



Major considerations and outcomes of clinical trials of vitamin D in athlete performance: a systematic review

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Abstract

Introduction: In addition to influencing physical performance, some studies verify the impact of vitamin D on body composition. It is known that their high levels favor the gain of fibers of fast contraction, favoring the increase of force due to the increase of muscular areas and it prevents loss of lean mass. **Objective:** It was present, through a systematic review, the main correlations and outcomes of clinical studies between vitamin D and physical exercise practitioners, analyzing the effects of vitamin D deficiency, sufficiency, and supplementation on sports performance. **Methods:** Following the criteria of literary search with the use of the Mesh Terms that were cited in the item below on "Search strategies", a total of 94 papers that were submitted to the eligibility analysis were collated and, after that, 65 studies were selected, following the rules of systematic review - PRISMA. The review protocol was based on literary search criteria using mesh terms in major databases such as PubMed, Scopus, Medline, Bireme, EBSCO, and Scielo. It followed the following steps: search for MeSH Terms: *Vitamin D. Clinical trials. Physical exercises. Athletes. Quality of life.* **Conclusion:** The present study aimed to present, through a systematic review, the main correlations and outcomes of clinical studies between vitamin D and physical exercise practitioners, analyzing the effects of vitamin D deficiency, sufficiency, and supplementation on sports performance.

Keywords: Vitamin D. Clinical trials. Physical exercises. Athletes. Quality of life.

Introduction

Vitamin D (VitD) is the only one in which the biologically active form is a hormone [1,2]. Popularly, and among the scientific community, it has been said that VitD is more of a hormone than a nutrient. However, this term is inappropriate, because the definition of vitamin is an essential substance, that the body needs to acquire from an external source to regulate its biological functions. The intake of vitamin D through the diet is necessary to maintain adequate levels [1]. Therefore, considering this concept, it is understood that VitD has to be considered a vitamin because it is an essential substance.

It is possible to conclude that there is a strong relationship between VitD and dermatological, immunological, neurological, and muscle functions, in addition to bone and joint functions [2,3]. However, its possible role in increasing strength and power, preventing loss of lean mass, accelerating the recovery of athletes after strenuous exercise, and preventing a drop in immune function after strenuous exercise are some of the reasons that justify the need for studies and investigations about of the real impact of VitD supplementation on physical exercise [4-10]. In addition to influencing physical performance, some studies verify the impact of VitD on body composition. It is known that its high levels favor the gain of fast-twitch fibers, favoring the increase in strength due to the increase in muscle areas and preventing loss of lean mass. VitD also favors an increase in bone mineral density, in addition to improving physical performance, which indirectly may facilitate lean mass gain and a decrease in fat mass, but some of these mechanisms are not completely clear as much as they are observed

[3,4,11-13].

Also, VitD appears to interact with the immune system through its action on the regulation and differentiation of cells such as lymphocytes, macrophages, and natural killer (NK) cells, in addition to interfering with the production of cytokines *in vivo* and *in vitro* [14-17]. Among the demonstrated immunomodulatory effects, the following stand out: decreased production of interleukin-2 (IL-2), interferon-gamma (INF γ), and tumor necrosis factor (TNF); inhibition of IL6 expression and inhibition of secretion and production of autoantibodies by B lymphocytes [18-20].

Thus, this study aimed to present, through a systematic review, the main correlations and outcomes of clinical studies between vitamin D and physical exercise practitioners, analyzing the effects of Vitamin D deficiency, sufficiency, and supplementation on sports performance.

Methods

Study Design

The present study followed a concise systematic review model, following the rules of systematic review - PRISMA (Transparent reporting of systematic review and meta-analysis [HTTP://www.prisma-statement.org/](http://www.prisma-statement.org/)).

Information Sources and Search Strategy

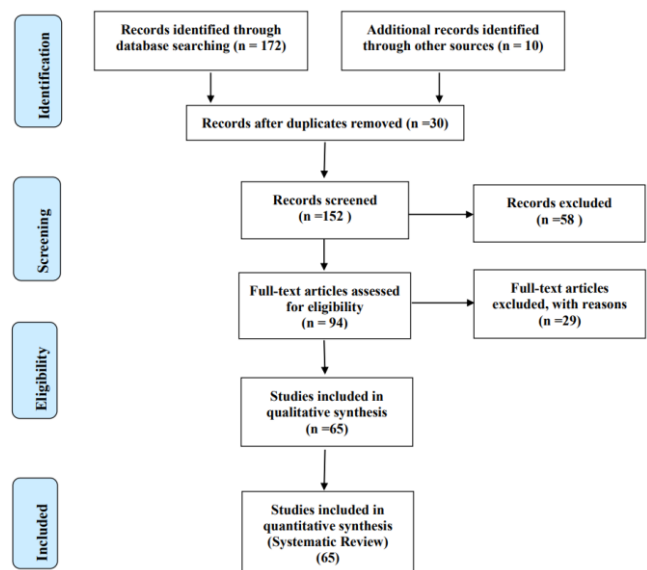
The review protocol was based on literary search criteria using mesh terms in major databases such as PubMed, Scopus, Medline, Bireme, EBSCO, and Scielo. The search strategy followed the following steps, search for *MeSH Terms: Vitamin D. Clinical trials. Physical exercises. Athletes. Quality of life*, and use of the Boolean “and” between mesh terms and “or” between historical findings.

Results and discussion

Summary of Findings

As a corollary of the literary search system, 182 studies were analyzed and submitted to eligibility analysis, and then 65 of the 94 final studies were selected for the present systematic review (Figure 1). The listed studies presented medium to high quality, considering in the first instance the level of scientific evidence of studies in study types such as meta-analysis, consensus, randomized clinical, prospective and observational. The biases did not compromise the scientific basis of the studies.

Figure 1. Eligibility flowchart for literary findings.



The primary source of vitamin D depends on the skin's exposure to sunlight and up to 20.0% comes from ingestion. It is still controversial whether the consumption of foods containing vitamin D has a direct impact on its circulating levels [1,2,21-26]. Vitamin D2 (ergocalciferol) is found in yeast, mushrooms, and some vegetables, and Vitamin D3 (cholecalciferol) is in animal foods. The latter is synthesized in the skin through ultraviolet radiation [27,28].

To be active, vitamin D undergoes hydroxylation in the liver mediated by 25-hydroxylase, and in the kidney by 1 α -hydroxylase. 1,25(OH) $_2$ D is recognized by its specific receptors (VDR) in various cells, mainly in the intestine to enhance calcium absorption, and the bone to regulate skeletal homeostasis [29-34]. Altered metabolic patterns result in metabolic disturbances of calcium and phosphorus, but as is well known, disturbances of vitamin D have been involved in some other diseases [35].

Vitamin D plays important roles in innate and adaptive immune responses, cell cycle, and metabolic processes, evidenced by the reported relationship between its deficiency and the prevalence of immune-mediated disorders, cancer, and cardiometabolic diseases [36-42]. An inverse correlation between their concentrations and the prevalence of obesity and type 2 diabetes mellitus has been described [43-49].

Because of advances and updates in research, the Institute of Medicine (IoM) has published new recommended RDA values for Ca (mg/day) and VitD (IU/day). It included the Estimated Average Requirement (EAR), Recommended Dietary Allowance (RDA), and Upper Levels of Intake (UL) [50,51].

Doses above 10,000 IU/day along with taking too many supplements that include calcium and fortified

foods can cause kidney damage. There is evidence that doses above 4,000 IU/day in this context add risks. Currently in the United States and Canada, the EAR, for all stages of development and also during pregnancy, except infancy up to 12 months of age, is 400 IU/day. The RDA or RDA for pregnant women and individuals between 1 and 70 years old is 600IU/day, but this value increases to 800UI in people over 70 years old. In babies up to 6 months, the UL is 1,000IU/day, between 6-12 months is 1,500IU/day, from 1 year of age to 3 years is 2,500IU and between 4-8 years of age is 3,000 IU/day [51].

The tolerable dose or UL among people aged 9 years or older is 4,000 IU/day, including pregnant women, above this value, as well as above 2000.0 mg of Ca maintained daily, which may be more harmful than beneficial for the normal population. This is due to the predominant public conducted in the research being North Americans, individuals who consume many supplements and are exposed to a high number of fortified foods with VitD and Ca. Renal lithiasis is associated with excessive consumption of calcium in food supplements. Very high doses of VitD, greater than 10,000 IU/day cause kidney and tissue damage. There is strong evidence that demonstrates the risk of consuming very high doses consumed daily and uninterruptedly, as well as studies that show the problems related to low levels [51].

Besides, VitD deficiency is a pandemic and high prevalence in young people is high. Latitude, winter, the habit of practicing sports performed exclusively indoors, and black skin are some factors that contribute to the increase in disabled individuals. This situation leads to reduced motivation, a high prevalence of muscle and bone injuries, myopathies, altered psychosocial function, and decreased muscle power, which causes great damage to the performance of practitioners of physical activity [6]. Given this, the need for vitamin D supplementation becomes relevant in some situations, considering that it reduces the risk of falls by 20.0%, and improves musculoskeletal function, as it has a neuromuscular and neuroprotective role [6].

Several studies have shown an increase in white fibers (type 2) and improvement in muscle atrophy in individuals treated with VitD supplementation. In addition, the sun proved to be an ergogenic resource, especially when deficiency is present [6]. Corroborating these findings, Hamilton (2010) demonstrated that the cardiovascular capacity to perform resistance exercises were greater when individuals were submitted to exposure to ultraviolet radiation.

Vitamin D and Exercise

Misinterpretation of guidelines and medical suggestions from new, unvalidated sets of guidelines (such as those suggested by Heaney and Holick [52] and Zittermann [53]) have led to supplemental vitamin D plans all athletes. Many studies have evaluated 25 [OH]D concentrations worldwide in elite and sub-elite athletes over different months of the year [54-59]. There are large variations between cohorts of non-supplemented athletes. For example, our laboratory showed large variations between cohorts of elite rugby players, soccer players, and jockeys [59]. Numerous factors, such as dietary differences, sunlight exposure, clothing, and lifestyle, may contribute to the disparities [60].

Athletes at risk of being deficient must be tested before proceeding to correct vitamin D inadequacy. Doctors and scientists must know what supplements athletes should be supplementing purely based on whether they have insufficient/deficient vitamin D concentrations. There is indeed an ergogenic effect of providing doses of vitamin D supplementation that would raise 25 [OH] D concentrations far above the threshold for sufficiency (75 nmol). When a need for supplementation has been identified, an appropriately selected supplemental form of vitamin D3 should be obtained that can deliver the correct dose. Recommendations, as to supplement dosage, vary widely and can often be confusing. Vitamin D dosing strategies in elite sport range from 1000 IU/day for manta supplementation to up to 100,000 IU boluses per week. The review should serve to direct practitioners to a need for a supplementation decision system that should be implemented individually and provide the most current advice for safe and effective supplementation protocols [1].

For protein synthesis and muscle contraction to be efficient, it is necessary to increase the concentration of P and adenosine triphosphate (ATP) in muscle tissue cells. This event is dependent on Ca uptake in the sarcoplasmic reticulum, therefore, taking into account that VitD acts on Ca absorption and homeostasis, it can be inferred that it indirectly contributes to muscle contraction and protein synthesis. Based on this, an association between the concentration of 25(OH)D levels and physical exercise performance has been reported. In addition, studies demonstrate that high doses of VitD in combination with Ca can confer benefits on physical performance [9].

Avoiding the decrease in 25(OH)D levels during the winter or carrying out the studies after obtaining optimal VitD levels, together with diet control may be necessary. This was the conclusion of the authors of a study carried

out with professional soccer players, where a protocol with 5,000UI/day + HIIT (High-Intensity Interval Training) compared to a placebo group did not demonstrate significant differences between the physical tests of the speed of running, vertical jump and counter-movement jump [12].

After evaluating the levels of 25(OH)D and performance in the sprint, jump in motion, VO₂max and vertical jump, in soccer players exempt from any supplementation, there was a direct relationship between the highest levels of 25(OH)D and the performance improvement for all variables. Proving that the concentration of 25(OH)D has a significant impact on sports performance parameters [14].

A study was carried out with the supplementation of 5000UI/day VitD in a group of athletes from different sports (n=61), compared to a control group of non-athletes (n=30), however, the first group competed and ran professionally and the control group was composed of amateur runners. It was observed that both increased serum levels of VitD proportionally. Both in the group of supplemented professional athletes and in the group of supplemented amateur runners, there was a significant increase in the 10m sprint and the vertical jump, showing that the concentration of VitD determines the musculoskeletal performance in both groups [15].

A well-controlled study of 22 athletes who avoided solar climates for 3 months preassessment. After that, one group was supplemented with 150,000UI of VitD3 and the other group with a placebo. The tests were performed in duplicate before training and the athletes rested for two days before the next tests. Supplementation of 150,000UI of VitD3 increased serum levels of 25(OH)D, and muscle strength was also increased between the 1st and 8th day when compared to the placebo group [16].

In an *in vivo* study, with 40 rats divided into 5 groups: G1-ovariectomized rats, G2-not ovariectomized, G3-ovariectomized + VitD supplementation, G4-ovariectomized + training, and G5- ovariectomized + training + VitD supplementation. In this research, it was observed that food intake and BMI decreased in groups supplemented with VitD (10,000UI/kg). These variables were not modified in groups G1 and G2. At the end of the research, the lipid profile (total cholesterol, triglycerides, HDL-C, and LDL-C), glucose, fasting basal insulin, and HOMA-R were improved in the experimental groups that trained without VitD supplementation and improved even more with training along with VitD supplementation [17].

Authors have reported that VitD supplementation exerts a possible ergogenic effect, as it increases muscle power, and cardiorespiratory capacity, positively

affecting muscle strength, improving the gain of type 2 fibers, in addition to preventing loss of lean mass and decreasing recovery time after PE [11]. It was also verified in another study that physical performance in PE is directly correlated with levels of 25(OH)D. This occurs because VitD has its specific receptor in the muscle (vitamin D receptor - VDR) and acts on the CYP27B1 enzyme (1- α -hydroxylase) and acts on myocytes through this pathway, improving the effects of myocyte proliferation and specialization, differentiation, growth, and inflammation [1].

Sun exposure exerts influence on physical performance variables in PEs, mainly in athletes with low blood levels of 25(OH)D, this result was observed in a review and in a research where the athletes were divided into two groups, G1: underwent controlled sun exposure, but without supplements and G2: were not subjected to sun exposure or supplements [9,14].

In athletes and practitioners of physical activities, low 25(OH)D means worse performance, therefore, in this situation, supplementation should be considered [9,11,14]. Furthermore, 25(OH)D insufficiency is associated with an increased risk of fractures in individuals with osteopenia, and osteoporosis (Kanis et al., 2000) and in runners and military personnel, a such correlation may be due to the inverse relationship between levels of VitD and PTH [10,19,20].

Muscle Repair and Remodeling

The goal of athletic training is to provide a stimulus that disrupts homeostasis to elicit an adaptive response that improves competitive performance. For athletes, maximizing the training stimulus is therefore a basic principle of the training program. Nutritional strategies complement the adaptive response to a physical/metabolic [54].

The challenge is heavily researched. Recently, based on animal testing and *in vitro* basic biology studies, data have emerged suggestive of a beneficial role for vitamin D in skeletal muscle repair and remodeling. In a randomized controlled trial (RCT), elevation of serum 25 [OH]D concentrations to [75 nmol L⁻¹ with supplemental vitamin D3 at 4000 IU/day has been shown to have a positive effect on strength recovery following exercise harmful eccentric [55].

Similar results were observed in studies correlating between serum 25 [OH] D and strength recovery after intense exercise [56,57]. These results imply that exposure to vitamin D can optimize the acute adaptive response to harmful physical work. Support the idea that vitamin D can be important for a long period of training. However, a recent training study provided evidence to support this idea [58]. The authors studied

40 young and old untrained men on vitamin D3 1920 IU (48 ng) 800.0 mg calcium daily from December to April (n = 20 per group), or calcium alone (placebo group) at a latitude of 56 N (little sun exposure). During the final 12 weeks of the supplementation period, participants underwent a resistance training program for the quadriceps muscles. There were no observable differences between groups in strength gains or hypertrophy, but a large change in fiber type (more type IIA fibers) and a reduction in myostatin messenger RNA (mRNA) expression was seen in the young men. Receiving Vitamin D. Interestingly, the elderly men receiving Vitamin D showed improvement in muscle quality above that of the placebo group.

Besides, *in vivo* studies have shown that where more drastic remodeling is needed, perhaps with a requirement for satellite cell recruitment, vitamin D may have more pronounced benefits in muscle. To definitively infer that vitamin D interacts with muscle to modulate some aspects of muscle remodeling, molecular mechanisms are essential. More studies have focused on the molecular actions of vitamin D in muscle than have focused on translation study designs, the challenge to the field remains to decipher the key vitamin D targets at play during the remodeling process [59,60].

One study analyzed global gene expression profiles during mechanical overload-induced skeletal muscle hypertrophy in the adult rat [59]. Interestingly, the vitamin D receptor (VDR) / retinoid X receptor (RXR) nuclear receptor signaling. The pathway showed significant elevation during the early stages of hypertrophy. Given the known protein interactions of the VDR, it is clear that VDR signaling interacts with pathways associated with the maintenance of skeletal muscle mass. In particular, it can be postulated that VDR signaling is important for satellite cell activity, consistent with *in vivo* observations discussed earlier. The evidence supports this notion. First, the VDR is expressed in satellite cells and can regulate cell fate decisions (ie, to differentiate or divide and maintain the stem cell pool) in satellite cell cultures [36]. Furthermore, a key regulator of satellite cell activation [61] has been reported in vitamin D-deficient myogenic cell cultures [62]. We have shown that migration and fusion of human-derived skeletal muscle precursor cells are enhanced in the presence of 1,25[OH]2D3 [55].

Also, VDR mRNA and protein expression appears higher in satellite cells than in mature muscle fibers, suggesting a more prominent role in muscle progenitors [57]. The signaling axes through which the VDR can mediate these effects are not well defined. However, the known and predicted VDR interaction partners such

as mothers against decapentaplegic homolog 3 (smad3) (implying bone morphogenetic protein (BMP)/transforming growth factor (TGF)-b), Src (Protooncogene tyrosine-protein Src kinase) / phosphoinositide 3 kinases (PI3K) and cAMP responsible element - binding protein (CREB) cascades are attractive. Candidates are assigned roles identified in progenitor muscle differentiation and muscle regeneration after damage [61,62].

In summary, large-scale gene expression assays and focused experimental studies performed *in vitro* and *in vivo* suggest that vitamin D can influence skeletal muscle remodeling, which is important for the athletic performer [63]. Future studies could use publicly available gene and protein array data to identify candidate validation pathways through which vitamin D might exert its effects on satellite cells and potentially mature skeletal muscle fibers [64,65].

Vitamin D Deficiency and the Benefits of its Supplementation

The musculoskeletal system suffers serious consequences from VitD insufficiency and deficiency. Most agree that concentrations below 20.0 ng/mL of 25(OH)D are considered deficient, and concentrations > 30.0 ng/mL are sufficient. However, a meta-analysis carried out in 2015 determined that levels below 30.0 ng/mL can be considered a deficiency, considering the assessment of the risk and benefits of these levels in different populations [21]. VitD deficiency has been associated with growth retardation in children, and in adults, it has been associated with mineralization defects. Joint pain, and bone and muscle discomfort are also related to low levels of this vitamin in the body [22].

Studies show that VitD improves muscle function. Symptoms such as muscle weakness, myopathies, generalized musculoskeletal pain, and difficulty walking, sitting, standing up, and climbing stairs are found in patients with low levels of this vitamin [6,7]. VitD plays an important role in the musculature of the cardiovascular system, which helps regulate blood pressure (BP). This function was observed in elderly people where supplementation with VitD and Ca determined the reduction of BP [23].

In a review, one of the studies presented concluded that adolescents aged 12-19 years showed a strong correlation between the development of high BP and low levels of 25(OH)D. Adolescents are 2.36 times more likely to develop hypertension, 2.54 times more likely to have high blood sugar levels, and 3.99 times more likely to develop metabolic syndrome when their 25(OH)D levels are low [6].

Moreover, VitD deficiency is a pandemic and high prevalence in young people is high. Latitude, winter, the habit of practicing sports performed exclusively indoors, and black skin are some factors that contribute to the increase in disabled individuals. This situation leads to reduced motivation, a high prevalence of muscle and bone injuries, myopathies, altered psychosocial function, and decreased muscle power, which causes great damage to the performance of practitioners of physical activity [6]. Thus, in some situations, the need for vitamin D supplementation becomes relevant, considering that it reduces the risk of falls by 20%, and improves musculoskeletal function, as it has a neuromuscular and neuroprotective role [6].

Several studies have shown an increase in white fibers (type 2) and improvement in muscle atrophy in individuals treated with VitD supplementation. In addition, the sun proved to be an ergogenic resource, especially when deficiency is present [6]. Corroborating these findings, Hamilton et al., 2010 [7] demonstrated that the cardiovascular capacity to perform resistance exercises were greater when individuals were submitted to exposure to ultraviolet radiation.

Based on these findings, it is necessary to normalize the levels of 25(OH)D, as it allows the cells to function properly, in addition to preventing a series of pathologies. Supplementation is a preventive factor to be considered, but it also helps in the treatment of diseases. Doses close to the UL (4,000 IU/day) should be administered with extreme caution and for short periods of time until 25(OH)D levels become adequate. Protocols of up to 8 weeks have been shown to normalize levels in case of deficiency, but protocols of up to 12 weeks of intervention did not pose risks and were equally safe and efficient in restoring 25(OH)D levels, allowing benefits to be obtained related to human performance.

There is no evidence that maintaining high doses of supplementation for more than 3 months to increase serum levels of vitamin D brings more benefits than harm to health, only indications that this conduct can promote toxicity. High doses should be warned, and at the sign of toxicity, such as headaches, weakness, nausea and vomiting, constipation, polyuria and excessive thirst, use should be discontinued, medical advice sought and a nutritionist notified. In biochemical tests, what can show toxicity is the increase in levels of markers that include renal (creatinine), hepatic (TGO and TGP) function, levels of calcium, phosphorus, magnesium and the decrease in the alkaline phosphatase marker.

Adequate levels, in addition to representing a protective factor against cardiovascular risks and

positively affecting aspects of body composition, allow for the improvement of certain physical exercise variables that are related to health. After normalization with high doses, followup to maintain 25(OH)D levels with lower doses may be indicated, as well as interruption of supplementation for later analysis and readjustment of doses. The current RDA is 400 IU/day and the EAR 600 IU/day, however, in Brazil, the RDI for the food sector is up to 200 IU.

Encouraging frequent sun exposure, without using sunscreen and with most of the body exposed, for periods of up to 45 minutes can confer benefits and help normalize levels without the need for high supplemental doses. The sunscreen can be used on the hands and face, which do not represent the largest areas of exposure and after sun exposure for a period determined by the type of skin. Adapting supplementary doses according to biological individuality and environmental factors may require long-term follow-up until a safe daily dose is established, but the seasons and sun exposure conditions may allow supplementation to be stopped.

Also, VitD supplementation may be necessary, especially when looking for maximum performance, where milliseconds can mean the difference between first and second place in a competition, one of the advantages of supplementation is the increase and improvement of muscle power, which is the ability to produce force over a given distance for some time. Depending on the physiological situation and environmental factors, the biochemical study should be more frequent.

Studies state that adjustments and normalization of supplementary doses may require an average of 3 months of observation, but monitoring regarding serum levels of VitD and other biochemical markers during periods of supplementation is essential to determine an appropriate dose for situations and physiological stresses, as well as seasonality and latitude so that maintaining levels ensures maximum gains in health and physical performance.

Protocols that verify the effects of VitD supplementation vary widely. Both in terms of diet and supplementation control, as well as differences between the researched groups, all these factors have a strong influence on 25(OH)D levels. There are still few studies that verify the impact of VitD on body composition free from the influence of diet or other dietary supplements, but positive effects of vitamin supplementation on muscle mass content and body fat reduction were observed, which minimizes the risks of cardiovascular disease.

Conclusion

According to literary findings, protocols with macronutrients and diet control had positive and synergistic effects with vitamin D supplementation. Due to the low number of studies with a similar pattern, more studies with controlled protocols that include vitamin D + EF (physical exercise) should be performed, as well as studies with EF + vitamin D + diet. There are no studies that verify whether a higher dose of supplementation is more advantageous than a smaller dose of the supplement in terms of performance, but studies have shown that the improvement in physical performance depends on adequate levels of vitamin D to obtain maximum performance.

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Informed consent

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

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