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Complete List of Authors:	zhao, jindong; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China, Jia, JingJing; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China Dong, PingShuan; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China Zhao, Di; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China Yang, XuMing; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China Li, DaoLin; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China Zhang, HuiFeng; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China
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Effect of Vitamin D on ventricular remodeling in Heart Failure: A Meta-analysis of Randomized Controlled Trials

Running title: Vitamin D treatment of Heart Failure

Jin-Dong Zhao, Jing-Jing Jia, Ping-Shuan Dong*, Di Zhao, Xu-Ming Yang, Lai-Jing Du, Hui-Feng Zhang

Author： Jin-Dong Zhao, The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China. Tel: 18437919892;

E-mail: zhaojindong123@outlook.com

***Corresponding author:** Ping-Shuan Dong, The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China. E-mail: pingshuandong@foxmail.com

Address of all author: The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China.

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ABSTRACT:

Objectives: The level of vitamin D is considered to be associated with the development and progress of heart failure. However, it is still unclear that whether supplementation of vitamin D could improve the ventricular remodeling of the patients with heart failure. This study aimed to systematically evaluate the influence of additional supplementation of vitamin D on ventricular remodeling of the patients with heart failure as well as its safety.

Design: This study is A Meta-analysis of Randomized Controlled Trials.

Setting: Make a retrieval of PubMed, EMbase, CNKI, Cochrane library and WEB SCINENCE was performed for randomized controlled trials (RCTs) pertinent to the effect of vitamin D on ventricular remodeling of the patients with heart failure (all from database creation to October 2017). RevMan5.3 software was employed for data analysis.

Participants: Eventually seven RCTs with a total of 465 patients including 235 cases in Vitamin D group and 230 cases in the control group were included.

Primary and Secondary outcome measures: LVEDD; LVEF, the incidence of adverse reactions.

Results: Compared with the control group, a significant decrease was observed in vitamin D group in LVEDD (mean difference [MD] =-2.31mm, 95% confidence interval [CI]: -4.15- -0.47, P =0.01), and a increase was indicated in LVEF (MD=4.18%, 95% CI: 0.36-7.99, P =0.03) has remarkable increase. Subgroup analysis also revealed a remarkably lowered LVEDD in adults (>18 years) and adolescents (<18 years) of vitamin D group in relative to the control group. High-dose vitamin D (＞4000IU/day) was more effective at reducing LVEDD than low-dose (＜4000IU/day).

Conclusion: Vitamin D supplementation can inhibit the ventricular remodeling, and improve the cardiac function in patients with heart failure.

Trial registration: PROSPERO CRD42017073893

Keywords: Vitamin D, ventricular remodeling, cardiac function, heart failure

Strengths and limitations of this study

- The results of this systematic review and meta-analysis will be highly dependent on the quality of the included primary research studies. Only RCTs were adopted in this study.
- Subgroup analysis were performed according to clinical heterogeneity analysis of the included studies.
- This will be the first review to systematically examine the impact of supplementation of vitamin D to the ventricular remodeling of the patients with heart failure. Result will help to guiding clinical medication.
- The results need to be interpreted with caution as there was a few study in the subgroup.

Introduction

Heart failure(HF) is the main factor leading to economic loss due to its characterized by bad prognosis and high mortality rate [1]. In the USA, there are at least 5,000,000 patients with decreased contractile function, and meanwhile, there is also the same amount of patients with the same disease in Western Europe [2,3]. In recent years, prognosis of heart failure has been improved remarkably, and the survival rate has been improved from 43% to 52% [4] in 5-year survival rate. At present, the main treatment methods for heart failure are still β-receptor blocking agents, ACEI/ARB, and aldosterone receptor antagonist, however, though they could reduce adverse cardiac events and improve prognosis of cardiac function [5], heart failure is still a main cause for global mortality rate. Therefore, there is an urgent need for supplementary treatment methods and strategies at present.

Lack or insufficiency of vitamin D may result in cardiovascular and cerebrovascular diseases [6-10]. Many studies have discovered that [11-14] there is a remarkable relation between lack of vitamin D and progression of HF. Studies showed that patients with heart failure were generally in lack of vitamin D and had bad prognosis, and supplementation of vitamin D could reduce mortality rate of patients with heart failure [15-17]. Several studies showed Vitamin D acts as a negative regulator of renin-angiotensin-aldosterone system (RAAS) [18-20], and modulates

myocardial extracellular matrix turnovers. Consistently, Vitamin D receptor(VDR) knockout mice show increased RAAS activity, leading to hypertension, cardiac hypertrophy, increased water intake and sodium retention [18], and VDR knockout mice show increased metallopreotease (MMP) activity, which promotes the destruction of myocardial tissue leading to ventricular remodelling [21,22]. Therefore, lack of vitamin D could result in deterioration of HF, and accelerate the myocardial remodeling.

At present, concerning the influence of vitamin D on ventricular remodeling of patients with heart failure, different studies have controversial conclusions. Therefore, this study makes a meta-analysis of influence of vitamin D on ventricular remodeling of patients with heart failure, so as to further clarify influence of vitamin D on ventricular remodeling of patients with heart failure.

Materials and Methods

Search strategy

PubMed, EMbase, Cochrane Central Register of Controlled Trials, CNKI and WEB of SCINENCE were retrieved. Medical subject headings: “heart failure”, “vitamin D”, “ventricular remodeling”, “heart function tests”, “randomized controlled Trials”; Keywords: “cardiac failure”, “myocardial failure”, “heart decompensation”, “left ventricular remodeling”, “ventricular remodelings”, “ventricular myocardial remodeling”,

"cholecalciferol", "vitamin D3", "controlled clinical trials". Time frame for the retrieval: establishment of the database to October 1, 2017. The reference lists of identified articles were also reviewed.

Study selection

Inclusion criteria: 1) Randomized controlled trials (RCTs) involving with the effect of Vitamin D on the Ventricular Remodeling of patients with heart failure, with or without blind method or allocation concealment employed; 2) Parallel or crossover trials; 3) Only the data before the washout period used in a crossover test; 4) Available baseline data and changes in left ventricular end-diastolic dimension(LVEDD), left ventricular ejection fraction(LVEF); 5) heart failure defined as New York Heart Association functional class ≥II, or a left ventricular ejection fraction (LVEF) ≤40%; 6) Participants of any gender, age or ethnicity; 7) Participants without using or changing any micronutrient except for Vitamin D, 8) A minimum 3 months of therapy was necessary for inclusion in the review to ensure the intervention had sufficient time to produce a better effect. Exclusion criteria: 1) Only the abstract reported for reference; 2) Studies with duplicated data, including same group of patients or for whom there were updated results available; 3) The study have no interest outcomes; 4) Animal test and review; 5) Conference

documents; 6) Non-RCTs, cohort studiers, retrospective studies. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Henan University of Science and Technology.

Data extraction and quality assessment

Data were independently extracted from each study by two authors (JD Zhao and JJ Jia) and entered onto a structured spreadsheet，followed by a cross check procedure. Disagreements were resolved by consensus or by a third investigator (P. Dong). The following data were extracted from each trial: the first author's surname, year of publication; demographic and methodological data; total number, mean age, gender distribution and race of enrolled patients; the using or changing drugs for heart failure; baseline seated LVEDD and LVEF at baseline, when available; number of patients randomized assigned to each intervention; duration of therapy; incidence and type of adverse events; number of dropouts or with drawals because of adverse events; and change from baseline of seated LVEDD and LVEF. Criteria for RCT bias risk evaluation listed in Cochrane Handbook for Systematic Reviewer 5.1.0 were adopted, including: 1) random sequence generation, 2) allocation concealment, 3) blinding of patients and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective reporting risk. Then an evaluation system with "low risk", "high risk" and "not clear" was established according to the six criteria as describes above [23].

Outcome assessed

Primary endpoints: LVEDD; Secondary endpoints: LVEF, the incidence of adverse reactions.

Data analysis and synthesis

RevMan5.3 software was employed for data analysis, with risk ratio (RR) and 95% confidence interval (CI) used for binary variables, mean difference (MD) and 95% CI for continuous variables, as well as a test level α=0.05. Following clinical heterogeneity analysis of the included studies, statistical heterogeneity was assessed using χ^2 based Cochran Q statistic and I^2 [24]. For the Q statistic, P $\geq$0.1 indicates homogeneity among multiple similar studies, and fixed effects model can be employed for Meta analysis; while P <0.1 indicates were considered to indicate statistically significant heterogeneity, analyzed by random-effects model. For the I^2 statistic, I^2 <25% indicates low heterogeneity, while I^2 >50% indicates moderate to high heterogeneity [25].

Results

Selection and description of studies

157 published papers were collected after the initial screening, and eventually seven RCTs [26-32] with a total of 465 patients including 235 cases in Vitamin D group and 230 cases in the control group were included through reviewing the title, abstract and full text, as well as eliminating duplicate documents, non-randomized controlled trials, and those failed to meet the inclusion criteria. See **Figure 1** for the screening process.

In the seven included studies [26-32], four studies reported a correct random method[27-29,32]; two study adopted allocation concealment[29,32], and six studies used double blind[26-30,32] . See **Figure 2** for evaluation on the methodology of the studies.

Data of the curative effect on the LVEDD were reported in five studies and LVEF in all the included studies, two studies mentioned adverse reactions [26,30]. Dropout or withdrawal from the research was covered in all the included studies. The study characteristics are shown in **Table 1**, and the basic information of the include population in **Table 2**.

Effects of Vitamin D on LVEDD

The changes in LVEDD of the patients were reported in five studies [26-30], which showed high levels of heterogeneity among the results of the studies (heterogeneity χ^2, P=0.07, I^2=55%), thus supporting the analysis using the random effect model. Compared with the control group, a significant decrease was observed in Vitamin D group in LVEDD (mean difference [MD] = -2.31mm, 95% confidence interval [CI]: -4.15- -0.47, P =0.01) (**Figure 3**).

Effects of Vitamin D on LVEF

The changes in LVEF of the patients were reported in all the seven studies [26-32], which showed high levels of heterogeneity among the results of the studies (heterogeneity χ^2, P <0.001, I^2 =88%), thus supporting the analysis using the random effect model. Compared with the control group, a significant increase was observed in Vitamin D group in LVEF (MD=4.18%, 95% CI: 0.36-7.99, P =0.03) (**Figure 4**).

Subgroup analysis

The analysis based on age stratification revealed that compared with the control group, both of the adults (aged≥18 years) and Non-adults (aged<18 years) with heart failure in the Vitamin D group showed a decrease in LVEDD (adults: heterogeneity χ^2, P =0.65, I^2 =0%; MD=-1.62mm, 95% CI: -2.83- -0.42, P =0.008; Non-adults: MD=-5.51mm, 95% CI, -8.08- -2.94, P<0.001) (**Figure 5**). These results, however, need to be interpreted with caution as there was only one study in the subgroup of Non-adults.

A subgroup analysis was performed according to dosage of Vitamin D. There was the effect of high-dose Vitamin D on reduction of LVEDD (MD=-1.71mm, 95% CI: -2.95- -0.46, P =0.007), but this effect was not seen with low-dose Vitamin D treatment (MD=-3.38mm, 95% CI: -8.23- 1.48, P =0.17). (**Figure 6**).

Publication bias

There was a significant asymmetry of the funnel plot for the effect of Vitamin D on LVEDD, which may be due to publication bias and other causes (**Figure 7).** On the other hand, no publication bias was found for the effect of Vitamin D on LVEF (**Figure 8**).

Adverse event

Two studies [26,30] reported the adverse events. During the follow-up, no significant adverse event was recorded. No data associated with the incidence of adverse events were recorded in the other three studies.

Discussion

At present, as for influence of vitamin D on ventricular remodeling of patients with heart failure, different studies have controversial conclusions. Results of this study show that, compared with the control group, among patients with heart failure, supplementation of vitamin D could reduce LVEDD (MD = -2.31 mm, 95% CI: -4.15- -0.47, P =0.01), and improve LVEF (MD=4.18%, 95% CI: 0.36-7.99, P =0.03). Besides, it has a more clear effect on high-dose Vitamin D (MD=-1.71mm, 95% CI: -2.95- -0.46, P =0.007).

Most of new treatment methods for chronic heart failure are expensive, and have a high requirement for technology [33], and most of them fail to conform to demand for strict Phase III clinical trial. For patients with heart failure, vitamin D is not only cheap but also safe, and they may obtain more benefits from it [34]. Heart failure refers to that cardiac contraction and diastole are affected due to overload of Ca ion in myocardial

cells. Lack of vitamin D may intervene with operation of Ca ion in myocardial cells, thus resulting in cardiomyocyte hypertrophy, and intra-organizational inflammatory reaction and fibrosis [35,36]. Low vitamin D level could activate the renin-angiotensin system [37], give rise to inflammatory reaction [38], and result in endothelium dysfunction [39]. The effects of Vitamin D on CV system are additionally mediated through elevated parathyroid hormone (PTH) levels, that is associated with development of left ventricular (LV) hypertrophy in patients with elevated PTH levels [40]. Although there are lots of evidences showing that lack of vitamin D could result in bad prognosis of patients with heart failure, as for whether supplementation of vitamin D could benefit the patients with heart failure, different studies have controversial conclusions.

In recent years, there have also been some relative small RCTs, which studied the influence of vitamin D on patients with heart failure. In 2014 World Heart Failure Conference, Louise et al [41] reported a RCT which made a 6-month study toward 32 patients with heart failure, and the result showed that supplementation of vitamin D had no influence on improving LVEF and improving pro-bnp. A recent system assessment [42] also showed that supplementation of vitamin D could not improve the LVEF (WMD: 4.11%, 95% CI: −0.91 to 9.12, P =0.11) of the patients with heart failure. However, other studies drew the opposite conclusions. In 2015 European Society of Cardiology, Lowry et al[43] reported a

12-month RCT, and the result showed that for patients with heart failure, supplementation of vitamin D could improve the ventricular remodeling (LVEDD −4.46 mm; p=0.047), and the LVEF showed a rising trend. It was also showed by a non-RCT [44] that supplementation of vitamin D could make EF value before and after the trial increase remarkably. Elidrissy et al [45] summarized 61 cases of children with cardiomyopathy, they thought the evidence available supports that the most likely cause of cardiomyopathy is hypocalcemia, and suggested for prevention maternal supplementation during pregnancy and lactation with up to 2000 units of vitamin D and 400 units for their infants, which was also similar to study result of Shedeed [29].

Since there are disputes among different study results, therefore, we conduct a meta-analysis of relevant RCT studies, so as to further clarify influence of supplementation of vitamin D on ventricular remodeling of patients with heart failure. Result of this study shows that, supplementation of vitamin D could inhibit myocardial remodeling of the patients, and improve the cardiac function.

Different studies have different results and conclusions, which may be related to different recommended dosages of vitamin; since there is no uniform standard for recommended dosage of vitamin D at present, therefore, there are differences in recommended dosage of vitamin D in

different trials, which may affect the result. However, there hasn't been a report related to adverse effects concerning dosage of vitamin D. Meanwhile, it has a great relation with the selected group, for example, study results of Schleithoff et al [28] showed that there were no remarkable changes in LVEF and LVEDD, and the people included in this study were more than those of NYHA 3-4 level, the degree of heart failure was high, and there was a high rate of lost to follow-up visit (37%).

The data in changes of LVEDD showed high levels of heterogeneity among the results of the studies. Shedeed [29] studied the cause of heterogeneity according to the subgroup analysis. There was a certain difference in metabolism of vitamin D and cardiac recovery capacity between newborns and adults, which might be the cause of heterogeneity.

Limitation of this study is considered to be although all trials included in this study are RCTs, there are still lots of limitations. 1) the quantity of the people included in the study is relative small, and more large-scale trials are still required to study the effect of vitamin D on patients with heart failure; 2) this study has heterogeneity, and through subgroup analysis and sensitivity analysis, it is discovered that, the age stratification of the studied group is the source of heterogeneity; 3) there is difference in recommended dosage of vitamin D in different trials, which may affect the study result, and more trials are required to explore the relationship between dosage and effect.

In conclusion, this study shows that supplementation of vitamin D could inhibit myocardial remodeling of patients with heart failure, and improve their cardiac function. Therefore, in clinical practices, for patients with heart failure, the treatment applying additional supplementation of vitamin D may bring more benefits to the patients.

Table 1 Study characteristics.

Author	Design	Blinding	Vitamin D Dose	Follow-up Duration	Study population	Primary Outcome
Turrini et al, 2017	Prospective RCT	Double-blind	300.000 IU at Baseline 50.000IU/mo	6 mo	Chronic HF, 25(OH)D <20 ng/mL, 60 y＜Age,	6MWD, echocardiography Parameters, hormonal
Witte et al, 2016	Prospective RCT	Double-blind	4000IU/d	12 mo	Chronic HF, NYHA class II–III, LVEF<45%, 25(OH)D <20 ng/mL	6MWD, echocardiography parameters

Qu et al, 2015	Prospective RCT	Single-blind	1000 IU/d	3 mo	NYHA class III–IV	echocardiography parameters, BNP, 25(OH)D
Dalbeni et al, 2014	Prospective RCT	Double-blind	4000IU/d	25 wk	Chronic HF, LVEF<55%, NYHA class>II, 25(OH)D <30ng/mL, Age >40 y,	Echocardiographic parameters, NYHA class, NT-proBNP
Boxer er al,2014	Prospective RCT	Double-blind	50000IU/wk	6mo	Age ≥50 y, NYHA class II–IV, 25(OH)D <37.5 ng/mL	Echocardiographic parameters, serum analysis, urine analysis
Shedeed, 2012	Prospective RCT	Double-blind	1000 IU/d	12 wk	Congestive HF, LVEF<40%, LV＞2 SD for age and sex	Echocardiographic parameters
Schleithoff et al, 2006	Prospective RCT	Double-blind	2000 IU/d	9 mo	Chronic HF, NYHA class II–IV	Survival rates, NT-proBNP, Pro-and anti-inflammatory cytokines, Echocardiographic parameters,

†25(OH)D; ‡6MWD; §HF; **IU; ††LV; ‡‡LVEF; §§NT-proBNP; ***NYHA;

Table 2 Study population characteristics.

Author	Intervention	Number (n)	Age (years)	Male (%)	LVEF (%)	NYHA Class II(%)	NYHA Class III(%)	NYHA Class IV(%)	LVEDD (mm)	25(OH)D (ng/mL)	Ischemic Cause (%)	Hypertension (%)	Diabetes (%)
Turrini et al, 2017	Vitamin D	17	77±7	35.3	54.7±13.8	64.7	35.3	0	51±1.58	9.4±5.2	41.2	64.7	35.3
	Placebo	16	79±7	43.8	49.2±19.1	68.7	21.3	0	54±3.48	9.6±7.3	43.7	43.7	18.7
Witte et al, 2016	Vitamin D	80	68.5±12.45	83.8	25.6±10.80	92.5	7.5	0	57.6±8.62	38.2±24.81	55.0	NR	21.3
	Placebo	83	69.0±13.78	74.7	26.5±10.62	85.5	14.5	0	58.0±6.49	36.4±20.24	60.2	NR	24.1

† 25-hydroxyvitamin D
‡ 6-minute walk distance
§ heart failure
** international units
†† left ventricular
‡‡ left ventricular ejection fraction
§§ N-terminal pro-B-type natriuretic peptide
*** New York Heart Association

Qu et al,	Vitamin D	22	70±7	59.3	34.9±3.8	NR	NR	NR	NR	NR	NR	66.7	81.5
2015	Blank	17	69±8	51.8	34.6±3.9	NR	NR	NR	NR	NR	NR	63.0	85.2
Dalbeni et	Vitamin D	13	71.2±6.22	84.6	39.08±8.00	58.8*	50.0**		53.9±6.81	16.2±6.59	76.9	100	NR
al, 2014	Placebo	10	73.4±13.78	60.0	43.6±7.63	41.2*	50.0**		50.6±7.04	16.0±6.15	90	100	NR
Boxer er	Vitamin D	19	65.8±10.6	48.4	39.2±13.2	55.0	73.0	0	NR	19.1±9.3	25.8	83.0	51.6
al,2014	Placebo	15	66.0±10.4	54.5	36.1±14.5	45.0	27.0	0	NR	17.8±9.0	30.3	84.8	42.4
Shedeed,	Vitamin D	42	0.86±1.3	64.29	36.4±2.26	NR	NR	NR	32.81±4.6	13.4±2.21	NR	NR	NR
2012	Placebo	38	0.93±1.0	57.89	37.2±2.62	NR	NR	NR	30.7±5.2	14.0±2.46	NR	NR	NR
Schleithoff et al, 2006	Vitamin D+ Calcium	42	57±7.41	85.25	32.5±8.67	NR	NR	NR	69.0±8.89	14.4±7.85	47	38	20
	Placebo+ Calcium	51	54±8.89	80.65	33.0±7.56	NR	NR	NR	69.0±9.26	15.3±7.48	40	32	23

†††NR

††† Not reported
*I and II
** III and IV

Contributor ship statement

Jin-Dong Zhao：Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND Drafting the work or revising it critically for important intellectual content; AND Final approval of the version to be published; AND Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Jing-Jing Jia：participated in writing

Ping-Shuan Dong*：served as scientific advisors

Di Zhao：participated in technical editing of the manuscript

Xu-Ming Yang：critically reviewed the study proposal

Dao-Lin Li：collected data

Hui-Feng Zhang：collected data

Disclosure of conflict of interest

None.

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Data sharing statement

The authors declare that they willing to share their data directly.

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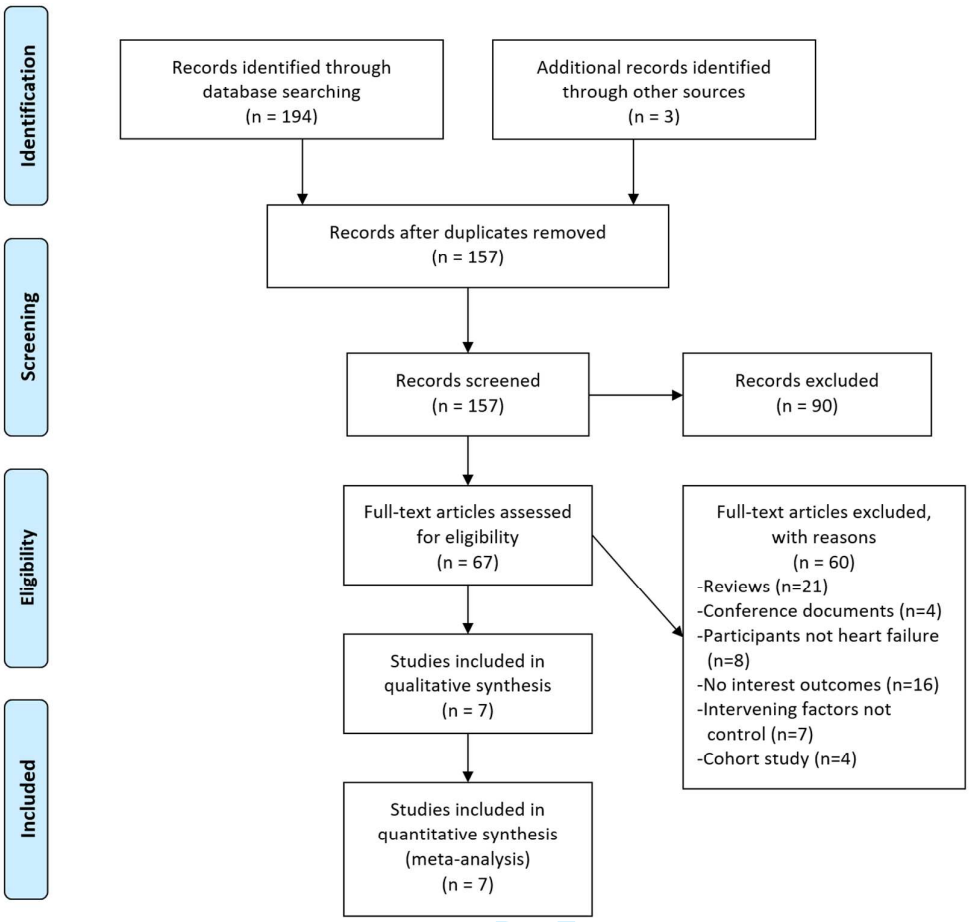

Figure 1 Flow diagram of study selection.

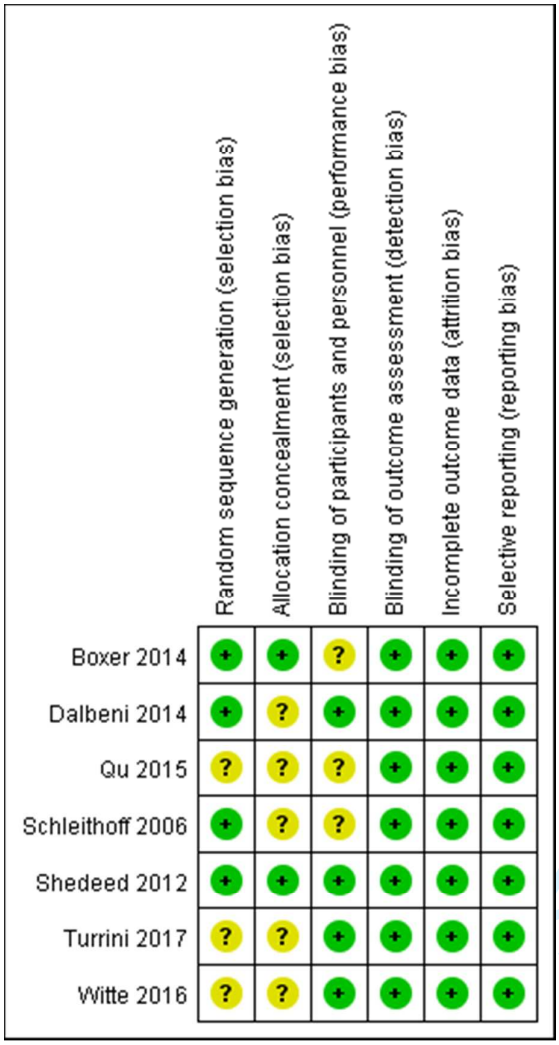

Figure 2 Quality assessment.

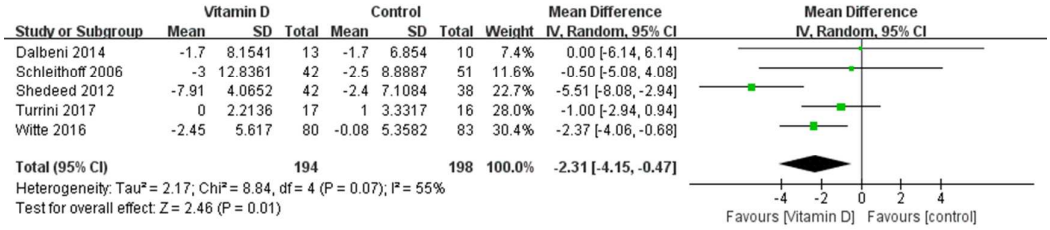

Figure 3 : Forest plot showing the effect of Vitamin D on LVEDD

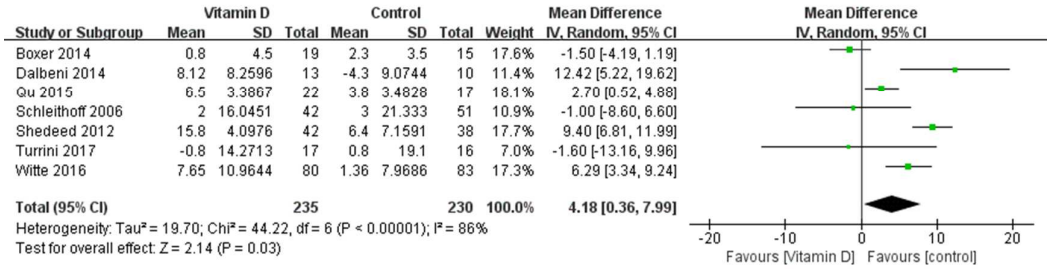

Figure 4: Forest plot showing the effect of Vitamin D on LVEF

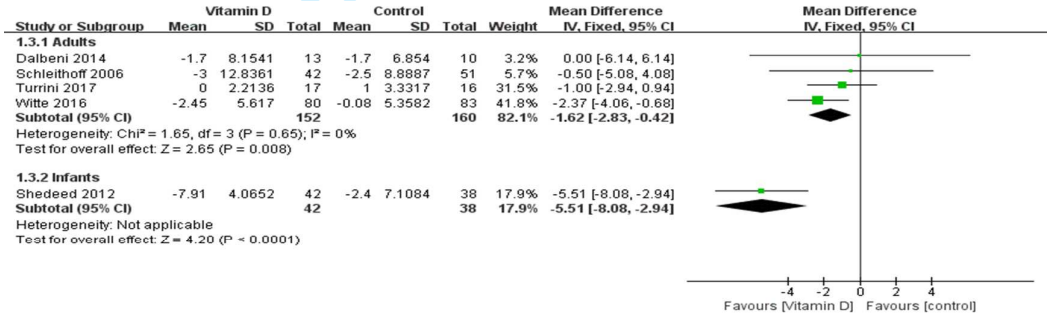

Figure 5: Subgroup analysis of effect of Vitamin D on LVEDD according to patients' age.

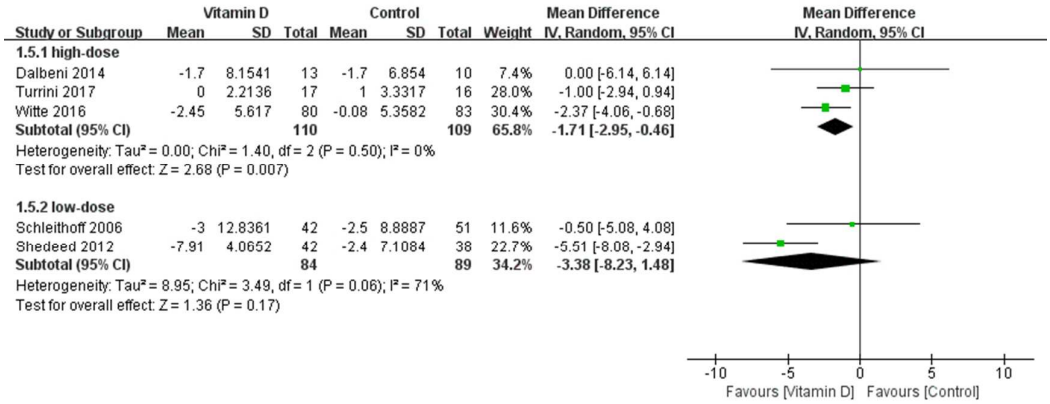

Figure 6: Subgroup analysis of effect of Vitamin D on LVEDD according to dose of Vitamin D.

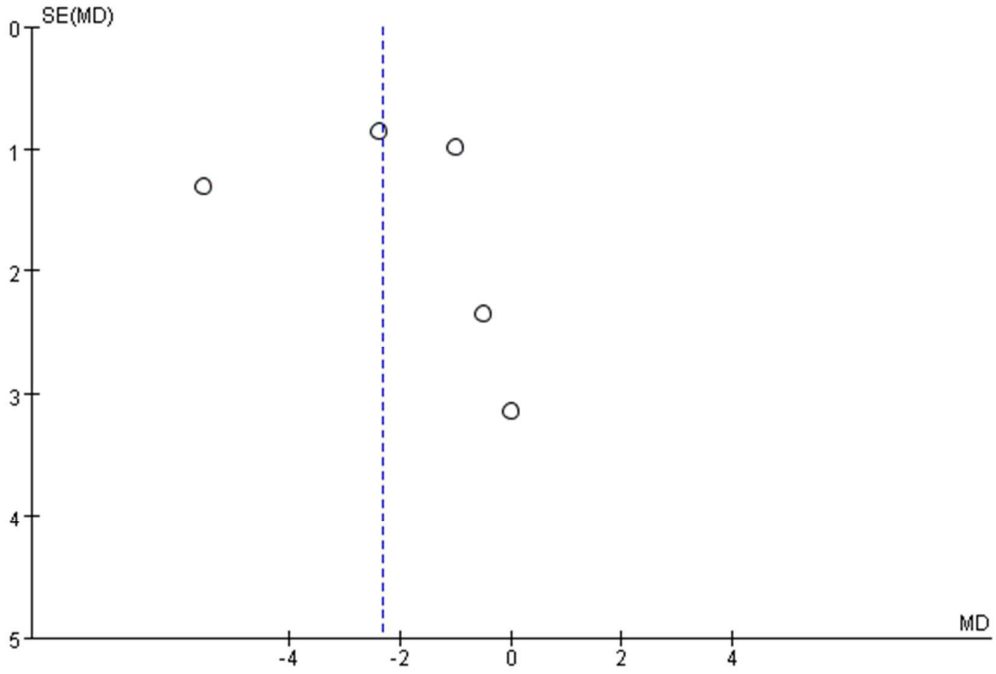

Figure 7: Funnel plots for the effect of Vitamin D on LVEDD

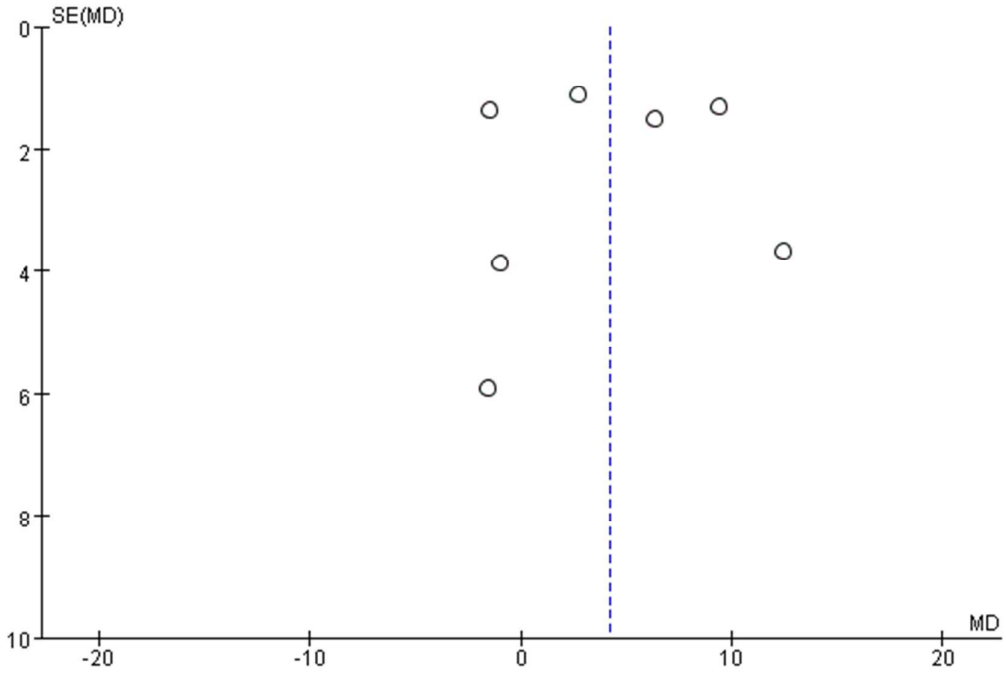

Figure 8: Funnel plots for the effect of Vitamin D on LVEF.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Effect of Vitamin D on Ventricular Remodeling in Heart Failure: A Meta-analysis of Randomized Controlled Trials.

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Complete List of Authors:	zhao, jindong; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China, Jia, JingJing; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China Dong, PingShuan; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China Zhao, Di; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China Yang, XuMing; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China Li, DaoLin; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China Zhang, HuiFeng; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Evidence based practice, Cardiovascular medicine
Keywords:	Meta-analysis, Vitamin D, ventricular remodeling, cardiac function, Heart failure < CARDIOLOGY

Effect of Vitamin D on Ventricular Remodeling in Heart Failure: A Meta-analysis of Randomized Controlled Trials

Running title: Vitamin D treatment of Heart Failure

Jin-Dong Zhao, Jing-Jing Jia, Ping-Shuan Dong*, Di Zhao, Xu-Ming Yang, Lai-Jing Du, Hui-Feng Zhang

Author: Jin-Dong Zhao, Department of Cardiology, The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China. Tel: 18437919892;

E-mail: zhaojindong123@outlook.com

***Corresponding author:** Ping-Shuan Dong, Department of Cardiology, The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China. E-mail: pingshuandong@foxmail.com

Address of all author: The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China.

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Main text: 2900

ABSTRACT:

Objectives: The level of vitamin D is considered to be associated with the development and progression of heart failure(HF). However, it is still unclear whether supplementation of vitamin D could improve ventricular remodelling in patients with HF. This study aimed to systematically evaluate the influence and safety of additional vitamin D supplementation on ventricular remodelling in patients with HF.

Design: This study is a meta-analysis of randomized controlled trials.

Setting: The PubMed, EMBASE, CNKI, Cochrane library, Web of Science databases and grey literature were searched for randomized controlled trials (RCTs) regarding the effect of vitamin D on ventricular remodelling in patients with HF (from database creation to October 2017). RevMan5.3 software was employed for data analysis.

Participants: Seven RCTs with a total of 465 patients, including 235 cases in the vitamin D group and 230 cases in the control group, were included.

Primary and secondary outcome measures: Left ventricular end-diastolic dimension(LVEDD), left ventricular ejection fraction(LVEF), and the incidence of adverse reactions.

Results: Compared with the control group, a decrease in the LVEDD (mean difference [MD] =-2.31mm, 95% confidence interval [CI]: -4.15- -0.47, P =0.01) and an increase in the LVEF (MD=4.18%, 95% CI: 0.36-7.99, P =0.03) were observed in the vitamin D group. Subgroup analysis also revealed a reduced LVEDD in adults

(>18 years) and adolescents (<18 years) of the vitamin D group relative to that in those of the control group. High-dose vitamin D (>4,000IU/day) was more effective at reducing the LVEDD than low-dose vitamin D (<4,000IU/day). Moreover, vitamin D supplementation was more effective at reducing the LVEDD and increasing the LVEF in patients with reduced ejection fraction than in patients without reduced ejection fraction.

Conclusion: Vitamin D supplementation inhibit ventricular remodelling and improve cardiac function in patients with HF.

Trial registration: PROSPERO CRD42017073893

Keywords: Vitamin D, ventricular remodeling, cardiac function, heart failure

Strengths and limitations of this study

- The results of this systematic review and meta-analysis is highly dependent on the quality of the included primary research studies. Only RCTs were included in this study.
- Subgroup analyses were performed according to clinical heterogeneity analysis of the included studies.
- This was the first review to systematically examine the impact of vitamin D supplementation on ventricular remodelling in patients with heart failure. The results

suggest that vitamin D may be utilized as adjunctive heart failure medication in heart failure patients with an underlying lack of or insufficiency in vitamin D.

- The results need to be interpreted with caution, as there were few studies in each subgroup.

Introduction

Heart failure(HF) is the main factor leading to economic loss due to poor prognosis and a high mortality rate [1]. In the USA, there are at least 5,000,000 patients with decreased contractile function; meanwhile, there is also the same number of patients with the same disease in Western Europe [2,3]. In recent years, the prognosis of HF has improved remarkably, and the 5-year survival rate has increased from 43% to 52% [4]. At present, the main treatment methods for HF are still β-receptor blocking agents, ACEI/ARB, and aldosterone receptor antagonists; although these medications can reduce the incidence of adverse cardiac events and improve cardiac function [5], HF is still a main cause of global mortality. Therefore, there is presently an urgent need for supplementary treatment methods and strategies.

lack of or insufficiency in vitamin D may result in cardiovascular and cerebrovascular diseases [6-10]. Many studies have discovered that [11-14] there is a remarkable association between lack of vitamin D and the progression of HF. Studies have shown that patients with HF generally lack vitamin D and have a poor prognosis; moreover, supplementation of vitamin D could reduce the mortality rate of patients with HF

[15-17]. Several studies have shown that vitamin D acts as a negative regulator of the renin-angiotensin-aldosterone system (RAAS) [18-20] and modulates myocardial extracellular matrix turnover. Consistently, vitamin D receptor (VDR) knockout mice show increased RAAS activity, which leads to hypertension, cardiac hypertrophy, increased water intake and sodium retention [18], and VDR knockout mice show increased metalloprotease (MMP) activity, which promotes the destruction of myocardial tissue, leading to ventricular remodelling [21,22]. Therefore, lack of vitamin D could result in deterioration of heart function and accelerate myocardial remodelling.

At present, different studies have reported controversial conclusions regarding the influence of vitamin D on ventricular remodelling in patients with HF. Therefore, the present study performed a meta-analysis to further clarify the influence of vitamin D on ventricular remodelling in patients with HF.

Materials and Methods

Search strategy

PubMed, EMBASE, Cochrane Central Register of Controlled Trials, CNKI and Web of Science were searched. Grey literature was also retrieved in Opengrey and ProQuest. The reference lists of identified articles and the bibliographies of original articles were also reviewed. The medical subject headings used in the search were as follows: “heart failure”, “vitamin D”, “ventricular remodelling”, “heart function tests”,

and “randomized controlled trials”. The keywords used in the search were as follows: “cardiac failure”, “myocardial failure”, “heart decompensation”, “left ventricular remodelling”, “ventricular remodelling”, “ventricular myocardial remodelling”, “cholecalciferol”, “vitamin D3”, and “controlled clinical trials”. The time frame for the retrieval was from the establishment of the database to October 1, 2017.

Study selection

The inclusion criteria were as follows: 1) Randomized controlled trials (RCTs) involving the effect of vitamin D on ventricular remodelling in patients with HF with or without blinding methods or allocation concealment methods; 2) Parallel or crossover trials; 3) Only the data before the washout period were used in a crossover test; 4) Available baseline data and changes in the left ventricular end-diastolic dimension (LVEDD) and left ventricular ejection fraction (LVEF); 5) HF defined as New York Heart Association functional class ≥II or LVEF ≤40%; 6) Participants of any gender, age or ethnicity; 7) Participants without or changing any micronutrient use except for vitamin D, and 8) A minimum of 3 months of therapy was necessary for inclusion in the review to ensure that the intervention had sufficient time to produce a better effect. The exclusion criteria were as follows: 1) Only the abstract was reported for reference; 2) Studies with duplicated data, including the same group of patients or patients for whom there were updated results available; 3) The study had no outcomes of interest 4) Animal studies and reviews; 5) Conference documents;

and 6) Non-RCTs, cohort studiers, and retrospective studies. This study was conducted in accordance with the Declaration of Helsinki and obtained approval from the Ethics Committee of Henan University of Science and Technology.

Data extraction and quality assessment

Data were independently extracted from each study by two authors (JD Zhao and JJ Jia) and entered into a structured spreadsheet followed by a cross-check procedure. Disagreements were resolved by consensus or by a third investigator (P. Dong). The following data were extracted from each trial: the first author's surname, year of publication; demographic and methodological data; total number, mean age, gender distribution and race of enrolled patients; use of or change in drugs for HF; seated LVEDD and LVEF at baseline, when available; number of patients randomly assigned to each intervention; duration of therapy; incidence and type of adverse events; number of dropouts or withdrawals because of adverse events; and change from baseline seated LVEDD and LVEF. Criteria for the RCT risk of bias evaluation listed in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 were adopted, including the following: 1) random sequence generation, 2) allocation concealment, 3) blinding of patients and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, and 6) selective reporting risk. Then, an evaluation system with "low risk", "high risk" and "not clear" was established according to the six criteria described above [23].

Outcomes assessed

The primary endpoint was LVEDD, and the secondary endpoints were LVEF and the incidence of adverse reactions.

Data analysis and synthesis

RevMan5.3 software was employed for data analysis. Continuous variables are reported as the mean difference (MD) and 95% CI, and the test level was $\alpha = 0.05$. Following clinical heterogeneity analysis of the included studies, statistical heterogeneity was assessed using χ^2-based Cochran Q statistic and I^2 [24]. For the Q statistic, $P \geq 0.1$ indicates homogeneity among multiple similar studies, and the fixed-effects model was employed for the meta-analysis, while $P < 0.1$ indicates statistically significant heterogeneity, and the random-effects model was used for analysis. For the I^2 statistic, $I^2 < 25\%$ indicates low heterogeneity, while $I^2 > 50\%$ indicates moderate to high heterogeneity [25].

Patient and public involvement

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

Results

Selection and description of studies

A total of 157 published papers were collected after the initial screening, and eventually, seven RCTs [26-32] with a total of 465 patients, including 235 cases in the vitamin D group and 230 cases in the control group, were included after reviewing the title, abstract and full text, as well as eliminating duplicate documents, non-RCTs, and studies that failed to meet the inclusion criteria. See **Figure 1** for the screening process.

In the seven included studies [26-32], four studies reported an appropriate randomization method [27-29,32]; two studies adopted allocation concealment [29,32], and six studies used double-blinding [26-30,32]. See **Figure 2** for the evaluation of the methodology of the studies.

Data of the curative effect on the LVEDD were reported in five studies, and the LVEF was reported in all the included studies; two studies mentioned adverse reactions [26,30]. Dropout or withdrawal from the research study was covered in all the included studies. The study characteristics are shown in **Table 1**, and the basic information of the include population is shown in **Table 2**.

Effects of vitamin D on the LVEDD

Changes in the LVEDD of patients were reported in five studies [26-30], which showed high levels of heterogeneity among the results of the studies (heterogeneity χ^2, P=0.07, I^2=55%), thus supporting analysis using the random-effects model. Compared with the control group, a decrease in the LVEDD was observed in the vitamin D group (mean difference [MD] = -2.31mm, 95% confidence interval [CI]: -4.15- -0.47, P =0.01) (**Figure 3**).

Effects of vitamin D on the LVEF

Changes in the LVEF of patients were reported in all seven studies [26-32], which showed high levels of heterogeneity among the results of the studies (heterogeneity χ^2, P <0.001, I^2 =88%), thus supporting analysis using the random-effects model. Compared with the control group, an increase in the LVEF was observed in the vitamin D group (MD=4.18%, 95% CI: 0.36-7.99, P =0.03) (**Figure 4**).

Subgroup analysis

The analysis based on age stratification revealed that compared with the control group, both the adults (aged≥18 years) and non-adults (aged<18 years) with HF in the vitamin D group showed a decrease in the LVEDD (adults: heterogeneity χ^2, P =0.65, I^2 =0%; MD=-1.62mm, 95% CI: -2.83- -0.42, P =0.008; non-adults: MD=-5.51mm, 95% CI, -8.08- -2.94, P<0.001) (**Figure 5**). These results, however, need to be interpreted with caution, as there was only one study in the subgroup of non-adults.

A subgroup analysis was performed according to the dosage of vitamin D. There was an effect from high-dose vitamin D on the reduction of the LVEDD (heterogeneity χ^2, P =0.50, I^2 =0%; MD=-1.71mm, 95% CI: -2.95- -0.46, P =0.007), but this effect was not seen with low-dose vitamin D treatment (heterogeneity χ^2, P =0.06, I^2 =71%; MD=-3.38mm, 95% CI: -8.23- 1.48, P =0.17). (**Figure 6**).

According to patients with or without reduced ejection fraction, subgroup analyses were performed. Vitamin D supplementation was effective at reducing the LVEDD in patients with reduced ejection fraction (patients with reduced ejection fraction: heterogeneity χ^2, P =0.07, I^2 =62%； MD=-3.11mm, 95% CI: -5.67- -0.55, P =0.02; patients without reduced ejection fraction: heterogeneity χ^2, P =0.76, I^2 =0%； MD=-0.91mm, 95% CI: -2.76- 0.94, P =0.34) (**Figure 7**). In addition, vitamin D supplementation was effective at increasing the LVEF in patients with reduced ejection fraction (patients with reduced ejection fraction: heterogeneity χ^2, P =0.02, I^2 =73%； MD=6.21%, 95% CI: 2.01- 10.41, P =0.004; patients without reduced ejection fraction: heterogeneity χ^2, P =0.002, I^2 =80%； MD=2.74%, 95% CI: -1.96- 7.45, P =0.25) (**Figure 8**).

Publication bias

There was significant asymmetry in the funnel plot for the effect of vitamin D on the LVEDD, which may be due to publication bias and other causes (**Figure 9).** On the other hand, no publication bias was found for the effect of vitamin D on the LVEF (**Figure 10**).

Adverse event

Two studies [26,30] reported adverse events. During the follow-up, no significant adverse event was recorded. No data associated with the incidence of adverse events were recorded in the other studies.

Discussion

At present, different studies have reported controversial conclusions regarding the influence of vitamin D on ventricular remodelling in patients with HF. The results of this study show that compared with the control group, supplementation of vitamin D could reduce the LVEDD (MD = -2.31 mm, 95% CI: -4.15- -0.47, P =0.01) and improve the LVEF (MD=4.18%, 95% CI: 0.36-7.99, P =0.03) among patients with HF. In addition, a more pronounced effect is achieved using high-dose vitamin D and on patients with a reduced ejection fraction.

Most new treatment methods for chronic HF are expensive and require advanced technologies [33]; in addition, most of these treatment methods have not passed strict phase III clinical trials. For patients with HF, vitamin D is not only cheap but also safe,

and these patients may obtain more benefits from vitamin D therapy [34]. Vitamin D toxicity is based not only on the dosing but also on circulating 25OHD levels. The Institute of Medicine [35] has set the dosage for vitamin D at 4,000IU daily for healthy adults, and the Endocrine Society [36] has set a dosage of 10,000IU daily for patients who are at risk of having circulating 25OHD levels <50 nmol/L. The Institute of Medicine [35] considers circulating 25OHD levels below 30 nmol/L as deficient, levels between 30 and 49.99 nmol/L as inadequate, levels between 50 and 125 nmol/L as adequate, and levels above 125 nmol/L as potentially harmful. In HF, cardiac contraction and diastole are affected due to overload of Ca^{2+} ions in myocardial cells. Lack of vitamin D may intervene with the functions of Ca^{2+} in myocardial cells, thus resulting in cardiomyocyte hypertrophy and intra-organizational inflammatory reaction and fibrosis [37,38]. Low vitamin D levels can activate the renin-angiotensin system [39], give rise to inflammatory reactions [40], and result in endothelial dysfunction [41]. The effects of vitamin D on the CV system are additionally mediated through elevated parathyroid hormone (PTH) levels, which are associated with the development of left ventricular (LV) hypertrophy [42]. Although there is much evidence showing that a lack of vitamin D could result in poor prognosis among patients with HF, different studies have reported controversial conclusions regarding whether supplementation of vitamin D could benefit patients with HF.

In recent years, there some relatively small RCTs have studied the influence of vitamin D on patients with HF. In the 2014 World Heart Failure Conference, Louise et al [43] reported an RCT that performed a 6-month study on 32 patients with HF, and the result showed that supplementation of vitamin D did not improve the LVEF or pro-BNP level. A recent meta-analysis [44] also reported that vitamin D supplementation could not improve the LVEF (WMD: 4.11%, 95% CI: -0.91 to 9.12, P =0.11) and 6-minute walk distance (6MWD) (WMD: 8.90 m, 95% CI: -48.47 to 66.26, P =0.76) in the treatment of chronic HF. In contrast, this study included three other studies, two of which showed a positive effect from vitamin D supplementation. The present studies have not shown that vitamin D supplementation can improve the 6MWD among patients [26,30,45,46]; thus, our meta-analysis did not evaluate this parameter. There are probably many factors that affect exercise tolerance, such as physical condition, obesity, habits, and environment, and these confounding factors may obscure the weak force from the remodelled ventricle. However, other studies have drawn opposite conclusions. In 2015, Lowry et al [47] reported in the European Society of Cardiology a 12-month RCT, and the result showed that for patients with HF, supplementation of vitamin D could improve ventricular remodelling (LVEDD −4.46 mm; P =0.047); in addition, the LVEF showed an increasing trend. A non-RCT [48] also showed that supplementation of vitamin D could remarkably increase the LVEF value compared to baseline. Elidrissy et al [49] evaluated 61 cases of children with cardiomyopathy; they concluded, based on the available evidence, that the most

likely cause of cardiomyopathy is hypocalcaemia and suggested maternal supplementation of vitamin D during pregnancy and lactation with up to 2,000 units of vitamin D and 400 units for their infants for prevention, which was also similar to the results reported by Shedeed [29].

Since there are disputes among different study results, we conducted a meta-analysis of relevant RCT studies to further clarify the influence of vitamin D supplementation on ventricular remodelling in patients with HF. Results of this study show that supplementation of vitamin D inhibit myocardial remodelling and improve cardiac function in patients with HF.

Different studies have different results and conclusions, which may be attributed to the different recommended dosages of vitamin D; since there is no standard recommended dosage of vitamin D at present, there are differences in the recommended dosage of vitamin D in different trials, which may affect the study results. However, there has not been a report related to adverse effects from the dosage of vitamin D. Meanwhile, the study results are related to the selected group; for example, the study results of Schleithoff et al [28] showed that there were no remarkable changes in the LVEF and LVEDD, and the participants included in this study were predominantly those with NYHA level 3-4 and a high degree of HF, and there was a high rate of lost to follow-up visit (37%).

The data on changes in the LVEDD showed high levels of heterogeneity among studies. Shedeed [29] studied the cause of heterogeneity according to subgroup. There was a difference in the metabolism of vitamin D and cardiac recovery capacity between new-borns and adults, which might be the cause of heterogeneity.

Although all trials included in this study are RCTs, there are still many limitations in this study: 1) because the current studies found that vitamin D has a weak and uncertain effect on ventricular remodelling and cardiac function in patients with HF and cannot improve exercise tolerance or reduce cardiac mortality, additional large-scale clinical studies are needed. Future research needs to focus on whether different vitamin D dosages would be superior; in addition, different selection criteria need to be defined (for example, ejection fraction, vitamin D threshold, PTH threshold, etc.) and additional echocardiographic parameters, the 6MWD and cardiovascular mortality need to be evaluated; 2) this study exhibits heterogeneity, and age stratification and whether there is reduced ejection fraction may be sources of clinical heterogeneity according to the subgroup analysis; 3) different recommended dosages of vitamin D are reported in different trials, which may affect study results; therefore, additional trials are required to explore the relationship between vitamin D dosage and effect; 4) the conclusions need to be interpreted with caution, as the extent of detected improvement in the remodelling parameters is close to the range of the inter- or

intra-observer variability of the echocardiographic method itself. The baseline vitamin D level of patients and the follow-up duration may affect the study results, and except for Dalbeni et al [27], whom have mentioned that no change in therapy was made during follow-up, other studies have not reported adjustments in HF medication. Therefore, whether the weak improvement in the remodelling parameters from vitamin D are attributed to other HF drugs is unclear.

In conclusion, this study shows that supplementation of vitamin D inhibit myocardial remodelling in patients with HF and improve their cardiac function. Vitamin D may be utilized as adjunctive HF medication for HF patients with an underlying lack of or insufficiency in vitamin D. This result is encouraging and of great clinical interest but still far from practical implications. The main implication is to encourage further research.

Figure legends

Figure 1 Flow diagram of study selection.

Figure 2 Quality assessment.

Figure 3 Forest plot showing the effect of Vitamin D on LVEDD.

Figure 4 Forest plot showing the effect of Vitamin D on LVEF.

Figure 5 Subgroup analysis of effect of Vitamin D on LVEDD according to patients' age.

Figure 6 Subgroup analysis of effect of Vitamin D on LVEDD according to dose of Vitamin D.

Figure 7 Subgroup analysis of effect of Vitamin D on LVEDD according to patients with or without reduced ejection fraction.

Figure 8 Subgroup analysis of effect of Vitamin D on LVEF according to patients with or without reduced ejection fraction.

Figure 9 Funnel plots for the effect of Vitamin D on LVEDD

Figure 10 Funnel plots for the effect of Vitamin D on LVEF.

Table 1 Study characteristics.

Author	Design	Blinding	Vitamin D Dose	Follow-up Duration	Study population	Primary Outcome
Turrini et al, 2017	Prospective RCT	Double-blind	300.000 IU at Baseline 50.000IU/mo	6 mo	Chronic HF, 25(OH)D <20 ng/mL, 60 y＜Age,	6MWD, echocardiography Parameters, hormonal
Witte et al, 2016	Prospective RCT	Double-blind	4000IU/d	12 mo	Chronic HF, NYHA class II–III, LVEF<45%, 25(OH)D <20 ng/mL	6MWD, echocardiography parameters
Qu et al, 2015	Prospective RCT	Single-blind	1000 IU/d	3 mo	NYHA class III–IV	echocardiography parameters, BNP, 25(OH)D
Dalbeni et	Prospective	Double-blind	4000IU/d	25 wk	Chronic HF, LVEF<55%,	Echocardiographic parameters,

al, 2014	RCT				NYHA class>II, 25(OH)D <30ng/mL, Age >40 y,	NYHA class, NT-proBNP
Boxer er al,2014	Prospective RCT	Double-blind	50000IU/wk	6mo	Age ≥50 y, NYHA class II–IV, 25(OH)D <37.5 ng/mL	Echocardiographic parameters, serum analysis, urine analysis
Shedeed, 2012	Prospective RCT	Double-blind	1000 IU/d	12 wk	Congestive HF, LVEF<40%, LV＞2 SD for age and sex	Echocardiographic parameters
Schleithoff et al, 2006	Prospective RCT	Double-blind	2000 IU/d	9 mo	Chronic HF, NYHA class II–IV	Survival rates, NT-proBNP, Pro-and anti-inflammatory cytokines, Echocardiographic parameters,

[†]25(OH)D; [‡]6MWD; [§]HF; [**]IU; [††]LV; [‡‡]LVEF; [§§]NT-proBNP; [***]NYHA;

[†] 25-hydroxyvitamin D
[‡] 6-minute walk distance
[§] heart failure

Table 2 Study population characteristics.

Intervention	Number	Age	Male	LVEF (%)	NYHA	NYHA	NYHA	LVEDD	25(OH)D	Ischemic	Hypertension	Diabetes (%)

** international units
†† left ventricular
‡‡ left ventricular ejection fraction
§§ N-terminal pro-B-type natriuretic peptide
*** New York Heart Association

Author		(n)	(years)	(%)		Class II(%)	Class III(%)	Class IV(%)	(mm)	(ng/mL)	Cause (%)		
Turrini et	Vitamin D	17	77±7	35.3	54.7±13.8	64.7	35.3	0	51±1.58	9.4±5.2	41.2	64.7	35.3
al, 2017	Placebo	16	79±7	43.8	49.2±19.1	68.7	21.3	0	54±3.48	9.6±7.3	43.7	43.7	18.7
Witte et al,	Vitamin D	80	68.5±12.45	83.8	25.6±10.80	92.5	7.5	0	57.6±8.62	38.2±24.81	55.0	NR	21.3
2016	Placebo	83	69.0±13.78	74.7	26.5±10.62	85.5	14.5	0	58.0±6.49	36.4±20.24	60.2	NR	24.1
Qu et al,	Vitamin D	22	70±7	59.3	34.9±3.8	NR	NR	NR	NR	NR	NR	66.7	81.5
2015	Blank	17	69±8	51.8	34.6±3.9	NR	NR	NR	NR	NR	NR	63.0	85.2
Dalbeni et	Vitamin D	13	71.2±6.22	84.6	39.08±8.00	58.8*	50.0**		53.9±6.81	16.2±6.59	76.9	100	NR
al, 2014	Placebo	10	73.4±13.78	60.0	43.6±7.63	41.2*	50.0**		50.6±7.04	16.0±6.15	90	100	NR
Boxer er	Vitamin D	19	65.8±10.6	48.4	39.2±13.2	55.0	73.0	0	NR	19.1±9.3	25.8	83.0	51.6
al,2014	Placebo	15	66.0±10.4	54.5	36.1±14.5	45.0	27.0	0	NR	17.8±9.0	30.3	84.8	42.4

Shedeed, 2012	Vitamin D	42	0.86±1.3	64.29	36.4±2.26	NR	NR	NR	32.81±4.6	13.4±2.21	NR	NR	NR
	Placebo	38	0.93±1.0	57.89	37.2±2.62	NR	NR	NR	30.7±5.2	14.0±2.46	NR	NR	NR
Schleithoff et al, 2006	Vitamin D+ Calcium	42	57±7.41	85.25	32.5±8.67	NR	NR	NR	69.0±8.89	14.4±7.85	47	38	20
	Placebo+ Calcium	51	54±8.89	80.65	33.0±7.56	NR	NR	NR	69.0±9.26	15.3±7.48	40	32	23

†††NR

††† Not reported
*I and II
** III and IV

Contributor ship statement

Jin-Dong Zhao：Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND Drafting the work or revising it critically for important intellectual content; AND Final approval of the version to be published; AND Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Jing-Jing Jia：participated in writing

Ping-Shuan Dong*：served as scientific advisors

Di Zhao：participated in technical editing of the manuscript

Xu-Ming Yang：critically reviewed the study proposal

Dao-Lin Li：collected data

Hui-Feng Zhang：collected data

Disclosure of conflict of interest

None.

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Data sharing statement

The authors declare that they willing to share their data directly.

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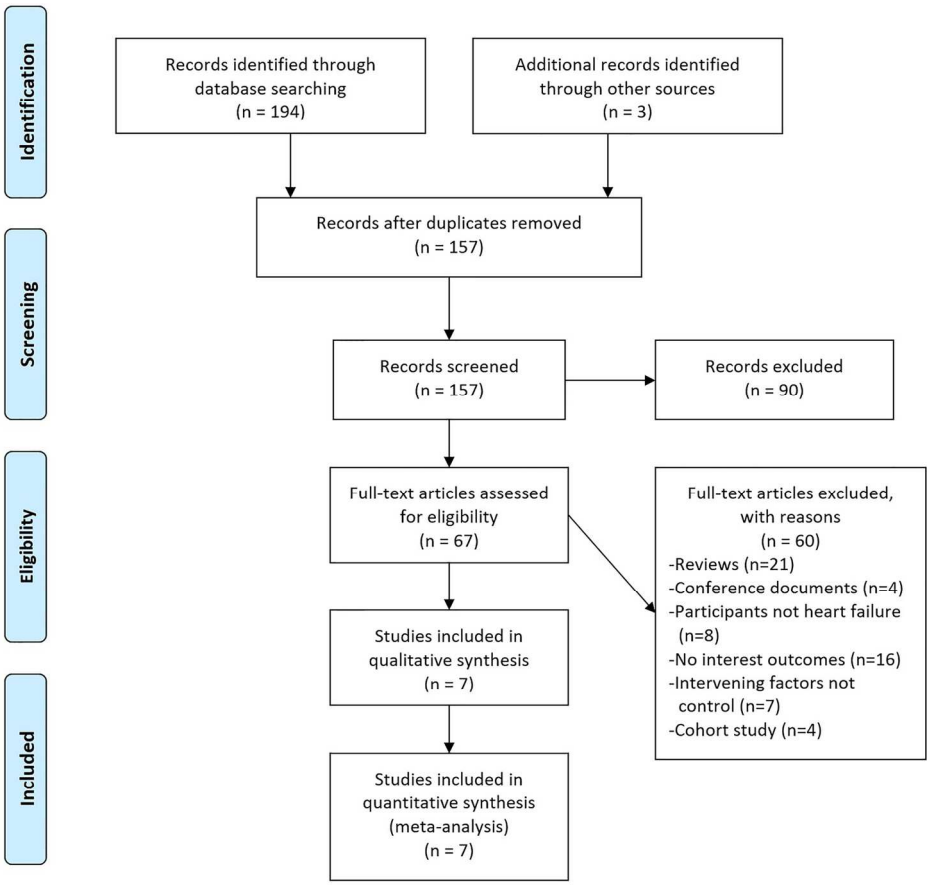

Figure 1 Flow diagram of study selection.

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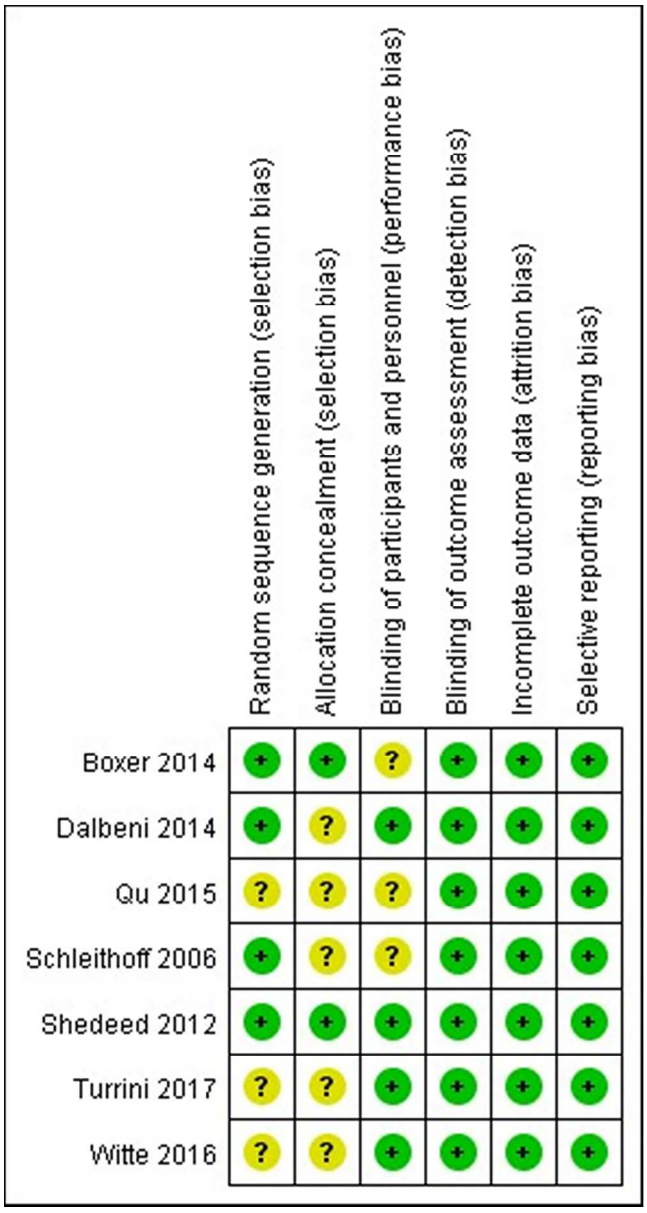

Figure 2 Quality assessment.

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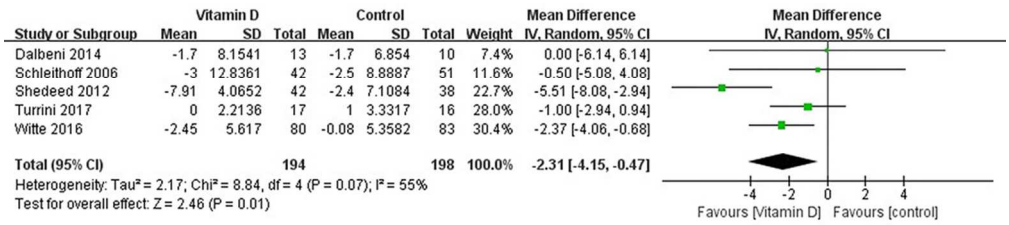

Figure 3 Forest plot showing the effect of Vitamin D on LVEDD.

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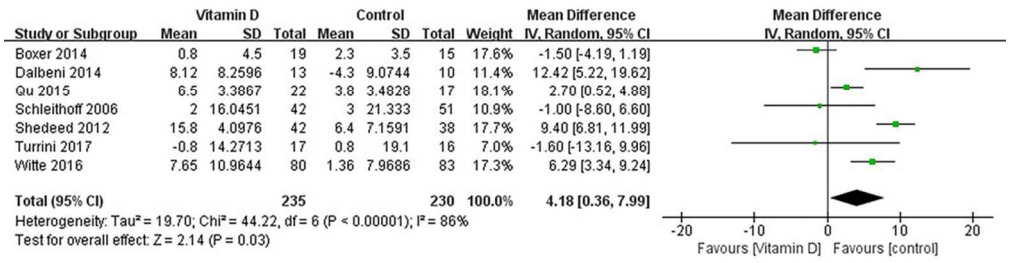

Figure 4 Forest plot showing the effect of Vitamin D on LVEF.

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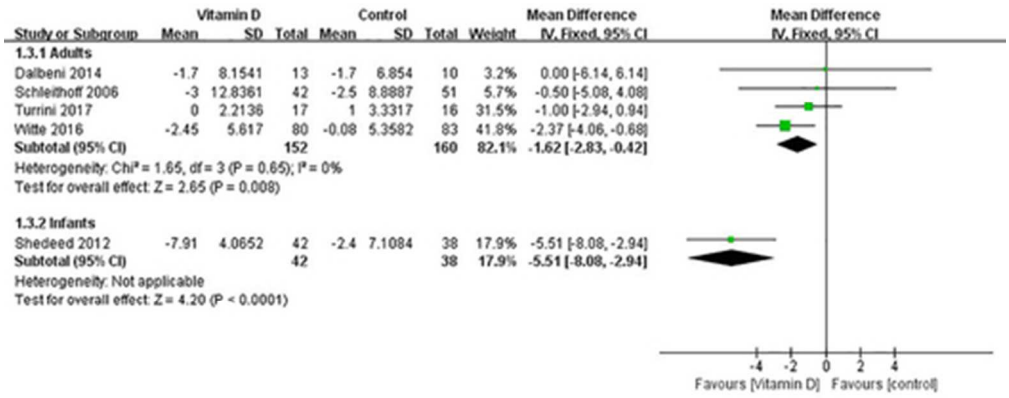

Figure 5 Subgroup analysis of effect of Vitamin D on LVEDD according to patients' age.

44x17mm (300 x 300 DPI)

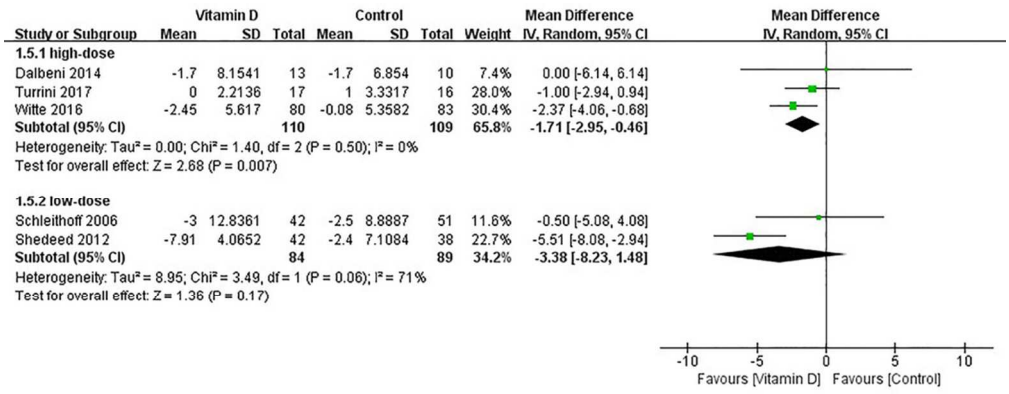

Figure 6 Subgroup analysis of effect of Vitamin D on LVEDD according to dose of Vitamin D.

88x34mm (300 x 300 DPI)

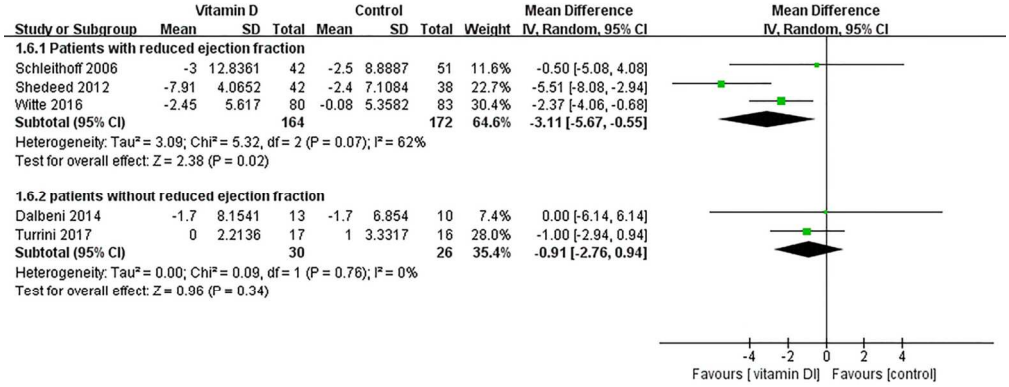

Figure 7 Subgroup analysis of effect of Vitamin D on LVEDD according to patients with or without reduced ejection fraction.

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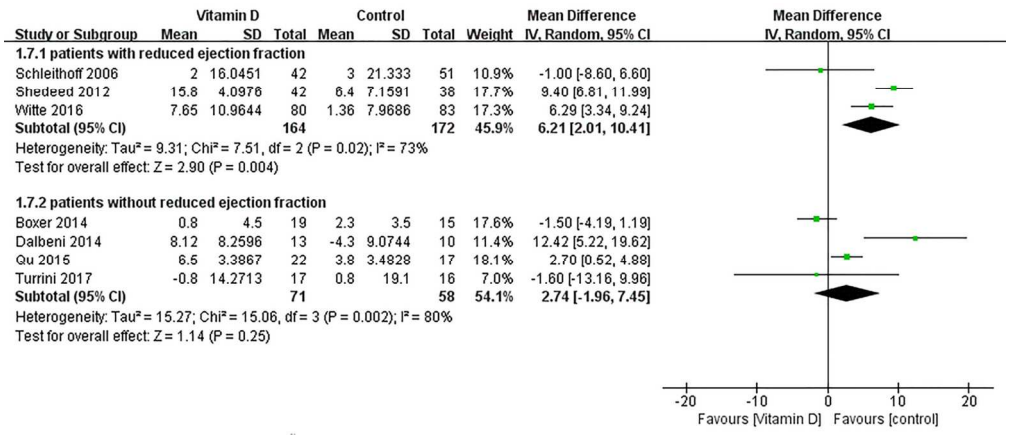

Figure 8 Subgroup analysis of effect of Vitamin D on LVEF according to patients with or without reduced ejection fraction.

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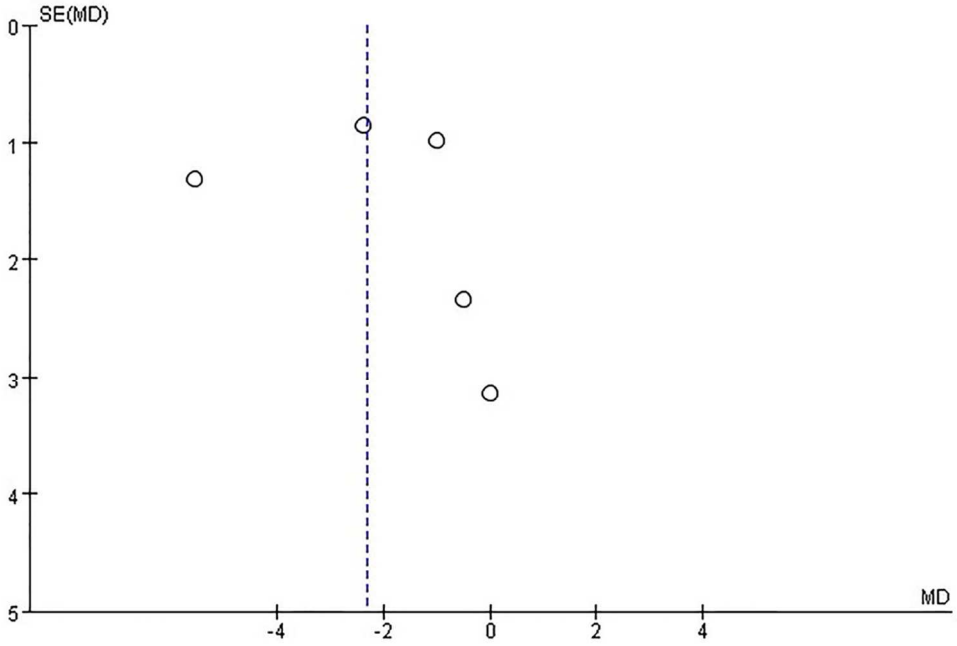

Figure 9 Funnel plots for the effect of Vitamin D on LVEDD

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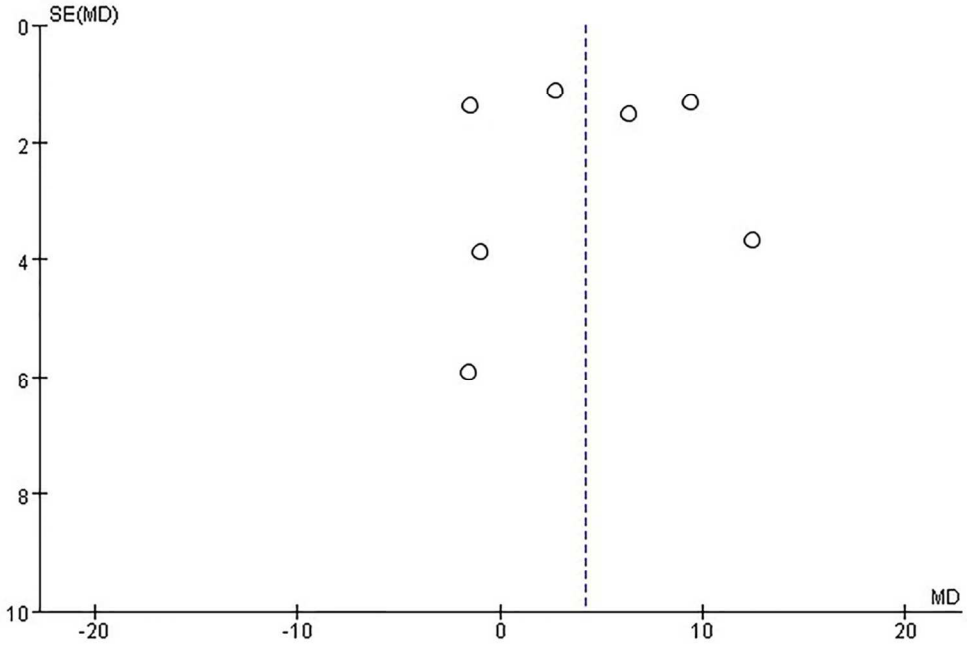

Figure 10 Funnel plots for the effect of Vitamin D on LVEF.

105x70mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

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Effect of Vitamin D on Ventricular Remodeling in Heart Failure: A Meta-analysis of Randomized Controlled Trials.

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Complete List of Authors:	zhao, jindong; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China, Jia, JingJing; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China Dong, PingShuan; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China Zhao, Di; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China Yang, XuMing; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China Li, DaoLin; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China Zhang, HuiFeng; Department of Cardiology, the First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China
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Keywords:	Meta-analysis, Vitamin D, ventricular remodeling, cardiac function, Heart failure < CARDIOLOGY

Effect of Vitamin D on Ventricular Remodeling in Heart Failure: A Meta-analysis of Randomized Controlled Trials

Running title: Vitamin D treatment of Heart Failure

Jin-Dong Zhao, Jing-Jing Jia, Ping-Shuan Dong*, Di Zhao, Xu-Ming Yang, Dao-Lin Li, Hui-Feng Zhang

Author: Jin-Dong Zhao, Department of Cardiology, The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China. Tel: 18437919892;

E-mail: zhaojindong123@outlook.com

***Corresponding author:** Ping-Shuan Dong, Department of Cardiology, The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China. E-mail: pingshuandong@foxmail.com

Address of all author: The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China.

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ABSTRACT:

Objectives: The level of vitamin D is considered to be associated with the development and progression of heart failure(HF). However, it is still unclear whether supplementation of vitamin D could improve ventricular remodelling in patients with HF. This study aimed to systematically evaluate the influence and safety of additional vitamin D supplementation on ventricular remodelling in patients with HF.

Design: This study is a meta-analysis of randomized controlled trials.

Setting: The PubMed, EMBASE, CNKI, Cochrane library, Web of Science databases and grey literature were searched for randomized controlled trials (RCTs) regarding the effect of vitamin D on ventricular remodelling in patients with HF (from database creation to October 2017). RevMan5.3 software was employed for data analysis.

Participants: Seven RCTs with a total of 465 patients, including 235 cases in the vitamin D group and 230 cases in the control group, were included.

Primary and secondary outcome measures: Left ventricular end-diastolic dimension(LVEDD), left ventricular ejection fraction(LVEF), and the incidence of adverse reactions.

Results: Compared with the control group, a decrease in the LVEDD (mean difference [MD] =-2.31mm, 95% confidence interval [CI]: -4.15- -0.47, P =0.01) and an increase in the LVEF (MD=4.18%, 95% CI: 0.36-7.99, P =0.03) were observed in the vitamin D group. Subgroup analysis also revealed a reduced LVEDD in adults

(>18 years) and adolescents (<18 years) of the vitamin D group relative to that in those of the control group. High-dose vitamin D (>4,000IU/day) was more effective at reducing the LVEDD than low-dose vitamin D (<4,000IU/day). Moreover, vitamin D supplementation was more effective at reducing the LVEDD and increasing the LVEF in patients with reduced ejection fraction than in patients without reduced ejection fraction.

Conclusion: Vitamin D supplementation inhibit ventricular remodelling and improve cardiac function in patients with HF.

Trial registration: PROSPERO CRD42017073893

Keywords: Vitamin D, ventricular remodeling, cardiac function, heart failure

Strengths and limitations of this study

- The results of this systematic review and meta-analysis is highly dependent on the quality of the included primary research studies. Only RCTs were included in this study.
- Subgroup analyses were performed according to clinical heterogeneity analysis of the included studies.
- This was the first review to systematically examine the impact of vitamin D supplementation on ventricular remodelling in patients with heart failure. The results

suggest that vitamin D may be utilized as adjunctive heart failure medication in heart failure patients with an underlying lack of or insufficiency in vitamin D.

- The results need to be interpreted with caution, as there were few studies in each subgroup.

Introduction

Heart failure(HF) is the main factor leading to economic loss due to poor prognosis and a high mortality rate [1]. In the USA, there are at least 5,000,000 patients with decreased contractile function; meanwhile, there is also the same number of patients with the same disease in Western Europe [2,3]. In recent years, the prognosis of HF has improved remarkably, and the 5-year survival rate has increased from 43% to 52% [4]. At present, the main treatment methods for HF are still β-receptor blocking agents, ACEI/ARB, and aldosterone receptor antagonists; although these medications can reduce the incidence of adverse cardiac events and improve cardiac function [5], HF is still a main cause of global mortality. Therefore, there is presently an urgent need for supplementary treatment methods and strategies.

lack of or insufficiency in vitamin D may result in cardiovascular and cerebrovascular diseases [6-10]. Many studies have discovered that [11-14] there is a remarkable association between lack of vitamin D and the progression of HF. Studies have shown that patients with HF generally lack vitamin D and have a poor prognosis; moreover, supplementation of vitamin D could reduce the mortality rate of patients with HF

[15-17]. Several studies have shown that vitamin D acts as a negative regulator of the renin-angiotensin-aldosterone system (RAAS) [18-20] and modulates myocardial extracellular matrix turnover. Consistently, vitamin D receptor (VDR) knockout mice show increased RAAS activity, which leads to hypertension, cardiac hypertrophy, increased water intake and sodium retention [18], and VDR knockout mice show increased metalloprotease (MMP) activity, which promotes the destruction of myocardial tissue, leading to ventricular remodelling [21,22]. Therefore, lack of vitamin D could result in deterioration of heart function and accelerate myocardial remodelling.

At present, different studies have reported controversial conclusions regarding the influence of vitamin D on ventricular remodelling in patients with HF. Therefore, the present study performed a meta-analysis to further clarify the influence of vitamin D on ventricular remodelling in patients with HF.

Materials and Methods

Search strategy

PubMed, EMBASE, Cochrane Central Register of Controlled Trials, CNKI and Web of Science were searched. Grey literature was also retrieved in Opengrey and ProQuest. The reference lists of identified articles and the bibliographies of original articles were also reviewed. The medical subject headings used in the search were as follows: “heart failure”, “vitamin D”, “ventricular remodelling”, “heart function tests”,

and “randomized controlled trials”. The keywords used in the search were as follows: “cardiac failure”, “myocardial failure”, “heart decompensation”, “left ventricular remodelling”, “ventricular remodelling”, “ventricular myocardial remodelling”, “cholecalciferol”, “vitamin D3”, and “controlled clinical trials”. The time frame for the retrieval was from the establishment of the database to October 1, 2017.

Study selection

The inclusion criteria were as follows: 1) Randomized controlled trials (RCTs) involving the effect of vitamin D on ventricular remodelling in patients with HF with or without blinding methods or allocation concealment methods; 2) Parallel or crossover trials; 3) Only the data before the washout period were used in a crossover test; 4) Available baseline data and changes in the left ventricular end-diastolic dimension (LVEDD) and left ventricular ejection fraction (LVEF); 5) HF defined as New York Heart Association functional class ≥II or LVEF ≤40%; 6) Participants of any gender, age or ethnicity; 7) Participants without or changing any micronutrient use except for vitamin D, and 8) A minimum of 3 months of therapy was necessary for inclusion in the review to ensure that the intervention had sufficient time to produce a better effect. The exclusion criteria were as follows: 1) Only the abstract was reported for reference; 2) Studies with duplicated data, including the same group of patients or patients for whom there were updated results available; 3) The study had no outcomes of interest 4) Animal studies and reviews; 5) Conference documents;

and 6) Non-RCTs, cohort studiers, and retrospective studies. This study was conducted in accordance with the Declaration of Helsinki and obtained approval from the Ethics Committee of Henan University of Science and Technology.

Data extraction and quality assessment

Data were independently extracted from each study by two authors (JD Zhao and JJ Jia) and entered into a structured spreadsheet followed by a cross-check procedure. Disagreements were resolved by consensus or by a third investigator (P. Dong). The following data were extracted from each trial: the first author's surname, year of publication; demographic and methodological data; total number, mean age, gender distribution and race of enrolled patients; use of or change in drugs for HF; seated LVEDD and LVEF at baseline, when available; number of patients randomly assigned to each intervention; duration of therapy; incidence and type of adverse events; number of dropouts or withdrawals because of adverse events; and change from baseline seated LVEDD and LVEF. Criteria for the RCT risk of bias evaluation listed in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 were adopted, including the following: 1) random sequence generation, 2) allocation concealment, 3) blinding of patients and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, and 6) selective reporting risk. Then, an evaluation system with "low risk", "high risk" and "not clear" was established according to the six criteria described above [23].

Outcomes assessed

The primary endpoint was LVEDD, and the secondary endpoints were LVEF and the incidence of adverse reactions.

Data analysis and synthesis

RevMan5.3 software was employed for data analysis. Continuous variables are reported as the mean difference (MD) and 95% CI, and the test level was $\alpha = 0.05$. Following clinical heterogeneity analysis of the included studies, statistical heterogeneity was assessed using χ^2-based Cochran Q statistic and I^2 [24]. For the Q statistic, $P \geq 0.1$ indicates homogeneity among multiple similar studies, and the fixed-effects model was employed for the meta-analysis, while $P < 0.1$ indicates statistically significant heterogeneity, and the random-effects model was used for analysis. For the I^2 statistic, $I^2 < 25\%$ indicates low heterogeneity, while $I^2 > 50\%$ indicates moderate to high heterogeneity [25].

Patient and public involvement

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

Results

Selection and description of studies

A total of 157 published papers were collected after the initial screening, and eventually, seven RCTs [26-32] with a total of 465 patients, including 235 cases in the vitamin D group and 230 cases in the control group, were included after reviewing the title, abstract and full text, as well as eliminating duplicate documents, non-RCTs, and studies that failed to meet the inclusion criteria. See **Figure 1** for the screening process.

In the seven included studies [26-32], four studies reported an appropriate randomization method [27-29,32]; two studies adopted allocation concealment [29,32], and six studies used double-blinding [26-30,32]. See **Figure 2** for the evaluation of the methodology of the studies.

Data of the curative effect on the LVEDD were reported in five studies, and the LVEF was reported in all the included studies; two studies mentioned adverse reactions [26,30]. Dropout or withdrawal from the research study was covered in all the included studies. The study characteristics are shown in **Table 1**, and the basic information of the include population is shown in **Table 2**.

The standard deviations for changes from baseline on the LVEF were reported in four studies [27,28,30,32]. According to the Cochrane Handbook, the Corr were imputed

by averaging the Corr of those four studies, and further imputed the standard deviations for changes from baseline for other studies [26,29,31].

The standard deviations for changes from baseline on the LVEDD were reported in three studies [27,28,30]. According to the Cochrane Handbook, the Corr were imputed by averaging the Corr of those three studies, and further imputed the standard deviations for changes from baseline for other studies [26,29].

Effects of vitamin D on the LVEDD

Changes in the LVEDD of patients were reported in five studies [26-30], which showed high levels of heterogeneity among the results of the studies (heterogeneity χ^2, P=0.07, I^2=55%), thus supporting analysis using the random-effects model. Compared with the control group, a decrease in the LVEDD was observed in the vitamin D group (mean difference [MD] = -2.31mm, 95% confidence interval [CI]: -4.15- -0.47, P =0.01) (**Figure 3**).

Effects of vitamin D on the LVEF

Changes in the LVEF of patients were reported in all seven studies [26-32], which showed high levels of heterogeneity among the results of the studies (heterogeneity χ^2, P <0.001, I^2 =88%), thus supporting analysis using the random-effects model.

Compared with the control group, an increase in the LVEF was observed in the vitamin D group (MD=4.18%, 95% CI: 0.36-7.99, P =0.03) (**Figure 4**).

Subgroup analysis

The analysis based on age stratification revealed that compared with the control group, both the adults (aged≥18 years) and non-adults (aged<18 years) with HF in the vitamin D group showed a decrease in the LVEDD (adults: heterogeneity χ^2, P =0.65, I^2 =0%; MD=-1.62mm, 95% CI: -2.83- -0.42, P =0.008; non-adults: MD=-5.51mm, 95% CI, -8.08- -2.94, P<0.001) (**Figure 5**). These results, however, need to be interpreted with caution, as there was only one study in the subgroup of non-adults.

A subgroup analysis was performed according to the dosage of vitamin D. There was an effect from high-dose vitamin D on the reduction of the LVEDD (heterogeneity χ^2, P =0.50, I^2 =0%; MD=-1.71mm, 95% CI: -2.95- -0.46, P =0.007), but this effect was not seen with low-dose vitamin D treatment (heterogeneity χ^2, P =0.06, I^2 =71%; MD=-3.38mm, 95% CI: -8.23- 1.48, P =0.17). (**Figure 6**).

According to patients with or without reduced ejection fraction, subgroup analyses were performed. Vitamin D supplementation was effective at reducing the LVEDD in patients with reduced ejection fraction (patients with reduced ejection fraction: heterogeneity χ^2, P =0.07, I^2 =62%； MD=-3.11mm, 95% CI: -5.67- -0.55, P =0.02;

patients without reduced ejection fraction: heterogeneity χ^2, P =0.76, I^2 =0%; MD=-0.91mm, 95% CI: -2.76- 0.94, P =0.34) (**Figure 7**). In addition, vitamin D supplementation was effective at increasing the LVEF in patients with reduced ejection fraction (patients with reduced ejection fraction: heterogeneity χ^2, P =0.02, I^2 =73%; MD=6.21%, 95% CI: 2.01- 10.41, P =0.004; patients without reduced ejection fraction: heterogeneity χ^2, P =0.002, I^2 =80%; MD=2.74%, 95% CI: -1.96- 7.45, P =0.25) (**Figure 8**).

Publication bias

There was significant asymmetry in the funnel plot for the effect of vitamin D on the LVEDD, which may be due to publication bias and other causes (**Figure 9).** On the other hand, no publication bias was found for the effect of vitamin D on the LVEF (**Figure 10**).

Adverse event

Two studies [26,30] reported adverse events. During the follow-up, no significant adverse event was recorded. No data associated with the incidence of adverse events were recorded in the other studies.

Discussion

At present, different studies have reported controversial conclusions regarding the influence of vitamin D on ventricular remodelling in patients with HF. The results of

this study show that compared with the control group, supplementation of vitamin D could reduce the LVEDD (MD = -2.31 mm, 95% CI: -4.15- -0.47, P =0.01) and improve the LVEF (MD=4.18%, 95% CI: 0.36-7.99, P =0.03) among patients with HF. In addition, a more pronounced effect is achieved using high-dose vitamin D and on patients with a reduced ejection fraction.

Most new treatment methods for chronic HF are expensive and require advanced technologies [33]; in addition, most of these treatment methods have not passed strict phase III clinical trials. For patients with HF, vitamin D is not only cheap but also safe, and these patients may obtain more benefits from vitamin D therapy [34]. Vitamin D toxicity is based not only on the dosing but also on circulating 25OHD levels. The Institute of Medicine [35] has set the dosage for vitamin D at 4,000IU daily for healthy adults, and the Endocrine Society [36] has set a dosage of 10,000IU daily for patients who are at risk of having circulating 25OHD levels <50 nmol/L. The Institute of Medicine [35] considers circulating 25OHD levels below 30 nmol/L as deficient, levels between 30 and 49.99 nmol/L as inadequate, levels between 50 and 125 nmol/L as adequate, and levels above 125 nmol/L as potentially harmful. In HF, cardiac contraction and diastole are affected due to overload of Ca^{2+} ions in myocardial cells. Lack of vitamin D may intervene with the functions of Ca^{2+} in myocardial cells, thus resulting in cardiomyocyte hypertrophy and intra-organizational inflammatory reaction and fibrosis [37,38]. Low vitamin D levels can activate the renin-angiotensin

system [39], give rise to inflammatory reactions [40], and result in endothelial dysfunction [41]. The effects of vitamin D on the CV system are additionally mediated through elevated parathyroid hormone (PTH) levels, which are associated with the development of left ventricular (LV) hypertrophy [42]. Although there is much evidence showing that a lack of vitamin D could result in poor prognosis among patients with HF, different studies have reported controversial conclusions regarding whether supplementation of vitamin D could benefit patients with HF.

In recent years, there some relatively small RCTs have studied the influence of vitamin D on patients with HF. In the 2014 World Heart Failure Conference, Louise et al [43] reported an RCT that performed a 6-month study on 32 patients with HF, and the result showed that supplementation of vitamin D did not improve the LVEF or pro-BNP level. A recent meta-analysis [44] also reported that vitamin D supplementation could not improve the LVEF (WMD: 4.11%, 95% CI: -0.91 to 9.12, P =0.11) and 6-minute walk distance (6MWD) (WMD: 8.90 m, 95% CI: -48.47 to 66.26, P =0.76) in the treatment of chronic HF. In contrast, this study included three other studies, two of which showed a positive effect from vitamin D supplementation. The present studies have not shown that vitamin D supplementation can improve the 6MWD among patients [26,30,45,46]; thus, our meta-analysis did not evaluate this parameter. There are probably many factors that affect exercise tolerance, such as physical condition, obesity, habits, and environment, and these confounding factors

may obscure the weak force from the remodelled ventricle. However, other studies have drawn opposite conclusions. In 2015, Lowry et al [47] reported in the European Society of Cardiology a 12-month RCT, and the result showed that for patients with HF, supplementation of vitamin D could improve ventricular remodelling (LVEDD −4.46 mm; P =0.047); in addition, the LVEF showed an increasing trend. A non-RCT [48] also showed that supplementation of vitamin D could remarkably increase the LVEF value compared to baseline. Elidrissy et al [49] evaluated 61 cases of children with cardiomyopathy; they concluded, based on the available evidence, that the most likely cause of cardiomyopathy is hypocalcaemia and suggested maternal supplementation of vitamin D during pregnancy and lactation with up to 2,000 units of vitamin D and 400 units for their infants for prevention, which was also similar to the results reported by Shedeed [29].

Since there are disputes among different study results, we conducted a meta-analysis of relevant RCT studies to further clarify the influence of vitamin D supplementation on ventricular remodelling in patients with HF. Results of this study show that supplementation of vitamin D inhibit myocardial remodelling and improve cardiac function in patients with HF.

Different studies have different results and conclusions, which may be attributed to the different recommended dosages of vitamin D; since there is no standard

recommended dosage of vitamin D at present, there are differences in the recommended dosage of vitamin D in different trials, which may affect the study results. However, there has not been a report related to adverse effects from the dosage of vitamin D. Meanwhile, the study results are related to the selected group; for example, the study results of Schleithoff et al [28] showed that there were no remarkable changes in the LVEF and LVEDD, and the participants included in this study were predominantly those with NYHA level 3-4 and a high degree of HF, and there was a high rate of lost to follow-up visit (37%).

The data on changes in the LVEDD showed high levels of heterogeneity among studies. Shedeed [29] studied the cause of heterogeneity according to subgroup. There was a difference in the metabolism of vitamin D and cardiac recovery capacity between new-borns and adults, which might be the cause of heterogeneity.

Although all trials included in this study are RCTs, there are still many limitations in this study: 1) because the current studies found that vitamin D has a weak and uncertain effect on ventricular remodelling and cardiac function in patients with HF and cannot improve exercise tolerance or reduce cardiac mortality, additional large-scale clinical studies are needed. Future research needs to focus on whether different vitamin D dosages would be superior; in addition, different selection criteria need to be defined (for example, ejection fraction, vitamin D threshold, PTH threshold,

etc.) and additional echocardiographic parameters, the 6MWD and cardiovascular mortality need to be evaluated; 2) this study exhibits heterogeneity, and age stratification and whether there is reduced ejection fraction may be sources of clinical heterogeneity according to the subgroup analysis; 3) different recommended dosages of vitamin D are reported in different trials, which may affect study results; therefore, additional trials are required to explore the relationship between vitamin D dosage and effect; 4) the conclusions need to be interpreted with caution, as the extent of detected improvement in the remodelling parameters is close to the range of the inter- or intra-observer variability of the echocardiographic method itself. The baseline vitamin D level of patients and the follow-up duration may affect the study results, and except for Dalbeni et al [27], whom have mentioned that no change in therapy was made during follow-up, other studies have not reported adjustments in HF medication. Therefore, whether the weak improvement in the remodelling parameters from vitamin D are attributed to other HF drugs is unclear.

In conclusion, this study shows that supplementation of vitamin D inhibit myocardial remodelling in patients with HF and improve their cardiac function. Vitamin D may be utilized as adjunctive HF medication for HF patients with an underlying lack of or insufficiency in vitamin D. This result is encouraging and of great clinical interest but still far from practical implications. The main implication is to encourage further research.

Figure legends

Figure 1 Flow diagram of study selection.

Figure 2 Quality assessment.

Figure 3 Forest plot showing the effect of Vitamin D on LVEDD.

Figure 4 Forest plot showing the effect of Vitamin D on LVEF.

Figure 5 Subgroup analysis of effect of Vitamin D on LVEDD according to patients' age.

Figure 6 Subgroup analysis of effect of Vitamin D on LVEDD according to dose of Vitamin D.

Figure 7 Subgroup analysis of effect of Vitamin D on LVEDD according to patients with or without reduced ejection fraction.

Figure 8 Subgroup analysis of effect of Vitamin D on LVEF according to patients with or without reduced ejection fraction.

Figure 9 Funnel plots for the effect of Vitamin D on LVEDD

Figure 10 Funnel plots for the effect of Vitamin D on LVEF.

Table 1 Study characteristics.

Author	Design	Blinding	Vitamin D Dose	Follow-up Duration	Study population	Primary Outcome
Turrini et al, 2017	Prospective RCT	Double-blind	300.000 IU at Baseline 50.000IU/mo	6 mo	Chronic HF, 25(OH)D <20 ng/mL, 60 y＜Age,	6MWD, echocardiography Parameters, hormonal
Witte et al, 2016	Prospective RCT	Double-blind	4000IU/d	12 mo	Chronic HF, NYHA class II–III, LVEF<45%, 25(OH)D <20 ng/mL	6MWD, echocardiography parameters
Qu et al, 2015	Prospective RCT	Single-blind	1000 IU/d	3 mo	NYHA class III–IV	echocardiography parameters, BNP, 25(OH)D
Dalbeni et	Prospective	Double-blind	4000IU/d	25 wk	Chronic HF, LVEF<55%,	Echocardiographic parameters,

al, 2014	RCT				NYHA class>II, 25(OH)D <30ng/mL, Age >40 y,	NYHA class, NT-proBNP
Boxer er al,2014	Prospective RCT	Double-blind	50000IU/wk	6mo	Age ≥50 y, NYHA class II–IV, 25(OH)D <37.5 ng/mL	Echocardiographic parameters, serum analysis, urine analysis
Shedeed, 2012	Prospective RCT	Double-blind	1000 IU/d	12 wk	Congestive HF, LVEF<40%, LV＞2 SD for age and sex	Echocardiographic parameters
Schleithoff et al, 2006	Prospective RCT	Double-blind	2000 IU/d	9 mo	Chronic HF, NYHA class II–IV	Survival rates, NT-proBNP, Pro-and anti-inflammatory cytokines, Echocardiographic parameters,

[†]25(OH)D; [‡]6MWD; [§]HF; [**]IU; [††]LV; [‡‡]LVEF; [§§]NT-proBNP; [***]NYHA;

[†] 25-hydroxyvitamin D
[‡] 6-minute walk distance
[§] heart failure

Table 2 Study population characteristics.

Intervention	Number	Age	Male	LVEF (%)	NYHA	NYHA	NYHA	LVEDD	25(OH)D	Ischemic	Hypertension	Diabetes (%)

** international units
†† left ventricular
‡‡ left ventricular ejection fraction
§§ N-terminal pro-B-type natriuretic peptide
*** New York Heart Association

Author		(n)	(years)	(%)		Class II(%)	Class III(%)	Class IV(%)	(mm)	(ng/mL)	Cause (%)		
Turrini et	Vitamin D	17	77±7	35.3	54.7±13.8	64.7	35.3	0	51±1.58	9.4±5.2	41.2	64.7	35.3
al, 2017	Placebo	16	79±7	43.8	49.2±19.1	68.7	21.3	0	54±3.48	9.6±7.3	43.7	43.7	18.7
Witte et al,	Vitamin D	80	68.5±12.45	83.8	25.6±10.80	92.5	7.5	0	57.6±8.62	38.2±24.81	55.0	NR	21.3
2016	Placebo	83	69.0±13.78	74.7	26.5±10.62	85.5	14.5	0	58.0±6.49	36.4±20.24	60.2	NR	24.1
Qu et al,	Vitamin D	22	70±7	59.3	34.9±3.8	NR	NR	NR	NR	NR	NR	66.7	81.5
2015	Blank	17	69±8	51.8	34.6±3.9	NR	NR	NR	NR	NR	NR	63.0	85.2
Dalbeni et	Vitamin D	13	71.2±6.22	84.6	39.08±8.00	58.8*	50.0**		53.9±6.81	16.2±6.59	76.9	100	NR
al, 2014	Placebo	10	73.4±13.78	60.0	43.6±7.63	41.2*	50.0**		50.6±7.04	16.0±6.15	90	100	NR
Boxer er	Vitamin D	19	65.8±10.6	48.4	39.2±13.2	55.0	73.0	0	NR	19.1±9.3	25.8	83.0	51.6
al,2014	Placebo	15	66.0±10.4	54.5	36.1±14.5	45.0	27.0	0	NR	17.8±9.0	30.3	84.8	42.4

Shedeed, 2012	Vitamin D	42	0.86±1.3	64.29	36.4±2.26	NR	NR	NR	32.81±4.6	13.4±2.21	NR	NR	NR
	Placebo	38	0.93±1.0	57.89	37.2±2.62	NR	NR	NR	30.7±5.2	14.0±2.46	NR	NR	NR
Schleithoff et al, 2006	Vitamin D+ Calcium	42	57±7.41	85.25	32.5±8.67	NR	NR	NR	69.0±8.89	14.4±7.85	47	38	20
	Placebo+ Calcium	51	54±8.89	80.65	33.0±7.56	NR	NR	NR	69.0±9.26	15.3±7.48	40	32	23

†††NR

††† Not reported
*I and II
** III and IV

Contributor ship statement

Jin-Dong Zhao：Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND Drafting the work or revising it critically for important intellectual content; AND Final approval of the version to be published; AND Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Jing-Jing Jia：participated in writing

Ping-Shuan Dong*：served as scientific advisors

Di Zhao：participated in technical editing of the manuscript

Xu-Ming Yang：critically reviewed the study proposal

Dao-Lin Li：collected data

Hui-Feng Zhang：collected data

Disclosure of conflict of interest

None.

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Data sharing statement

The authors declare that they willing to share their data directly.

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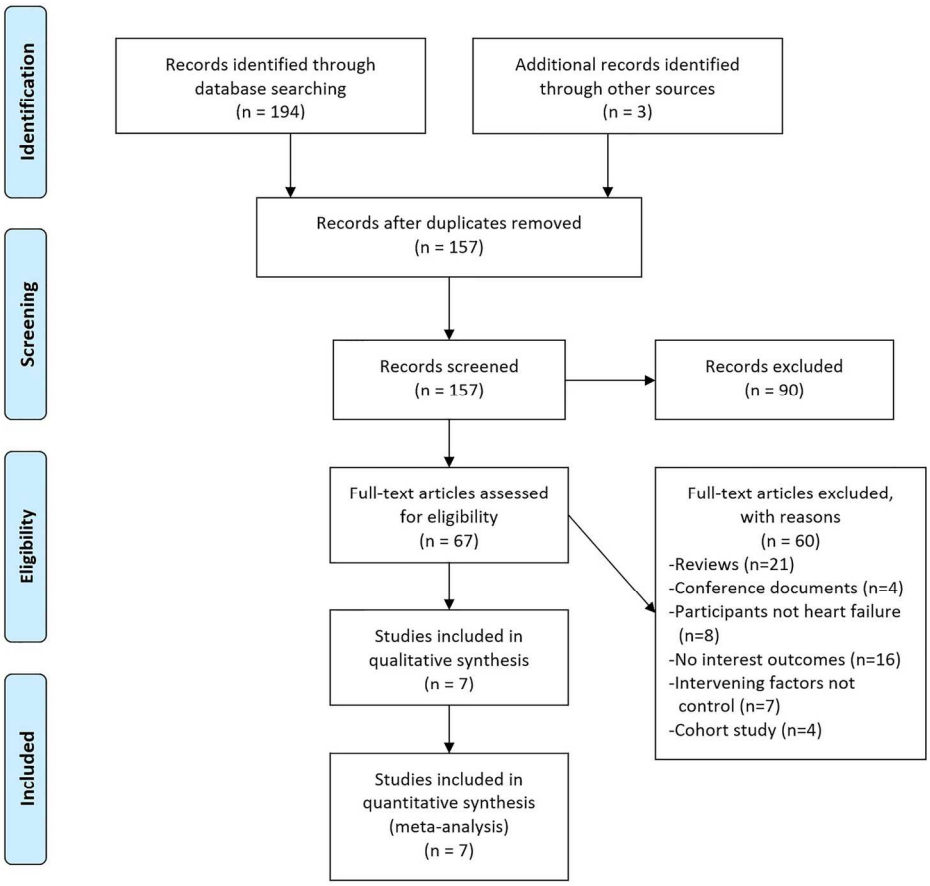

Figure 1 Flow diagram of study selection.

176x155mm (300 x 300 DPI)

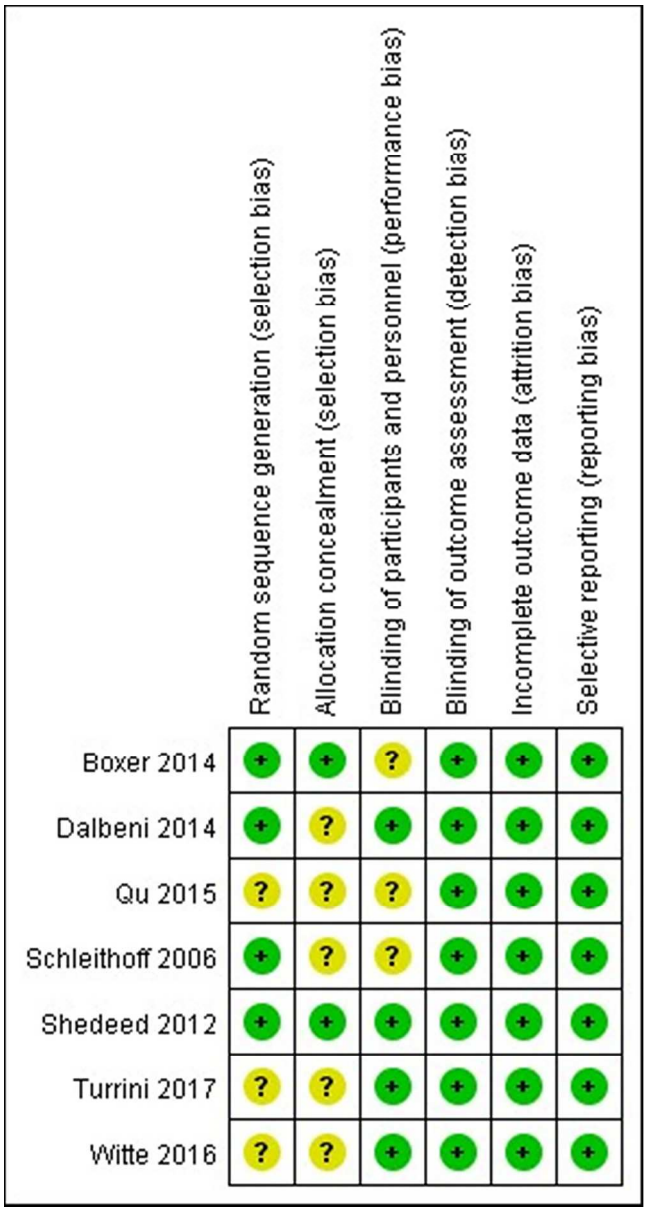

Figure 2 Quality assessment.

422x794mm (300 x 300 DPI)

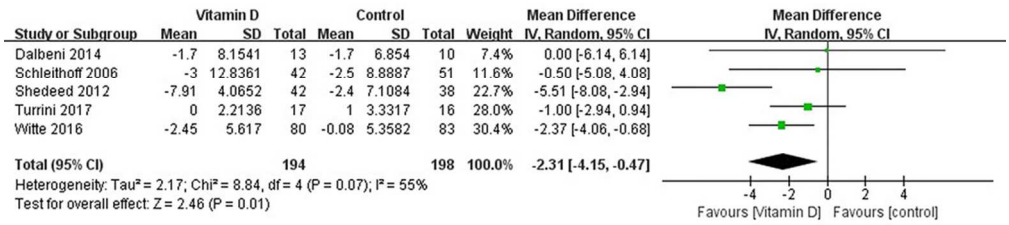

Figure 3 Forest plot showing the effect of Vitamin D on LVEDD.

92x20mm (300 x 300 DPI)

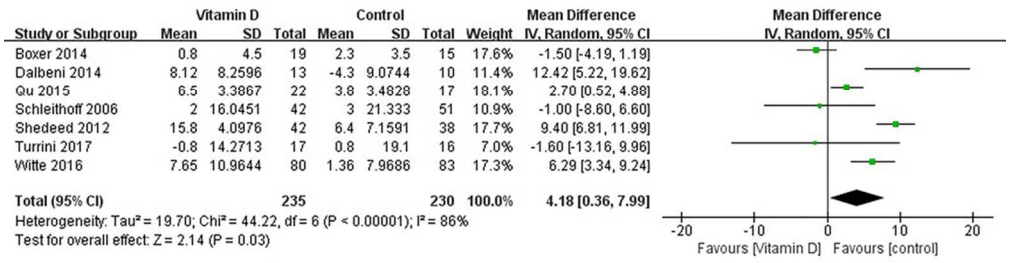

Figure 4 Forest plot showing the effect of Vitamin D on LVEF.

92x24mm (300 x 300 DPI)

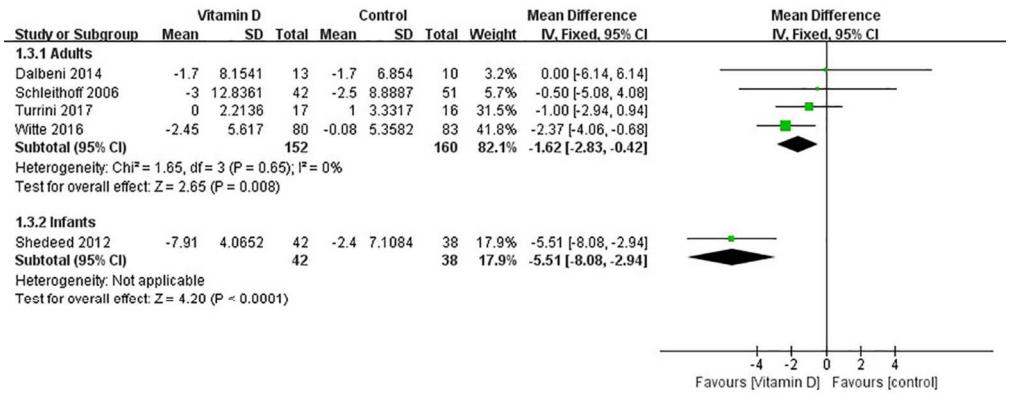

Figure 5 Subgroup analysis of effect of Vitamin D on LVEDD according to patients' age.

123x48mm (300 x 300 DPI)

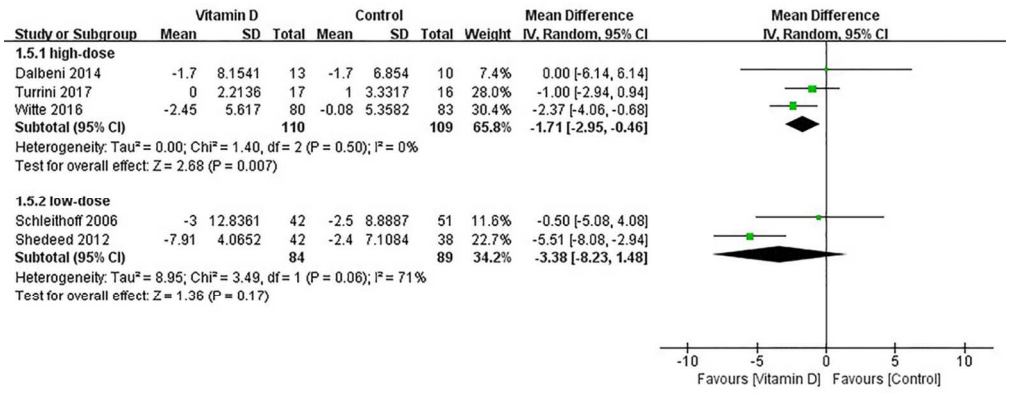

Figure 6 Subgroup analysis of effect of Vitamin D on LVEDD according to dose of Vitamin D.

99x38mm (300 x 300 DPI)

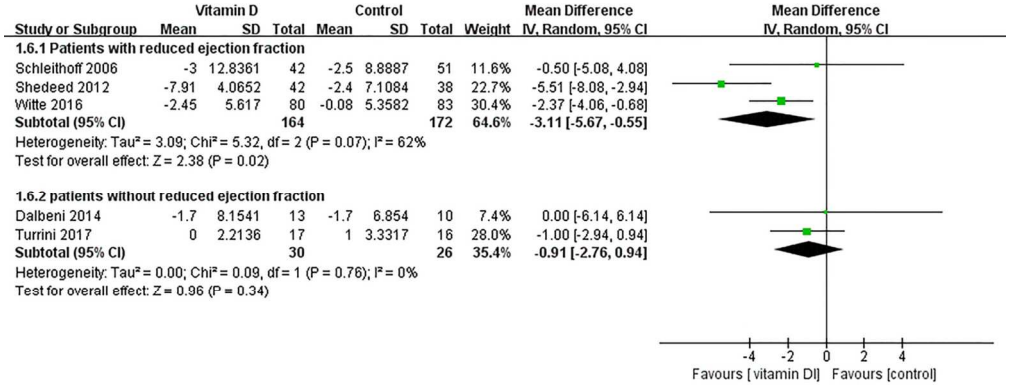

Figure 7 Subgroup analysis of effect of Vitamin D on LVEDD according to patients with or without reduced ejection fraction.

118x46mm (300 x 300 DPI)

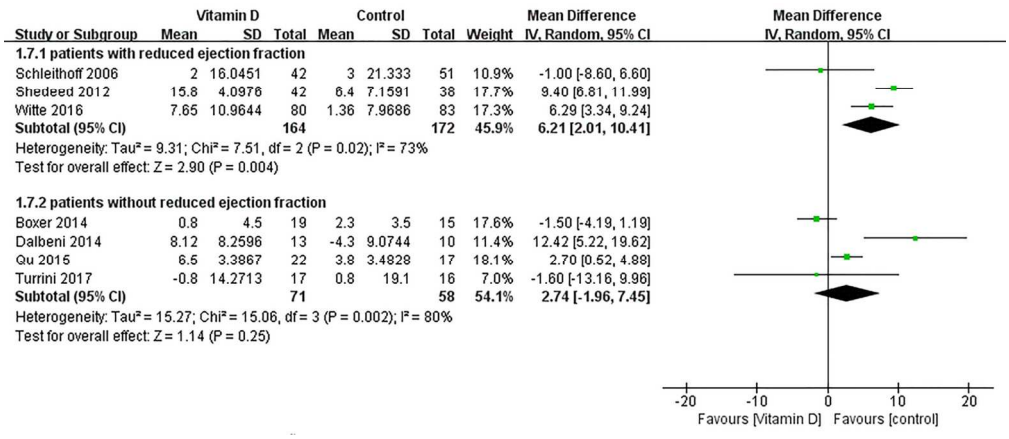

Figure 8 Subgroup analysis of effect of Vitamin D on LVEF according to patients with or without reduced ejection fraction.

129x55mm (300 x 300 DPI)

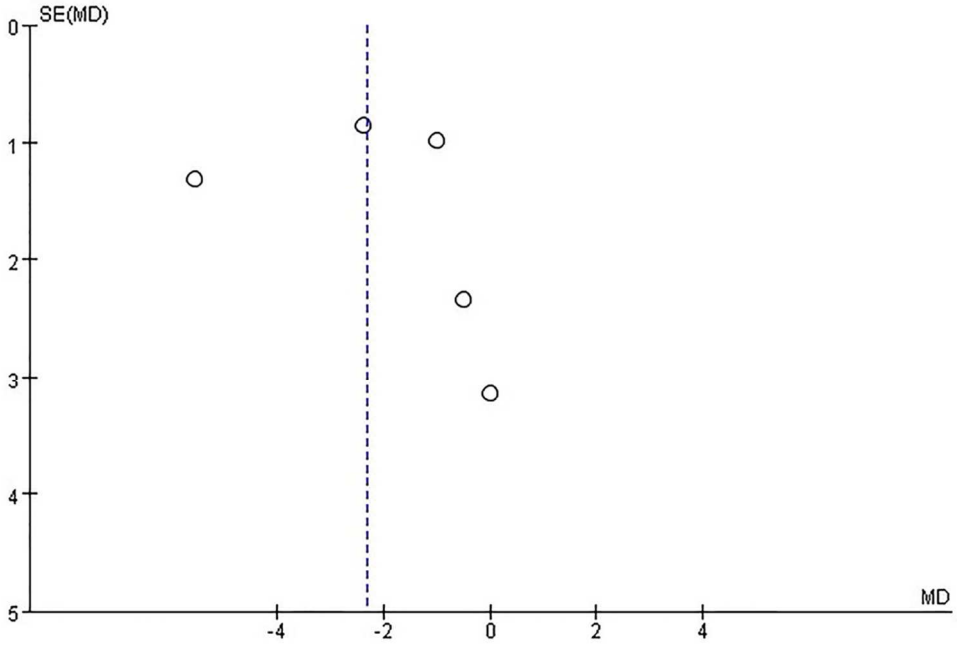

Figure 9 Funnel plots for the effect of Vitamin D on LVEDD

105x70mm (300 x 300 DPI)

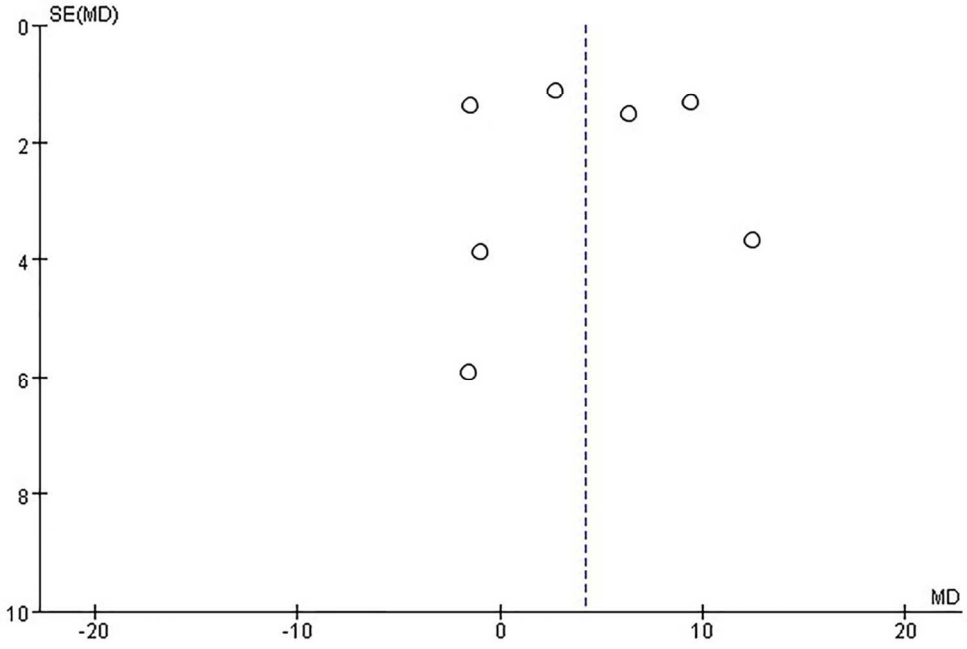

Figure 10 Funnel plots for the effect of Vitamin D on LVEF.

105x70mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	24

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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