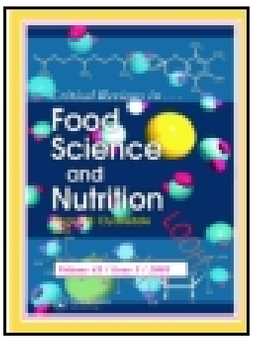

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REVIEW

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Vitamin D status and vitamin D receptor genotypes in celiac disease: a meta-analysis

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ABSTRACT

Background: There have been various articles reporting relationship between Vitamin D (VitD) and celiac disease (CeD), but results remain controversial. This study aimed to conduct a meta-analysis to systematically review and quantify the relationship between VitD and CeD. Moreover, difference in Vitamin D Receptor (VDR) genotypes between CeD patients and controls was also analyzed.

Methods: Articles published until July 20, 2019 in the PubMed, MEDLINE, and EMBASE databases were searched. According to the inclusion and exclusion criteria, relevant statistical data were collated and extracted, which were finally analyzed by STATA15.1.

Results: 27 articles and 28 sets of data were included. It showed that average 25(OH)D level in CeD patients was 8.36 nmol/L lower than controls (Weighted Mean Difference (WMD) = −8.36, 95% CI = [−14.63, −2.09] nmol/L). After gluten-free diet treatment, we found that average 25(OH)D level in treated patients was 15.6 nmol/L higher than untreated patients (WMD = 15.6, 95% CI = [5.96, 25.23] nmol/L). In addition, 25(OH)D level in treated patients was close to healthy controls (WMD = −2.82, 95% CI = [−6.45, 0.73] nmol/L). However, genetic polymorphism analysis showed that there is no difference in VDR genotypes between CeD and control.

Conclusions: CeD had decreased serum 25(OH)D levels, which returned to normal after treatment, suggesting that VitD may play a role in the development of CeD. The directionality of this association cannot be confirmed from cross-sectional studies. Demonstration of a causal role of VitD deficiency in CeD development in future studies could have important therapeutic implications.

KEYWORDS
Vitamin D; celiac disease; Vitamin D Receptor; single nucleotide polymorphism

Introduction

Celiac disease (CeD) is an autoimmune disorder that occurs in genetically predisposed individuals who develop an immune reaction to gluten (Lebwohl, Sanders, and Green 2018). The disease primarily affects the small intestine; however, the clinical manifestations are broad, with both intestinal and extra-intestinal symptoms (Lebwohl, Sanders, and Green 2018). CeD affects about 1% of the population and there are differences in prevalence worldwide (Rubio-Tapia et al. 2012; Choung et al. 2017). Globally, the prevalence of CeD is increasing: for example, a 4–4.5 times increase over approximately 50 years in USA (Rubio-Tapia et al. 2009) and a 2 times increase over approximately 20 years in Finland (Lohi et al. 2007). However, the pathogenesis of CeD is not clear. The major environmental factor responsible for the development of CeD is gluten, and gluten-free diet remains mainstay of treatment of CeD (Lebwohl, Sanders, and Green 2018; Murray et al. 2004). In addition, genetic factors (DQ2 and DQ8) (Karell et al. 2003), breast-feeding and infant feeding practices (Ivarsson et al. 2000), microbiome may also play important roles in CeD (Galipeau et al. 2015).

As early as 25 years ago, Corazza et al had found that CeD patients had lower vitamin D (VitD) levels than healthy volunteers (Corazza et al. 1995). Since then, more and more scholars became to study the relationship between VitD and CeD. VitD is more than just a vitamin, which is synthesized in the skin and mediates numerous actions in many tissues of the body. VitD regulates calcium and phosphate metabolism and is essential for bone mineralization (Holick 2007). However, accumulating data indicate that VitD deficiency raises the risk of developing extraskeletal actions, such as cancer or many other diseases, and it worsens outcomes for these diseases (Feldman et al. 2014). The above biological actions of VitD are mediated by the Vitamin D Receptor (VDR), which belongs to the steroid receptor family (Christakos et al. 2016). VDR gene has numerous single nucleotide polymorphisms (SNPs), of which Fok I (SNP rs2228570), Bsm I (SNP rs1544410), Apa I (SNP rs7975232) and Taq I (SNP rs731236) are the most studied. San-Pedro et al reported that Fok I (SNP rs2228570) is a risk factor for CeD (San-Pedro et al. 2005).

However, there were controversial views on VitD and CeD. For example, Stein et al had opposite view, which

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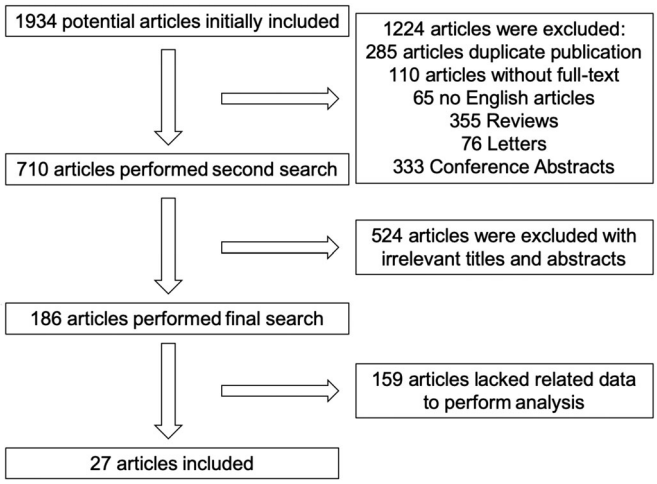

Figure 1. Screening flow chart.

revealed that VitD plays a dangerous role in CeD (Stein et al. 2015). Therefore, this study aimed to conduct a meta-analysis to systematically review and quantify the relationship between VitD and CeD. We were also interested in the change of VitD levels in CeD after gluten-free diet treatment. In addition, VDR gene polymorphism were also heavily analyzed in this study.

Materials and methods

Data selection

Articles published in the PubMed, MEDLINE and EMBASE databases until July 20, 2019 with restrictions of English-language were searched. In order to cover whole potential articles, we used following terms to search: ((Celiac disease) OR (Celiac disease) OR (gluten-sensitive enteropathy) OR (gluten-induced enteropathy)) AND ((Vitamin D) OR (VD) OR (25(OH)D) OR (Cholecalciferol) OR (25-Hydroxyvitamin D)). The inclusion and exclusion criteria were used to limit the screening conditions. Articles would be considered for inclusion if they met all the following criteria: (1) Published as full research articles; (2) Definite diagnosis of CeD; (3) Data of VitD can be calculated in CeD. Articles which did not meet the above criteria or duplicate publication were excluded.

Articles were independently screened by title and abstract by two authors, and both of them subsequently performed full articles. If a disagreement arose, a third author would evaluate it again and form a final result after the trade.

Risk of bias and Quality assessment were assessed through elements of the STROBE checklist for studies included (Vandenbroucke et al. 2007). The genetic model-free approach was used to estimate the genetic effects and mode of inheritance if an overall gene effect was confirmed (Minelli et al. 2005). In addition, the work was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al. 2009).

Data extraction

Data were extracted to Microsoft Excel (2019 edition; Microsoft, Redmond, WA, USA) for effective organization. 25(OH)D was the main form of VitD, which was used to be tested and represented VitD level. In addition, 25(OH)D unit was defined as 1 ng/mL = 2.5 nmol/L, and 25(OH)D level lower than 50 nmol/L defined as deficiency. The following data were obtained from included studies: basic characteristics; 25(OH)D levels (mean ± standard deviation (SD)) of CeD and controls; 25(OH)D levels (mean ± SD) of untreated CeD and treated CeD; 25(OH)D levels (mean ± SD) of treated CeD and controls; VDR SNPs data of CeD and controls; diagnostic method of CeD; treatment method of CeD. All data were double-checked by two authors. According to the data provided, four VDR SNPs including Fok I (SNP rs2228570), Bsm I (SNP rs1544410), Apa I (SNP rs7975232) and Taq I (SNP rs731236) were analyzed. And these four SNPs are also representative of VDR SNPs.

Statistical analysis

Weighted Mean Difference (WMD) was used to combined mean and SD values for 25(OH)D levels. For some article providing quartile instead of SD, we calculated a final SD using reduction formula (Jean Dunn and Clark 2009). The odds ratio (OR, 95% confidence intervals [CIs]) was used to describe the ratio of 25(OH)D deficiency in CeD patients and controls, and data of VDR SNPs. In addition, statistical heterogeneity was assessed by Cochran's Q test and the I^2 statistic. For heterogeneous results, publication bias was estimated by Begg's test. Pooled estimates were obtained using the fixed-model (Mantel and Haenszel) method (if $I^2 \leq 50\%$, $P > 0.1$) or random-model (M-H heterology) method (if $I^2 > 50\%$, $P \leq 0.1$). To enhance the credibility of the results, sensitivity analysis was used to evaluate stability and reliability of results. Meta-regression was used to look for potential sources of heterogeneity (Monte Carlo permutation test). All analyses were carried out through the application of STATA (StataCorp.).

Results

Basic characteristics

We searched 1934 potential related articles, of which 27 papers and 28 sets of data met our inclusion criteria (Supplementary material). The flowchart describing the process of study selection was shown in Figure 1. The articles reported were mainly from Europe and the United States. Of the articles included, eight reported on pediatric CeD, eight reported on gluten-free diet treatment of CeD, and three reported on VDR genotypes. In this study, a total of four SNPs were used for comparison (Fok I SNP rs2228570 in exon 2, Bsm I SNP rs1544410 and Apa I SNP rs7975232 in intron 8, Taq I SNP rs731236 in exon 9).

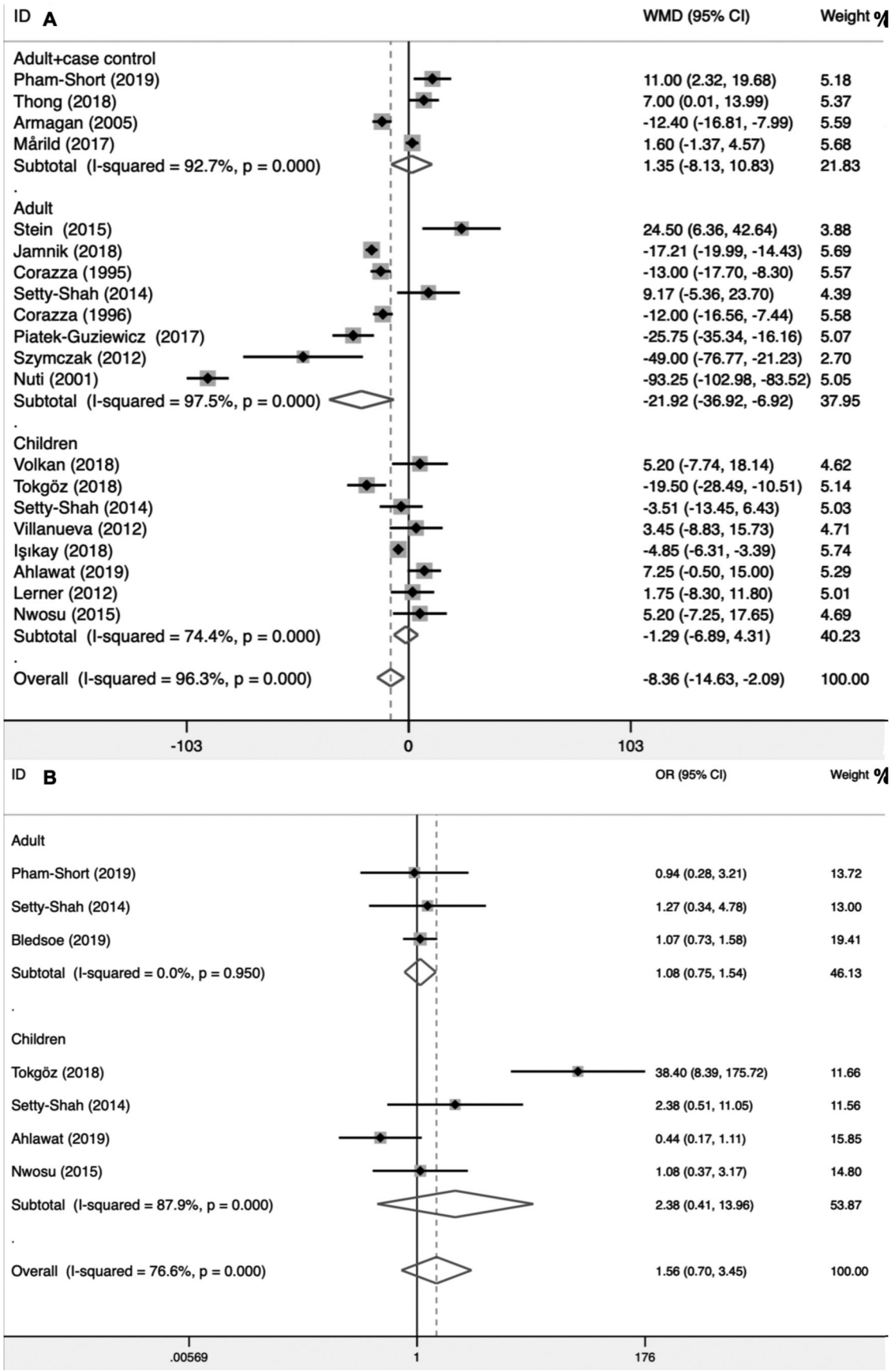

Figure 2. (A) the average 25(OH)D level in CeD patients was 8.36 nmol/L lower than that in controls (WMD = −8.36, 95% CI = [−14.63, −2.09] nmol/L) (I^2 = 96.3%, $P < 0.01$); (B) 25(OH)D deficiency individuals had no difference in CeD and controls (OR = 1.56, 95% CI = [0.7, 3.45], I^2 = 76.7%, $P < 0.01$).

Table 1. VDR genotypes difference between CeD and control.

SNP	Author	Year	VDR genotypes (Allele)			
			CeD		Control	
Fok I (rs2228570)			**F**	**f**	**F**	**f**
	San-Pedro (San-Pedro et al. 2005)	2005	46	32	121	55
	Mårild (Marild et al. 2017)	2017	152	636	179	917
Bsm I (rs1544410)			**B**	**b**	**B**	**b**
	San-Pedro (San-Pedro et al. 2005)	2005	26	52	78	98
	Mårild (Marild et al. 2017)	2017	341	447	456	640
Apa I (rs7975232)			**A**	**a**	**A**	**a**
	San-Pedro (San-Pedro et al. 2005)	2005	33	45	99	77
	Vogelsang (Vogelsang et al. 2000)	2000	112	72	128	94
Taq I (rs731236)			**T**	**t**	**T**	**t**
	San-Pedro (San-Pedro et al. 2005)	2005	55	23	105	71
	Vogelsang (Vogelsang et al., 2000)	2000	107	77	128	94

VDR: Vitamin D Receptor;
CeD: Celiac disease;
SNP: Single nucleotide polymorphism.

Comparison of 25(OH)D levels between CeD patients and controls

The corresponding data were listed in Supplementary material 1 (Table S1). A total of 24 articles and 25 sets of data, contained 1137 CeD patients and 2613 controls. Mean value of 25(OH)D was 54.39 nmol/L in CeD patients and 63.1 nmol/L in controls. The pooled results of meta-analysis showed that the average 25(OH)D level in CeD patients was 8.36 nmol/L lower than that in controls (WMD = −8.36, 95% CI = [−14.63, −2.09] nmol/L) (Figure 2A). In subgroup analysis, it showed that there was no statistical difference in 25(OH)D level between pediatric CeD and controls (WMD = −1.29, 95% CI = [−6.89, 4.31] nmol/L) (Figure 2A). In subgroup of underlying diseases with or without CeD, it also showed no statistical difference (WMD = 1.35, 95% CI = [−8.13, 10.83] nmol/L) (Figure 2A). While in adult stratified analysis, we found that the average 25(OH)D level in CeD patients was 21.92 nmol/L lower than that in controls (WMD = −21.92, 95% CI = [−36.92, −6.92] nmol/L) (Figure 2A). There was no publication bias (Supplement 2) and abnormal sensitivity analysis (Supplement 3). In addition, meta-regress revealed that heterogeneity did not come from location ($P = 0.891$), adult or child ($P = 0.462$), patient or healthy volunteers ($P = 0.535$).

Analyzed data from seven included articles showed that the ratio of 25(OH)D deficiency individuals to normal individuals was 106–322 in CeD and 172 to 738 in control. The pooled result of meta-analysis found that there is no statistical difference in the ratio of 25(OH)D deficiency between CeD and control (OR = 1.56, 95% CI = [0.7, 3.45]) (Figure 2B).

Changes in 25(OH)D levels after CeD treatment

In this part, we aimed to analyze changes in 25(OH)D levels after gluten-free diet treatment of CeD. Eight articles listed in Supplementary material 1 (Table S2) contained changes in 25(OH)D levels before and after treatment, and five articles which were listed in Supplementary material 1 (Table S3) contained comparison of 25(OH)D levels between post-treatment and healthy controls. First, it revealed that the average 25(OH)D level in treated patients was 15.6 nmol/L higher than untreated patients (WMD = 15.6, 95% CI = [5.96, 25.23] nmol/L) (Figure 3A). Next, we found that 25(OH)D level had no difference between post-treated patients and healthy controls (WMD = −2.82, 95% CI = [−6.45, 0.73] nmol/L) (Figure 3B). Meta-regress revealed that heterogeneity was neither from location ($P = 0.949$) nor adult or child ($P = 0.395$). Publication bias and sensitivity analysis were listed in Supplementary material 2 and Supplementary material 3. The results were stable and reliable.

Comparison of VDR SNPs between CeD patients and controls

Three articles reported four VDR SNPs totally, which were Fok I (SNP rs2228570), Bsm I (SNP rs1544410), Apa I (SNP rs7975232) and Taq I (SNP rs731236). The basic characteristics were listed in Table 1. Although some individual studies reported SNP difference, changes in Fok I (SNP rs2228570) (OR = 0.94, 95% CI = [0.51, 1.73]) (Figure 4A), Bsm I (SNP rs1544410) (OR = 0.88, 95% CI = [0.53, 1.45]) (Figure 4B), Apa I (SNP rs7975232) (OR = 0.83, 95% CI = [0.42, 1.63]) (Figure 4C) or Taq I (SNP rs731236) (OR = 1.19, 95% CI = [0.86, 1.64]) (Figure 4D) had no statistic difference in this meta-analysis.

Discussion

In previous clinical studies, comparison results of VitD levels between CeD and control were inconsistent. In this study, our results suggested that VitD levels were indeed low in patients with CeD. In addition, VitD levels were higher in treated patients than untreated patients, and VitD levels in treated patients were close to healthy controls. Combining these results, we hypothesized that VitD might be part of the pathogenesis of CeD. In addition, there was no difference in VDR genotypes between CeD and controls.

The results suggested that VitD and VDR may play key roles in the pathogenesis of CeD. First, we confirmed the consistency of VitD and VDR expression, which was helpful

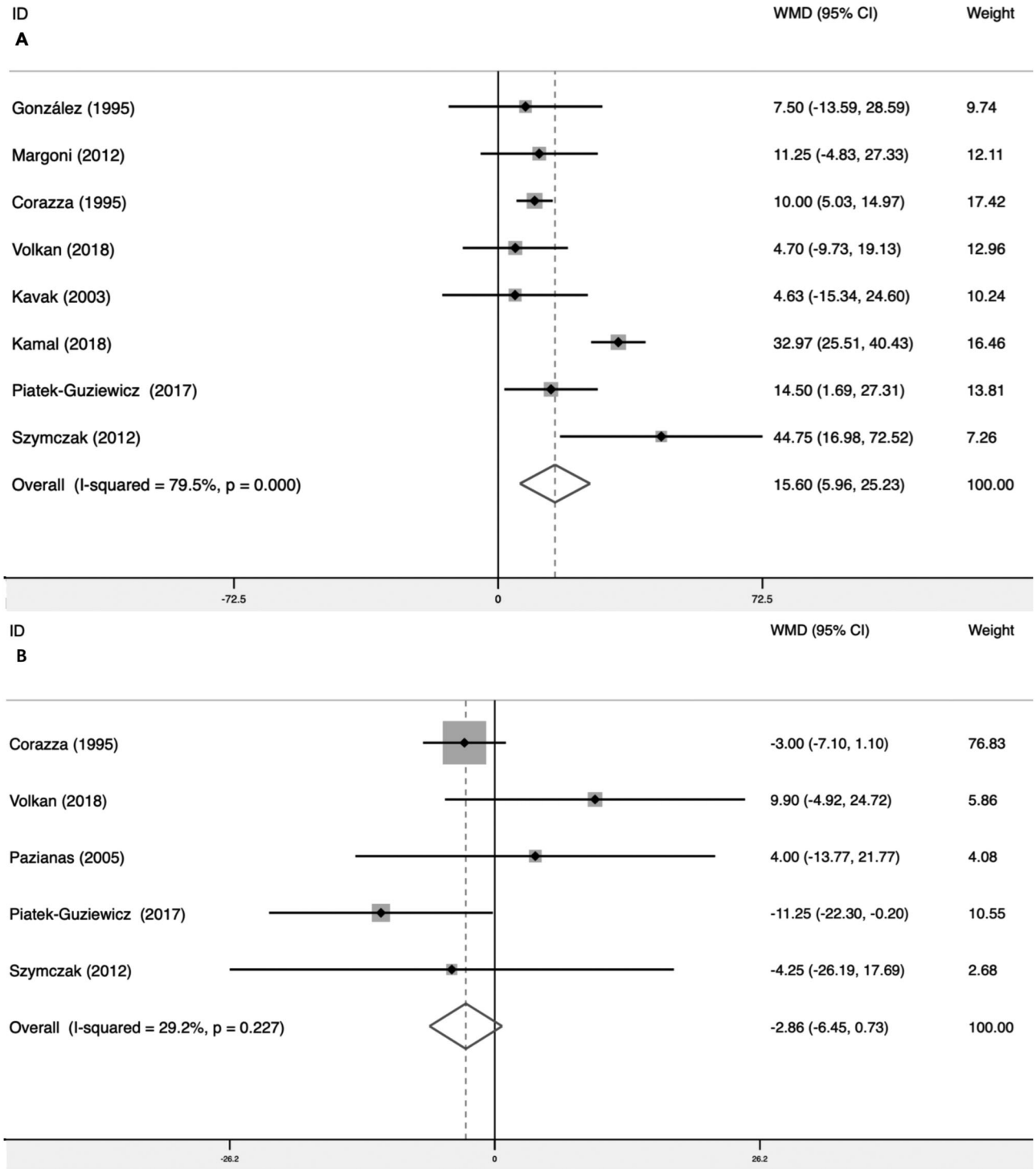

Figure 3. (A) the average 25(OH)D level in treated patients was 15.6 nmol/L more than untreated patients (WMD = 15.6, 95% CI = [5.96, 25.23] nmol/L) (I^2 = 79.5%, $P < 0.01$); (B) 25(OH)D levels had no difference between treated patients and healthy controls (WMD = −2.82, 95% CI = [−6.45, 0.73] nmol/L) (I^2 = 29.2%, $P = 0.227$).

for the interpretation of the results. In dextran sulfate sodium (DSS)-induced colitis mouse model, we found that VDR expression was significantly reduced by feeding on VitD-deficient diet (Supplementary material 4). The complex interaction of the microbiome might be crucial to the development of CeD. Nistal et al revealed that healthy adults have a different fecal microbiota from that of untreated CeD patients, and treated CeD patients significantly reduce diversity of *Lactobacillus* and *Bifidobacterium* (Nistal et al. 2012). In addition, another study found that pediatric CeD patients had a higher incidence of duodenal Gram-negative and pro-inflammatory bacteria at diagnosis than controls (Nadal et al. 2007). VitD may be beneficial to the intestinal microbiome. Ooi et al had proved that there were more beneficial bacteria, including *Lactobacillaceae* and *Lachnospiraceae* families, in feces from VDR knockout mice than that from wild-type (Ooi et al. 2013). Moreover, it reported that VDR can negatively regulates bacterial-induced intestinal NF-κB

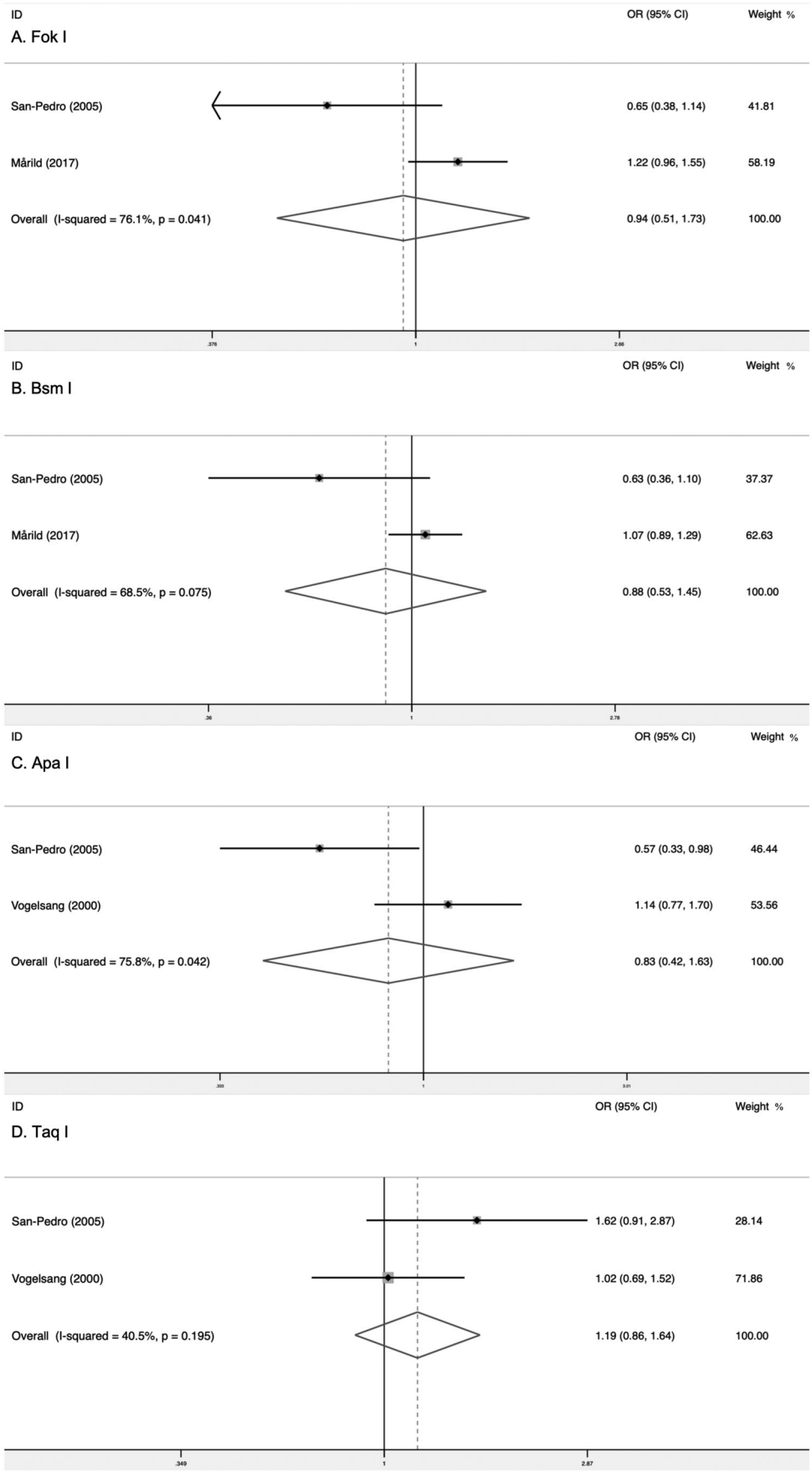

Figure 4. VDR SNPs of Fok I (SNP rs2228570), Bsm I (SNP rs1544410), Apa I (SNP rs7975232) and Taq I (SNP rs731236) between CeD patients and controls. It showed no statistical difference.

activation and attenuates response to infection (Wu et al. 2010). Combined with our results, these contents suggested that VitD deficiency may promote CeD progression through the microbiome.

Except for that, gastrointestinal infections may also be closely related to CeD (Canova et al. 2014). Rotavirus infection in children and *campylobacter* infection in adults, have been reported as risk factors (Stene et al. 2006; Riddle et al. 2013). Antibiotic exposure (Marild et al. 2013) and early life infections (Marild et al. 2015) may have a role in CeD development. In addition, Bouziat et al supported a role for infection with reovirus in triggering the development of CeD (Bouziat et al. 2017). The importance of infection in the pathogenesis of CeD is self-evident, and VitD happens to have anti-infective effect. The antibacterial peptide cathelicidin is induced by the active form of VitD (White 2010). Cathelicidin has been shown to have direct antibacterial, antifungal, antiviral, and immunoregulatory properties when added to infected cells and cultures in vitro (Bandurska et al. 2015).

For CeD, clinical symptoms of malabsorption syndrome including diarrhea would result in low nutrition absorption, and thus, VitD deficiency and CeD progress might be parallel. In addition, the evidence of that VitD levels improved significantly after gluten-free diet treatment indicated that VitD deficiency might be the consequence of CeD. Based on published studies, a persistent shortage of VitD and VDR might aggravate CeD and influence prognosis. Nevertheless, we cannot confirm whether VitD is the cause in the pathogenesis of CeD based on the current evidence.

As far as we know, CeD is the only one for which there is broad consensus on the identity of immunodominant epitopes consistently recognized by pathogenic $CD4^+$ T cells among all the autoimmune diseases (Hardy et al. 2015). $CD4^+$ T cells of CeD patients will recognize gluten peptides when presented by disease associated HLA-DQ molecules (Sollid et al. 2012). The regulation of CeD may be closely related to VitD. Nodehi et al found that in Hashimoto's thyroiditis, VitD supplementation can change frequency of $CD4^+$ T cell subsets, and the expression of IFN-γ, IL-10, IL-4 and IL-17 by $CD4^+$ T-cell subsets (Nodehi et al. 2019). Sheikh et al observed that the stimulation of $CD4^+$ T cells with VitD, suppressed proliferation capacity, enhanced the expression of inhibitory markers on $CD4^+$ T cells, and diminished the percentage of pro-inflammatory cytokines (Moore et al., 2018).

One study did identify an association of genotype "ff" (Fok I) with risk to CeD, which identified "ff" as a risk genotype in CeD (San-Pedro et al. 2005). Previous study has shown that the Fok I genotype results in the incorporation of three extra amino-acids in the NH2 terminal of VDR protein in contrast to other VDR genotypes, which can influence transcriptional activity by modulating interaction with the transcription factor IIB (TFIIB) (Whitfield et al. 2001). Different genotypes have different biological function. Through genotype analysis, we can selectively improve the expression of disease genotypes without affecting the function of other genes. In this study, no differences in the frequency of any single allele (Fok I, Bsm I, Taq I and Apa I) has been found between CeD patients and controls by meta-analysis. However, we still can find some associated trend of Taq I between CeD and control (Figure 4).

Although we have achieved certain results, there were still some defects in this study. The main problem was that we did not have clear evidence of whether VitD deficiency causes CeD progression, or the disease itself causes VitD deficiency, or both. The most important reason was the lack of prospective studies or randomized controlled trials (RCTs). In this study, we can only determine the changes of VitD in CeD patients rather than the causal relationship. If studies about VitD supplementation alleviating CeD were provided, it can provide strong evidence that VitD is the cause of CeD. Second, more studies are needed to fully demonstrate VDR gene polymorphism. In our study, only two articles reported the difference of Fok I, Bsm I, Taq I and Apa I, respectively, which led to a lack of convincing results. Third, the original studies did not adjust for potentially important confounders, such as body mass index, basic gastrointestinal symptoms, race or dietary habit. Finally, the existence of heterogeneity may bias the results. We have excluded some sources of heterogeneity, and the current studies suggest no major clinical heterogeneity. Hence, we thought that it was appropriate to provide the pooled analyses.

In conclusion, we have demonstrated that VitD deficiency was prevalent in CeD subjects, and VitD level was close to normal after treatment, suggesting that VitD may play a role in the development of CeD. The microbiome diversity/action and immune-modulatory properties provide plausible mechanisms by which VitD-VDR may impact on disease progression in CeD. Due to the nature of cross-sectional surveys in our study, directionality of the results cannot be ascertained. Future study should focus on investigating the association between VitD and CeD prospectively, as well as on RCTs of VitD supplementation in CeD patients. Hence, VitD supplementation may prove to be beneficial in the treatment of CeD.

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Authors contributions: Chao Lu designed research; Chao Lu and Weihua Zhou searched articles and collected data; Xinjue He evaluated the disagreement; Xinxin Zhou performed the statistical analysis; Chao Lu wrote the paper; Chaohui Yu revised the paper.

Disclosure statement

The authors declare that they have no competing interests.

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