | YES | YES | N/A | YES |
| Liu 2021 [46] | YES | YES | YES | No | N/A | YES | YES | YES | No | YES | YES |
| Ran 2021 [47] | YES | YES | YES | No | YES | YES | YES | YES | YES | YES | YES |
| Zhai 2020 [48] | YES | YES | YES | U | No | YES | YES | YES | No | YES | YES |
| Yu 2016 [49] | YES | YES | YES | No | YES | YES | N/A | YES | U | YES | YES |
| Wang 2014 [50] | YES | YES | U | No | N/A | YES | YES | YES | No | N/A | YES |
| Tizaoui 2014 [51] | YES | YES | U | No | YES | YES | N/A | YES | No | YES | YES |
| Wang 2012 [52] | YES | YES | YES | No | YES | YES | YES | YES | YES | N/A | YES |
| Present study | YES | YES | YES | YES | YES | YES | YES | YES | No | YES | YES |

Note: The questions are used according to the reference value (Q1 to Q11). Q1, Is the evaluation question unambiguous?; Q2, Were there sufficient inclusion criteria to answer the research question?; Q3, Was the search strategy appropriate?; Q4, Were there insufficient means or sources used to find studies?; Q5, Were the study-evaluation standards adequate?; Q6, Did at least two separate reviewers each make their own critical judgments?; Q7, Was there a way to reduce human error during data collection?; Q8, Were the strategies for combining studies adequate?; Q9, Was the potential for bias in the publication process evaluated?; Q10, Were the reported data sufficient to back up the suggested changes to policy and/or practice?; Q11, Were the detailed instructions for new studies adequate?

## 4. Discussion

VD plays a crucial role in diabetes development by affecting inflammation, insulin synthesis, and insulin resistance [53,54]. Polymorphisms in the gene responsible for VDR may also disturb the listed functions. We conducted a review to elucidate the relationship between polymorphisms in the gene responsible for VDR and the risk of DM, aiming to address the conflicting results from previous research with small sample sizes. The study also observed the connection between *FokI* polymorphisms and the vulnerability to both T1D and T2D. The meta-analysis shows a considerable link between the FokI polymorphism in the gene responsible for VDR and the susceptibility to T2D, especially in individuals of Asian origin. No significant correlation was discovered between this gene variation and the likelihood of developing T1D. Umbrella review showed that 50% of the published SRMA reported technically significant findings. We assessed RoB in all SRMAs that were selected. Common criticisms focused on the dependence on central studies that compared all patients using a uniform dietary intervention test.

Most participants in the T2D study were from Asian countries, with a particular focus on China. Liu et al. [46] conducted an updated SRMA to explore further the association between polymorphism in the gene responsible for VDR and T2D risk. In general, the risk of T2D was found to be significantly lower in Asians with the VDR *BsmI* polymorphism, in Asians and African countries as a whole with the VDR *FokI* polymorphism. A mixed-race population has a substantially greater risk of T2D due to the VDR *ApaI* polymorphism. To determine if polymorphisms in the DBP increase the likelihood of T2D, Wang et al. [50] analyzed Asians and showed that the DBP polymorphism was somewhat associated with an elevated T2D risk, whereas in Caucasians, no such association was found. Yu et al. [49] attempted to measure the relationship between variations in the *BsmI* and *FokI* polymorphisms in the gene responsible for VDR and developing T2D risk by reviewing existing literature. Based on an analysis of twenty-three papers comprising thirty case-control published articles, they claimed that *BsmI* polymorphism has a modest connection with T2D risk. In contrast, *FokI* polymorphism is strongly associated with T2D risk. This suggests that the *FokI* polymorphism could be considered a probable factor for T2D risk.

Zhai et al. [48] performed an SRMA including 29 studies to thoroughly assess how VDR gene variations impact the likelihood of developing T1D. The overall population data indicated no significant correlation between polymorphism in the gene responsible for and the probability of developing T1D. Nevertheless, the combined findings of subgroup analysis demonstrated noteworthy inverse and direct correlations between *FokI* and *BsmI* genetic variations with T1D in African and American populations, respectively. Tizaoui et al. [51] conducted a study to examine the impact of polymorphism in the gene responsible for T1D. They demonstrated that specific variations in the VDR gene might not be associated with the likelihood of developing T1D. Nevertheless, haplotypes made a substantial contribution to the vulnerability to the disease. The relationship between polymorphism in the gene responsible for T1D was influenced by the specific attributes of the study. These findings indicate that in the development of T1D, variations in the VDR gene interact with one another and with environmental factors. Yu et al. [44] comprehensively analyzed the existing scientific research on the relationship between VD and T1D. This analysis involved reviewing 22 publications that observed the impact of VD on pancreatic cells, as well as 28 articles that explored the impact of VD on humans or human islets. Much evidence in the literature illustrates a connection between T1D and low levels of VD in the bloodstream.

Wang et al. [50] analyzed whether variations in the DBP contribute to the risk of T2D. Among Asians, the DBP polymorphism was found to be somewhat correlated with a higher risk of T2D, although no such connection was observed in Caucasians. Yu et al. [39] conducted a study to assess the relationship between *BsmI* and *FokI* polymorphisms in the gene responsible for VDR and the likelihood of developing T2D. They analyzed twenty-three papers with 30 studies, revealing a non-significant relationship between the polymorphism in the *BsmI* gene and T2D. Conversely, the *FokI* polymorphism exhibited a significant correlation with T2D. This indicates that the polymorphism in the *FokI* gene might be a potential factor for T2D risk.

Zheng et al. [43] performed a comprehensive SRMA and subgroup analysis employing five genetic models to evaluate the relationship between the rs739837 polymorphism in genes responsible for VDR and T2D. There were 9 papers included in the study. The thorough investigation found a connection between the VDR gene variation and an increased vulnerability to T2D. The majority of participants in the T2D study were from Asian countries, with a specific emphasis on China. Liu et al. [46] performed a recent SRMA to investigate the possible connection between polymorphisms in the gene responsible for VDR and T2D risk. Overall, Asians with the VDR *BsmI* polymorphism and individuals of Asian and African descent with the polymorphism in the *FokI* gene responsible for VDR had a notably reduced chance of developing T2D. A multiracial community had a significantly increased risk of T2D as a result of the VDR *ApaI* polymorphism. To determine if polymorphisms in the DBP increase the likelihood of T2D, Wang et al. 50] analyzed Asians. They showed that the polymorphism in DBP was associated with an elevated T2D risk, while in Caucasians, no such association existed. Yu et al. [49] attempted to measure the link between variations and polymorphism in the *BsmI* and *FokI* genes responsible for the VDR and the developing T2D risk. Based on an analysis of twenty-three papers comprising thirty studies, it was shown that the polymorphism in the *BsmI* gene showed a modest connection with T2D. In contrast, the polymorphism in the *FokI* gene exhibited a substantial relationship with T2D. This may suggest that the polymorphism in the *FokI* gene may be a risk factor for T2D.

Najjar et al. [45] performed an SRMA to evaluate the connection between certain genetic variants associated with 25-hydroxyvitamin D variation levels and the susceptibility to developing T1D. So far, no association has been detected between polymorphism in a gene responsible for VDR and T1D in a subset of Caucasian individuals. Zhai et al. 2020 [48] conducted an SRMA comprising twenty-nine studies to comprehensively estimate the influence of variation in the gene responsible for VDR on developing T1D risk. The population-based analyses revealed a non-significant link between polymorphism in the gene responsible for VDR and the likelihood of having T1D. Consequently, further analysis exposed significant inverse and direct relationships between polymorphism in the *FokI* and *BsmI* genes responsible for VDR with T1D risk in people living in African and American countries. Tizaoui et al. [51] investigated the influence of polymorphism in the gene responsible for VDR on the development and the risk of T1D. The study showed that particular polymorphisms in the gene responsible for VDR were not linked with the risk of acquiring T1D. However, haplotypes significantly influenced the susceptibility to the disease. The relationship between polymorphism in genes responsible for VDR and T1D was impacted by the particular characteristics of the research. The findings suggest that mutations in the VDR gene interact with environmental factors that are chief components in the development of T1D. Yu et al. [46] thoroughly examined the current scientific studies on the correlation between VD and T1D. This research included examining 22 articles that studied the influence of VD

on pancreatic cells, along with 28 articles that appraised the impacts of VD on individuals or human islets. Extensive pieces of evidence indicate that a considerable and significant correlation exists between T1D and insufficient levels of VD in the blood.

## 5. Advantages and Disadvantages of the Study in Comparison to Other Research

This umbrella review offers a thorough overview of the published literature regarding the impact of polymorphism in the *FokI* gene responsible for VDR on susceptibility to both T1D and T2D. We analyzed the SRMA literature on polymorphism in the gene responsible for VDR to determine the level of bias and heterogeneity and synthesized the data across several outcomes. The quality of a review is strongly linked to the quality of the selected studies. Several health-related outcomes need to be more adequately addressed, and we have identified this deficiency. In the component observational studies, we could not assess the impact of using other comparison groups (e.g., thirds, quarters, fifths) or varied distributions of polymorphism in the *FokI* gene responsible for VDR and median differences. We incorporated observational meta-analyses of polymorphism in the *FokI* gene responsible for VDR. SRMA studies are considered the norm for comparing studies about VDR polymorphism. SRMA of supplement intake studies is not necessarily more dependable than those studies on the associations of polymorphism in the gene responsible for VDR, particularly the *FokI* gene. Therefore, they are not a gold standard for evaluating bias, size, or heterogeneity mapping. Like our research, this summary noted a difference in results from studies, with most polymorphisms in the *FokI* gene responsible for VDR not indicating an impact of VDR variation on DM occurrence and risk. Our review is more comprehensive than the overview regarding the number and range of outcomes. It differs in the types of studies included (SRMA instead of original studies), the population analyzed (not limited to adults or specific clinical settings), and the statistical analyses conducted (including bias tests).

## 6. Strengths and Limitations

Given that this study is an umbrella review, in summary, data were extracted as reported in the SRMAs and are usually not reanalysed. This method is more cost-effective, but the preference for one method over the other depends on the purpose of the umbrella review. If the goal is to summarize and describe existing SRMA on a topic, then summarization is an appropriate method. On the other hand, if, for example, the umbrella review aims to answer a different question than the included systematic reviews, or if the systematic reviews do not include meta-analysis, then reanalysis of the data would be the preferred method [55]. It is worth noting that the reanalysis is performed using standard meta-analysis methods [56]. Though the study showed an association and differences between various types of diabetes with the polymorphism of interest, high heterogeneity in the meta-analyses' results could be related to the various sample sizes used in different studies. Another possible source could be differences in the ethnicities of the study population [57].

Our review has some limitations. First, it is important to note that umbrella review findings should not be used to make indirect comparisons between interventions [37]. In such comparisons, the assumption of transitivity must hold [58]. Testing the assumption of transitivity is usually not possible with the information provided in systematic reviews. Second, given that the findings of an umbrella review may be presented in a way that encourages the reader to make such comparisons, it is suggested that the authors specifically caution readers against such interpretations [59].

## 7. Conclusion

Our SRMA reveals no considerable and significant association between the polymorphism in the *FokI* gene responsible for VDR and the likelihood of developing T1D in all ethnic groups. In addition, we discovered a substantial correlation between these polymorphisms and the susceptibility to T2D in individuals of Asian descent. Nevertheless, additional investigation is necessary to scrutinize these associations by considering the interplay between genes and the environment. Moreover, further extensive research is required to clarify the processes behind the associations between VDR polymorphisms and DM despite substantial research done so far. Based on the findings of this analysis, there is a potential link between polymorphism in the *FokI* gene responsible for VDR and DM risk. However, more extensive investigations and well-planned trials are necessary to establish more specific conclusions. One of the most important benefits of immunotherapy is its ability to stimulate targeted immune responses

that help wounds heal faster and reduce inflammation. These features make immunotherapy an attractive option for diabetic patients who may not improve with traditional treatment methods. The use of monoclonal antibodies, immune cells, and immunotherapy vaccines has shown that these methods can be effective in reducing the size of wounds and preventing new infections. Vitamin D may play a role in reducing the risk of diabetes, especially type 2 diabetes. Evidence suggests that VD deficiency may be associated with an increased risk of DM, and VD supplementation may help improve glucose tolerance and reduce insulin resistance. Studies have shown that VD intake can reduce the risk of T2D by up to 15%, and during pregnancy, it may also help reduce the risk of gestational diabetes. However, more randomized controlled trials are needed to definitively confirm these effects and determine the optimal dose of VD. Special attention should also be paid to dosage and safety. Therefore, although the evidence is promising, it is important to consult a doctor and conduct further research to determine the exact role of VD in diabetes prevention.

## Author Contributions

Conceptualization, K.R.K., M.D., K.H.O., Y.K., S.S.A.-M., and T.K.; validation, K.H.O. and Y.K.; formal analysis, K.R.K., M.D., S.S.A.-M., and T.K.; data curation, K.R.K., M.D., S.S.A.-M., and T.K.; writing—original draft preparation, K.R.K. and M.D.; writing—review and editing, K.H.O. and Y.K. All authors have read and agreed to the published version of the manuscript.

## Funding

This work received no external funding

## Institutional Review Board Statement

The article is comprehensive in its consideration of ethical concepts. The ethics committee gave the study the all-clear.

## Informed Consent Statement

Not applicable.

## Data Availability Statement

No data used in the present research.

## Acknowledgments

The authors would like to thank all participants of the research, and Osh State University for their support.

## Conflicts of Interest

The authors declare no conflict of interest.

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