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Basic study

Effects of vitamin D supplementation on patients with chronic heart failure: A meta-analysis

Effets de la supplémentation en vitamine D chez les patients souffrant d'insuffisance cardiaque chronique : une méta-analyse

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ABSTRACT

Objective. – To systematically evaluate the effect of vitamin D supplementation on cardiac function in patients with chronic heart failure.
Methods. – Search multiple databases to find randomized controlled trials of vitamin D for chronic heart failure from the self-built database until September 1, 2023. Meta-analysis was performed using RevMan5.3 and Stata15.0 software.
Results. – Eighteen articles were included. Vitamin D supplementation has improved left ventricular ejection fraction [WMD = 3.18%, 95%CI (1.07, 5.3), $P < 0.05$] and 6-minute walking distance [MD = −11.54, 95%CI (−22,215, −0.871), $P < 0.05$], has decreased left ventricular end-diastolic diameter [MD = −1.67, 95%CI (−2.88, −0.46), $P < 0.05$], left ventricular end-diastolic volume [MD = −11.94, 95%CI (−20.59, −3.29), $P < 0.05$], N-terminal forebrain natriuretic peptide [WMD = −0.7, 95%CI (0.24, 1.16), $P < 0.05$].
Conclusion. – Vitamin D supplementation can improve cardiac function, inhibit ventricular remodeling, and increase exercise endurance inpatients with chronic heart failure.
INPLASY registration number. – 202440032.

Keywords :
Heart failure
Vitamin D
Cardiac function
Meta-analysis
Randomized controlled trial

RÉSUMÉ

Objectif. – Évaluer systématiquement l'effet de la supplémentation en vitamine D sur la fonction cardiaque chez les patients souffrant d'insuffisance cardiaque chronique.
Méthodes. – Recherche dans plusieurs bases de données pour trouver des essais contrôlés randomisés sur la vitamine D pour l'insuffisance cardiaque chronique à partir de la base de données auto-construite jusqu'au 1er septembre 2023. Une méta-analyse a été réalisée à l'aide des logiciels RevMan5.3 et Stata15.0.
Résultats. – Dix-huit articles ont été inclus. La supplémentation en vitamine D a amélioré la fraction d'éjection du ventricule gauche [WMD = 3,18 %, 95 %IC (1,07, 5,3), $p < 0,05$] et la distance de marche de 6 minutes [MD = −11,54, 95 %IC (−22 215, −0,871), $p < 0,05$], a diminué le diamètre de fin de diastole du ventricule gauche [MD = −1,67, 95 %IC (−2,88, −0,46), $p < 0,05$], du volume ventriculaire gauche en fin de diastole [MD = −11,94, 95 %IC (−20,59, −3,29), $p < 0,05$], du *N-terminal forebrain natriuretic peptide* [WMD = −0,7, 95 %IC (0,24, 1,16), $p < 0,05$].
Conclusion. – La supplémentation en vitamine D peut améliorer la fonction cardiaque, inhiber le remodelage ventriculaire et augmenter l'endurance à l'exercice chez les patients souffrant d'insuffisance cardiaque chronique.

Mots clés :
Insuffisance cardiaque
Vitamine D
Fonction cardiaque
Méta-analyse
Essai contrôlé randomisé

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1. Introduction

Chronic heart failure (CHF) is a disorder of cardiac structure and function caused by multiple causes, and ventricular ejection capacity is impaired, resulting in cardiac systolic and diastolic dysfunction, resulting in insufficient cardiac output [1]. The main manifestations of the disease are dyspnea, weakness, pulmonary stasis, and limb edema. Once the disease deteriorates, it is the final stage and one of the most important causes of death. Therefore, timely detection and treatment are essential. CHF has a high incidence, as well as a high readmission rate, poor quality of life, and high mortality [2]. With the aggravation of population aging, the incidence of diabetes, hypertension, coronary heart disease and other common causes has increased, and the incidence of heart failure has also been increasing. The treatments for CHF include angiotension converting enzyme inhibitors, sodium-dependent glucose transporters 2 inhibitors, β-blockers, and aldosterone receptor antagonists [3]. Many studies have consistently shown that vitamin D deficiency may exacerbate the occurrence of cardiovascular events and cardiovascular death [4]. But is vitamin D supplementation beneficial for CHF? There have been several articles, but this issue is still controversial. There are a few meta-analyses on the efficacy of vitamin D supplementation and CHF, but the included articles are few, the sample size is small, the outcome indicators are different, and the results of the analysis are inconsistent. Therefore, this study is to add data to previous studies and further verify the effect of vitamin D supplementation for CHF by meta-analysis.

2. Methods

Inclusion criteria are:

- study type: randomized controlled trials (RCT);
- subjects: meeting the diagnostic criteria for chronic heart failure;
- interventions: the control group received conventional treatment, including diuretics, etc. Experimental group received vitamin D treatment on the basis of conventional treatment;
- outcome indicators: left ventricular end-diastolic dimension (LVEDD), left ventricular end-diastolic volume (LVEDV), left ventricular ejection fraction (LVEF), brain natriuretic peptide (BNP)/N-terminal pro-brain natriuretic peptide (NT-proBNP), 6-minute walk distance (6MWD).

2.1. Exclusion criteria

Repeated publication of literature; animal experiments and reviews.

2.2. Study search strategy

We searched Pubmed, Web of Science, Google Scholar, the Cochrane, Library, China National Knowledge Internet database. Systematic reviews were also browsed. Our search queries were heart failure AND (vitamin D or cholecalciferol or calcitriol). This search agreement is limited to studies published before September 1, 2023.

2.3. Data extraction

The data were independently evaluated and extracted by two evaluators, and the data were extracted from the original literature using a table. Data extraction included:

- basic information: first author, publication time, study type, follow-up time, etc.;
- intervention measures of experimental group and control group;

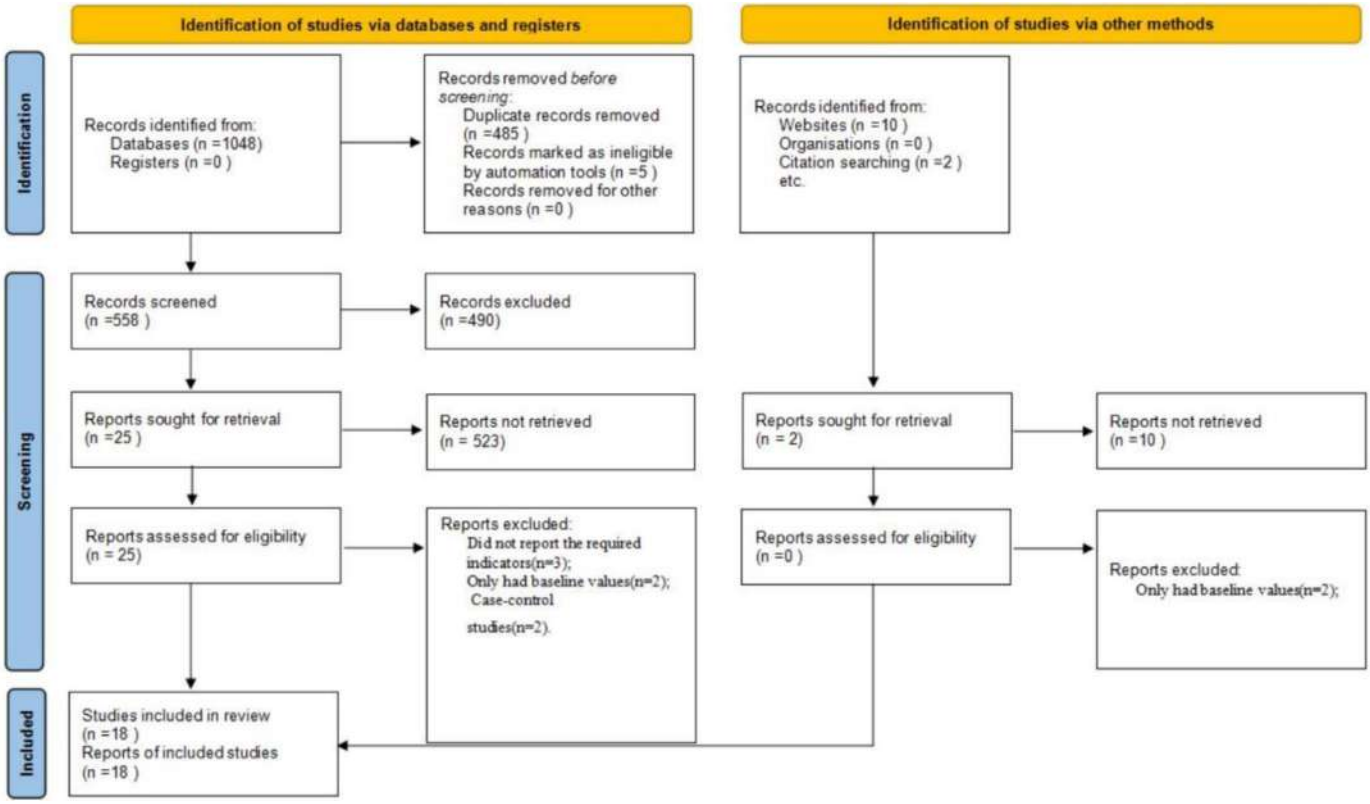

Fig. 1. Study flow diagram.

Table 1
Studies and patients' characteristics.

First author	Publication year	Study design	Duration of treatment	Vitamin D dosage	Sample size		Age	The type of heart failure	Baseline 25-OHD	
					Treatment	Placebo			Treatment	Placebo
Witte	2016	Double-blinded/randomized	12 months	VD3 4000 IU/d	80	83	68.7 ± 13.1	HF with reduced LVEF	–	–
Reza	2020	Double-blinded/randomized	8 weeks	VD3 50,000 IU/wk	41	41	VD: 61.6 ± 19.8 CO: 62.1 ± 18.2	HF with reduced LVEF	18.05 ± 7.48 ng/mL	16.85 ± 8.08 ng/mL
Dalbeni	2014	Double-blinded/randomized	6 months	VD3 4000 IU/d	13	10	VD: 71.2 (67.0–75.4) CO: 73.4 (64.1–82.7)	EF < 55% and NYHA class > II	17.2 ± 18.6 ng/mL	17.6 ± 18.2 ng/mL
Schleithoff	2006	Double-blinded/randomized	9 months	VD3 4000 IU/d	61	62	VD: 57 (53, 63) CO: 54 (50, 62)	HF with reduced LVEF	14.4 ± 7.8 ng/mL	15.3 ± 7.4 ng/mL
Witham	2010	Double-blinded/randomized	20 weeks	VD2 100,000 IU/10wk	53	52	VD: 78.8 ± 5.6 CO: 80.6 ± 5.7	HF with reduced LVEF	20.5 ± 8.9 nmol/L	23.7 ± 10.0 nmol/L
Mckeag	2014	Double-blinded/randomized	12 months	VD2 400 IU/d	38	36	38.6 ± 10.9	HF with reduced LVEF	38.7 ± 13.8 nmol/L	38.6 ± 23.7 nmol/L
Boxer	2013	Double-blinded/randomized	6 months	VD3 50,000 IU/wk	31	33	65.9 ± 10.4	–	19.1 ± 9.3 ng/mL	17.8 ± 9.0 ng/mL
Moretti	2017	–/randomized	6 months	VD3 10,000 IU/d	20	20	67 ± 14	NYHA class II or III	19 ± 7 ng/mL	20 ± 7 ng/mL
Schroten	2013	Double-blinded/randomized	6 weeks	VD3 2000 IU/d	50	51	64 ± 10	HF with reduced LVEF	48 ± 17.0 nmol/L	46 ± 17.7 nmol/L
Turrini	2017	Double-blinded/randomized	6 months	VD3 300,000 U +50,000 U/month	17	16	VD: 77.0 ± 7.0 CO: 79.0 ± 7.0	Either preserved or reduced ejection fraction	9.4 ± 5.2 ng/mL	9.6 ± 7.3 ng/mL
Witte	2005	Double-blinded/randomized	9 months	VD3 400 IU/d	14	14	75.4 ± 4.2	HF with reduced LVEF	–	–
Zittermann	2019	Double-blinded/randomized	36 months	VD3 4000 IU/d	199	201	30.7 ± 10.6	HF with reduced LVEF	36.9 ± 16.8 nmol/L	38.0 ± 16.7 nmol/L
Shao	2021	Double-blinded/randomized	24 weeks	VD3 200 IU/d	34	34	82. 98 ± 1.32		19. 07 ± 5.81 μg/L	18. 58 ± 2.32 μg/L
Tian	2020	–/randomized	6 months	VD3 200 IU/d	42	38	–	HF with reduced LVEF	–	–
Qu	2015	–/randomized	3 months	VD3 1000 IU/d	27	27	VD: 70.0 ± 7.0 CO: 69.0 ± 8.0	–	–	–
Wu	2022	Double-blinded/randomized	1.6 years	VD3 100,000 IU/d	395	384	67 ± 8	–	66.5 ± 23.5 nmol/L	66.4 ± 23.1 nmol/L
Woo	2022	Double-blinded/randomized	6 months	VD3 4000/d	39	34	66.0 ± 9.6	–	11.9 ± 3.2 ng/mL	13.3 ± 3.0 ng/mL
Shedeed	2012	Double-blinded/randomized	12 weeks	25 μg (1000 IU) chole-calciferol/d	42	38	VD: 10.3 ± 4.6 CO: 11.2 ± 3.5	HF with reduced LVEF	13.4 ± 2.21 ng/mL	14.0 ± 2.46 ng/mL

Age is reported in mean ± SD. VD: treatment group. CO: control group. –: unclear.

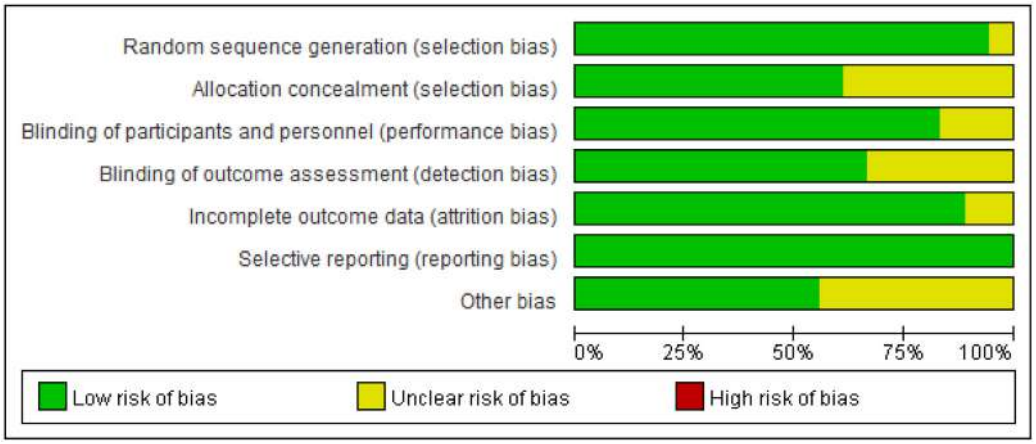

Fig. 2. Risk of bias graph.

- outcome indicators included LVEDD, LVEDV, LVEF, BNP/NT-proBNP, and 6MWD.

2.4. Risk of bias assessment

We evaluated the quality of the literature using the Cochrane Risk of Bias tool [5]. All included articles were independently assessed by two authors, and disagreements were resolved by a third author. If the information is not described in the study, an unclear risk of bias is selected.

2.5. Statistical analysis

RevMan5.3 and Stata15.0 software were used for meta-analysis. The results of our study are continuous variables so weighted mean difference (WMD) is used for analysis. We used chi-square test to analyze the heterogeneity of the included studies. If $P \geq 0.1$, the homogeneity of the studies was indicated, and the fixed-effect model was used for analysis. If $P < 0.1$, there is significant heterogeneity, and the random effects model is used for analysis. Publication bias was assessed qualitatively by funnel plots and quantitatively by Berg and Egger plots, where a two-tailed P-value < 0.1 of the Berg and Egger tests was considered statistically significant. Finally, the sensitivity analysis was performed using the "delete a study" method.

3. Results

3.1. Literature search results and process

A total of 1060 studies were retrieved, resulting in 570 remaining after removing duplicates. After reviewing titles and abstracts, 545 studies were excluded. Following the exclusion of two non-RCT studies and five unnecessary outcome measures, a total of 18 randomized controlled trials were included [6–23] (Fig. 1). Eighteen studies involving 2182 people, 1157 in the vitamin D group, and 1122 in the control group. The mean age of the patients ranged from 21 to 85 years. The duration of vitamin D treatment varied from 12 weeks to 3 years, with doses ranging from 200 IU/day to 50,000 IU/week (Table 1).

3.2. Study quality assessment

Out of the 18 studies included, 17 employed appropriate randomization methods, 11 utilized allocation concealment, and 15 implemented double-blinding (Figs. 2 and 3).

3.3. Results of meta-analysis

There were 14 studies [6–9,11,12,15–20,22,23] reported the changes in LVEF in the two groups. $P < 0.1$, $I^2 = 79.5\% > 50\%$, and the heterogeneity was high. The result showed that after vitamin D treatment, LVEF was improved [WMD = 3.18%, 95%CI (1.07, 5.3), $P = 0.003$] (Fig. 4). To reduce inter-study heterogeneity, different subgroup analyses were performed according to treatment duration, vitamin D dose and different HF categories, but none of them reduced inter-study heterogeneity.

The associated funnel plot showed no publication bias, and the Egger's test $P = 0.903$ and Begg's test $P = 0.661$ also indicated that there was no publication bias (Fig. 5).

NT-proBNP was reported in seven studies [8,9,11,14,19–21], a total of 1315 patients; four studies reported BNP results [10,13,15,18], a total of 230 cases; results using WMD analysis, the combined effect model $P > 0.1$, $I^2 = 38.1\% > 50\%$, using random effect model analysis. There was no significant difference between the two groups [WMD = −0.34, 95%CI (−0.65, −0.03), $P < 0.05$]. Shao et al.'s article reported BNP in mmol/L, we analyzed again after excluding this study, and subgroup analysis was performed by grouping BNP and NT-proBNP. The results showed high homology within the two groups, both $P > 0.1$, $I^2 = 0\%$. Fixed effect model was used to merge the effect size, and the results showed vitamin D supplementation could reduce the level of NT-proBNP in patients with heart failure [WMD = −0.7, 95%CI (0.24, 1.16), $P < 0.05$]. However, there was no significant difference in BNP [WMD = −40.18, 95%CI (−0.96.8, 16.48), $P = 0.165$], which may be caused by the small sample size (Fig. 6). The funnel plot showed no publication bias. And Egger's test and Begg's test all indicated no publication bias (Fig. 7).

Six studies [6,10–12,15,22] reported the 6-minute walk distance at the end point, and a total of 509 were included people, combined effect model $P > 0.1$, $I^2 = 0\%$, no heterogeneity among the studies. The result showed 6-minute walk distance was significantly increased in the vitamin D group [WMD = −11.54, 95%CI (−22.215, −0.871), $P = 0.09$] (Fig. 8).

Eight studies [6,8,9,15,17,20,22,23] reported changes in LVEDD. Combined effect model $P > 0.1$, $I^2 = 79.5\%$, the decrease of LVEDD was more obvious in the vitamin D group [MD = −1.67, 95%CI (−2.88, −0.46), $P < 0.05$]. The sensitivity analysis showed the heterogeneity came from the study of Shedeed and Tian, and the results were not statistically significant after removing these two studies [WMD = −0.21 95%CI (−0.62, 0.2), $P = 0.084$] (Fig. 9).

Four studies [6,7,16,22] reported the end point of LVEDV level. The pooled effect model $P > 0.1$, $I^2 = 0\%$, and there was no heterogeneity among the studies. The decrease of LVEDV was more

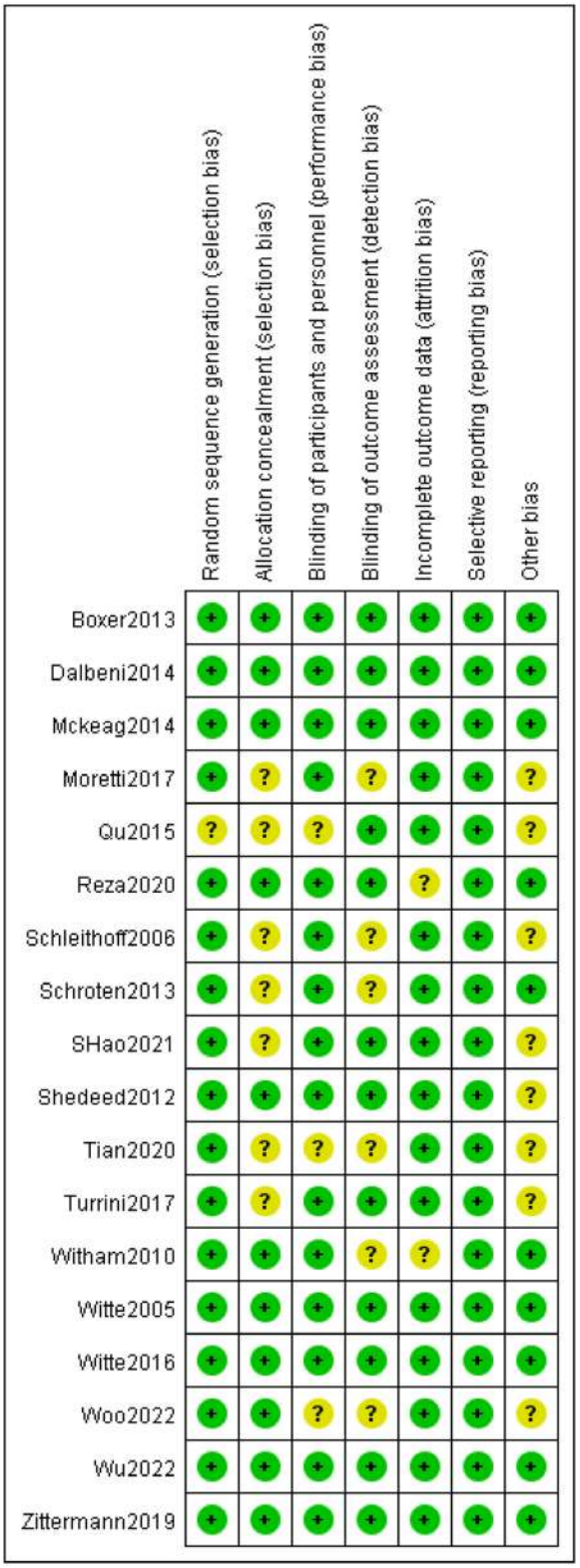

Fig. 3. Risk of bias summary.

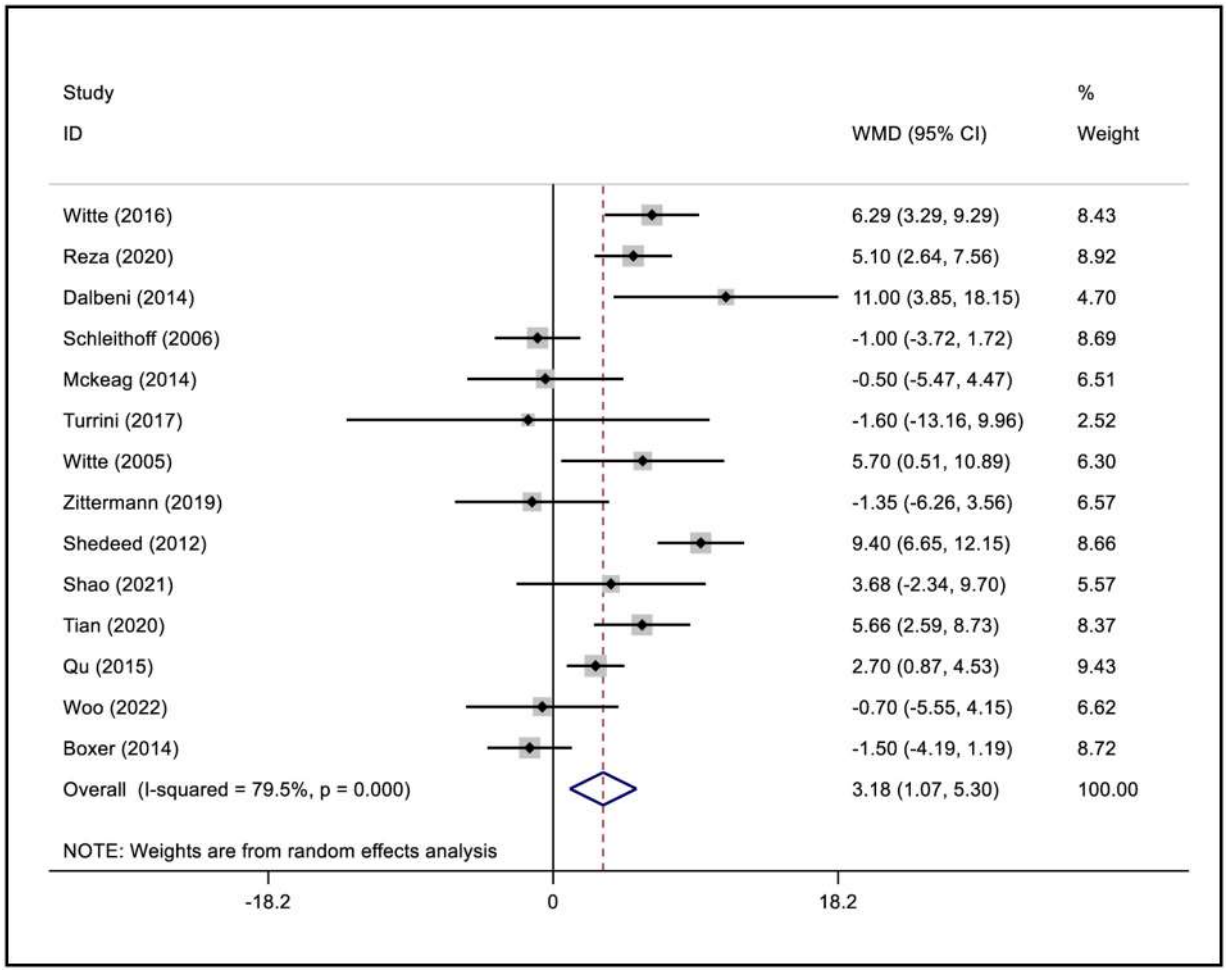

Fig. 4. Forest plot: effect of vitamin D supplements on LVEF.

significant in vitamin D group [WMD = −11.94, 95%CI (−20.59, −3.29), $P < 0.05$] (Fig. 10).

4. Discussion

This study is to evaluate the effect of vitamin D supplementation on cardiac function in patients with chronic heart failure. The study includes only adult or children with heart failure. All the included literatures were high-quality RCT studies, and it was a high quality meta-analysis.

A case of congestive HF brought on by hypocalcemic cardiomyopathy in a three-and-a-half-month-old newborn was described by Gillor et al. in 1989 [24], which paved the way for further investigation into the relationship between vitamin D and HF. A following observational clinical research revealed that newborns with severe and potentially fatal heart failure also had hypocalcemia as a result of vitamin D deficiency [25]. The pathophysiology and management of chronic heart failure have also been shown to affect bone and mineral homeostasis, according to Shane et al. [26], and there is mounting proof that the hormone calcitonin may influence cardiovascular function, with concentrations correlated with the degree of cardiovascular damage. This conclusion was also supported by animal tests. Mice lacking the vitamin D receptor exhibited heart hypertrophy and malfunction [27]. Two Mendelian randomization experiments suggested that 25 (OH)D may have a causal influence on lowering the risk of heart failure. The findings are consistent in that lower levels of vitamin D may be linked to heart failure, and prompt vitamin supplementation or maintaining a healthy

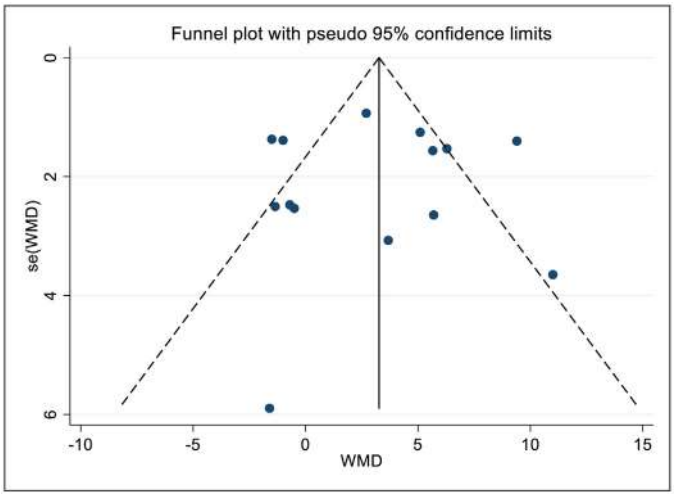

Fig. 5. Funnel plot: vitamin D supplements on LVEF.

level of 25(OH)D may be crucial steps in preventing heart failure in the general population [28,29]. Many studies have explored the pathogenesis of heart failure caused by vitamin D deficiency. These include activation of the renin-angiotensin-aldosterone system, induction of inflammatory responses to endothelial cell injury, and dysfunction of calcium processing in cardiomyocytes [30]. Inflammatory cytokines regulate the phenotype and progression of

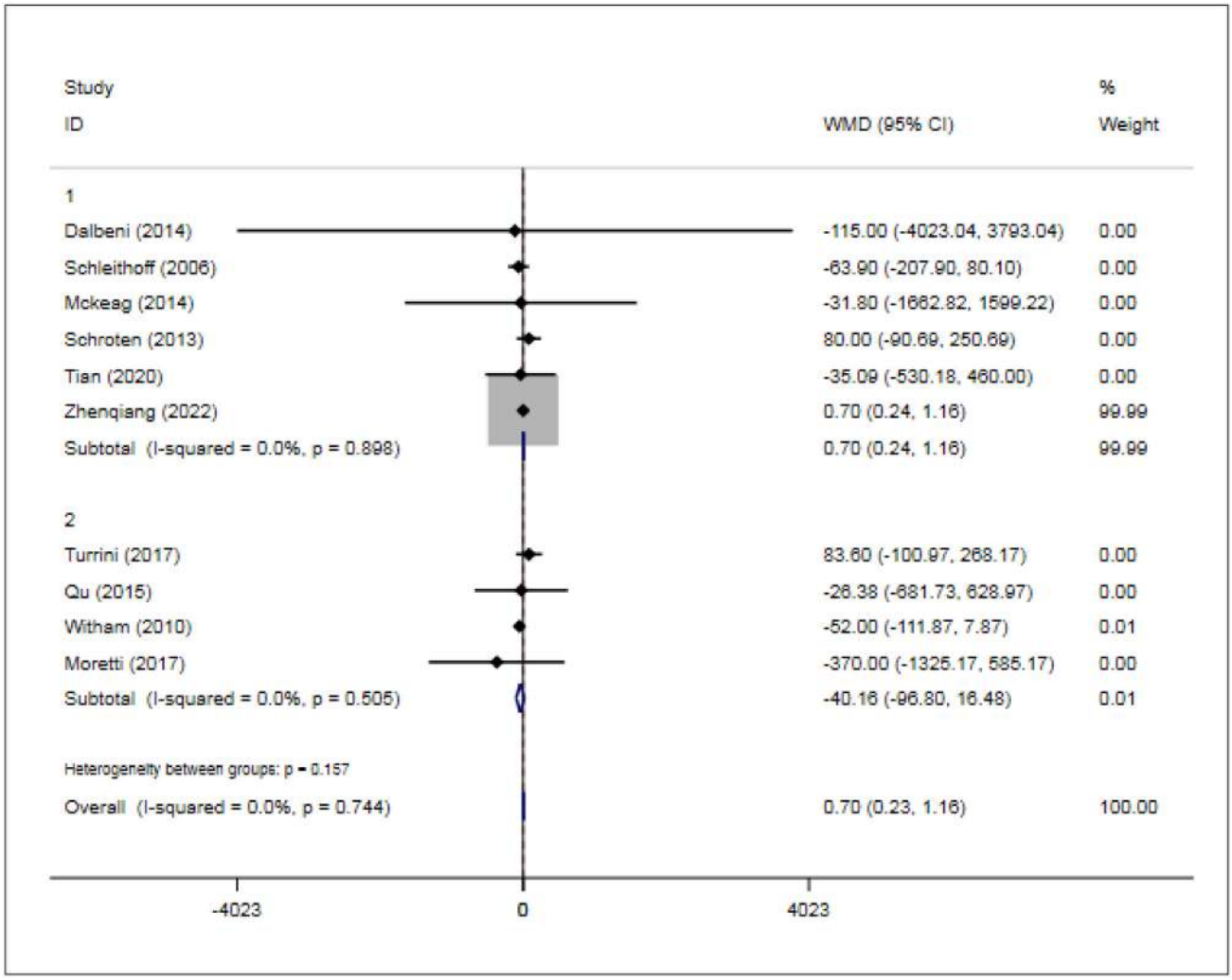

Fig. 6. Forest plot. 1: effect of vitamin D supplements on NT-proBNP; 2: effect of vitamin D supplements on BNP.

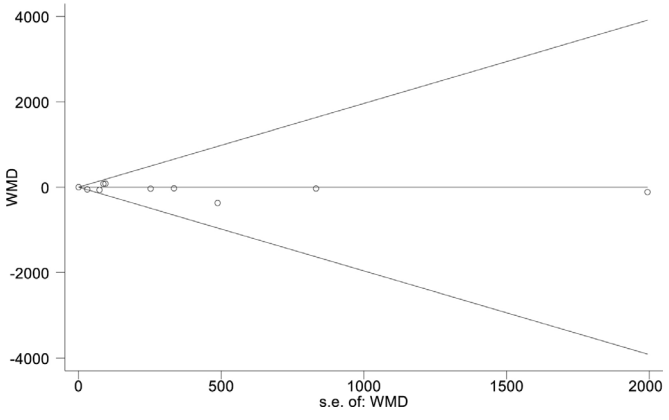

Fig. 7. Begg's funnel plot: effect of vitamin D supplements on BNP/NT-proBNP.

chronic heart failure [31]. A study from 2006 put forth the theory that treating low vitamin D levels would both prevent heart failure and enhance cardiac function in people who already had the condition [32]. Studies on the impact of vitamin D supplementation on HF subsequently began to emerge; these studies included studies on inflammatory indicators, heart color Doppler ultrasound indicators, and left ventricular ejection fraction [33]; these studies included RCTS, case-control studies, and meta-analyses, but the outcomes were not entirely consistent.

A 2018 study examining the relationship between vitamin D levels and the risk of mortality and hospitalization in patients with HF showed that vitamin D deficiency may lead to a significant increase in cardiovascular hospitalization, but there was no association with mortality, ejection fraction, or diastolic dysfunction [34]. Another long-term study investigated the reasons for the higher hospitalization and mortality rates in patients with vitamin D deficiency [35]. The study showed that vitamin D deficiency was associated with higher mortality, but not hospitalization rates. However, Busa's study showed that vitamin D deficiency is associated with hospitalization, adverse outcomes, and death [36]. This may be due to the sample size, which requires a larger sample to prove.

Rodriguez et al. [37] conducted a meta-analysis of the effect of vitamin D supplementation on inflammatory markers, and showed that the vitamin D supplementation group had lower tumor necrosis factor-α (TNF-α) concentrations at follow-up. The meta-analysis [38] also showed that vitamin D supplementation could reduce serum inflammatory markers, inhibit ventricular remodeling and improve cardiac function in patients with CHF.

A 2021 meta-analysis [39] evaluated the effect of vitamin D supplementation on EF, and the results showed that vitamin D supplementation could effectively improve EF values in patients with heart failure, which was consistent with the results of Zhao et al.

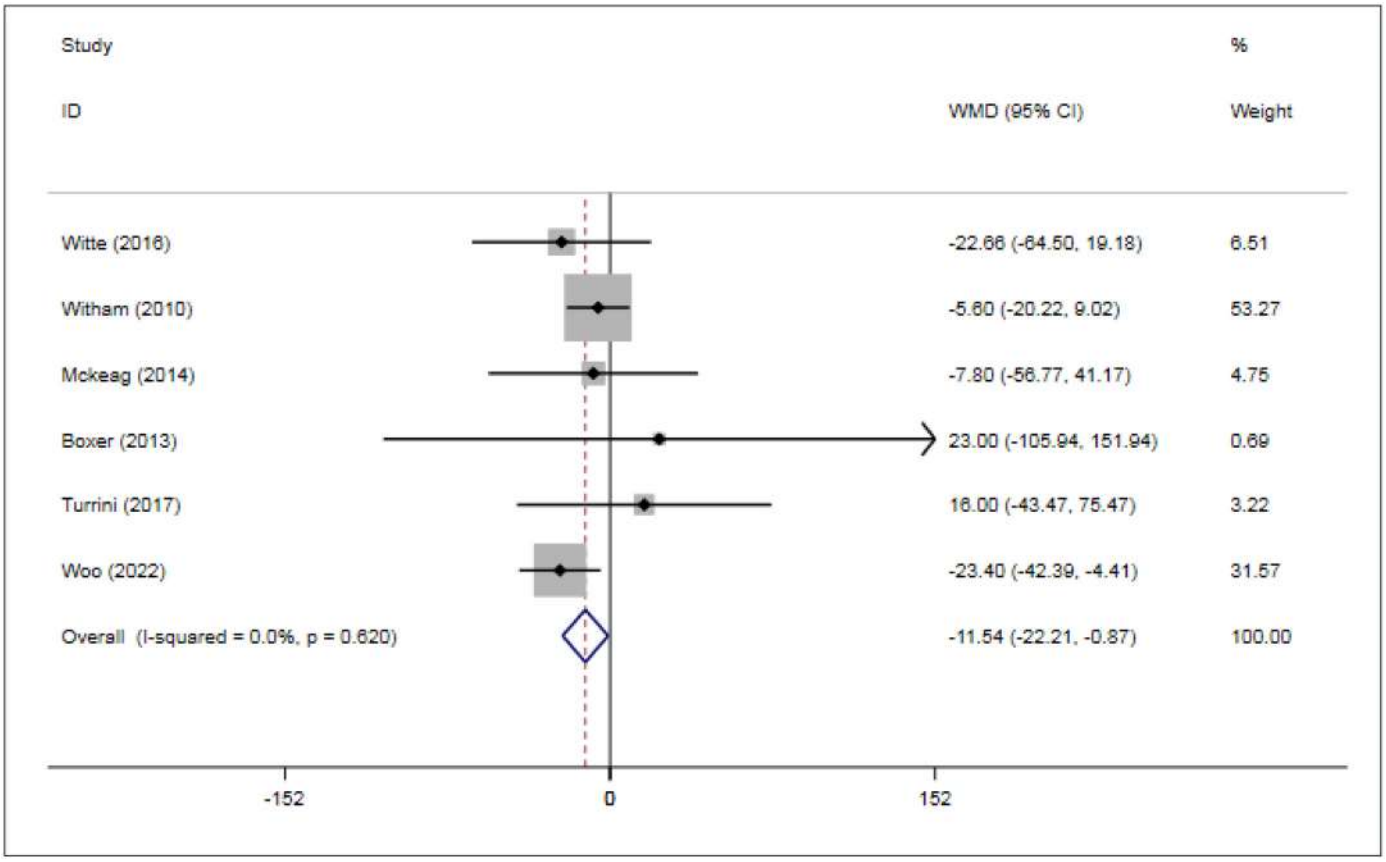

Fig. 8. Forest plot: effect of vitamin D supplements on 6WM.

[40]. However, the study by Wang et al. [41] revealed the opposite result.

In summary, the indicators of the current meta-analysis studies are not exactly the same, and the results are also controversial. We are not sure whether patients with chronic heart failure can benefit from vitamin D supplementation, and a larger sample is still needed to explore the effect of vitamin D supplementation. As clinicians, we need to combine exercise endurance, myocardial injury markers, and cardiac color Doppler ultrasound to evaluate cardiac function. So far, there is no meta-analysis to fully evaluate the above results. This study is all RCT with a large sample size, and the selected indicators include BNP, 6MWD, LVEF, LVEDD, and LVEDV are the most important and commonly used indicators of cardiac function evaluation in clinical practice, so our study is completely necessary.

Our study showed that vitamin D supplementation could significantly improve LVEF [WMD = 3.18%, 95%CI 1.07–5.3, $P = 0.003$], but the results were highly heterogeneous. Subgroup analysis was performed by age, but heterogeneity was still not significantly reduced. This result was consistent with the previous study by Naghedi et al. and the study by Nie [42] [MD = 2.57, 95% CI (0.35–4.79), $P < 0.05$]. We conducted a subgroup analysis of BNP, and there was no heterogeneity within or between groups. The final results showed that vitamin D supplementation could improve NT-proBNP but could not improve BNP. However, there are few studies using BNP as an outcome, and the sample size is small, so more samples are needed to confirm the results. We found that LVEDD and LVEDV decreased more significantly in the vitamin D group, which was consistent with the results of Nie [MD = 2.57, 95% CI (0.35–4.79), $P < 0.05$]. In addition, we also found that vitamin D supplementation improved 6MWD, in contrast to Nie's findings, possibly because 6MWD is more susceptible to confounding factors such as age or comorbid diseases affecting physical activity.

The limitations of this study are as follows: first, the vitamin D formulation, dose, and frequency used are not all identical, and the baseline vitamin D levels and baseline cardiac function of the patients are not all identical, which may be a source of bias. In addition, the main source of vitamin D depends on light, and our study could not rule out that patients with HF who live in sunny areas have adequate 25-OHD levels.

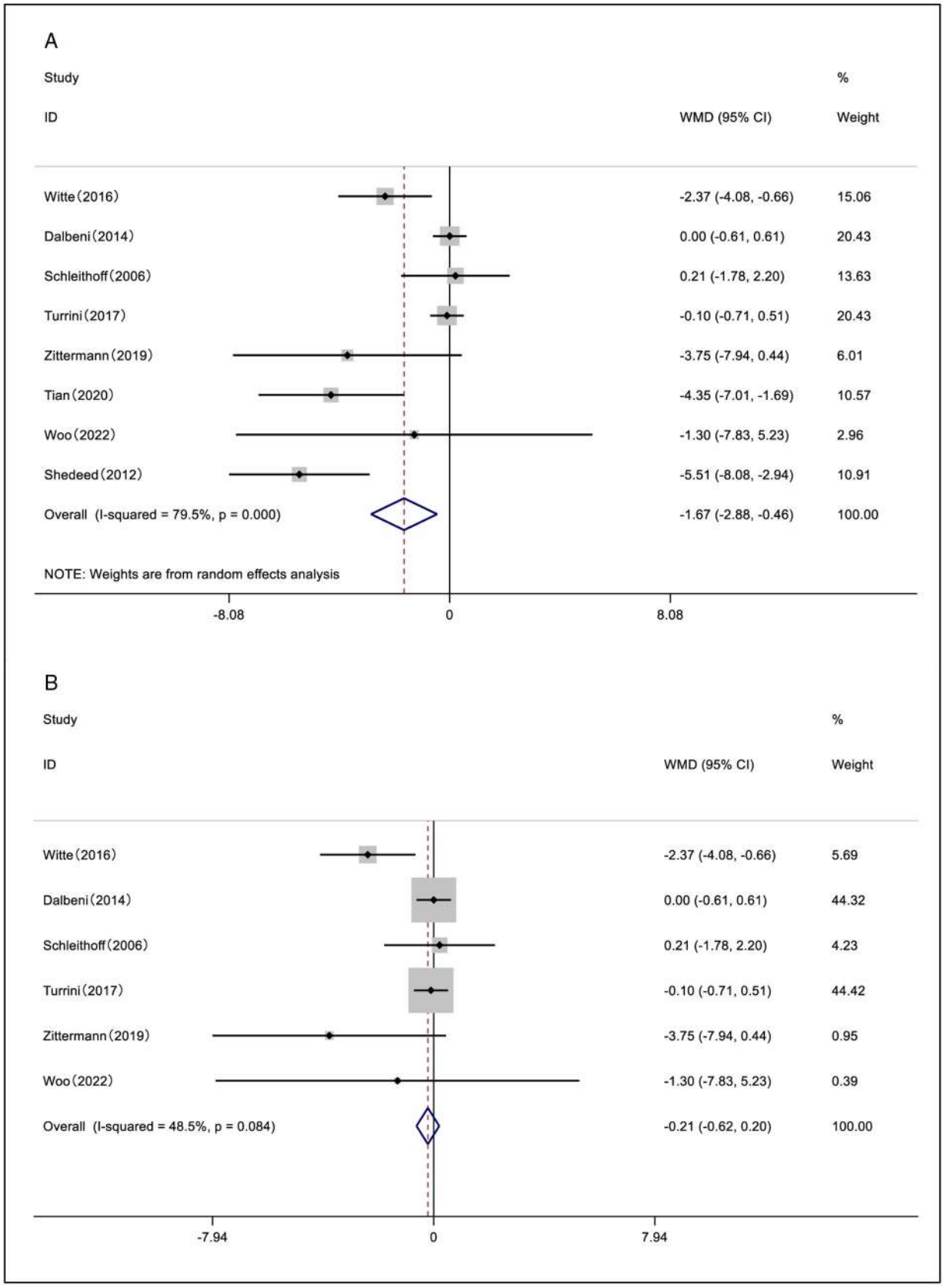

Fig. 9. Forest plot: effect of vitamin D supplements on LVEDD. A. Forest plot before excluding heterogeneity studies. B. Forest plot after excluding Shedeed and Tian's study.

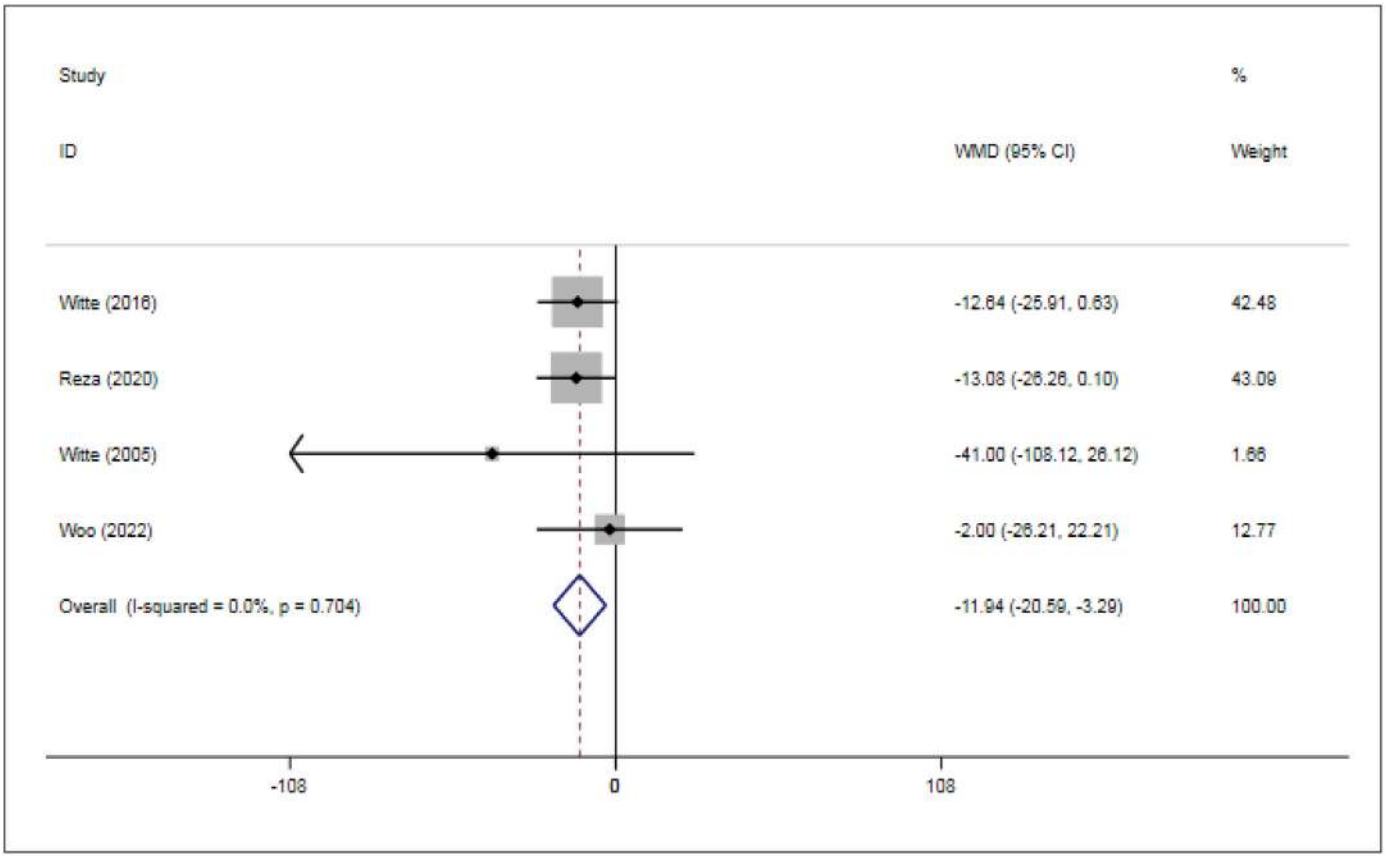

Fig. 10. Forest plot: effect of vitamin D supplements on LVEDV.

5. Conclusion

Vitamin D supplementation can significantly and effectively improve cardiac function, inhibit ventricular remodeling, and improve exercise endurance in patients with CHF.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Disclosure of interest

The authors declare that they have no competing interest.

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Authors' contributions

All authors participated in the design of the paper and the quality evaluation of the included literature, and Qian Tang wrote the paper. Lin Liu_a and Liu Lin_b completed the collection of literature and related data. Min Chen revised the design of the article and participated in the discussion of the results of the article. All authors reviewed the manuscript.

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Not applicable.

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