Changes in 25-hydroxyvitamin D levels post-vitamin D supplementation in people of Black and Asian ethnicities and its implications during COVID-19 pandemic : A systematic review

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Abstract

Objective: People of Black and Asian ethnicities have higher infection rate and mortality due to COVID-19. It has also been reported that vitamin D deficiency may play a role in this, possibly due to the multi-gene regulatory function of the vitamin D receptor. As a result, increased dietary intake and/or supplementation to attain adequate 25-hydroxyvitamin D (25(OH)D) levels could benefit people in these ethnicities. The aim of this study was to review the literature examining the changes in 25(OH)D in different types of vitamin D supplementation from randomised controlled trials in this population.

Design: This systematic review was conducted using the PRISMA guidelines. Electronic databases were systematically searched using keywords related to vitamin D supplementation in Black and Asian ethnicities.

Results: Eight studies were included in the review. All the included studies found that supplementation of vitamin D (D_2 and D_3), regardless of dosage, increased 25(OH)D levels when compared to a placebo. All trials in which participants were vitamin D deficient at baseline showed increased 25(OH)D levels to a level considered adequate. Two studies that used food fortification yielded smaller 25(OH)D increases compared to similar studies that used oral supplementation (10.2 vs 25.5 nmol·L^{-1}, respectively). Furthermore, vitamin D_2 supplementation yielded significantly lower 25(OH)D increases than vitamin D_3 supplementation.

Conclusions: Oral vitamin D supplementation may be more efficacious in increasing 25(OH)D levels than food fortification of Black and Asian ethnicities, with vitamin D_3 supplementation possibly being more efficacious than vitamin D_2. It is recommended that people with darker skin supplement their diet with vitamin D_3 through oral tablet modes where possible, with recent literature suggesting a daily intake of 7000-10000IUs to be potentially protective from unfavourable COVID-19 outcomes. Due to the paucity of studies, these findings should be treated as exploratory.

Introduction

Vitamin D is a major contributor to the regulation of calcium and phosphate in the body and can potentially play a role in preventing many diseases ([1–3]). Moreover, insufficient concentrations of vitamin D have been reported as significant risk factor of mortality ([4,5]). Although the majority of vitamin D is synthesised in the human body via sunlight ([6]), this may not be sufficient in some people. For example, if the inability to go outdoors (such as in the elderly) is impaired, or due to opaque clothes that cover up the majority of the skin. Furthermore, it is known that people with darker skin do not convert vitamin D from ultraviolet radiation as effectively as people with lighter skin types. Moreover, it has been reported that people with darker skin are more prone to vitamin D deficiency in countries where the majority of the population is of the Fitzpatrick skin type V or VI, such as Afghanistan, India, Mongolia, Pakistan and Tunisia ([7]). Indeed, it has been reported that people with darker skin require nearly three times the exposure of sunlight than Caucasians to attain similar changes in serum 25-hydroxyvitamin D (25(OH)D) levels ([8]) and therefore and may need to increase dietary intake of vitamin D, thereby increasing serum 25(OH)D levels ([9]), to reduce the likelihood of deficiency. Moreover, it has also been reported that 25(OH)D levels are positively associated with several health outcomes in African Americans, including Alzheimer's disease and multiple sclerosis ([10]).

Historically, several studies have examined the efficacy of vitamin D supplementation in participants of Black and Asian ethnicities. Of these, several randomised controlled trials (RCTs) have reported that vitamin D supplementation can minimise the likelihood of deficiency, and have examined serum 25(OH)D changes for several dosages and intervention

lengths ([11–13]). A number of these studies have also compared changes in serum 25(OH)D levels following vitamin D supplementation in people of different skin colours, and shown significant improvements ([11,14]).

The influence of vitamin D has received interest in the light of the COVID-19 pandemic in people with Black and Asian ethnicities. COVID-19 has been found to disproportionally affect people of Black and Asian ethnicities ([15,16]). Primary studies have yielded conflicting results regarding vitamin D associations and COVID-19 outcomes. For example, a recent large, nationally representative, study reported non-significant associations between vitamin D levels, COVID-19 infection, or COVID-19 mortality in adjusted models ([17]), while others have found significant associations ([10,18–21]). Furthermore, recent systematic reviews have concluded that there is not enough evidence to conclude whether vitamin D levels are conclusively associated with COVID-19 ([22]). When stratifying by ethnicity, reports suggest that people of Black and/or Asian ethnicities consistently yield significant associations between low circulating vitamin D concentrations and poor COVID-19 outcomes ([20,23,24]), with policy makers recommending vitamin D supplementation as a possible protective measure for COVID-19 ([25]). Because people of Black and Asian ethnicities have been reported to yield significant associations between vitamin D status and poor COVID-19 outcomes, it is important to understand to what extent vitamin D supplementation increases serum 25(OH)D levels.

To date, no studies have systematically reviewed RCTs that have explored the efficacy of different dosages, modes of entry, and duration of vitamin D supplementation in Black and Asian communities. It is, therefore, the aim of this exploratory study to review all available

literature that examined the efficacy of vitamin D supplementation (via changes in 25(OH)D levels) in Black or Asian participants. The results from this study have the potential to inform future research, identify gaps in the current literature, and inform COVID-19 related nutrition advice, especially regarding the general efficacy of vitamin D supplementation in this potentially vulnerable population.

METHODS

Study registration

This study was registered with the international prospective register of systematic reviews, and the full protocol can be found on PROSPERO (Protocol ID: CRD42021239233), and was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines ([26]).

Search strategy

Electronic databases were searched from inception to 31 July 2021, including PubMed, Scopus, Web of Science and EMBASE. Searching methodology included terms and synonyms relating to vitamin D supplementation in Black and Asian populations and have been outlined below:

(Vitamin D* OR 25-hydroxyvitamin D OR hypovitaminosis D) AND (Black OR Asia* OR Ethnic*) AND (Therap* OR treatment)

Results of the searches were imported into a bibliographic database (Covidence) and duplicates automatically removed. Titles and abstracts of studies were screened for inclusion by two independent authors (MV & GP), using the following criteria for inclusion:

Population

Healthy adults with Black or Asian ethnicity were included. Children <18yrs, studies with pregnant women and animal studies were excluded.

Intervention

Any intervention designed to increase vitamin D levels including oral tablets, injection and food fortification.

Control

Control groups were defined as a placebo treatment with no vitamin D supplementation.

Outcomes

Studies had to report the efficacy of the respective vitamin D deficiency treatment in terms of changes in serum concentration of 25-hydroxyvitamin D in both populations.

Study design

Only RCTs were included.

Following title and abstract screening, full texts of potential papers were reviewed independently by the same two reviewers (MV & GP) using the same inclusion criteria. Any discrepancies between reviewers were resolved by discussion and consultation with a third senior author (SP) if required.

Data extraction

A bespoke data extraction form was created according to the requirements of the review. Two authors piloted the data extraction form in a random sample of studies to ensure that the relevant information was selected by the review authors. The data was independently extracted by two reviewers (MV & RS) and included: first author, year of study, country, number of participants, outcomes, inclusion and exclusion criteria, method of assessing vitamin D levels, details of randomisation, quality of study, limitations and conclusions. Where information was missing or variables of interest were not reported in the paper, or clarification was required, corresponding authors were contacted. If no response was received within a two-week window, these studies were excluded.

Quality assessment

The risk of bias was assessed by two independent researchers (MV, RS) with the Joanna Briggs Institute (JBI) checklist for randomised control trials ([27]), a non-scoring appraisal tool for assessing the validity of articles, which requires the identification of whether or not relevant information is present in each article using a yes, no, unclear or not applicable rating. Any discrepancies between the review authors over the risk of bias in particular studies was made by consensus, with the involvement of a third review author (SP) where necessary.

RESULTS

A total of 9178 studies were initially identified from the database searches. After the removal of 3890 duplicates, 5105 studies were excluded based on their title and abstract. This left 183 studies selected for full-text review. Of these studies screened, 164 were excluded (full exclusion reasons are broken down and can be seen in PRISMA flow diagram Figure 1), and one study was added from the reference lists, leaving eight studies included in the review.

Full characteristics of included studies can be found in Table 1. In brief, all studies were published 2010-2020, with a total of 1,108 participants at follow-up (baseline number of participants was incomplete). Study follow-up ranged from 30 days to one year. Two studies comprised of an African American population ([12,13]), one comprised an Indian population ([28]), one Bangladeshi ([29]), one Pakistani ([11]), and Japanese ([30]), one non-specific South Asian population ([14]), and the one remaining study's population was mixed ([31]). All included studies were placebo-controlled, with the placebo group being the same ethnicity as the treatment group. Two studies investigated the effect of food/drink fortification ([11,14]), two studies investigated the effect of increasing dosage (1,000, 2,000, 4,000 IU) of vitamin D_3 combined with 200mg calcium carbonate·day^{-1} ([12,13]), one study investigated the effect of vitamin D_3 sachets in combination with lactose or calcium carbonate tablets ([28]), one study investigated the difference between 10 μg vitamin D·day^{-1}, 10μg of vitamin D_3 + 600 mg of calcium lactate·day^{-1} and multiple micronutrients + 10μg of vitamin D_3 + 600mg of calcium lactate·day^{-1} ([29]), one study investigated a combination of calcium (200 mg·d^{-1}) and vitamin D_3 (800 IU·d^{-1}) ([30]), and one study investigated 4 x 1000 IU capsules of vitamin D_3 per day ([31]). Of the eight included studies, one had a five-arm placebo-controlled method, four had used a four-arm placebo-controlled method, while three studies used a placebo and single-arm assessment

group. All studies used 25(OH)D assays using plasma/serum samples at baseline and follow up. All eight studies were evaluated with the JBI RCT checklist and were deemed of sufficient quality to be included. Full scoring information is shown in Supplementary Table 1.

Regarding baseline vitamin D status, there were three studies where the baseline population had a 25(OH)D of <25nmol·L^{-1}. Of these studies, all treatment groups (regardless of dosage or duration) showed significant 25(OH)D increases compared to the placebo group(s), and all treatment groups' mean 25(OH)D levels increased to >25 nmol·L^{-1} (range 47.2-118.75 nmol·L^{-1}). Furthermore, all but two studies reported treatment groups' follow up 25(OH)D levels at >50 nmol·L^{-1}, see Table 2 for full details.

DISCUSSION

In this systematic review, we have summarised the outcomes of eight RCTs (1,108 participants) relating to the relative efficacy of vitamin D supplementation in people of Black and/or Asian ethnicities.

In the trials in which participants had 25(OH)D levels of <25nmol·L^{-1} at baseline, the intervention, regardless of dosage, mode of delivery, or duration, increased the levels to >25nmol·L^{-1}. In all but two studies the intervention increased 25(OH)D levels to >50nmol·L^{-1} effectively lifting them out of VD deficient status. The study with the smallest intervention dosage (400IU; 10 µg·d^{-1}) [29] reported that all of their participants were no longer vitamin deficient, indicating that high dosage may not be necessary to increase 25(OH)D levels above 50 nmol·L^{-1}. It is worth noting that the study with the shortest duration of treatment (30 days) [30] did not increase the serum 25(OH)D levels to > 50 nmol·L^{-1}, therefore it is likely that higher dosages may be required in Black and Asian populations especially when sun exposure does not contribute enough to allow enough vitamin D synthesis. Whether this would be sustainable after sufficient vitamin D levels were attained require further investigation. In participants who had a baseline 25(OH)D of >25 nmol·L^{-1}, significant increases in 25(OH)D levels were also observed in their respective treatment groups, regardless of dosage, duration or modality of supplementation.

Modality of vitamin D supplementation

The modality of intake makes a difference. One study [11] that used foods fortified with vitamin D$_3$ as a mode of supplementation yielded much smaller changes in 25(OH)D levels than another included study [12] (10.2 vs 25.5 nmol·L^{-1}, respectively) in which participants

received similar dosages and durations ('approx' 20 µg/800IU vs 25µg/1000IU, respectively) of oral vitamin D_3, suggesting that oral vitamin D_3 supplementation may be more efficacious than food fortification. It has been argued that food fortification may be an easier way to add vitamin D to the diet than other modes [14], particularly for some South Asian populations who have a vegan or vegetarian diet [32], as vitamin D is primarily present in animal sources such as meat and poultry [33]. Furthermore, it has been reported that food fortification can have a significant role in increasing serum 25(OH)D levels in other ethnicities as well [34–36], and is ranked as a priority intervention to reduce malnutrition in Southeast Asians [37] and internationally [38]. The results of this review, however, suggest that compared to oral supplementation, food fortification may be less efficacious. Further research to confirm or refute this is warranted.

South Asian vs populations with lighter skin

The two studies [11,14] that used food fortification as a vitamin D delivery mode were also the only ones that directly compared results of different skin types (in other arms of their respective RCTs). Grønborg and colleagues [11] found that, while both populations (Danish vs Pakistani) significantly increased 25(OH)D levels, the Danish group's 25(OH)D levels increased more than the Pakistani group. However, the authors argue that adherence to the fortified foods was higher amongst the Danish group, which may go towards explaining their findings. Tripkovic and colleagues [14] found no interaction effects between 25(OH)D changes and ethnicity; however, they also reported that fewer South Asian women increased their 25(OH)D levels to >50nmol·L^{-1}, predominantly because their baseline 25(OH)D levels were much lower.

Vitamin D_2 vs vitamin D_3 supplementation

A comparison of the type of vitamin D supplementation showed that while vitamin D_2 supplementation did increase 25(OH)D levels, there was significantly less change than the group who received vitamin D_3 supplementation, regardless of ethnicity. This concurs with previous literature that suggests vitamin D_2 is less efficacious than vitamin D_3 for increasing serum 25(OH)D levels ([39–41]). One possible mechanism is vitamin D_3's enhanced ability to bind to the vitamin D receptor (VDR) after the formation of $1,24,25(OH)_3$ in the kidneys ([42]).

Vitamin D, COVID-19, and supplementation recommendations

With reference to COVID-19, several studies have reported negative associations between serum 25(OH)D levels and disease severity ([20,43]), resulting in recommendations that policy makers should include dietary intake/ supplementation as a potential protective measure against the infection and mortality ([20,21,25,44]). Vitamin D has been advocated to reduce viral replication rates and expression of pro-inflammatory cytokines ([20,45]). Specific 'one-size fits all' vitamin D dosages and treatment lengths are difficult to recommend, partly due to the potential effect of VDR gene activation on the responsiveness of vitamin D supplementation in African Americans ([46]), and general human variability. Grimes and colleagues have recommended a dosage of 75-125µg (7000-10000 IU) per day for adults who are people 'of colour' to attain a potential protective effect against COVID-19 ([47]), which is a much higher dosage than any of the included studies in this review. Our review suggests that oral supplementation may be more beneficial than food fortification in people with darker skin and that vitamin D_3 is more efficacious than vitamin D_2, and therefore may therefore provide better protection against adverse COVID-19 outcomes. Further RCTs to test these hypotheses are required.

Although this is the first systematic review to assess the efficacy of vitamin D supplementation for Black and Asian populations, the results should be considered within the study's limitations. Firstly, there was a paucity of studies found, making robust conclusions challenging. More RCTs in Black and Asian populations are needed to confirm or refute these purely preliminary findings. Secondly, the studies were highly heterogeneous, with different treatment durations, dosages, and populations, making the direct comparison of results challenging. In particular, the baseline levels of 25(OH)D and intervention lengths were highly heterogeneous. Future studies should robustly examine previous literature to ascertain comparability of results in the future, which would enable future reviews to use established nutrient review guidelines ([48]). Lastly, due to limitations in translation resources, only studies published in English were included, which could mean that relevant information may not be included based on language barriers.

CONCLUSION

Our review suggests that oral vitamin D supplementation could be more efficacious than food fortification in Black and Asian populations, and vitamin D_3 is more efficacious than VD_2. It is recommended that people with darker skin supplement their diet with vitamin D_3 through oral modes in order to reduce the risk of adverse outcomes of COVID-19, with current literature suggesting a dosage of 7000-10000IUs for people of Black or Asian ethnicity. Further study to determine differences between supplementation in different ethnicities are warranted.

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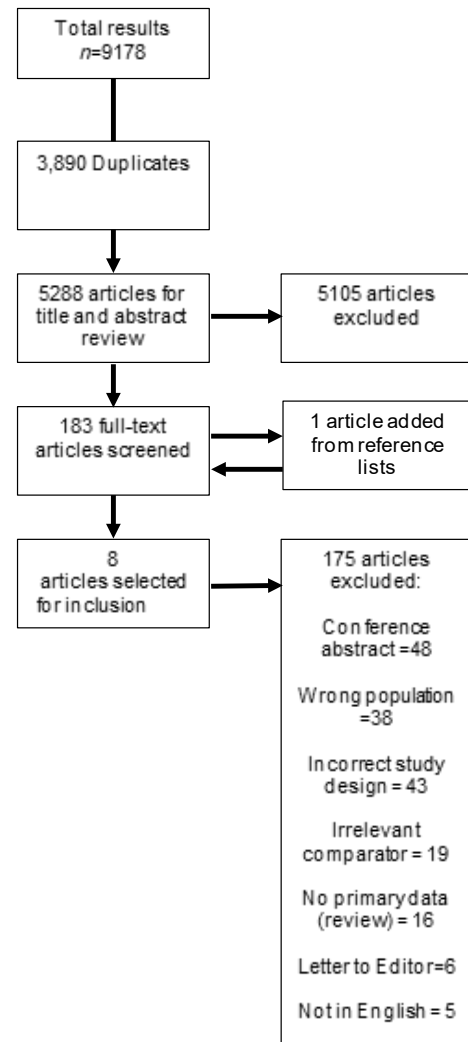
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Figure 1: Flowchart of included studies


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Total results
n=9178
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↓
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3,890 Duplicates
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↓
```
5288 articles for          →     5105 articles
title and abstract                 excluded
review
```
↓
```
183 full-text             →      1 article added
articles screened         ←      from reference
                                 lists
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↓
```
8                        →      175 articles
articles selected               excluded:
for inclusion
                                Conference
                                abstract =48

                                Wrong population
                                =38

                                Incorrect study
                                design = 43

                                Irrelevant
                                comparator = 19

                                No primary data
                                (review) = 16

                                Letter to Editor=6

                                Not in English = 5
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Table 1: Descriptive characteristics of each study

Study	Country	Treatment group	Treatment type	Ethnicity	N participants baseline	N participants follow-up	Mean age (SD)	Percentage female	Method of vitamin D measurement	Follow up
Chandler 2014	USA	Placebo	Placebo tablets (200mg calcium carbonate/day)	African-American	81	71	**51 (44-58)	66.7%	Blood sample*	3 months*
		Treatment Group 1	1000 IU (25µg) Vitamin D_3 + 200mg calcium carbonate/day		81	67	**51 (43-60)	72.8%		
		Treatment Group 2	2000 IU (50µg) Vitamin D_3 + 200mg calcium carbonate/day		83	76	**50 (44-58)	66.3%		
		Treatment Group 3	4000 IU (100µg) Vitamin D_3 + 200mg calcium carbonate/day		83	78	**51 (44-60)	65.1%		
Goswami 2012	India	Double Placebo	Lactose tablets and sachets	Indian	43	37	22 (4.9)	100%	Blood sample*	6 months*
		Treatment Group 1	Lactose sachets and Calcium carbonate tablets (1g/day)		42	38	22 (4.4)	100%		
		Treatment Group 2	Vitamin D_3 sachets (60,000 IU/wk for first 8wk followed by 60,000IU twice/month for 4months), and Lactose tablets		42	39	21 (3.2)	100%		
		Treatment Group 3	Vitamin D_3 sachets (60,000 IU/wk for first 8wk followed by 60,000IU twice/month for 4months), and Calcium carbonate tablets (1g/day for 6 months)		43	39	22 (3.5)	100%		
Gronborg 2020	Denmark	Placebo	Unfortified food supplements	Pakistani	37	31	36 (9)	100%	Blood sample*	12 weeks*
		Treatment Group 1	Fortified food supplements (approx. 20 µg /day vitamin D_3)		35	33	36 (10)	100%		
Islam 2010	Bangladesh	Placebo	Placebo tablets 1/day	Bangladeshi	50	35	23 (3.9)	100%	Blood sample*	1 year*
		Treatment Group 1	10µg vitamin D/day		50	40	22 (3.9)	100%		
		Treatment Group 2	10µg of vitamin D_3 + 600mg of Calcium Lactate/day		50	41	23 (3.6)	100%		
		Treatment Group 3	Multiple micronutrients +10µg of VD + 600mg of Calcium Lactate/day		50	37	22 (3.3)	100%		

Study	Country	Group	Intervention	Ethnicity						
Kim 2020 (total sample)	USA	Placebo	Placebo tablets (200mg calcium carbonate/day)	African-American	NR	61	30-80*	NR	Blood sample*	3 months*
		Treatment Group 1	1000 IU (25µg) Vitamin D_3 + 200mg calcium carbonate/day		NR	65		NR		
		Treatment Group 2	2000 IU (50µg) Vitamin D_3 + 200mg calcium carbonate/day		NR	61		NR		
		Treatment Group 3	4000 IU (100µg) Vitamin D_3 + 200mg calcium carbonate/day		NR	63		NR		
Kim 2020 (obese only)		Placebo	Placebo tablets (200mg calcium carbonate/day)	African-American	NR	31	NR	77%*		
		Treatment Group 1	1000 IU (25µg) Vitamin D_3 + 200mg calcium carbonate/day		NR	36	NR			
		Treatment Group 2	2000 IU (50µg) Vitamin D_3 + 200mg calcium carbonate/day		NR	33	NR			
		Treatment Group 3	4000 IU (100µg) Vitamin D_3 + 200mg calcium carbonate/day		NR	41	NR			
Kim 2020 (non-obese only)		Placebo	Placebo tablets (200mg calcium carbonate/day)	African-American	NR	30	NR	58%*		
		Treatment Group 1	1000 IU (25µg) Vitamin D_3 + 200mg calcium carbonate/day		NR	29	NR			
		Treatment Group 2	2000 IU (50µg) Vitamin D_3 + 200mg calcium carbonate/day		NR	28	NR			
		Treatment Group 3	4000 IU (100µg) Vitamin D_3 + 200mg calcium carbonate/day		NR	22	NR			
Kuwabara 2009	Japan	Placebo	200mg calcium/day	Japanese	30	30	86 (8.5)	67%	Blood sample*	30days
		Treatment Group 1	200mg calcium + 800IU vitamin D_3 (20µg)/day		32	32	84 (7.6)	74%		
Tripkovic 2017	UK	Placebo	Placebo juice and placebo biscuit/day	South Asian	17	14	44. (12)***	100%	Blood sample*	12 weeks
		Treatment Group 1	Juice fortified with 600 IU (15µg) Vitamin D_2 and placebo biscuit.		18	13	44 (11)***			
		Treatment Group 2	Placebo juice and biscuit fortified with 600 IU (15µg) Vitamin D_2		17	14	43 (13)***			
		Treatment Group 3	Juice fortified with 600 IU (15µg) Vitamin D_3 and placebo biscuit.		19	11	43 (13)***			

		Treatment Group 4	Placebo juice and biscuit fortified with 600 IU (15µg) Vitamin D$_3$		19	11	44 (13)***				
von Hurst 2010 (pre-menopausal)	New Zealand	Placebo	4 placebo capsules/day	91% Indian; 6% Sri Lankan; 3% Pakistani*	106*	29	>20*	100%*	Blood sample*	6 months*
		Treatment Group 1	4 x 1000 IU (100µg) vitamin D$_3$ capsules/day			26				
von Hurst 2010 (post-menopausal)		Placebo	4 placebo capsules/day			13				
		Treatment Group 1	4 x 1000 IU (100µg) vitamin D$_3$ capsules/day			13				

*Statistics for the whole cohort - stratified characteristics not reported; **Median (Inter-quartile range); *** Mean ages are for both South Asian and white European cohorts; IU=international unit; µg=microgram

Table 2. Change in vitamin D values from baseline to follow up.

Ethnicity	Study	Intervention duration	Placebo		Treatment group 1		Treatment group 2		Treatment group 3		Treatment group 4	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
African-American	Kim et al 2020† (all)	3 months	40 (23)	34 (19)**	44 (23)	70 (23)**	41 (23)	91 (28)**	45 (23)	119 (25)**	NA	
	Kim et al 2020† (Obese only)		39 (22)	32 (18)	45 (21)	71 (15)**	38 (23)	88 (20)**	46 (23)	113 (25)**	NA	
	Kim et al 2020† (Non-obese only)		42 (25)	36 (21)	44 (25)	69 (29)**	45 (22)	95 (35)**	44 (23)	131 (22)**	NA	
	Chandler et al. 2014†‡	3 months	38 (26-59)	34 (18-47)	41 (28-57)	74 (64-82)**	35 (24-56)	87 (72-103)**	39 (28-58)	115 (99-138)**	NA	
Japanese	Kuwabara et al. 2009†	30days	24 (9.0)	28 (11)	24 (7)	48 (10)**	NA					
South Asian	Goswami et al. 2012†	6 months	22 (8.2)	19 (9.1)	25 (8.4)	20 (7.3)	23 (8.5)	75 (52)*	24 (8.7)	68 (24)*	NA	
	vonHurst et al. 2010 (pre-menopausal)	6 months	18 (NR)	30 (NR)*	20 (NR)	75 (NR)**	NA					
	vonHurst et al. 2010 (post-menopausal)		32 (NR)	40 (NR)	31 (NR)	74 (NR)*	NA					
	Islam et al 2010	1 year	35 (9.4)	36 (NR)	37 (12)	69 (NR)**	38 (11)	70 (NR)**	37 (13)	65 (NR)**	NA	
	Gronborg et al. 2020	12 weeks	49 (23)	37 (16)	45 (21)	55 (18)	NA					
	Tripkovic et al. 2017‡	12 weeks	31 (18-43)	23 (13-33)	30 (17-42)	47 (37-57)	31 (18-43)	49 (39-59)	27 (16-39)	60 (50-71)	21 (8.7-32)	53 (43-63)

The unit of measurement in all data is reported in nmol/l; data reported in mean and standard deviation (SD) unless otherwise stated †Original data was in ng/mL and have been converted to nmol/l post-hoc. ‡ data reported as median and interquartile range (IQR). *indicates a significant change from baseline values p=<0.05 **indicates a significant change from baseline values p=<0.001

Supplementary Table 1: Full results of the quality control assessment, measured with the Joanna Briggs Institute checklist for randomized control trials

Study	1	2	3	4	5	6	7	8	9	10	11	12	13
Chandler 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Goswami 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Grønborg 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Islam 2010	Yes	Yes	No	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Kim 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kuwabara 2009	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Tripkovic 2017	Yes	Unclear	No	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
vonHurst 2010	Yes	Unclear	No	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes

1= Was true randomization used for assignment of participants to treatment groups?; 2= Was allocation to treatment groups concealed?; 3= Were treatment groups similar at the baseline?; 4= Were participants blind to treatment assignment?; 5= Were those delivering treatment blind to treatment assignment?; 6= Were outcomes assessors blind to treatment assignment?; 7= Were treatment groups treated identically other than the intervention of interest?; 8= Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?; 9= Were participants analyzed in the groups to which they were randomized?; 10= Were outcomes measured in the same way for treatment groups?; 11= Were outcomes measured in a reliable way?; 12= Was appropriate statistical analysis used?; 13= Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?