Is Calcium the Main Nutrient in the Diet Plan for Sarcopenia among the Elderly? A Systematic Review and Meta-Analysis

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Research Article

Keywords: sarcopenia, vitamin D, protein, calcium, older

Posted Date: February 18th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1359964/v1

Abstract

Background: The effect of nutrients such as vitamin D, protein and calcium, to increase muscle mass and stimulate muscle synthesis has been verified. While the latent association between these nutrients and sarcopenia was poorly investigated. Therefore, this study summarized current studies reporting vitamin D, protein and calcium among patients with sarcopenia vs. people without sarcopenia (controls) with meta-analysis to explore their possible relationship.

Methods: An electronic search of PubMed and Science Direct from January 1, 1989 to May 30, 2018 was conducted for data collection and meta-analysis of cross-sectional studies was performed. Out of 105,700 initial hits, 6 studies with a total of 6,221 participants (1,156 with sarcopenia vs. 5,065 without) were meta-analyzed.

Results: Sarcopenic participants had significantly lower levels of 25(OH)D (SMD = 0.791; 95%CI 0.073, 1.510; $p < 0.05$; $I^2 = 98.790\%$), protein (SMD = 0.574; 95%CI 0.088, 1.060; $p < 0.05$; $I^2 = 97.276\%$) and calcium (SMD =1.258; 95%CI 0.429, 2.087; $p < 0.01$; $I^2 = 99.067\%$) than controls.

Conclusions: In conclusion, sarcopenia is associated with intake level of vitamin D, protein and calcium. Among these nutrients, calcium has the greatest impact. Therefore, the significance of calcium to the prevention of sarcopenia should be well-focused.

Introduction

Sarcopenia, an important age-related health condition, is known to be the cause of metabolic disorders in the aging population and carries the risk of adverse outcomes such as the loss of independence, falls and fractures, poor quality of life, and eventually, death [1–3]. Sarcopenia has become an important public health problem, especially in countries which have a numerous aging population such as South Korea. The prevalence of sarcopenia is estimated to range from 6 to 26% depending on age, sex, the definition and measurement of muscle mass. After the age of 80, the prevalence of sarcopenia increases to over 50% [4, 5].

To date, no medical treatment has inhibited the development of sarcopenia. Therefore, nutritional intervention is currently considered to be the most effective strategy for the prevention of sarcopenia. Available evidence suggests that a high-quality diet plays a significant role in ensuring adequate protein, vitamin D and calcium intake in the elderly [6, 7]. Protein is considered a key nutrient in older age [7]. Dietary protein provides amino acids which are necessary for the synthesis of muscle protein, and more importantly, absorbed amino acids have a stimulatory effect on muscle protein synthesis after feeding [8]. Recently, an increasing number of researches have been performed in the elderly to emphasize the importance of the role of vitamin D. The potential mechanisms that link vitamin D status to muscle function are complex. The vitamin D receptor (VDR) has been isolated from skeletal muscle, indicating that it is a target organ [9], and polymorphisms of the VDR have been shown to be related to differences in muscle strength [10]. Although, vitamin D and calcium are generally considered to be closely associated, there is currently no research concentrating on the relationship between calcium and muscle.

Therefore, optimizing diet and nutrition may be vital to the prevention of sarcopenia and the improvement of the physical functioning of the elderly. This study conducted a meta-analysis of the previous literature to explore the relationship among sarcopenia and these main point nutrients to find which of these three nutrients have the greatest impact on muscle. In order to prevent muscle reduction in the elderly as soon as possible, it is pivotal to recognize how to intervene as early as possible.

Materials And Methods

Although a meta-analysis is not a primary research method, it does include steps such as the formulation of a problem, collection of data (studies), coding of data, and data analysis and interpretation [11].

Search strategy

First, a preliminary search is conducted for data collection, and the Medical Subject heading (MeSH) searched is divided into four categories: sarcopenia, vitamin D, protein and calcium. Sarcopenia's entry terms: Sarcopenias; Entry terms of proteins: Proteins, Gene Products, proteins, proteins, Gene Products; Entry terms of calcium: Blood Coagulation Factor IV, Coagulation Factor IV, Factor IV, Coagulation, Calcium-40, Calcium 40, Factor IV. Then, a comprehensive collection of international academic literature and other data was collected in PubMed and Science Direct databases, and the retrieval time range was From January 1989 to May 2018. According to the method of Preferred Reporting Items for Systematic Reviews and meta-analyses (PREISMA), literatures were selected and determined [12]. In order to make the retrieval more perfect, the snowball retrieval method is further adopted, that is, continue to search relevant literatures from the initial selected literatures.

Study selection

Included studies were those: 1) compared data on vitamin D between sarcopenic participants vs. those without, 2) reported on the blood 25(OH)D, protein and calcium. Studies were excluded if the 1) did not use clear data for 25(OH)D, protein and calcium, 2) subjects under 65 years or used animal models, or 3) did not measure or did not report 25(OH)D, protein and calcium in both sarcopenia and no sarcopenia subjects.

Data extraction

Two authors independently extracted data from the selected studies into a standardized Microsoft Excel spreadsheet. Any disagreement was resolved by consensus. The following information was extracted: 1) study population characteristics (e.g., sample size, demographic), 2) survey site in which the study was performed, 3) parameters related to 25(OH)D, protein and calcium in sarcopenia and no sarcopenia subjects.

Statistical analysis

The meta-analysis was performed using comprehensive meta-analysis V2.0 (CMA) for Windows (https://www.meta-analysis.com/). Only outcomes with at least two studies can be termed as meta-analysis, while outcomes with only one study were reported in the descriptive analyses. When combining studies, the random effects model was used to account for study heterogeneity (I^2) with utilizing the standardized mean difference (SMD) with its 95% confidence interval (CI). Study heterogeneity was measured using the chi-squared and I-squared statistics, with chi-squared $p \leq 0.05$ and I-squared $\geq 50\%$ indicating the presence of crucial heterogeneity [13]. Publication bias was assessed with a visual inspection of funnel plots and the Egger bias test [14]. What's more, this study also utilized Nfs to verify the reliability of the research.

Results

The search identified 105,700 potentially eligible studies, of which 46,635 duplicates were excluded due to duplication. After excluding 55,703 papers through title and abstract review, 3,365 full text articles were examined. Altogether, 6 studies were included in meta-analysis which can be seen in Fig. 1 [15–20].

Studies and patients

Studies and patients' characteristics are summarized in Table 1. The 6 meta-analyzed studies included a total of 6,221 participants (1,156 with sarcopenia and 5,065 without). The definition and criteria of sarcopenia varied from different areas or countries, but the six studies we used for data analysis were mostly conducted in Asia (five in Asia and one in Britain) and they shared very similar criteria of sarcopenia. All of six studies were published in the after 2010. The sample sizes for vitamin D, protein, and calcium in the six meta-analysis studies were 9, 7, and 9, respectively, because of differences between the male and female groups.

Table 1
The characteristics of the included studies.

First author (year)	Place of study	Sample size (with/without sarcopenia)	Participants' age	Critieria of sarcopenia	Vitamin D, protein and calcium of dietary intake or those levels
Kim et al., (2014)	South Korean	2264 (540/1724)	65	ASM divided by height^2; 7.04 kg/m^2 for men and 5.04 kg/m^2 for women	Vitamin D: 22.6ng/mL (male), 18.8ng/mL (female); protein: 54.6g (male), 40.3g (female); calcium: 414mg (male), 296.1mg (female).
Oh et al., (2015)	South Korean	923 (325/598)	60	ASM divided by height^2	Vitamin D: 19.33ng/mL (male), 17.66ng/mL (female); protein: 66.90g (male), 47.3g (female); calcium: 282.47mg (male), 403.25mg (female).
Hwang et al., (2012)	South Korean	1436 (137/1326)	60	ASM divided by height^2	Vitamin D: 17.9ng/mL (male), 15.8ng/mL (female); protein: 58.3g (male), 44.7g (female); calcium: 490.5mg (male), 511.6mg (female).
Verlaan et al,. (2017)	UK	132 (66/66)	65	Low skeletal muscle mass index (SMI: skeletal muscle mass/ BW x 100):≤37% (men)and ≤ 28% (women)	Vitamin D: 52.9ng/mL; protein: 72.5g; calcium: 813mg .
Seo et al., (2013)	South Korean	1339 (59/1280)	60	ASM divided by height^2; 29.5% (ASM/Wt) for men, 23.2% (ASM/Wt) for women,	Vitamin D: 17.1ng/mL; calcium: 316.37 mg .
Souza et al., (2017)	South Korea	100 (29/71)	73.59	ASM divided by height^2; 7.26 kg/m^2 for men and 5.5 kg/m^2 for women	Vitamin D: 29.58ng/dL; calcium: 9.08 mg/dL

Effect sizes

It was found in this study that vitamin D, protein and calcium have a significant effect on sarcopenia (see in Table 2). Overall effect sizes (ESs) under random-effects assumptions indicate that the 25(OH)D (SMD = 0.791; 95% CI 0.073, 1.510; $p < 0.05$; $I^2 = 98.790\%$), protein (SMD = 0.574; 95%CI 0.088, 1.060; $p < 0.05$; $I^2 = 97.276\%$) had a significant overall effect on sarcopenia. But a significant positive effect on sarcopenia calcium (SMD = 1.258; 95%CI 0.429, 2.087; $p < 0.01$; $I^2 = 99.067\%$) and the corresponding forest plots of these three effect sizes were illustrated in Fig. 2. There was large heterogeneity between studies with I^2 ranging from 97.276–99.067%.

Table 2
Summary of results, overall effect sizes and homogeneity.

Outcome	**N**	**d (95% CI)**	**Homogeneity of d's**		
		Random-Effects	**Q**	**I^2(%)**	**P**
25(OH)D	9	0.791 (0.073, 1.510)*	661.189	98.790	0.031
Protein	7	0.574 (0.088, 1.060)*	220.224	97.276	0.021
Calcium	9	1.258 (0.429, 2.087)**	857.711	99.067	0.003

Note: d, overall effect size; *** indicates a significant effect (*p≤ 0.05, **p≤ 0.01, ***p≤ 0.001); N indicated the number of adjusted variables; Q represents Cochran's Q indicating significance of heterogeneity; I^2 represents the magnitude of heterogeneity; p-value represents the significance of heterogeneity;

Publication bias

Publication bias was evaluated to examine the validity of the results of this study. The effect size of the included studies was not visually symmetrical in the funnel plot which was illustrated in Fig. 3. Using Egger linear regression test inferred the severity of the publication bias [21]. As a result, there were no new studies which were added to convert the effect size of the included studies from asymmetry to symmetry. Therefore, the pooled effect size did not convert. To sum up, it could not ensure that the included studies had no publication bias; however, there was also no evidence to question the validity of the results.

Discussion

According to previous studies [22, 23], malnutrition is the main cause of sarcopenia. This study investigated the effect of vitamin D, protein and calcium intake on sarcopenia and found that calcium has the most effect on sarcopenia. Results of this study may be largely related to previous studies in the meta-analysis process [24]. In muscle synthesis, studies which investigated the association between protein, vitamin D and muscle were often mentioned, while the effects of calcium on muscle were seldomly concerned [25]. In particular, the lack of calcium in korean elderly people has always been a national nutritional problem [26]. Therefore, the significance of calcium to public health has been verified and this is also one of our research objectives.

This study analyzed the relationship between protein, vitamin D, calcium and sarcopenia, and to the best our knowledge, this study was, so far, the only study that reported calcium in these three nutrients with having the greatest impact on sarcopenia. The decrease in calcium intake in the elderly leads to an increase in the concentration of $1,25(OH)_2D$ and parathyroid hormone, which in turn, may cause the increase the intracellular calcium concentration [27, 28]. Alteration in calcium signaling may play a role in regulating muscle contractile force in differentiated muscle fibers. More recently, Brotto [29] revealed that altered calcium homeostasis was associated with skeletal muscle weakness during the aging process, and the sarcoplasmic reticulum (SR) have less calcium available to be released for contractions, ultimately translating into less contractile force, which, when coupled with the aging-related shift of faster into slower myosin/myosin light chain is forms, unequivocally results in decreased muscle power [29]. In addition, the study by Seo et al. [19] showed that calcium intake (278 mg per day) was negatively correlated with total body fat mass and positively correlated with appendicular skeletal mass. Other studies have shown the significant role of calcium intake in muscle mass [30–32]. Increased fat infiltration and fatty degeneration in skeletal muscle may cause subsequent atrophy of skeletal muscle, resulting in impaired muscular performance in older individuals.

From other perspectives, Denke et al. [33] revealed that increased dietary calcium may combine with fatty acids in the intestine to form insoluble soaps that are therefore not absorbed. Some other researches confirmed that low dietary calcium intakes lead to increased adiposity triglyceride deposition [34, 35]. Calcium intake status may be associated with body weight, body composition, and insulin resistance [36–38]. This may be due to the essential role of calcium in insulin edited intracellular processes in skeletal muscle. From the 2015 National Nutrition Survey of Korea, it was found that the rate of insufficient intake of Korean calcium was as high as 70.3% [39]. Taking these findings into consideration, the supplement of calcium is short of public attention.

A great number of researches have focused on the linkage between protein and muscle synthesis [40]. The results of this study confirmed the relationship between these two. Verlaan et al. [41] found that there were significantly lower intakes of protein, vitamin and phosphorus by the sarcopenic adults compared to the non-sarcopenic control. This is similar to the finding of our previous research which is related to the association between dairy product and sarcopenia [42]. Although the mean intake in the sarcopenic group was within the low range of the most recent recommendations for healthy older adults (1.0-1.2 g/kg bw/day) [43, 44], this intake level may still not be adequate to prevent or treat sarcopenia. However, another study found that an excess intake of protein resulted in renal dysfunction via reduction of calcium-sensing receptor function and decreased calcium reabsorption [45]. Therefore, adequate protein intake should be considered with other nutrients and depend on the individual’s health condition. The reduction of muscle mass often coexists with low calcium intake and vitamin D insufficiency. The study of Pleasure et al. [46] demonstrated that vitamin D deficiency has effects on skeletal muscle calcium metabolism. A low 25-OH-vitamin D level was also directly cross-section ally related to appendicular lean mass, leg strength and leg muscle quality [47], and also to functional outcomes such as increased rates of falls and nursing home admissions [48, 49]. The role of vitamin D in preventing rickets depends on its ability to increasing the expression of Ca^+ pumps and buffers to facilitate the uptake of Ca^+ across the intestine as part of vitamin D's role in regulating whole body Ca^+ homoeostasis [50].

Although the study has been completed, the study needs to be interpreted in view of certain limitations. First, a small amount of research was covered and the sample size was relatively limited. Second, research subjects were from different countries, therefore, some data deviation could be existed based on the diverse criteria of sarcopenia. Finally, obese patients may be included in the study for people with sarcopenia and may have a certain impact on outcomes which in some studies, researcher prefer to distinguish sarcopenia and sarcopenia obese [51]. Therefore, in the future, we may also conduct further meta-analysis of nutrients for the elderly sarcopenia obesity and sarcopenia. A unified measurement of sarcopenia is needed for a stronger meta-analysis.

In conclusion, although there is ample evidence that protein, vitamin D and calcium have important health benefits, there is no general understanding of how calcium works. Therefore, to develop a nutrition prevention strategy, we must have a better understanding of the mechanisms that affect muscle loss. The research results of this paper also provide relevant scientific basis for health workers to concentrate on the nutritional supplement of the elderly.

Declarations

Authors' contributions

YD & CO designed the study; YD & JN collected the data; YD analyzed the data; YD, CO & JN interpreted the data; YD wrote the first draft; All authors read and confirmed the manuscript.

Funding

Not applicable

Availability of data and materials

The authors confirm that the data supporting the findings of this study are available.

Ethical Approval and Consent to participate

Not applicable

Consent for publication

All authors consent to the publication of the manuscript in Nutrition Journal.

Competing interests

We declare that we have no conflict of interest.

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Figures

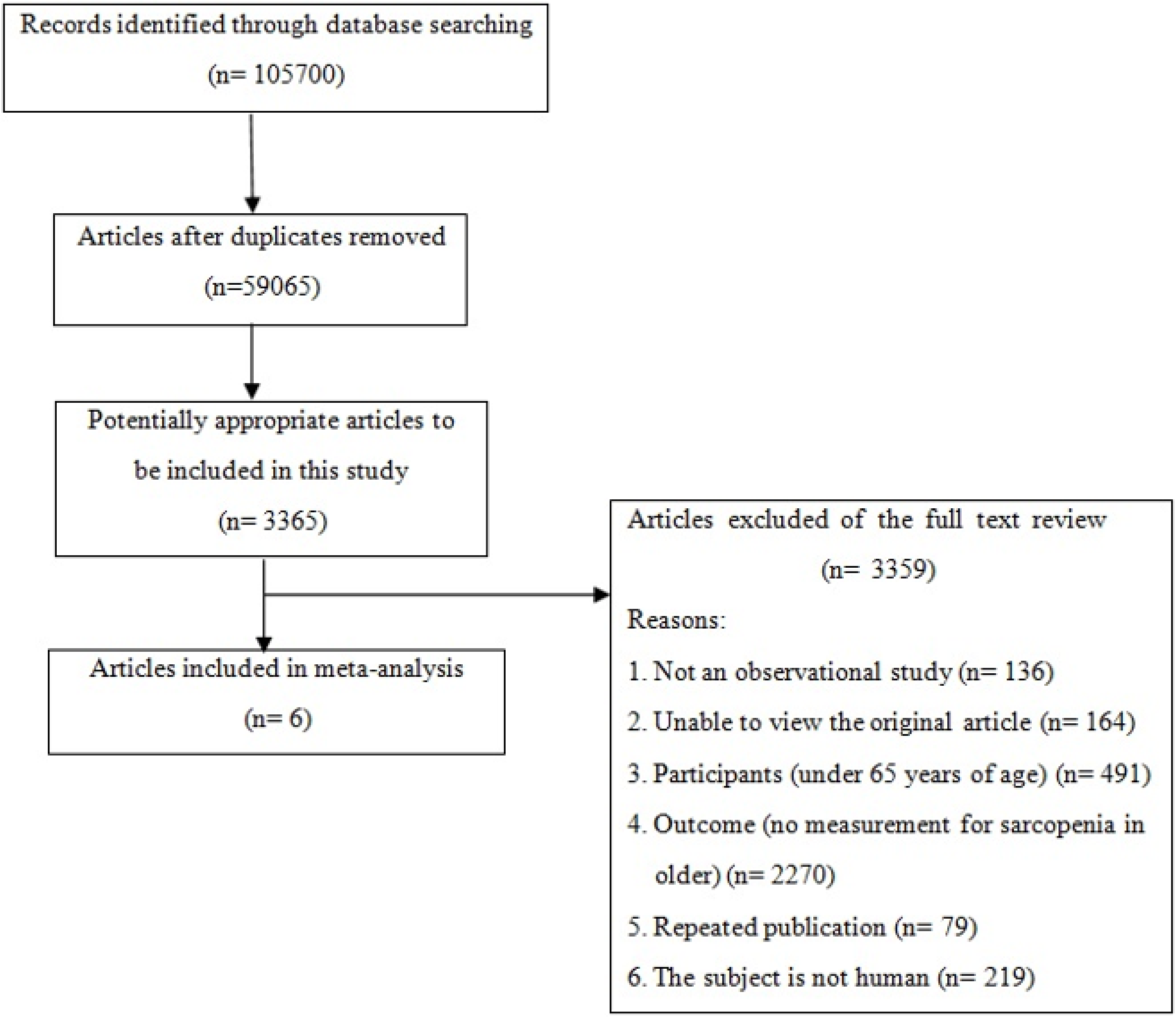
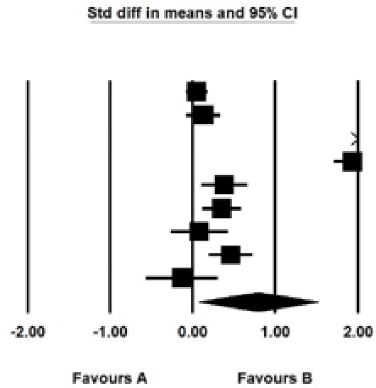


Figure 1

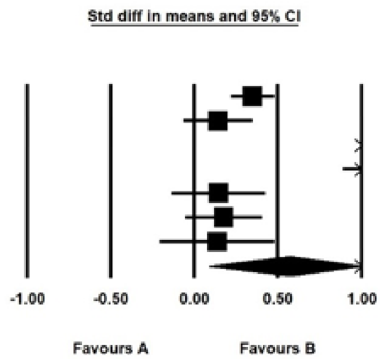
Flow of study analysis through different phases of the meta-analysis (from January 1, 1989 to May 30, 2018)

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Kim et al. M	0.053	0.065	0.004	-0.075	0.181	0.811	0.417
Kim et al. F	0.132	0.104	0.011	-0.071	0.336	1.273	0.203
Oh et al. M	3.843	0.160	0.026	3.529	4.156	24.014	0.000
Oh et al. F	1.941	0.116	0.014	1.713	2.168	16.696	0.000
Hwang et al. M	0.383	0.142	0.020	0.105	0.662	2.696	0.007
Hwang et al. F	0.353	0.117	0.014	0.125	0.581	3.029	0.002
Verlaan et al. M/F	0.083	0.174	0.030	-0.258	0.425	0.478	0.632
Seo et al. M/F	0.461	0.133	0.018	0.199	0.723	3.455	0.001
Souza et al. M/F	-0.128	0.221	0.049	-0.560	0.305	-0.579	0.562
	0.791	0.367	0.134	0.073	1.510	2.159	0.031



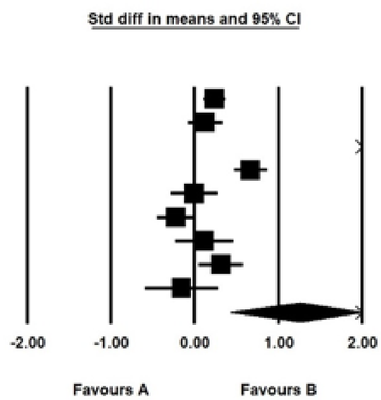
Meta Analysis

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Kim et al. M	0.350	0.066	0.004	0.221	0.479	5.309	0.000
Kim et al. F	0.141	0.104	0.011	-0.062	0.345	1.360	0.174
Oh et al. M	1.955	0.117	0.014	1.725	2.184	16.696	0.000
Oh et al. F	1.094	0.104	0.011	0.891	1.298	10.563	0.000
Hwang et al. M	0.145	0.142	0.020	-0.133	0.423	1.025	0.306
Hwang et al. F	0.176	0.116	0.014	-0.052	0.404	1.511	0.131
Verlaan et al. M/F	0.139	0.174	0.030	-0.203	0.481	0.797	0.425
	0.574	0.248	0.062	0.088	1.060	2.313	0.021



Meta Analysis

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Kim et al. M	0.232	0.066	0.004	0.104	0.361	3.545	0.000
Kim et al. F	0.128	0.104	0.011	-0.076	0.331	1.226	0.220
Oh et al. M	10.923	0.373	0.139	10.191	11.654	29.272	0.000
Oh et al. F	0.665	0.100	0.010	0.470	0.860	6.675	0.000
Hwang et al. M	-0.009	0.142	0.020	-0.287	0.269	-0.063	0.950
Hwang et al. F	-0.221	0.116	0.014	-0.449	0.007	-1.903	0.057
Verlaan et al. M/F	0.112	0.174	0.030	-0.230	0.453	0.642	0.521
Seo et al. M/F	0.313	0.133	0.018	0.052	0.575	2.351	0.019
Souza et al.	-0.157	0.221	0.049	-0.589	0.276	-0.710	0.478
	1.258	0.423	0.179	0.429	2.087	2.973	0.003



Meta Analysis

Figure 2

Forrest plots of 25(OH)D, protein, calcium(by order) in sarcopenic vs. no sarcopenic subjects. (Abbreviations: Std diff: standard difference; CI: confidence interval)

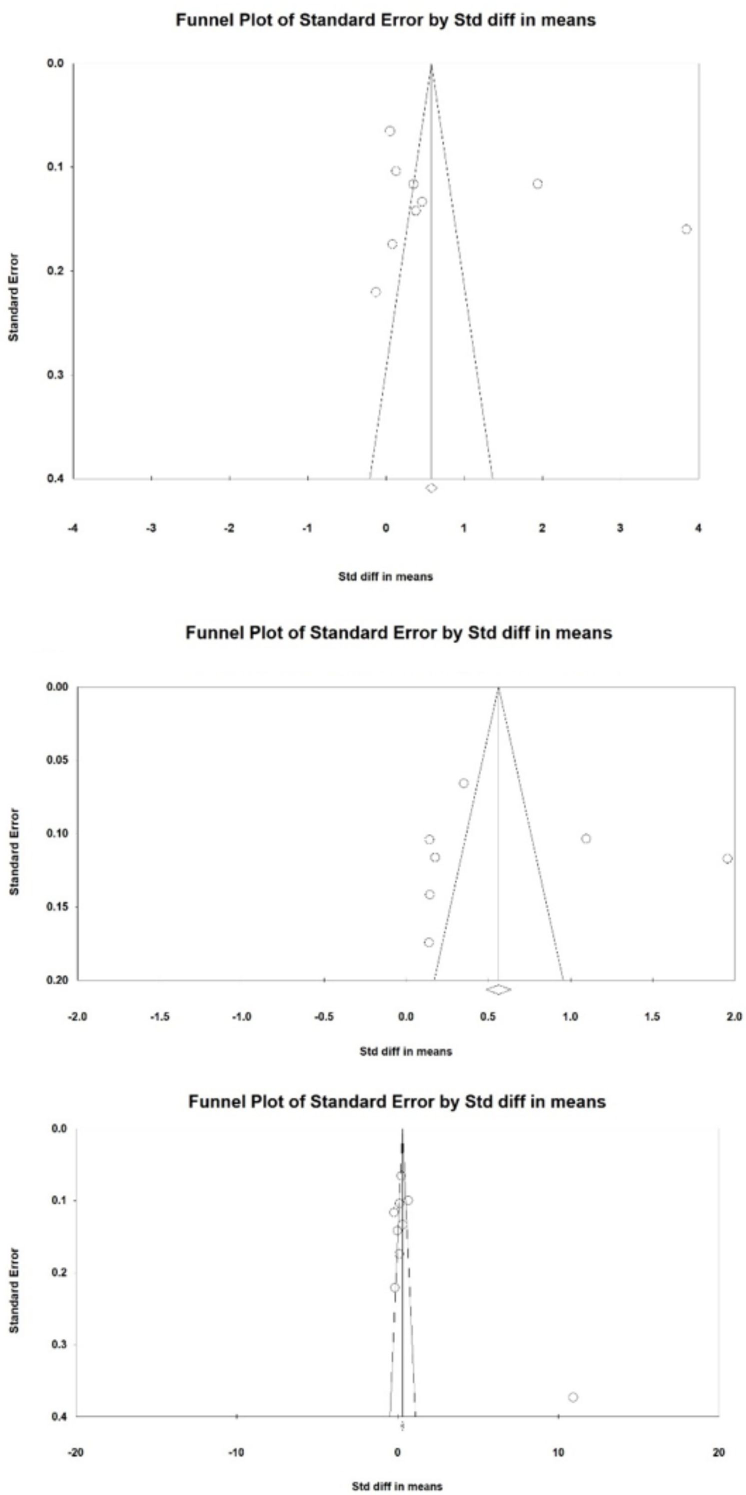


Figure 3

Funnel plots of 25(OH)D, protein, calcium (by order) in sarcopenic vs. no sarcopenic subjects. (Abbreviation: Std diff: standard difference)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2020checklist.docx