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The relationship between neuropsychological function and responsiveness to vitamin D supplementation using artificial neural networks

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Abstract

Background: Vitamin D has recently attracted interest for its pleiotropic effects. Vitamin D supplements are a potentially important public health intervention, but the response to supplementation varies between individuals. **Aim:** We aimed to assess the association between several neuropsychological parameters and the magnitude of response to vitamin D supplementation using an artificial neural network method. **Methods:** Neuropsychological function was assessed in 619 participants using standard questionnaires. The study participants received vitamin D capsules containing 50,000 IU vitamin D per week over 9 weeks. To assess the relationship between responsiveness to vitamin D supplements and the impact on these neuropsychological parameters, the best-performing artificial neural network algorithms were selected from a combination of different transfer functions in hidden and output layers and variable numbers of hidden layers (between two and 50). The performance of the artificial neural network algorithm was assessed by receiver operating characteristic analysis and variables of importance were identified. **Results:** The artificial neural network algorithm with sigmoid transfer function in both hidden and output layers could predict responsiveness to vitamin D supplementation effectively. The sensitivity and specificity were between 0.60 and 0.70 and 0.66 and 0.70, respectively. Cognitive abilities (42.5%), basal vitamin D (21.3%), body mass index (9.5%), and daytime sleepiness (8%) are the most widely used variables to predict changes in serum vitamin D levels. **Conclusions:** Cognitive abilities status and baseline 25-hydroxyvitamin D are important novel modifiers of the enhancement in circulating 25-hydroxyvitamin D after vitamin D supplementation.

Keywords

Cognitive abilities, depression, sleep disorders, sleepiness, insomnia, artificial intelligence

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Introduction

Cholecalciferol, or 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), plays a critical role in overall health and in preventing all causes of mortality and morbidity including musculoskeletal disorders, inflammatory and cardiovascular disease, diabetes mellitus (Holick, 2007; Skaaby, 2015; Husemoen et al., 2012; Skaaby et al., 2012; Skaaby et al., 2013a; Skaaby et al., 2013b), respiratory disorders (Skaaby et al., 2014), malignances (Yin et al., 2013), and autoimmune disease (Skaaby et al., 2015). Vitamin D (VitD) is necessary for the absorption of calcium by the gut. Low serum VitD levels may result in secondary hyperparathyroidism, and slow irreversible detrimental defects of bone mineralization and bone loss (McKenna, 1992; Malabanan et al., 1998; Parfitt et al., 1985) and is linked with development of rickets and osteomalacia in children and adults, respectively (Holick, 2007). Most of the circulating VitD is synthesized endogenously following dermal exposure to solar ultraviolet (UV) B radiation on 7-dehydrocholesterol, and lesser amounts are derived from dietary intake (Holick et al., 2007). The prevalence of VitD deficiency is estimated to be over one billion people globally (Holick and Chen, 2008). Measurements of serum 25(OH)D is a reliable and accepted index of VitD status. The current recommended dietary allowance for VitD is 600 IU daily for persons aged 1–70 years old and 800 IU daily for those older than 70 years (DRI, 2005), which is assumed to achieve sufficient serum 25(OH)D levels in 97.5% of healthy populations.

Previous studies have reported that several factors increase the likelihood of VitD deficiency, such as low body surface area exposed to sunlight, usage of sunscreen, less time spent on outside physical activity, and a greater tendency to indoor activities (Puri et al., 2008). Natural dietary sources of VitD are limited, and fortification or supplementation is often needed (Comptson, 1998). Recently oral VitD supplementation has been considered as one of the most effective public health interventions. Advantages of VitD supplementation have been observed to a reduction in fractures in the elderly (Trivedi et al., 2003; Bischoff-Ferrari et al., 2005), decrements the risk of metabolic syndrome, diabetes and coronary artery diseases (von Hurst et al., 2010; Wang et al., 2012; Giovannucci et al., 2008), prevention of cancer (Garland et al., 2006; Bolland et al., 2011; Lowe et al., 2005), multiple sclerosis (Munger et al., 2006), and enhanced immune system response (Ginde et al., 2009; Laaksi et al., 2007; Urashima et al., 2010).

In response to a similar administration dose of VitD supplement, the increment in serum 25(OH)D concentrations varies between individuals (Aloia et al., 2008; Gallagher and Sai, 2012; Heaney et al., 2003; Talwar et al., 2007). But there is little evidence on the parameters that may influence the magnitude of serum responsive to VitD supplementation, such as serum baseline 25(OH)D, body weight, body mass index (BMI), age, calcium intake, genetics, type/duration of supplement, and season (Gallagher and Sai, 2012; Mazahery and von Hurst, 2015; Ng et al., 2014; Shab-Bidar et al., 2014).

Adolescence is associated with a transition in the psychological, mental, and behavioral activity (Awasthi et al., 2012). VitD is a neurosteroid that appears to be involved in many brain processes such as neuroimmunomodulation, neuroprotection, and neuroplasticity (Eyles et al., 2005). VitD metabolites can cross the blood-brain barrier, and VitD receptors (VDR) and 1α-hydroxylase (the enzyme accountable for transforming 25(OH)D into the active form of VitD) are found on neurons and glia in various areas of the brain that have been involved in the pathophysiology of mode disorders (Cass et al., 2006).

It has been speculated that there are complicated interactions between host-related psychological factors and variance in serum 25(OH)D levels following supplementation. Due to the interplay between corresponding risk factors, the prediction of VitD responsiveness remains difficult and depends on combinations of different risk factors. The determinants of the magnitude of response to VitD treatment are very poorly understood by the classical linear statistical methods formerly used for the identification of these factors (Gallagher and Sai, 2012; Mazahery and von Hurst, 2015; Ng et al., 2014; Shab-Bidar et al., 2014). Investigating novel statistical techniques to enhance the identification of neuropsychological factors related to degree of response is an important objective. Bioinformatic predictions with a form of artificial intelligence, the artificial neural network (ANN), is frequently used for improving our understanding of the complex interplay of potential preliminary causes and risk factors with the aim of providing valid support regarding to its potency to recognize patterns in data consisting of multiple variables (Anselmino et al., 2009). We aimed to evaluate the effects of the neuropsychological profile of individuals on the magnitude of response to high-dose VitD supplementation using the ANN method among adolescent girls to provide a recommended specific supplementation to achieve the desirable 25(OH)D status.

Methods

Study population

This cross-sectional study was undertaken in adolescent female students aged between 12 and 19 years old in January 2015 (Bahrami et al., 2018; Khayyatzadeh et al., 2017). In brief, participants were recruited from six geographic areas in two cities from north-eastern Iran, Mashhad and Sabzevar, using a multi-stage cluster sampling way. Four high schools from each of the six geographic areas were chosen, and one class from each grade (three classes from each school) was randomly selected for inclusion. In each class about 15 students were included. Schools, classes, and students were recruited using

computer-generated random selection. Written consent was gathered from the participants and their parents. We excluded girls with any autoimmune disorders, malignancies, kidney failure, cardiovascular diseases, malabsorption or thyroid, parathyroid, or adrenal diseases. Participants who were receiving anti-inflammatory, antidepressive, anti-glycemic or antiobesity drugs, VitD or calcium supplement use, or hormone therapy within the last 6 months were also excluded. A total of 1026 participants were recruited; from this, 940 met the inclusion criteria. Participants were assigned to receive nine soft gel capsules containing 50,000 IU of cholecalciferol ($VitD_3$)/weekly during a 9-week interval. All study procedures were approved by the Ethics Committee of Mashhad University of Medical Sciences (MUMS).

Emotional function test

To assess the degree of depression, participants were asked to complete the Beck Depression Inventory II questionnaire (Beck et al., 1996), which was validated (Cronbach's $\alpha = 0.87$) for the Iranian population previously (Mohammadi, 2006). This is a 21-item self-report questionnaire, in which each item is scored as 0, 1, 2, or 3 and the minimum and maximum of total scores are 0 and 63, respectively. Degree of depression based on the obtained score is classified as follows: 0–13 (no/minimal), 14–19 (mild), 20–28 (moderate), and 29–63 (severe).

Sleep assessment

Participants also completed the Epworth Sleepiness Scale (ESS) to find the intensity of the daytime sleepiness (Johns, 1991). Total scores for each question of ESS ranged from 0 to 24 with following interpretation: total score of 0–10 (normal), 10–16 (mild/moderate obstructive sleep apnea), and above 16 (severe obstructive sleep apnea/narcolepsy). This questionnaire was verified for Iranian participants (Cronbach's $\alpha = 0.8$) previously (Haghighi et al., 2013).

Cognitive ability task

Cognitive functions were evaluated using Cognitive Abilities Questionnaire (CAQ), which consists of 30 questions, each rated on a five-point scale (1–5) with a total score ranging from 30–150. The CAQ validity with high internal consistency (Cronbach's $\alpha = 0.83$) was established in Iranians (Nejati, 2013). Higher scores indicate favorite cognition abilities. The CAQ examines seven cognitive skills: memory, inhibitory control and selective attention, decision making, planning, sustain attention, social cognition, and cognitive flexibility.

VitD measurements

Blood specimens were collected at 8 am at baseline and post 9 weeks' intervention after a 14-hour overnight fast. The serum samples were collected into non-heparinized tubes and were centrifuged (Hettich model D-78532) at room temperature to separate the serum. They were stored at -80°C in acid-washed Eppendorf tubes at the reference laboratory in MUMS until analysis. An electrochemical-luminescence technique was used for the quantification of serum 25(OH)D.

Evaluation of other variables

Demographic data were collected via an expert interviewer. The height and weight of each participant was determined in a standard manner then their BMI was calculated. A validated questionnaire was applied for physical activity and illustrated as metabolic equivalents (METs) in hours per day (Delshad et al., 2015).

Evaluation method

The ANN model imitates human brain neural systems in three layers, input (variables), hidden, and output, which provide artificial adaptive systems capable of modifying their internal structure in relationship with the function objective; thus, this algorithm is particularly suitable for answering nonlinear questions (Basheer and Hajmeer, 2000). We used an ANN model to classify responsiveness to VitD supplementation in our study; input variables were age, BMI, physical activity, basal VitD, depression, daytime sleeping, and seven cognitive skills —memory, inhibitory control and selective attention, decision making, planning, sustain attention, social cognition, and cognitive flexibility. The output layer in the ANN model was categorized by variables for the difference between the level of serum VitD before and after intervention (Δ25(OH)D). Low, moderate, and high response categories were < 20.89 ng/mL, between 20.89 and 34.85 ng/mL, and >34.85 ng/mL, respectively. The levels of 20.89 ng/mL and 34.85 ng/mL used for categorization were the 33th and 66th percentile of magnitude of response. But hidden layers that formed the structure of a neural network were dependent on the number of hidden neurons, transfer functions, and the training algorithm (Amato et al., 2013). We used a feed-forward ANN with back-propagation as the training algorithm in 70% of data as training set and 30% of data as the validation set. Optimal transfer functions and number of hidden neurons were selected between sigmoid or hyperbolic tangent transfer functions in hidden layers with 2–50 neurons and hyperbolic tangent, linear, or sigmoid transfer function in the output layer. Finally, a receiver operating characteristic (ROC) analysis was used to determine model performance by the sensitivity, specificity, and accuracy area under the ROC curve (AUC). All data analysis was performed using IBM SPSS 22 (SPSS Inc., Chicago, Illinois, USA).

Table 1. Description of the study population at the beginning of study.

Variable	Mean ± *SD*	Min	Max
Serum vitamin D (ng/mL)	9.40 ± 8.67	3	61
Physical activity (MET/h)	45.51 ± 3.69	41.50	68.45
Age (year)	14.57 ± 1.58	12	19
BMI (kg/m^2)	21.02 ± 4.04	12.42	27.89

BMI: body mass index; MET: metabolic equivalent.

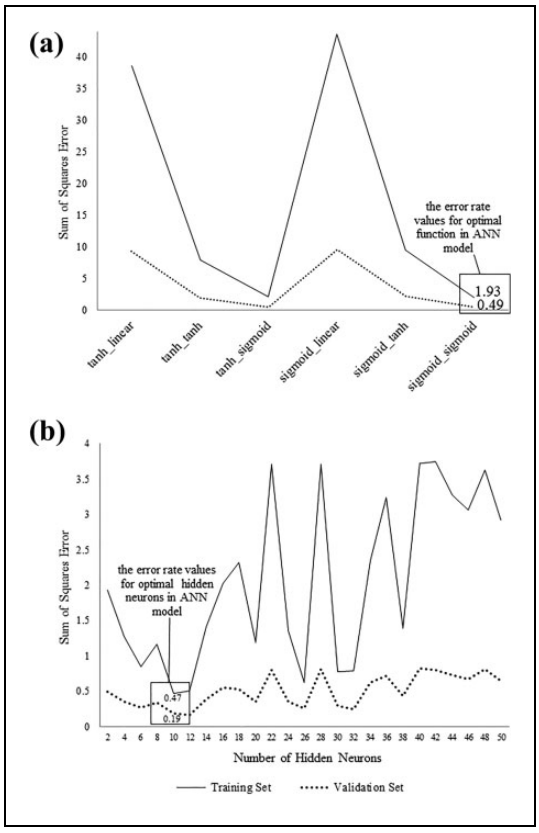

Figure 1. (a) The sum of square error of artificial neural network (ANN) models for different transfer functions**. (b)** The sum of square error of selected ANN transfer function models for different hidden neurons.

Results

A complete set of information was available for 619 adolescent girls in the present study. The mean total serum VitD, levels of physical activity, and BMI were 9.40 ± 8.67 (ng/mL), 45.51 ± 3.69 (MET/h), and 21.02 ± 4.04 (kg/m^2) at the beginning of study, respectively (Table 1). Using supplementation extensively increased average of VitD to 36.44 ± 15.71 ng/mL after 9 weeks.

Model selection is provided in Figure 1. Figure 1(a) displays a different combination of transfer functions in the hidden and output layers. When the linear function is used to connect the hidden and output layers, the sum of square error was about 40 in the training set and 10 in validation set regardless of the transfer function between input and hidden layers. However, ANN models had a sum of square error about 10 and 3 in training and validation sets for hyperbolic tangent function that connected hidden and output layers. But ANN models have the lowest sum of square error when the sigmoid function linked the hidden and output layers, and near performance of training and validation sets. Thus, the sigmoid transfer function in both input-hidden and hidden-output layers had a minimum sum of square error in both the training and validation sets. Figure 1(b) presents performance of this function with different neurons in the hidden layer. However, the validation set was similar for different hidden neurons and the training set shows the greatest improvement when the number of neurons increases into 10. For more than 10 neurons in hidden layers, the sum of square error had a high fluctuation and increased by more than six-fold when the number of neurons reached more than 40. Therefore, the ANN model is optimal when we use a sigmoid transfer function in both hidden and output layers with 10 hidden neurons to predict responsiveness to VitD supplementation by neuropsychological parameters as in Figure 2.

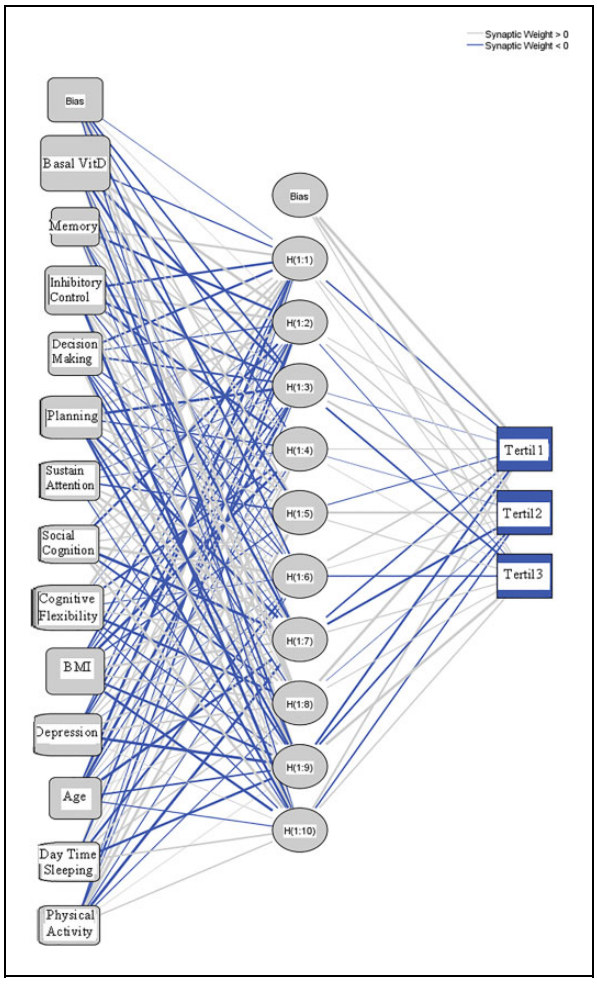

Figure 2. The final structure of artificial neural network mode.

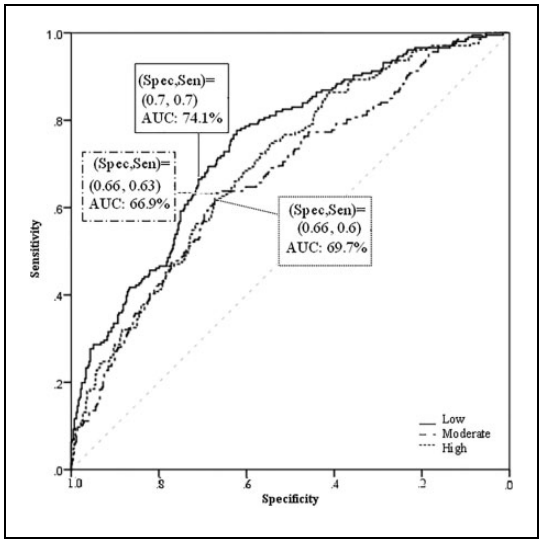

Figure 3. Roc curve of the artificial neural network model.

Table 2. Power of the ANN model based on triple threshold values in the validation set.

	Predicted / observed	Tertile 1	Tertile 2	Tertile 3
Validation set	Tertile 1	44 (63.8%)	21	4
	Tertile 2	22	33 (55%)	5
	Tertile 3	26	37	7 (10%)

ANN: artificial neural network.

The specificity, sensitivity, and AUC were 70%, 70%, and 74.1% in low, 66%, 63%, and 66.9% in moderate, and 66%, 60%, and 69.7% in participants with a high level of response to VitD supplementation (Figure 3). As can be seen in Table 2, the selected ANN model was able to correctly predict 63.8% of responses in the first tertile and 50% in the second tertile. However, it could classify only 10% of the participants with a high level of response to VitD supplementation. Figure 4 shows the best variable for predicting responsiveness to VitD supplementation was the cognitive ability task, which predicted 42.5% of the response to supplementation and was even twice as predictive as basal serum VitD, at 21.3%. Furthermore, physical activity (7.2%) and depression (6.6%) came after BMI (9.5%) and daytime sleepiness (8%), respectively. However, age (4.9%) was the least important variable.

Discussion

There is an ongoing debate about the requirement of VitD supplementation in healthy individuals. Evidence from several observational studies has shown that to attain optimal serum 25(OH)D status, the amount of VitD supplementation needed relies on genotype, baseline serum levels, BMI, etc. (Gallagher and Sai, 2012; Mazahery and

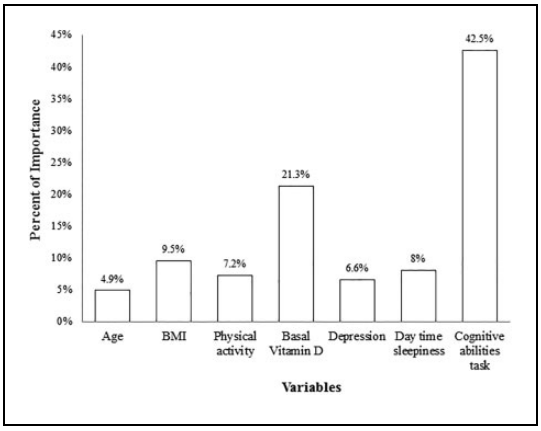

Figure 4. The variable importance from the selected artificial neural network.

von Hurst, 2015; Ng et al., 2014; Shab-Bidar et al., 2014). Results from a systematic review focused on the effect of VitD supplements on circulating 25(OH)D concentrations showed that identical doses across different trials led to increases in serum 25(OH)D levels that varied three- to four-fold in some trials in comparison with others. The overall between-study variation in serum 25(OH)D concentrations was greater than 25 ng/ml, even at similar doses (Autier et al., 2012). Often VitD recommendations do not take into consideration inter-individual parameters. At present, there is no definite view about the ideal 25(OH)D level or the size of the therapeutic window. Assuming this window is narrow, choosing the most appropriate dose for supplementation will be critical and dose adjustments are important. But it seems the window is somewhat broad as it has been challenging to demonstrate a clinical impact of increments the serum 25(OH)D concentrations from 20–30 ng/ml to close to 60 ng/ml (Grimnes et al., 2012; Grimnes et al., 2011; Kjærgaard et al., 2012; Jorde et al., 2010a; Jorde et al., 2010c; Jorde et al., 2010b). Moreover, usually total serum 25(OH)D concentrations were measured, and it is plausible the free or biologically active proportion is different and should be considered.

The current paper shows a neuropsychological-associated augmentation in circulating 25(OH)D by VitD supplements in adolescent girls. To best of our knowledge, the novel significant determinant of increments in serum 25(OH)D levels in response to supplementation noticed in this work is cognitive ability status. There is no similar work that compares with our results but many studies have illustrated the relationship between VitD status and cognition. Epidemiological studies demonstrate that low circulating VitD levels are correlated with a higher risk of incident Alzheimer's disease and dementia. For instance, VitD deficiency was associated with about 2.2–2.3 times the hazard ratios of incident Alzheimer disease's and dementia (Littlejohns et al., 2014). Moreover, decreased VitD concentrations are related with vascular risk factors, which are also linked to dementia (Reitz et al., 2007; Whitmer et al., 2005; Kivipelto et al., 2006). Miller et al.

reported that the mean $\pm$ *SD* of serum 25(OH)D levels were significantly decreased in the dementia individuals than mild cognitive impairment and normal control participants (16.2 ± 9.4 vs 20.0 ± 10.3 and 19.7 ± 13.1 ng/mL, respectively). After a mean of 4.8 years follow-up, the frequency of decline in episodic memory and executive function in sufficient VitD were lower than VitD deficiency and insufficiency cases after adjusting for potential confounders (Miller et al., 2015). In a recent systematic review and meta-analysis including 26 observational and three intervention studies, low VitD was associated with 1.2 and 1.3 odds of deteriorate neurocognitive functioning and cognitive decline (95% confidence interval (CI) = 1.1–1.3 and 95% CI = 1.1–1.2, respectively) (Goodwill and Szoeke, 2017). There are various possible explanations for the role of VitD in cognitive performance. It has been found that not only 1,25(OH)2D3 but also 25-hydroxyvitamin D trans over the blood-brain barrier (Kesby et al., 2011). VitD is able to regulate the generation of serotonin, a neurotransmitter that is linked with mood elevation (Stockmeier, 2003). Furthermore, VitD response elements were identified on two tryptophan hydroxylase genes that have been related to serotonin synthesis (Zhang et al., 2004).

Baseline 25(OH)D was found to be the second most important predictor (21.3%) that independently affected the variance of 25(OH)D in response to VitD treatment. Recently, a comprehensive systematic review and meta-analysis of clinical trials disclosed that baseline 25(OH)D was a significant determinant of variances in 25(OH)D post VitD treatment (Mo et al., 2019). Drincic and colleagues reported that 2.5 U/kg VitD is needed to increase 25(OH)D level in serum by as much as 1 ng/ml (Drincic et al., 2013). Recently, Kaykhaei observed that the increase in VitD levels were 26.4, 18.5, and 8.3 ng/ml, in participants with baseline VitD concentrations below 10, 10–20, and 20–30 ng/ml, respectively (Kaykhaei et al., 2019). Because hepatic hydroxylation of VitD is possibly a saturable trend, response to VitD supplementation may be influenced via baseline 25(OH)D levels (Barger-Lux et al., 1998). Higher baseline serum 25(OH)D leads to higher free 25(OH)D, which leads to the conversion of more 25(OH)D to inactive 24, 25(OH)2VitD. In agreement with our study, the baseline serum 25(OH)D level accounts for 20.2% of the increments in 25(OH)D response to VitD supplementation among Middle Eastern women (Mazahery et al., 2015). Additionally, a recent review reported there was an inverse relationship between the increment in serum VitD and baseline 25(OH)D serum after oral intake of cholecalciferol, but this relationship was not found after supplementation with calcifediol (Quesada-Gomez and Bouillon, 2018).

Another finding from our study is that the magnitude of responsiveness of serum VitD levels to Vit therapy were best predicted by physical activity. Similar observations were reported in nearly 4500 participants from the NHANES study (Forrest and Stuhldreher, 2011). Physically active individuals had a significantly higher 25(OH)D level compared to those who were inactive, possibly due to more time spent outdoors thus exposing them to more UV irradiation, which produces more VitD in the skin. VitD controls calcium transport and inorganic phosphate uptake for the generation of energy-rich phosphate contents during muscle action. Indeed, VitD promotes muscle protein synthesis (Pfeifer et al., 2001).

Our models explained that nearly 8.0% and 6.6% of the variability in serum 25(OH)D post-treatment are associated to severity of daytime sleepiness and depression. Consistently, experimental studies revealed that VDR animal knock-out models presented higher anxiety, lower activity, and muscular/motor impairments, resembling phenotypic models of depression (Gracious et al., 2012). It has been suggested that VitD may implicated in manifestations of sleepiness through sleep-regulating metabolites, namely TNF-α, and NF-κB (Peterson and Heffernan, 2008; Jablonski et al., 2011), which can regulate various substances involved in homeostatic sleep pressure (Krueger et al., 2009). VitD has a neuroprotective effect on hippocampal cells, via regulation of calcium ion channels and activation of PKC and MAPK cascades (Gracious et al., 2012).

Carlander et al. reported that serum 25(OH)D levels were lower in patients suffering from narcolepsy with cataplexy versus normal controls. Patients with narcolepsy with cataplexy (NC) had significantly greater VitD deficiency compared to controls (72.5% vs 50.9%, $p < 0.005$) (Carlander et al., 2011). In another study a significant association between sleepiness and VitD was observed. However, ESSs and 25(OH)D are related, the association is complex and mainly influenced by race (McCarty et al., 2012). Observational studies indicate a role of VitD in emotional disturbance, such as depression, anxiety, and stress (Tepper et al., 2016; Gracious et al., 2012). The connection between VitD inadequacy and lower physical activity (Öberg et al., 2014) and higher emotional and peer relationship problems in adolescents have been investigated (Husmann et al., 2017). VitD supplementation has led to a decreased frequency of psychosis and depression in adolescents (Gracious et al., 2012). In a 12-week interventional study, VitD and probiotic co-administration led to significant improvements in scores of Beck Depression/Anxiety Inventory and general health questionnaire (Raygan et al., 2018).

There is ample evidence supporting a role of VitD in brain development, behavior, and mood. The present study adds to the existing knowledge of and evidence for the role of neuropsychological function in the magnitude of response to VitD supplementation measured as increment in serum 25(OH)D by using an novel statistical analysis, ANN. Neurocognitive function, baseline 25(OH)D level, and BMI are strong predictors of the serum 25(OH)D response to VitD supplementation. The strengths of the current work include the large population, the mega supplementation dose, and the fact that all serum specimens were measured to the same 25(OH)D

evaluation techniques, with standard tools for neuropsychological assessments.

In conclusion, cognitive ability status, baseline 25(OH)D, BMI, severity of daytime sleepiness, physical activity level, and depression status are important novel modifiers of the enhancement in circulating 25(OH)D after VitD supplementation. These factors should be taken into account in persons with deficient or inadequate circulating 25(OH)D values to estimate the VitD supplement dose that is essential for reaching adequate circulating 25(OH)D amount.

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Authors contributions

EA, MG, and AB conceived the idea for this qualitative study and contributed to its design. AB designed the interview schedules, conducted the interviews, and analyzed them with EA and PC. FA and TEK drafted the article with GF and edited all subsequent drafts. All authors read and revised the article and approved the final version.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Informed consent

All participants and their parents gave written informed consent to be interviewed, and for the interviews to be audio recorded and used for research purposes and publication.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of MUMS (931188).

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References

Aloia JF, Patel M, DiMaano R, et al. (2008) Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. *The American Journal of Clinical Nutrition* 87(6): 1952–1958.

Amato F, López A, Peña-Méndez EM, et al. (2013) *Artificial neural networks in medical diagnosis* 11(2): 47–58.

Anselmino M, Malmberg K, Rydén L, et al. (2009) A glucometabolic risk index with cardiovascular risk stratification potential in patients with coronary artery disease. *Diabetes and Vascular Disease Research* 6(2): 62–70.

Autier P, Gandini S and Mullie P (2012) A systematic review: Influence of vitamin D supplementation on serum 25-hydroxyvitamin D concentration. *The Journal of Clinical Endocrinology & Metabolism* 97(8): 2606–2613.

Awasthi S, Agnihotri K, Chandra H, et al. (2012) Assessment of Health-Related Quality of Life in school-going adolescents: Validation of PedsQL instrument and comparison with WHO-QOL-BREF. *National Medical Journal of India* 25(2): 74.

Bahrami A, Bahrami-Taghanaki H, Afkhamizadeh M, et al. (2018) Menstrual disorders and premenstrual symptoms in adolescents: prevalence and relationship to serum calcium and vitamin D concentrations. *Journal of Obstetrics and Gynaecology* 38(7): 989–995.

Barger-Lux M, Heaney R, Dowell S, et al. (1998) Vitamin D and its major metabolites: Serum levels after graded oral dosing in healthy men. *Osteoporosis International* 8(3): 222–230.

Basheer IA and Hajmeer M (2000) Artificial neural networks: Fundamentals, computing, design, and application. *Journal of Microbiological Methods* 43(1): 3–31.

Beck AT, Steer RA and Brown GK (1996) *Beck depression inventory-II*. Vol 78. San Antonio, TX: Psychological Corporation, 1996, pp. 490–498.

Bischoff-Ferrari HA, Willett WC, Wong JB, et al. (2005) Fracture prevention with vitamin D supplementation: A meta-analysis of randomized controlled trials. *Jama* 293(18): 2257–2264.

Bolland MJ, Grey A, Gamble GD, et al. (2011) Calcium and vitamin D supplements and health outcomes: A reanalysis of the Women's Health Initiative (WHI) limited-access data set. *The American Journal of Clinical Nutrition* 94(4): 1144–1149.

Carlander B, Puech-Cathala AM, Jaussent I, et al. (2011) Low vitamin D in narcolepsy with cataplexy. *PloS one* 6(5): e20433.

Cass WA, Smith MP and Peters LE (2006) Calcitriol protects against the dopamine-and serotonin-depleting effects of neurotoxic doses of methamphetamine. *Annals of the New York Academy of Sciences* 1074(1): 261–271.

Comptson J (1998) Vitamin D deficiency-a time for action. *British Medical Journal* 317: 1466–1467.

Delshad M, Ghanbarian A, Ghaleh NR, et al. (2015) Reliability and validity of the modifiable activity questionnaire for an Iranian urban adolescent population. *International Journal of Preventive Medicine* 6: 3.

DRI (2005) *Institute of Medicine, Food and Nutrition Board, Dietary Reference Intakes: energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids*. The National Academy Washington.

Drincic A, Fuller E, Heaney RP, et al. (2013) 25-Hydroxyvitamin D response to graded vitamin D3 supplementation among obese adults. *The Journal of Clinical Endocrinology & Metabolism* 98(12): 4845–4851.

Eyles DW, Smith S, Kinobe R, et al. (2005) Distribution of the vitamin D receptor and 1α-hydroxylase in human brain. *Journal of Chemical Neuroanatomy* 29(1): 21–30.

Forrest KY and Stuhldreher WL (2011) Prevalence and correlates of vitamin D deficiency in US adults. *Nutrition Research* 31(1): 48–54.

Gallagher JC and Sai A (2012) Dose response to vitamin D supplementation in postmenopausal women response: a randomized trial. *Annals of Internal Medicine* 156(6): 425–437.

Garland CF, Garland FC, Gorham ED, et al. (2006) The role of vitamin D in cancer prevention. *American Journal of Public Health* 96(2): 252–261.

Ginde AA, Mansbach JM and Camargo CA (2009) Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Archives of Internal Medicine* 169(4): 384–390.

Giovannucci E, Liu Y, Hollis BW, et al. (2008) 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Archives of Internal Medicine* 168(11): 1174–1180.

Goodwill AM and Szoeke C (2017) A systematic review and meta-analysis of the effect of low vitamin D on cognition. *Journal of the American Geriatrics Society* 65(10): 2161–2168.

Gracious BL, Finucane TL, Friedman-Campbell M, et al. (2012) Vitamin D deficiency and psychotic features in mentally ill adolescents: A cross-sectional study. *BMC Psychiatry* 12(1): 38.

Grimnes G, Figenschau Y, Almås B, et al. (2011) Vitamin D, insulin secretion, sensitivity, and lipids: Results from a case-control study and a randomized controlled trial using hyperglycemic clamp technique. *Diabetes* 60(11): 2748–2757.

Grimnes G, Joakimsen R, Figenschau Y, et al. (2012) The effect of high-dose vitamin D on bone mineral density and bone turnover markers in postmenopausal women with low bone mass: A randomized controlled 1-year trial. *Osteoporosis International* 23(1): 201–211.

Haghighi KS, Montazeri A, Mehrizi AK, et al. (2013) The Epworth Sleepiness Scale: Translation and validation study of the Iranian version. *Sleep and Breathing* 17(1): 419–426.

Heaney RP, Davies KM, Chen TC, et al. (2003) Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *The American Journal of Clinical Nutrition* 77(1): 204–210.

Holick MF (2007) Vitamin D deficiency. *New England Journal of Medicine* 357(3): 266–281.

Holick MF and Chen TC (2008) Vitamin D deficiency: A worldwide problem with health consequences. *The American Journal of Clinical Nutrition* 87(4): 1080S–1086S.

Holick MF, Chen TC, Lu Z, et al. (2007) Vitamin D and skin physiology: AD-lightful story. *Journal of Bone and Mineral Research* 22(S2): V28–V33.

Husemoen L, Skaaby T, Thuesen B, et al. (2012) Serum 25 (OH) D and incident type 2 diabetes: A cohort study. *European Journal of Clinical Nutrition* 66(12): 1309.

Husmann C, Frank M, Schmidt B, et al. (2017) Low 25 (OH)-vitamin D concentrations are associated with emotional and behavioral problems in German children and adolescents. *PloS one* 12(8): e0183091.

Jablonski KL, Chonchol M, Pierce GL, et al. (2011) 25-Hydroxyvitamin D deficiency is associated with inflammation-linked vascular endothelial dysfunction in middle-aged and older adults. *Hypertension* 57(1): 63–69.

Johns M (1991) A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep* 14: 540–545.

Jorde R, Sneve M, Torjesen P, et al. (2010a) No improvement in cardiovascular risk factors in overweight and obese subjects after supplementation with vitamin D3 for 1 year. *Journal of Internal Medicine* 267(5): 462–472.

Jorde R, Sneve M, Torjesen PA, et al. (2010b) No effect of supplementation with cholecalciferol on cytokines and markers of inflammation in overweight and obese subjects. *Cytokine* 50(2): 175–180.

Jorde R, Sneve M, Torjesen PA, et al. (2010c) No significant effect on bone mineral density by high doses of vitamin D3 given to overweight subjects for one year. *Nutrition Journal* 9(1): 1.

Kaykhaei MA, Khodadoost M, Dashipour AR, et al. (2019) Baseline levels determine magnitude of increment in 25 hydroxy vitamin D following vitamin D3 prescription in healthy subjects. *Endocrine* 64(2): 378–383.

Kesby JP, Eyles DW, Burne TH, et al. (2011) The effects of vitamin D on brain development and adult brain function. *Molecular and Cellular Endocrinology* 347(1–2): 121–127.

Khayyatzadeh SS, Vatanparast H, Avan A, et al. (2017) Serum transaminase concentrations and the presence of irritable bowel syndrome are associated with serum 25-hydroxy vitamin D concentrations in adolescent girls who are overweight and obese. *Annals of Nutrition and Metabolism* 71(3–4): 234–241.

Kivipelto M, Ngandu T, Laatikainen T, et al. (2006) Risk score for the prediction of dementia risk in 20 years among middle aged people: A longitudinal, population-based study. *The Lancet Neurology* 5(9): 735–741.

Kjærgaard M, Waterloo K, Wang CE, et al. (2012) Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: Nested case-control study and randomised clinical trial. *The British Journal of Psychiatry* 201(5): 360–368.

Krueger J, Szentirmai E and Kapas L (2009) Biochemistry of sleep function: A paradigm for brain organization of sleep. In: *Basics of sleep guide*, *2nd ed*. Westchester, IL: Sleep Research Society, pp. 69–74.

Laaksi I, Ruohola J-P, Tuohimaa P, et al. (2007) An association of serum vitamin D concentrations < 40 nmol/L with acute respiratory tract infection in young Finnish men. *The American Journal of Clinical Nutrition* 86(3): 714–717.

Littlejohns TJ, Henley WE, Lang IA, et al. (2014) Vitamin D and the risk of dementia and Alzheimer disease. *Neurology* 83(10): 920–928.

Lowe LC, Guy M, Mansi JL, et al. (2005) Plasma 25-hydroxy vitamin D concentrations, vitamin D receptor genotype and breast cancer risk in a UK Caucasian population. *European Journal of Cancer* 41(8): 1164–1169.

Malabanan A, Veronikis I and Holick M (1998) Redefining vitamin D insufficiency. *The Lancet* 351(9105): 805–806.

Mazahery H, Stonehouse W and Von Hurst P (2015) The effect of monthly 50 000 IU or 100 000 IU vitamin D supplements on vitamin D status in premenopausal Middle Eastern women living in Auckland. *European Journal of Clinical Nutrition* 69(3): 367.

Mazahery H and von Hurst PR (2015) Factors affecting 25-hydroxyvitamin D concentration in response to vitamin D supplementation. *Nutrients* 7(7): 5111–5142.

McCarty DE, Reddy A, Keigley Q, et al. (2012) Vitamin D, race, and excessive daytime sleepiness. *Journal of Clinical Sleep Medicine* 8(06): 693–697.

McKenna MJ (1992) Differences in vitamin D status between countries in young adults and the elderly. *The American Journal of Medicine* 93(1): 69–77.

Miller JW, Harvey DJ, Beckett LA, et al. (2015) Vitamin D status and rates of cognitive decline in a multiethnic cohort of older adults. *JAMA Neurology* 72(11): 1295–1303.

Mo M, Wang S, Chen Z, et al. (2019) A systematic review and meta-analysis of the response of serum 25-hydroxyvitamin D concentration to vitamin D supplementation from RCTs from around the globe. *European Journal of Clinical Nutrition* 73: 816–834.

Mohammadi N (2006) Primary survey of psychometric index of Buss-Perry questionnaire. *Farsi. Journal of Human and Social Science of Shiraz University, Iran* 25(4): 135–151.

Munger KL, Levin LI, Hollis BW, et al. (2006) Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *Jama* 296(23): 2832–2838.

Nejati V (2013) Cognitive abilities questionnaire: Development and evaluation of psychometric properties. *Advances in Cognitive Science* 15(2): 11–19.

Ng K, Scott JB, Drake BF, et al. (2014) Dose response to vitamin D supplementation in African Americans: Results of a 4-arm, randomized, placebo-controlled trial. *The American journal of clinical nutrition* 99(3): 587–598.

Öberg J, Jorde R, Almås B, et al. (2014) Vitamin D deficiency and lifestyle risk factors in a Norwegian adolescent population. *Scandinavian Journal of Public Health* 42(7): 593–602.

Parfitt A, Rao DS, Stanciu J, et al. (1985) Irreversible bone loss in osteomalacia. Comparison of radial photon absorptiometry with iliac bone histomorphometry during treatment. *The Journal of Clinical Investigation* 76(6): 2403–2412.

Peterson CA and Heffernan ME (2008) Serum tumor necrosis factor-alpha concentrations are negatively correlated with serum 25 (OH) D concentrations in healthy women. *Journal of Inflammation* 5(1): 10.

Pfeifer M, Begerow B, Minne H, et al. (2001) Vitamin D status, trunk muscle strength, body sway, falls, and fractures among 237 postmenopausal women with osteoporosis. *Experimental and Clinical Endocrinology & Diabetes* 109(02): 87–92.

Puri S, Marwaha RK, Agarwal N, et al. (2008) Vitamin D status of apparently healthy schoolgirls from two different socioeconomic strata in Delhi: Relation to nutrition and lifestyle. *British Journal of Nutrition* 99(4): 876–882.

Quesada-Gomez J and Bouillon R (2018) Is calcifediol better than cholecalciferol for vitamin D supplementation? *Osteoporosis International* 29(8): 1697–1711.

Raygan F, Ostadmohammadi V, Bahmani F, et al. (2018) The effects of vitamin D and probiotic co-supplementation on mental health parameters and metabolic status in type 2 diabetic patients with coronary heart disease: a randomized, double-blind, placebo-controlled trial. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 84: 50–55.

Reitz C, Tang M-X, Manly J, et al. (2007) Hypertension and the risk of mild cognitive impairment. *Archives of Neurology* 64(12): 1734–1740.

Shab-Bidar S, Bours S, Geusens PP, et al. (2014) Serum 25 (OH) D response to vitamin D 3 supplementation: A meta-regression analysis. *Nutrition* 30(9): 975–985.

Skaaby T (2015) The relationship of vitamin D status to risk of cardiovascular disease and mortality. *Danish Medical Journal* 62(2).

Skaaby T, Husemoen LLN, Martinussen T, et al. (2013a) Vitamin D status, filaggrin genotype, and cardiovascular risk factors: A Mendelian randomization approach. *PloS one* 8(2): e57647.

Skaaby T, Husemoen LLN, Pisinger C, et al. (2012) Vitamin D status and changes in cardiovascular risk factors: A prospective study of a general population. *Cardiology* 123(1): 62–70.

Skaaby T, Husemoen LLN, Pisinger C, et al. (2013b) Vitamin D status and 5-year changes in urine albumin creatinine ratio and parathyroid hormone in a general population. *Endocrine* 44(2): 473–480.

Skaaby T, Husemoen LLN, Thuesen BH, et al. (2015) Prospective population-based study of the association between vitamin D status and incidence of autoimmune disease. *Endocrine* 50(1): 231–238.

Skaaby T, Husemoen LLN, Thuesen BH, et al. (2014) Vitamin D status and chronic obstructive pulmonary disease: A prospective general population study. *PloS one* 9(3): e90654.

Stockmeier CA (2003) Involvement of serotonin in depression: Evidence from postmortem and imaging studies of serotonin receptors and the serotonin transporter. *Journal of Psychiatric Research* 37(5): 357–373.

Talwar SA, Aloia JF, Pollack S, et al. (2007) Dose response to vitamin D supplementation among postmenopausal African American women. *The American Journal of Clinical Nutrition* 86(6): 1657–1662.

Tepper S, Dabush Y, Shahar D, et al. (2016) Vitamin D status and quality of life in healthy male high-tech employees. *Nutrients* 8(6): 366.

Trivedi DP, Doll R and Khaw KT (2003) Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: Randomised double blind controlled trial. *BMJ* 326(7387): 469.

Urashima M, Segawa T, Okazaki M, et al. (2010) Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *The American Journal of Clinical Nutrition* 91(5): 1255–1260.

von Hurst PR, Stonehouse W and Coad J (2010) Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient: A randomised, placebo-controlled trial. *British Journal of Nutrition* 103(4): 549–555.

Wang L, Song Y, Manson JE, et al. (2012) Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: A meta-analysis of prospective studies. *Circulation: Cardiovascular Quality and Outcomes* 5(6): 819–829.

Whitmer RA, Sidney S, Selby J, et al. (2005) Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology* 64(2): 277–281.

Yin L, Ordóñez-Mena JM, Chen T, et al. (2013) Circulating 25-hydroxyvitamin D serum concentration and total cancer incidence and mortality: A systematic review and meta-analysis. *Preventive Medicine* 57(6): 753–764.

Zhang X, Beaulieu J-M, Sotnikova TD, et al. (2004) Tryptophan hydroxylase-2 controls brain serotonin synthesis. *Science* 305(5681): 217–217.

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