Systematic Review and Meta-Analysis

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The effect of vitamin D_3 on blood pressure in people with vitamin D deficiency

A system review and meta-analysis

Silu He, BS*, Xiyuan Hao, MS

Abstract

Objective: To evaluate the effect of vitamin D_3 on blood pressure in people with vitamin D deficiency.

Methods: Randomized controlled trials (RCTs) were electronically searched databases including CNKI, VIP, WanFang Data, the Cochrane Library, PubMed, and EMbase which were about oral vitamin D_3 among people with vitamin D deficiency from inception to December 2017. Two reviewers independently screened literature according to the inclusion and extracted data; meta-analysis was performed using RevMan5.3.

Results: A total of 17 RCTs with 22 arms involving 1687 participants were included. The results of meta-analysis showed that, there were no significant differences between the vitamin D deficiency group and the control group on the level of change in systolic pressure (ΔSBP) [weighted mean difference (WMD) = −1.94, 95% confidence interval (CI) (−3.93,0.04) $P = .06$] and on the level of change in diastolic pressure (ΔDBP) [WMD = −0.50, 95% CI (−1.17, 0.17) $P = .14$]. The results of subgroups showed that, there were statistically significant differences in the age of >50 years subgroup on ΔSBP [WMD = −2.32, 95% CI (−4.39, −0.25) $P = .03$]; there were statistically significant differences in the hypertension subgroup on ΔSBP [WMD = −6.58, 95% CI (−8.72, −4.44) $P < .00001$]; there were statistically significant differences in the hypertension subgroup on ΔDBP [WMD = −3.07, 95% CI (−4.66, −1.48) $P = .0002$]; there were statistically significant differences in the body mass index (BMI) >30 subgroup on ΔSBP [WMD = −3.51, 95% CI (−5.96, −1.07) $P = .005$].

Conclusion: Oral vitamin D_3 has no significant effect on blood pressure in people with vitamin D deficiency. It reduces systolic blood pressure in people with vitamin D deficiency that was older than 50 years old or obese. It reduces systolic blood pressure and diastolic pressure in people with both vitamin D deficiency and hypertension.

Abbreviations: 25-OHD = 25-hydroxyvitamin D, BMI = body mass index, CI = confidence interval, DBP = diastolic pressure, PTH = parathyroid hormone, RCT = randomized controlled trial, SBP = systolic pressure, WMD = weighted mean difference.

Keywords: blood pressure, meta-analysis, vitamin D deficiency, vitamin D_3

1. Introduction

Vitamin D is 1 kind of steroid hormone. It can promote the absorption of calcium, phosphorus and other elements in the gastrointestinal tract. Vitamin D plays a key role in the skeleton and mineral metabolism which is an importance of human health.[1] The Institution of Endocrinology Clinical Practice Guidelines[2] pointed out that vitamin D deficiency was defined as a serum 25-hydroxyvitamin D (25-OHD) content less than 20ng/mL (or 50 nmol/L). Vitamin D deficiency is prevalent in Chinese population with.[3] There is a large volume of published studies describing that vitamin D deficiency can not only cause osteoporosis or other common diseases, but also lead to cardiovascular diseases, metabolic diseases, and tumors. Hypertension is an important factor that causes cardiovascular disease. Recent evidence indicated that serum 25-OHD levels were negatively correlated with the risk of hypertension.[4] It is considered that blood pressure changes in people with vitamin D deficiency would be related to vitamin D supplementation. This study aims to compare the changes in blood pressure in people with vitamin D deficiency after administration of vitamin D_3 by meta-analysis.

2. Methods

2.1. Search strategy

CNKI, VIP, WanFang Data, The Cochrane Library, PubMed, and Embase were searched by tow reviewers independently by computer from the database to December 2017. The search terms included vitamin D_3, cholecalciferol, and 25-OHD. Randomized controlled trials (RCTs) published in English language which were reported the effects of vitamin D_3 supplementation in people with vitamin D deficiency on blood pressure would be included.

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The authors declare that they have no conflicts of interest.

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2.2. Inclusion and exclusion criteria

The subjects were people with vitamin D deficiency. The baseline serum 25-OHD of them should be lower than 20ng/mL (or 50nmol/L). The RCTs mentioned that the observation group was administered a dose of vitamin D_3 and the control group was the placebo. The subjects were with no vitamin D deficiency and the form of vitamin D was not mentioned in the articles as vitamin D_3 was not included. Articles that data cannot be extracted from were not included. Studies that were published repeatedly were included only once. No ethical review is needed in this study.

2.3. Data extraction

The 2 reviewers extracted the data according to inclusion and exclusion criteria, then used self-made Excel forms and hand-drawn forms to record data. Mean age, male ratio, body mass index (BMI), mean serum 25-OHD baseline, sample size, subjects, nationality (or ethnicity), intervention measures, and course of treatment from the studies were extracted.

2.4. Quality assessment

The quality of studies was assessed via using the Cochrane Handbook: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Publication bias was generated by using a funnel plot to examine whether there was a bias towards studies.

2.5. Data synthesis and analysis

Data synthesis and analysis were carried out by RevMan 5.3 software and Stata 14.0 software. Relative risk (RR) was used as the statistic of curative effect analysis, and weighted mean difference (WMD) was used as the statistic of continuous variables. 95% confidence interval (CI) was given as the statistic of curative effect analysis. Heterogeneity analysis was performed by χ^2 statistics. Fixed effect model was used when $P > .1$ and $I^2 < 50\%$ and random effect model was used when $P < .1$ or $I^2 \geq 50\%$. The mean changes of systolic pressure (ΔSBP) and the mean changes of DBP (ΔDBP) were performed to evaluate the effects of vitamin D_3 of intervention groups and placebo of control groups. If the ΔSBP or ΔDBP are not mentioned in the articles, the mean and SD of ΔSBP and ΔDBP should be calculated by formulas. $\text{Mean (change)} = \text{Mean (Final)} - \text{Mean (baseline)}$, $\text{SD(change)} = \sqrt{\text{SD(Baseline)}^2 + \text{SD(Final)}^2 - \text{SD(Baseline)} + \text{SD(Final)}}$. Subgroup analysis was used to compare ΔSBP and ΔDBP according to age, course of treatment, treatment regimen, average daily dose, hypertension, and BMI index. We assessed publication bias by using Egger test.

3. Results

3.1. Study selection

The screening process is detailed in Figure 1. A total of 861 published articles were screened. Of those articles, 174 were first excluded due to duplicate publications. 575 were excluded after reading the titles and abstracts and then 112 articles were further screened. 62 of these did not fit the specific inclusion criteria and data from 33 articles cannot be extracted. Finally, a total of 17 RCTs[5–21] were included, including 22 arms and 1687 participants.

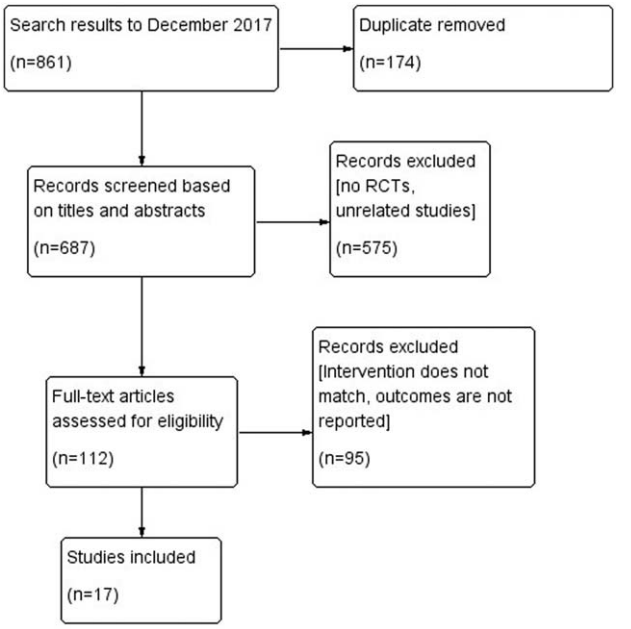

Figure 1. Flow chart of study selection.

3.2. Study characteristics

The characteristics of the studies are shown in Table 1. The mean serum 25-OHD of the participants from all articles are lower than 20ng/mL (or 50 nmol/L). The mean age of the participants is between 18 and 74 years old. The duration of intervention is 6 weeks to 12 months. Participants of 5 articles were hypertension. 5 arms of 3 articles were diabetic participants. The BMI is between 23.9 and 36.1.

3.3. Quality assessment

The quality evaluation of the study is shown in Figure 2. 17 RCTs were all double-blind and reported dropouts. There were no selective reports or other sources of bias that were mentioned in the articles. Only 3 articles[5,8,14] were not explained the randomization methods. Only 5 references[11,16–19] were used the correct allocation concealment. All of the 17 articles included are of high quality.

3.4. Outcome results

3.4.1. Primary outcome. The forest plots of ΔSBP and ΔDBP are shown in Figure 3. A total of 17 RCTs and 22 arms were included.

Compared with the control group, there was no significant difference between ΔSBP in vitamin D deficiency participants by oral administration of vitamin D_3 [WMD = −1.94, 95% CI (−3.93, 0.04) $P = .06$]. There was an indication of heterogeneity ($P < .00001$, $I^2 = 68\% > 50\%$, random effect model).

Compared with the control group, there was no significant difference between ΔDBP in vitamin D deficiency participants by oral administration of vitamin D3 [WMD = −0.50, 95% CI

Table 1

Trial characteristics.

Study	Age	Male, %	BMI	Serum 25-OHD Baseline (O/C)	Sample Size (O/C)	Trial crowd	Nationality/ Race	Intervention method O	Intervention method C	Duration
Bressendoff 2016[5]	>18	57.5	24.9	31/32*	22/18	Healthy	Denmark	$VD_3$3000IU/d	Placebo/d	16 wk
Chen 2014[6]	62	58	23.9	19.4/19.5**	63/63	Hypertension	China	$VD_3$2000IU/d	Placebo/d	6 mo
Dalbeni 2014[7]	74	61	28.6	16.2/16**	18/18	Hypertensio+ Heart failure	Italy	$VD_3$60000IU-100000IU/10w	Placebo/10w	6 mo
				16.3/6.3**	68/72			$VD_3$1000IU/d+Ca0.2g/d		
Forman 2013[8]	51	34.6	31	14.5/16.3**	73/72	Healthy	Black	$VD_3$2000IU/d+Ca0.2g/d	Placebo/d+Ca0.2g/d	3 mo
				15.6/16.3**	70/72			$VD_3$4000IU/d+Ca0.2g/d		
Longenecker 2012[9]	44	78	28.5	9.0/6.2**	30/15	AIDS	USA	$VD_3$4000IU/d	Placebo/d	12 wk
Mozaffari-K 2014[10]	43	36	28.7	17.6/18.4**	19/20	Hypertension	Iran	$VD_3$5000IU/d	Placebo/d	8 wk
Nagpal 2008[11]	44	100	26	36.5/30*	35/36	Healthy	India	$VD_3$120000IU/2w+Ca 1g/d	Placebo+Ca 1g/d	6 wk
Raja-K 2014[12]	18–45	0	37.2	19.95/20**	13/15	Polycystic ovary syndrome	USA	$VD_3$12000IU/d	Placebo/d	12 wk
Sadiay 2015[13]	49	18.4	37.8	28.5/30.5*	45/42	Diabetes mellitus	Arab	$VD_3$6000IU/d-3000 IU/d	Placebo/d	6 mo
Salehpour 2012[14]	38	0	30.1	36.8/46.9*	42/43	Healthy	Iran	$VD_3$1000IU/d	Placebo/d	12 wk
Schleithoff 2006[15]	57	52	26	14.4/15.3**	42/51	Heart failure	Germany	$VD_3$2000IU/d+Ca 0.5g/d	Placebo/d+Ca 0.5g/d	9 mo
Stricker 2012[16]	74	61	-	16.3/17.0**	31/31	Peripheral arterial disease	White	$VD_3$100000IU/mon	Placebo/mon	1 mo
Tabesh 2015[17]	44	50	30.3	30.3/45.5*	30/30	Diabetes mellitus	Iran	$VD_3$50000IU/w+Ca 1g/d	Placebo/w+Ca 1g/d	8 wk
				27.8/45.5*	29/30			$VD_3$50000IU/w	Placebo/w	
Witham 2010[18]	65	67	31.4	41/45*	19/21	Hypertension+Diabetes mellitus	UK	$VD_3$100000IU/8w	Placebo/8w	16 wk
				48/45*	18/21			$VD_3$200000IU/8w		
Witham 2013[19]	41	0	26.8	27/27*	25/25	Healthy	South Asia	$VD_3$100000IU/4w	Placebo/4w	8 wk
Wood 2012[20]	64	0	26.7	32.74/36.18*	97/100	Healthy	White	$VD_3$400IU/d+Ca0.5g/d	Placebo/d+ Ca0.5g/d	2 mo
					96/100					
				32.41/36.18*				$VD_3$1000IU/d+Ca0.5g/d		
Zittermann 2009[21]	48	24	36.1	30.0/30.3*	82/83	Overweight	Germany	$VD_3$3332IU/d	Placebo/d	12 mo

C = control group, O = observation group.

*Unit of 25-OHD is nmol/L.

**Unit of 25-OHD is ng/mL.

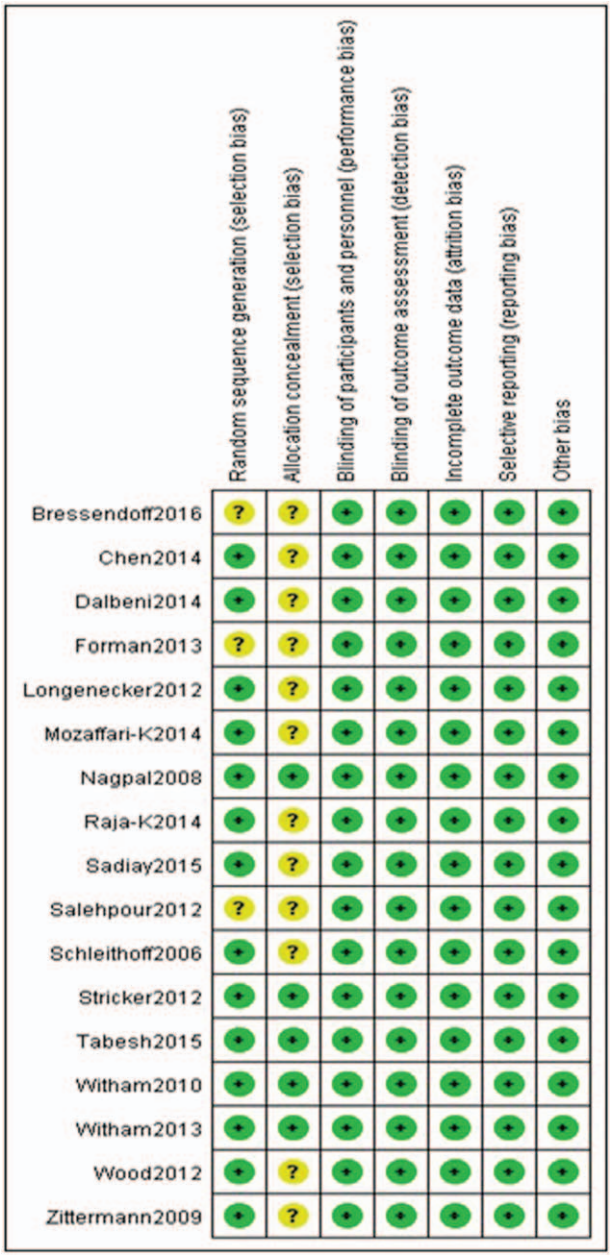

Figure 2. Risk of bias in the included studies.

(−1.17, 0.17) $P=.14$]. There was no indication of heterogeneity ($P=.03>.01$, $I^2=39\%<50\%$, fixed effect model).

3.4.2. Subgroup outcome

3.4.2.1. ΔSBP Subgroup. Compared with the control group, there was a significant difference in the age >50 years subgroup of ΔSBP [WMD = −2.32, 95% CI (−4.39, −0.25) $P=.03$]. There was a significant difference in the hypertension subgroup [WMD = −6.58, 95% CI (−8.72, −4.44) $P<.00001$]. There was a significant difference in the BMI >30 subgroup [WMD = −3.51, 95% CI (−5.96, −1.07) $P=.005$]. The outcomes of ΔSBP subgroup are listed in Table 2.

3.4.2.2. ΔDBP Subgroup. Compared with the control group, there was a significant difference only in the hypertension subgroup [WMD = −3.07, 95% CI (−4.66, −1.48) $P=.0002$]. The outcomes of ΔDBP subgroup are listed in Table 2.

3.5. Publication bias

There was no publication bias based on Egger test ($t=-0.95$, $P=.355$ for ΔSBP, $t=-0.48$, $P=.634$ for ΔDBP, Fig. 4).

4. Discussion and conclusion

Vitamin D_3 is one of the most active forms of vitamin D with the highest biometabolic rate. It is synthesized in skin by ultraviolet radiation and is less obtained from usual diet. A meta-analysis[22] of 7 RCTs indicated that vitamin D_3 is more efficacious at increasing serum 25-OHD than is vitamin D_2, and vitamin D_3 supplementation intake was the preferred treatment for vitamin D deficiency.[23] Numerous studies have attempted to explain the possible mechanisms of vitamin D deficiency that induced hypertension. Presently, there are 3 mainstream theories: First, it is that the renin-angiotensin-aldosterone system (RAAS) is activated. An animal experiment has shown that mice lacking the vitamin D receptor has had elevated production of renin and angiotensin II.[24] The second is vitamin D deficiency leads to hyperparathyroidism. Serum 25-OHD levels and parathyroid hormone (PTH) levels are negatively correlated and high PTH level causes hypertension. The last is that vitamin D deficiency causes endothelial dysfunction. The reducing of NO in the blood vessels caused by endothelial dysfunction affects the vasodilation and then raised blood pressure. It suggests that vitamin D deficiency might be a risk factor of hypertension.

All the studies reviewed so far, however, the RCTs included from each study had larger individual differences and the conclusions of them are not the same. The relationship between vitamin D_3 and blood pressure has been widely investigated in several previous meta-analysis. For the purpose of exploring the relationship between vitamin D deficiency and blood pressure, a total of 17 articles including 22 arms involving 1687 participants were included in this study. The results showed that vitamin D_3 made no effect on ΔSBP or ΔDBP in people with vitamin D deficiency. A meta-analysis of Beveridge[26] shown no effect of vitamin D supplementation was seen on SBP or DBP in the subgroup of mean baseline 25OHD level ≤20 ng/mL. In this study, another 3 RCTs were included which were published after Beveridge's study. Furthermore, the participants of Beveridge's study were administered vitamin D2 , vitamin D3 or 1-α-Hydroxylated vitamin D and participants of this study were only administered vitamin D3. These reasons may lead to different conclusions of the 2 studies. Another meta-analysis in 2016 including 30 RCTs by Golzarand[25] reported that there was no significant difference in the effects of vitamin D3 supplementation on systolic and diastolic blood pressure. The conclusion was similar to this study but the participants in that study were not limited to vitamin D deficiency. This is the first meta-analysis of blood pressure after vitamin D3 supplementation for people with vitamin D deficiency.

In this subgroup analysis, there is a significant difference in the group of age >50. There is an evidence suggests that the prevalence of hypertension increases from age.[27] The ability to absorb and metabolize vitamin D of humans decreases in age growing, resulting in vitamin D deficiency in the elderly. The systolic blood pressure on vitamin D deficient folks whose age over 50 years old will decrease significantly when their vitamin D

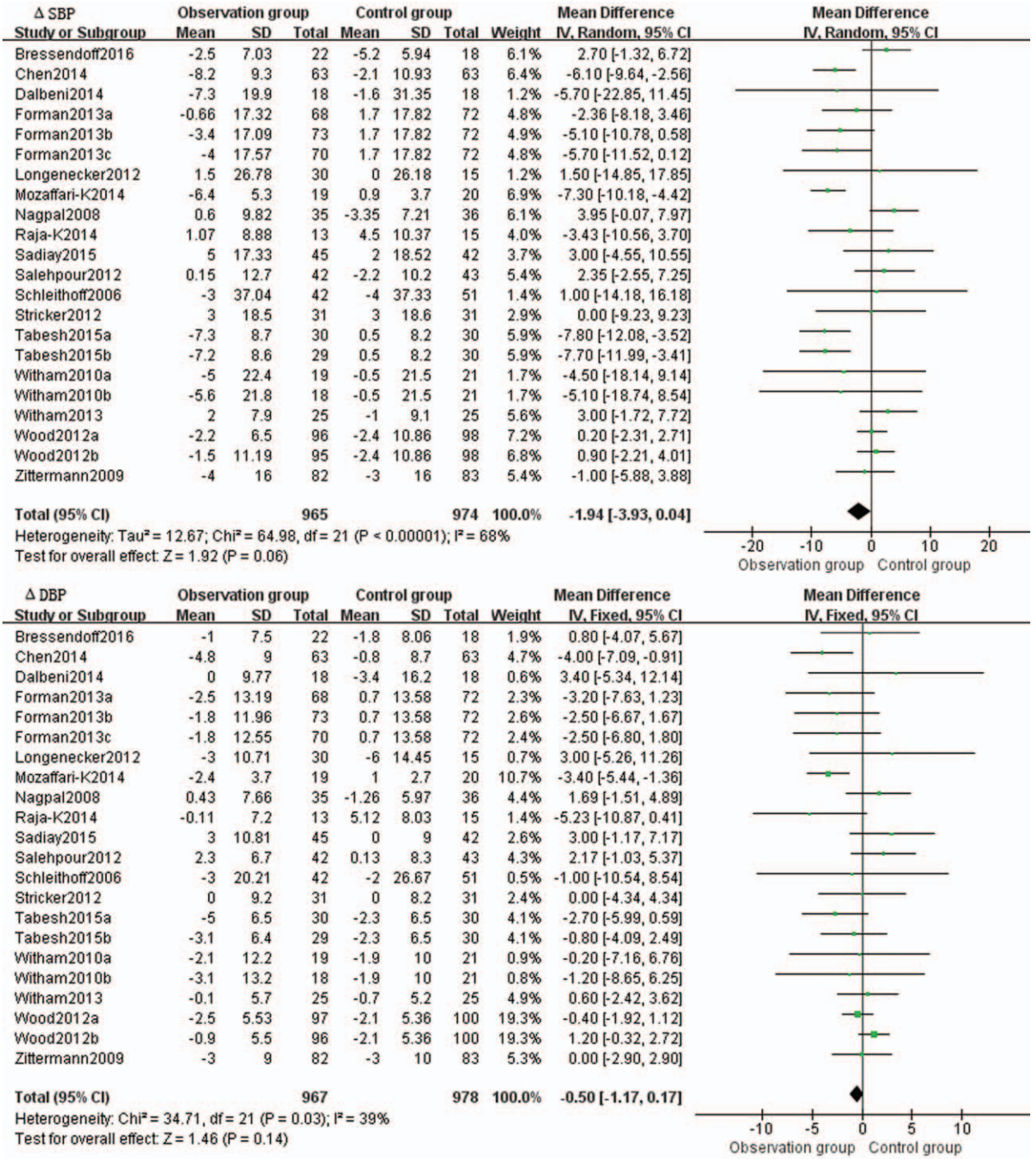

Figure 3. Forest plot of comparison for ΔSBP and ΔDBP. DBP = diastolic pressure, SBP = systolic pressure.

levels returned to normal after vitamin D_3 supplementation. The differences between the observation group and control group of ΔSBP and ΔDBP in the hypertension subgroup are statistically significant. The results of subgroup analysis from Wei Zhen's meta-analysis[28] published in 2017 showed that oral vitamin D_3 supplementation could reduce the systolic and diastolic blood pressure levels in patients with essential hypertension, but could not affect the blood pressure level in people without hypertension. It was similar to the subgroup analysis in this study. It is concluded that vitamin D_3 has a hypotensive effect on hypertension patients but useless on non-hypertension patients. The difference of ΔSBP is statistically significant in BMI >30 subgroup. BMI index is positively correlated with blood pressure level. The aggregate analysis of the follow-up data of 240,000 Chinese adults shows that the risk of hypertension in people with BMI >24 is over triple higher than that in people with normal weight.[27] Overweight or obese people are prone to vitamin D deficiency because they lack of exercise and rarely stay outside

Table 2

Outcomes of ΔSBP subgroup.

Subgroup	Arm	Heterogeneity	WMD (95% CI)	*P*
Age <50	10	$P<.00001$ $I^2=79\%$	−1.75 [−5.22, 1.73]	.32
Age >50	11	$P=.14$ $I^2=32\%$	−2.32 [−4.39, −0.25]	.03
Duration <3 months	14	$P<.00001$ $I^2=75\%$	−2.15 [−4.64, 0.33]	.09
Duration >3 months	8	$P=.08$ $I^2=45\%$	−1.34 [−4,68, 2.00]	.43
Daily dosing	14	$P=.0003$ $I^2=66\%$	−1.77 [−3.97, 0.42]	.11
Intermittently dosing	8	$P=.0003$ $I^2=74\%$	−2.49 [−7.11, 2.13]	.29
Average daily dose ≤2000IU/d	9	$P=.06$ $I^2=46\%$	−1.56 [−3.92, 0.81]	.20
Average daily dose >2000IU/d	13	$P<.00001$ $I^2=75\%$	−2.04 [−5.05, 0.96]	.18
Hypertension	5	$P=.93$ $I^2=0\%$	−6.58 [−8.72, −4.44]	<.00001
No Hypertension	17	$P=.0005$ $I^2=61\%$	−0.98 [−2.98, 1.01]	.33
BMI <30	10	$P<.00001$ $I^2=78\%$	−0.54 [−3.55, 2.47]	.72
BMI >30	11	$P=.06$ $I^2=44\%$	−3.51 [−5.96, −1.07]	.005

Outcomes of ΔDBP subgroup

Subgroup	Arm	Heterogeneity	WMD (95% CI)	*P*
Age <50	10	$P=.01$ $I^2=56\%$	−0.34 [−1.98, 1.31]	.69
Age >50	11	$P=.16$ $I^2=30\%$	−0.80 [−2.09, 0.49]	.22
Duration <3 months	14	$P=.02$ $I^2=50\%$	−0.73 [−1.90, 0.43]	.22
Duration >3 months	8	$P=.22$ $I^2=26\%$	−0.20[−2.18, 1.78]	.85
Daily dosing	14	$P=.005$ $I^2=56\%$	−0.87 [−2.20, 0.46]	.20
Intermittently dosing	8	$P=.70$ $I^2=0\%$	−0.15 [−1.57, 1.27]	.84
Average daily dose≤2000IU/d	9	$P=.06$ $I^2=46\%$	−0.11 [−1.02, 0.79]	.81
Average daily dose>2000IU/d	13	$P=.10$ $I^2=35\%$	−0.96 [−1.95, 0.03]	.06
Hypertension	5	$P=.49$ $I^2=0\%$	−3.07 [−4.66, −1.48]	.0002
No Hypertension	17	$P=.27$ $I^2=16\%$	0.05 [−0.68, 0.79]	.89
BMI <30	10	$P=.01$ $I^2=58\%$	−0.31[−1.83, 1.21]	.69
BMI >30	11	$P=.23$ $I^2=22\%$	−0.91 [−2.31, 0.49]	.20

BMI = body mass index, DBP = diastolic pressure, WMD = weighted mean difference.

under ultraviolet radiation. Increased activity in these groups not only reduces body weight but also reduces the risk of hypertension by synthesizing vitamin D from skin exposure to ultraviolet light. Intervention duration less than 6 months, average daily dose over 800IU/d and daily doses appeared to be more effective at reducing blood pressure in the meta-analysis of Golzarand.[25] However, the daily dosage of vitamin D3, intervention measures or the course of treatment are not the factors that influenced the outcomes in this study.

Limitations of this study are as follows:

(1) This study may have language bias because all the RCTs included are in English.
(2) The dosage of vitamin D_3 in the 17 RCTs differs individually which may have an impact on the results of meta-analysis.

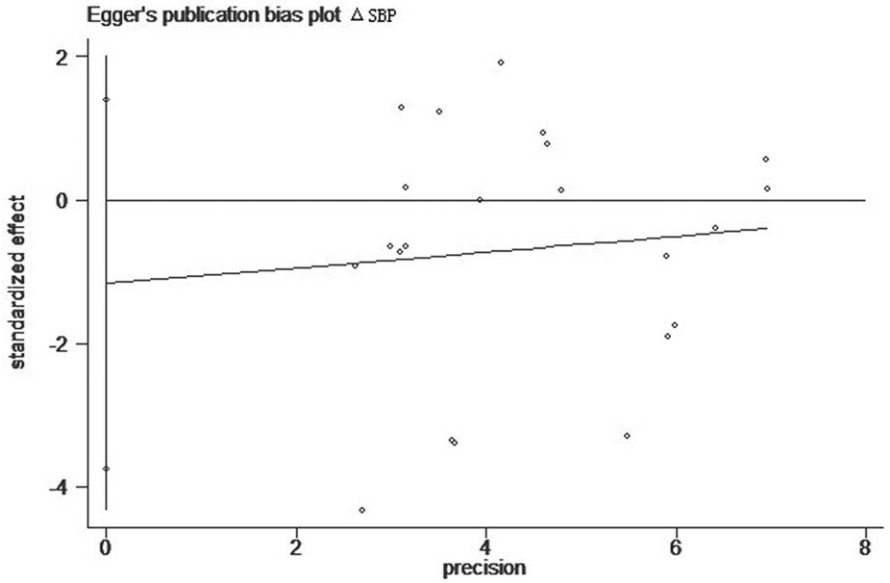

Figure 4. Egger test for ΔSBP. SBP = systolic pressure.

(3) The participants from quite a few RCTs included in this study took other non-experimental drugs at the same time in the observation group and control group that may affect the reliability of the results.
(4) Only RCTs were included in these studies. More multi-center, large-sample, well-designed clinical reports and prospective studies are needed to further summarize this study.

In conclusion, vitamin D_3 can be taken as a prophylactic drug for hypertension by the elderly and obese folks with vitamin D deficiency who are at high risk of hypertension. Vitamin D_3 can be used as an adjuvant drug to control the blood pressure on hypertension patients with vitamin D deficiency.

Author contributions

Conceptualization: Silu He, Qingchun Zhao, Xiyuan Hao.
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Writing – original draft: Silu He, Xiyuan Hao.
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