

ORIGINAL ARTICLE

Can vitamin D status influence the effect of stress on planning and problem-solving? A randomized control trial

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Popular scientific summary

- Higher vitamin D status seemed to prevent the effect of stress on easy planning and problem-solving tasks, as accuracy improved from pre- to post-test when controlling for age and IQ.
- Improved performance caused by vitamin D supplementation was not related to a speed-accuracy trade off effect.
- A classic nadir in vitamin D status during spring caused impaired resilience to stress manifested by no learning effect of pre-test.

Abstract

Background: Nutritional interventions may serve as a stress resilience strategy with important implications for human health.

Objective: The aim of this study was to investigate the effect of vitamin D supplementation throughout wintertime on problem-solving and planning abilities during stressful circumstances.

Design: A total of 77 male inpatients with a mean age of 48 years (range 31–81) and stress-related mental health disorders were randomly assigned into a Vitamin D supplement group (daily intake of 40 µg) or a placebo supplement group (Control) (daily intake of 120 mg olive oil). The intervention period was from January 2018 to May 2018. The means and standard deviations for vitamin D status (25-hydroxyvitamin D3, nmol/L), pre- and post-test, respectively, were 58(21) and 46(15) for the Control group, and 63(18) and 76(21) for the Vitamin D group. Problem-solving and planning abilities were measured by the Tower of London (ToL) task pre- (midwinter) and post- (spring) supplement intervention. The ToL task was performed during exposure to distracting noise.

Results: The results revealed that vitamin D supplementation throughout the winter had a significant effect on number of correct responses on easier (1 and 2 move) ToL problems during stress; the Vitamin D group improved significantly from pre- to post-test, whereas the Control group did not. In addition, the Vitamin D group had significantly more correct responses than the Control group on post-test. The improved performance was not related to a speed-accuracy trade off effect; both groups showed significantly decreased planning times from pre- to post-test. The intervention did not differentially affect task performance on the more difficult (3 to 5 move) ToL problems. For the more demanding problems, IQ seemed to explain most of the variance regarding accuracy. Age explained most of the variance associated with task planning time.

Conclusion: Vitamin D supplementation seemed to improve resilience to stress, but it was limited to performance of easier tasks.

Keywords: *vitamin D status; wintertime; problem-solving; planning; stress resilience*

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It has been argued that vitamin D is important for the development of the brain and brain functioning throughout the lifespan (1). Both the major circulatory form 25-hydroxyvitamin D3 (25(OH)D3) and the active hormonal form 1,25-hydroxyvitamin D3 (1,25(OH)2D3) can be found in the brain (2, 3). The 25(OH)D3 can cross the blood–brain barrier and enter glia and neuronal cells and further be converted to the 1,25(OH)2D3, which can bind to the vitamin D receptors (VDRs) (see 4 for an overview). Vitamin D receptors have been found in the temporal (e.g., auditory) and frontal cortex (e.g., prefrontal cortex), deep grey matter (e.g., basal ganglia, hypothalamus, amygdala, and hippocampus), and cerebellum (see 2 for an overview). Vitamin D deficiency in adults has been associated with reduced hippocampal volume (5). The prefrontal cortex is important for executive functioning (e.g., working memory), while the hippocampus plays a key role in memory formation, such as transformation of short-term memory to long-term memory (5). The prefrontal cortex and the hippocampus are sensitive to stress. Mobilization of stress-response systems releases neurotransmitters, which, in some cases, can damage these structures in the brain (depending on the type and timing of the stressors) and cause impaired cognitive performance (6). Vitamin D is a steroid hormone that can regulate and act on many underlying mechanisms, e.g., axonal growth, and neurotropic factors, such as nerve growth factors important for both development and survival of hippocampus. Vitamin D can also act on neurotransmitters (e.g., dopamine, serotonin, and noradrenaline) (3, 4). Thus, the question is whether vitamin D supplementation can prevent the effect of stress on cognition.

Vitamin D deficiency has been shown to be associated with different neurodevelopmental disorders and adverse brain-related outcomes (3, 7). In a recent previous paper on this larger randomized control trial (RCT) investigating vitamin D supplementation during winter, we reported that vitamin D status (i.e., serum 25(OH)D3) also influenced psychophysiological mechanisms of resilience to stress in patients with stress-related mental health disorders (8). Pre- and post-vitamin D intervention, this study investigated heart rate (HR) and heart rate variability (HRV) to a stress procedure consisting of both resting and stressful conditions. The Control group, with a classic nadir in vitamin D during spring, showed impaired resilience to stress at post-test, i.e., no variations in physiological responses from resting baseline to stress conditions, or from stress conditions to resting recovery. In contrast, the Vitamin D group, with an optimal level of vitamin D status during spring, showed significant differences in physiological responses between rest and stress conditions. Thus, at post-test, the Control group was in a constant state of stress (i.e., high HR and low HRV) throughout

the whole experimental procedure (8). In general, resting HRV has shown to be a useful index of flexibility and adaptability to novel situations (9, 10). The importance of physiological recovery, or the ability to shut off a stress response after stress exposure, has also been emphasized by many investigators (see 11 for an overview). The results from our RCT (8) demonstrated a relationship between vitamin D status and physiological recovery to stress.

Another important aspect of stress resilience is the ability to solve problems and plan future behavior during stress, as this is essential for management and coping in everyday life. Problem-solving and planning abilities depend on executive functioning such as working memory (12). In a study investigating prisoners, vitamin D status was associated with accurate performance on an executive function task measuring working memory, and this was not related to a speed-accuracy trade off. However, there was no relationship between vitamin D and performance on easier automatic non-executive functioning (13).

To expand knowledge about potential effects of vitamin D supplementation on stress resilience, the investigation of the effects of vitamin D supplementation on problem-solving and planning abilities during stress is of particular importance. One way to test problem-solving and planning under stress is to use the Tower of London (ToL) task in combination with exposure to aversive noise. The ToL task is an experimental executive functioning task designed to measure problem-solving and planning abilities (14, 15). Aversive noise is known to elicit stress and psychophysiological stress responses (e.g., [16, 17]) and impair cognitive performance (18). The study by Alimohammadi et al. (18) found that the addition of noise negatively impacted the number of correct responses on the ToL task. The ToL task consists of problems requiring a different number of moves to solve, which is typical for many different versions of tower tasks (e.g., Tower of Hanoi). In general, it is assumed as the number of required moves increases, so does the load on working memory (12). Thus, it is possible to distinguish between easy and difficult tasks (19).

To learn more about the potential importance of vitamin D status in relation to stress resilience, this study aimed to investigate the effects of regular consumptions of vitamin D supplements throughout wintertime. Vitamin D status varies through the year, and for people living at higher latitudes in the Northern hemisphere, there is a natural decrease in vitamin D status during spring due to a long winter with diminished natural daylight and sun exposure (UV-radiation) (e.g., [20, 21, 22]). As we have shown before (8), the timing of the study makes it possible to gain insight into potential *adverse effects of a natural decrease* in vitamin D status without additional manipulation or harm, such as intentionally putting participants on a diet with low or non-vitamin D content or

denying participants the opportunity to go outside during summer.

The aim of this study was to investigate the effects of vitamin D supplementation throughout wintertime on problem-solving and planning abilities during stress in a group of patients with stress-related disorders. Based on previous research (8), it was expected that vitamin D supplementation would cause enhanced stress resilience, manifesting as improved accuracy on the more demanding ToL tasks. No speed-accuracy trade-off effect was expected (cf. [13]).

Materials and methods

Study design

This study is one of a series of studies from a larger parallel randomized double-blind placebo-controlled trial, aiming to investigate the effects of vitamin D supplementation during wintertime on different stress resilience mechanisms (see also [8, 23]). The study protocol was approved by the Regional Committee for Medical Research Ethics, Western Norway (REK-West; 2017/1520; October 6, 2017) and the Sand Ridge Secure Treatment Center Institutional Review Board (IRB00002675; FWA00021540; August 7, 2017). The procedure used in the present study was in accordance with the Helsinki Declaration and the US federal regulations. The preregistration number at ClinicalTrials.gov for this trial is NCT03336125.

Based on a study conducted by Armas et al. (24), an a priori analysis found that 50 participants per group were needed to reliably identify a statistically significant effect at $\alpha = 0.05$ with a statistical power of 80% (i.e., $1 - \beta = 0.80$).

Subjects

All patients at a secure inpatient treatment facility were considered for trial participation, and 161 male participants were assessed for eligibility. A total of 75 of these did not participate due to different reasons: they were on vitamin D supplements; had an IQ < 70; had a severe mental illness (e.g., schizophrenia and schizoaffective disorder); had a major neurocognitive disorder, neurodevelopmental disorder, or history of traumatic brain injury; or were unable to complete the protocol (i.e., did not speak fluent English, tremor, and legally blind). In addition, 20 inpatients declined to participate. Fig. 1 presents a flow diagram of the number of participants who were excluded due to the different reasons and the progress of the current study (see also [8, 23]). As illustrated in the flow diagram (Fig. 1), a total of 86 participants were randomized into a placebo group, i.e., the Control group, or an intervention group, i.e., the Vitamin D group. For the current study, we have complete data on 77 participants. Tower of London data were available for 38 and 39 participants for the Control and Vitamin D groups, respectively

(see Fig. 1). Mean age for the two groups is reported in Table 1.

The randomization procedure conformed to CONSORT criteria. Each participant was assigned a participant number. Participants were paired using age and IQ. In each pair, one participant was randomly assigned to one of two groups. The randomization was carried out using the Mersenne twister random number generator in MATLAB (MathWorks, Natick, MA, USA). The current time was used as seed. Personnel outside of the project decided which group received vitamin D or placebo. This information was not available to neither the US nor the Norwegian teams. The random allocations to the groups were completed before all participants were enrolled and had completed baseline testing (pre-intervention battery). Thus, all researchers, staff, and participants were blinded.

As it has been described before (8), the participants in the present study were characterized with stress-related mental health disorders such as antisocial and borderline personality disorders, as well as substance use disorders. These disorders were common in both groups. Even if mood and trauma-related disorders or diagnoses were less common among the participants, scores on questionnaires measuring symptoms of such disorders indicated that both childhood trauma and post-traumatic symptoms were common in this sample. Scores on Childhood Trauma Questionnaire-Short Form and the Impact of Event Scale-Revised (IES-R), as well as the number of prescribed medications for each group (i.e., antidepressant and cardiovascular) have been reported before. No significant differences between the groups were found (8).

The recruitment process began on October 12, 2017. Participants received both oral and written information about the aim of the study, and they were informed of their rights, including the right to withdraw from the study at any time for any reason. All participants signed an informed consent statement. Agreement or refusal to participate had no ramifications for their confinement status, services, privileges, or liberties available to them at the secure treatment center.

Intervention

All participants received their vitamin D supplements or placebo pearls along with their daily medication delivered by the health services staff. The health services staff also tracked compliance with taking the supplements by recording '1' if the participants took the capsules and '0' if the participant did not take the capsules. If a participant had to leave the institution for a reason (e.g., court appearance in another county), the supplements were packaged with their other medications to be administered off-site. Compliance in this study was about 97% (8, 23). The intervention period started on January 7, 2018 and ended on May 22, 2018.

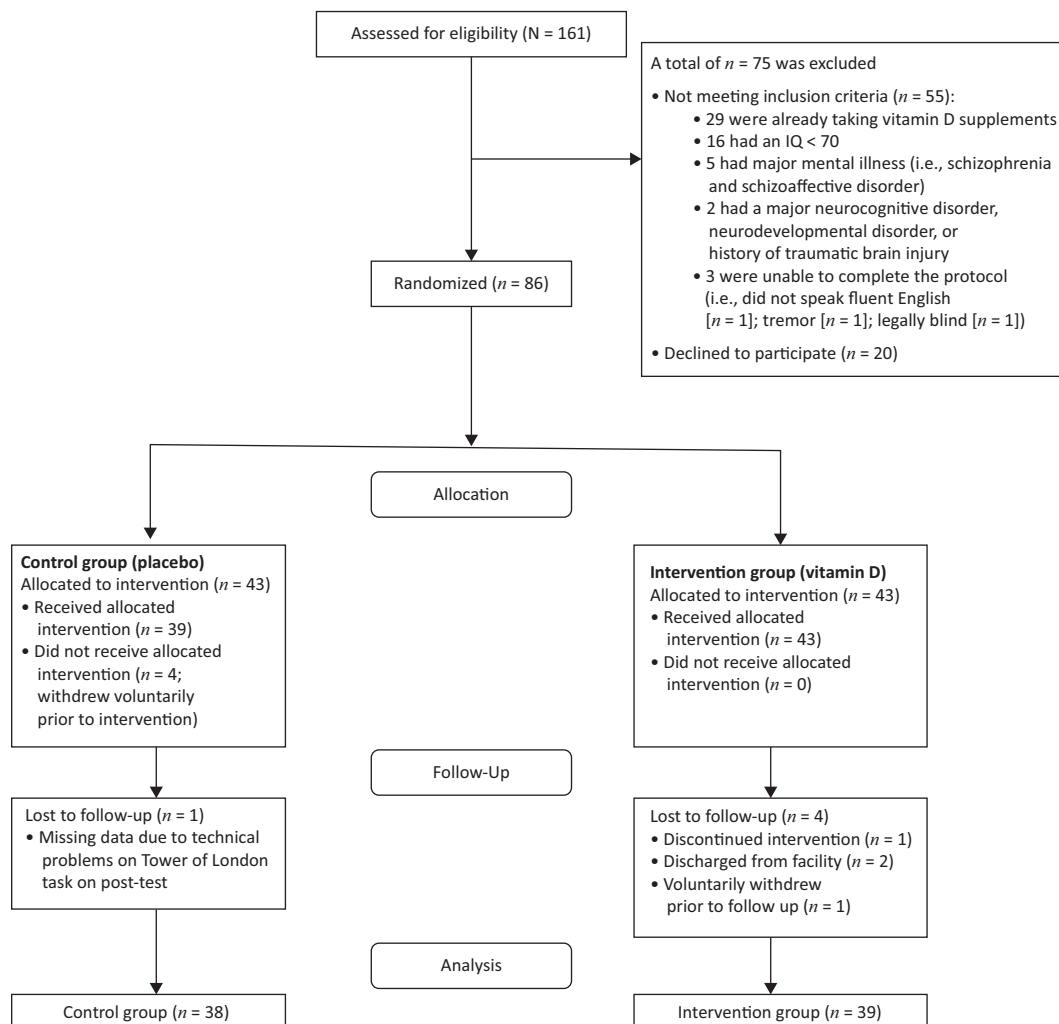


Fig. 1 CONSORT flowchart of participants.

Table 1. Means and standard deviations for the current sample (N = 77)

Groups	Sample characteristics	Pre-test	Post-test
Control (N = 38)	IQ	91(14)	
	Age	49(11)	
	Vitamin D (nmol/L)	58(21)	46(15)*:**
Vitamin D (N = 39)	IQ	92(14)	
	Age	48(11)	
	Vitamin D (nmol/L)	63(18)	76(21)*:**

* P < 0.001 within group differences on the pre- versus post-test.

** P < 0.001 between group differences on the post-test.

Both the vitamin D and placebo pearls (120 mg olive oil) were produced by Pharma Nord, Denmark, and were Halal and Kosher certified. The vitamin D dose of 40µg cholecalciferol corresponding to 1600 IU was based on the Nordic Nutrition Recommendations (25).

The vitamin D supplement in the present study contributed 38% of the upper limit intake level (see also [8, 23]).

Measures

Before and after the intervention, the participants were exposed to an experimental stress procedure. The pre-intervention test procedure was carried out between November 16, 2017 and December 29, 2017. The post-intervention test procedure was carried out between April 2, 2018 and May 22, 2018. Thus, the participants were tested while they were still taking the supplements.

To investigate the effects of vitamin D supplementation on planning and problem-solving abilities during stress, the ToL task was used (14). The ToL task used was a computerized version programmed in the E-prime system (Psychology Software Tools, Pittsburgh, PA). All participants received standardized instructions about the task, including a directive to respond as quickly and accurately as possible. The task consisted of five different

problem-solving conditions with 10 trials in each condition. The order of presentation was randomized. For each trial, a picture of the *starting* and final *target* configuration was presented on the computer screen. Our ToL task configuration consisted of three colored balls (red, yellow, and blue) positioned in three pockets. The left pocket could contain a maximum of three balls, the middle pocket could contain maximum of two balls, and the last pocket could contain only one ball. Participants were instructed to imagine how many moves, according to set rules, would be necessary to transform the *starting configuration* into the *target configuration* and then to press the corresponding key (1, 2, 3, 4, or 5) on the keyboard. Thus, this task required visualization in the mind of the number of necessary moves before entering the solution. Accuracy data, defined as the number of correct responses to problems requiring a set number of moves, were recorded by the computer (see also [19]).

For statistical analysis, a sum score of correct responses of the 1–5 move problems was made. In addition, sum scores were made for the easier 1–2 move problems and the more difficult 3–5 move problems. This categorization of easy vs more difficult move problems was based on previous findings (19, 26). Also planning time (in milliseconds) before correct responses was registered by the computer. Planning time in the current study is defined as the time from the picture of the starting and target configuration entering the screen (i.e., onset of the stimulus) to when a response was given. Thus, planning time in this version of the task was from the onset of the stimulus until a key was pressed. Planning time data were log transformed.

During the task, participants were exposed to aversive noise through headphones. The noise varied in intensity and frequency. The noise was an excerpt of mass spectrometry data of a fillet of salmon. This was further converted to a WAV file using the function ‘audiowrite’ in MATLAB (The MathWorks, Natick, MA, USA) (8). Presentation of aversive noise is a common stress procedure used in laboratory studies to elicit psychophysiological stress responses (16). Results from Hansen et al. (8) validate the stress-inducing characteristic of the procedure. For ethical reasons, participants were allowed to select a noise level between 80 and 100dB, such that the noise was experienced as ‘annoying, but not painful’ (see also [8]).

Statistics

To investigate the effects of vitamin D supplementation on problem-solving and planning abilities during stress, repeated-measures analysis was used. Vitamin D group and Control group were treated as independent variables. Performance on the ToL, both the number of correct responses and the planning time, was treated as dependent variables. For the number of correct responses, a

total sum score for the 1–5 move problems was calculated. In addition, a sum score for the easier 1–2 move problems was calculated, together with a sum score for the more difficult 3–5 move problems. This procedure was based on previous investigation, showing a significant drop in correct performance from the third move problem, indicating that there is a difference in difficulty between the second and third move problem (26). Furthermore, we looked at the overall planning time for the 1–5 move problems, as well as planning time for the easier and the more difficult move problems.

Significant interactions were followed-up by Fishers LSD-test. Because of our specific expectations based on previous research (8, 13), non-significant interactions were followed-up by Bonferroni corrections (27, 28). Cohen’s *d* was calculated for significant differences to test the effect sizes (29).

IQ has been shown to impact performance on the ToL task (30), and executive functioning is sensitive to aging (31). In the present study, IQ ranged from 72 to 130 in the Control group and from 72 to 124 in the Vitamin D group. The age range was 32–81 for the Control group, and it was 31–79 for the Vitamin D group. Consequently, we conducted our analyses controlling for age and IQ.

Results

Descriptive statistics

Means and standard deviations for sample characteristics such as age, IQ as well as vitamin D status (nmol/L) for both groups pre- and post-test have been reported before (8). However, Table 1 shows means and standard deviations for the *current* sample (N = 77).

There was no significant relationship between the two covariates age and IQ, $r = 0.045$, $P = 0.689$.

Means and standard deviations for all the dependent variables are presented in Table 2.

Number of correct responses on Tower of London

For the total sum score of correct responses on the ToL, the repeated measures analyses showed no main effect of group, $F(1,75) = 1.840$, $P = 0.179$, $\eta^2 = 0.02$. However, there was a main effect of the intervention period (i.e., from pre- to post-test for the whole sample), $F(1,75) = 4.358$, $P = 0.040$, $\eta^2 = 0.055$. Follow-up tests revealed that for the whole sample pooled together, there was a significant increase in total number of correct responses from pre- to post-test ($P = 0.038$, $d = 0.14$). Moreover, there was a marginal interaction effect between the pre- and post-test conditions and groups, $F(1,75) = 3.919$, $P = 0.051$, $\eta^2 = 0.050$. Follow-up with Bonferroni test, the results revealed the Vitamin D group had a significant increase in correct responses from pre- to post-test ($P = 0.030$, $d = 0.30$).

Table 2. The means and standard deviations for all the dependent variables: number of correct responses on Tower of London such as total number of correct responses (sum of 1–5 move problems), correct responses to easy sub-tasks (sum of 1–2 move problems), correct responses to difficult sub-tasks (sum of 3–5 move problems), and total planning time (in milliseconds) for the different categories of correct responses

Groups	Dependent variables (Tower of London)	Pre-test	Post-test
<i>Number of correct responses</i>			
Control (N = 38)	Total score (1–5)	33.21(12.05)	33.29(12.02)
	Easy tasks (1–2)	15.55(5.53)	15.55(4.86)**
	Difficult tasks (3–5)	17.66(7.27)	17.74(7.64)
Vitamin D (N = 39)	Total score (1–5)	35.00(10.53)	37.97(8.98)*
	Easy tasks (1–2)	15.82(4.32)	17.56(2.68)**
	Difficult tasks (3–5)	19.18(6.75)	20.41(6.47)
<i>Planning time to correct responses</i>			
Control (N = 38)	Total score (1–5)	14.61(0.32)	14.44(0.28)
	Easy tasks (1–2)	13.66(0.36)	13.53(0.30)
	Difficult tasks (3–5)	14.12(0.30)	13.91(0.31)*
Vitamin D (N = 39)	Total score (1–5)	14.64(0.26)	14.51(0.32)
	Easy tasks (1–2)	13.76(0.28)	13.61(0.35)
	Difficult tasks (3–5)	14.10(0.27)	13.99(0.32)*

* $P < 0.05$ within group differences on the pre- versus post-test.

** $P < 0.05$ between group differences on the post-test. Planning time data were log transformed.

This was not true for the Control group ($P = 1.000$, $d = 0.007$). See Table 2.

Analyses of the easier 1–2 move problems revealed no effects of groups, $F(1,75) = 1.403$, $P = 0.240$, $\eta^2 = 0.018$, but again, there was an effect of the intervention period, $F(1,75) = 6.928$, $P = 0.010$, $\eta^2 = 0.085$. Follow-up tests showed there was a significantly higher rate of correct responses on post-compared to pre-test ($P = 0.009$, $d = 0.20$). There was also a significant interaction between the intervention period and groups, $F(1,75) = 6.928$, $P = 0.010$, $\eta^2 = 0.085$. Follow-up tests showed the Vitamin D group had improved performance from pre- to post-test ($P < 0.001$, $d = 0.48$). No changes were observed from pre- to post-test for the Control group ($P = 0.793$, $d = 0.0$). The results further revealed a marginal difference between the groups at post-test ($P = 0.051$, $d = 0.51$), where the Vitamin D group had more correct responses than the Control group (Table 2).

For the more difficult 3–5 move problems, no statistically significant effects of vitamin D supplementations were found. However, looking at the sum scores for the 3–5 move problems, the Vitamin D group showed a slight increase in correct responses from pre- to post-test, with a small effect size ($d = 0.19$). The effect size from pre- to post-test for the Control group was $d = 0.01$. In addition, at post-test, the Vitamin D group's performance was slightly better than the Control group's performance on these difficult sub-tasks (i.e., $d = 0.38$) (Table 2).

Planning time to correct responses

The results revealed no effects of groups looking at the overall planning time for correct responses to the

ToL, $F(1,75) = 0.6$, $P = 0.443$, $\eta^2 = 0.008$. However, there was a significant effect of the intervention period, $F(1,75) = 39.7$, $P < 0.001$, $\eta^2 = 0.346$. Thus, the planning time decreased significantly from pre- to post-test ($P < 0.001$, $d = 0.51$) looking at the whole sample pooled together. There was no significant interaction between the intervention period and groups, $F(1,75) = 0.7$, $P = 0.415$, $\eta^2 = 0.008$. Follow-up with Bonferroni revealed that both the Control and the Vitamin D groups had significant faster planning times at post-compared to pre-test ($P < 0.001$, $d = 0.57$ and $P = 0.001$, $d = 0.45$, respectively) (Table 2).

Planning time to the easier 1–2 move problems showed no effect of groups, $F(1,75) = 1.5$, $P = 0.222$, $\eta^2 = 0.020$, but there was a significant effect of the intervention period, $F(1,75) = 21.4$, $P < 0.001$, $\eta^2 = 0.222$, showing an overall decrease in planning time from pre- to post-test ($P < 0.001$, $d = 0.44$). There was no significant interaction between the intervention period and groups, $F(1,75) = 0.1$, $P = 0.725$, $\eta^2 = 0.002$. In a follow-up of this non-significant interaction, the Bonferroni showed both the Control and the Vitamin D groups had a significant decrease in planning time from pre- to post-test ($P = 0.022$, $d = 0.39$ and $P = 0.004$, $d = 0.47$, respectively) (Table 2).

Looking at planning time for the more difficult 3–5 move problems, there was no effect of groups, $F(1,75) = 0.2$, $P = 0.659$, $\eta^2 = 0.003$. However, there was a significant main effect of the intervention period, $F(1,75) = 39.1$, $P < 0.001$, $\eta^2 = 0.343$. Again, for the whole sample pooled together, there was a significant decrease in planning time from pre- to post-test ($P < 0.001$, $d = 0.53$). There was no significant interaction effects between the intervention

period and groups, $F(1,75) = 3.1$, $P < 0.084$, $\eta^2 = 0.039$. However, the Bonferroni showed both the Control and the Vitamin D groups had a significant decrease in planning time from pre- to post-test ($p = 0.001$, $d = 0.69$ and $P = 0.012$, $d = 0.37$, respectively) (Table 2).

Number of correct responses controlling for age and IQ

For the total number (1–5) of correct responses on the ToL, controlling for age and IQ, the results revealed a significant effect of age, $F(1,73) = 13.482$, $P < 0.001$, $\eta^2 = 0.156$, and IQ, $F(1,73) = 44.20$, $P < 0.001$, $\eta^2 = 0.377$. Controlling for age and IQ, the results also showed a significant interaction effect between the intervention period and groups, $F(1,73) = 4.099$, $P = 0.047$, $\eta^2 = 0.053$. Follow-up tests revealed the Vitamin D group had a significant increase in total number of correct responses from pre- to post-test ($P = 0.005$). At post-test, there was also a significant difference between the groups as the Vitamin D group had significantly more correct responses than the Control group ($P = 0.019$). No changes in number of correct responses were found for the Control group ($P = 0.940$) (Table 3).

Moreover, looking at number of correct responses to the easier 1–2 move problems, there was a main effect

of age, $F(1,73) = 8.413$, $P = 0.005$, $\eta^2 = 0.103$, and IQ, $F(1,73) = 27.699$, $P < 0.001$, $\eta^2 = 0.275$. There was also a significant interaction between the intervention period and IQ, $F(1,73) = 4.70$, $P = 0.033$, $\eta^2 = 0.061$. Controlling for age and IQ, the results again revealed a significant interaction between the intervention period and groups, $F(1,73) = 7.682$, $P = 0.007$, $\eta^2 = 0.095$. Follow-up tests showed the Vitamin D group improved significantly from pre- to post-test ($P < 0.001$). At post-test, the Vitamin D group also showed more correct responses compared to the Control group ($P = 0.022$). The Control group showed no changes from pre- to post-test ($P = 1.00$). See Fig. 2.

Controlling for age and IQ, the results revealed for the difficult 3–5 move problems a main effect of age, $F(1,73) = 14.702$, $P < 0.001$, $\eta^2 = 0.168$, and IQ, $F(1,73) = 48.10$, $P < 0.001$, $\eta^2 = 0.397$. Thus, both age and IQ had large effects, but IQ explained most of the variance with regard to correct responses on the most difficult move problems. No other significant results were found.

Planning time to correct responses controlling for age and IQ

Controlling for age and IQ, there was a significant effect of age looking at overall/total planning time for all the sub-tasks pooled together, $F(1,73) = 19.07$, $P < 0.001$,

Table 3. Estimated means (M), standard errors (SE), and confidence intervals (CI) for dependent variables, i.e. number of correct responses and planning time (in milliseconds) to correct responses, controlling for age and IQ

Groups	Dependent variables (Tower of London)	Pre-test		Post-test			
		M(SE)	95% CI		M(SE)	95% CI	
			Lower	Upper		Lower	Upper
<i>Number of correct responses</i>							
Control (N = 38)							
	Total score (1–5)	33.55(1.41)	30.73	36.37	33.59(1.38)	30.84	36.34**
	Easy tasks (1–2)	15.68(0.68)	14.33	17.03	15.65(0.55)	14.56	16.74
	Difficult tasks (3–5)	17.87(0.87)	16.13	19.61	17.94(0.91)	16.13	19.76
Vitamin D (N = 39)							
	Total score (1–5)	34.67(1.40)	31.88	37.45	37.68(1.36)	34.96	40.40*:**
	Easy tasks (1–2)	15.70(0.67)	14.36	17.02	17.47(0.54)	16.39	18.55
	Difficult tasks (3–5)	18.97(0.86)	17.25	20.69	20.21(0.90)	18.42	22.00
<i>Planning time to correct responses</i>							
Control (N = 38)							
	Total score (1–5)	14.61(0.04)	14.52	14.69	14.44(0.04)	14.35	14.52
	Easy tasks (1–2)	13.66(0.04)	13.56	13.76	13.53(0.05)	13.44	13.62**
	Difficult tasks (3–5)	14.12(0.04)	14.03	14.20	13.91(0.05)	13.81	14.01
Vitamin D (N = 39)							
	Total score (1–5)	14.65(0.04)	14.56	14.73	14.52(0.04)	14.43	14.60
	Easy tasks (1–2)	13.76(0.05)	13.67	13.86	13.61(0.04)	13.52	13.70*:**
	Difficult tasks (3–5)	14.11(0.04)	14.02	14.19	13.99(0.04)	13.90	14.09

* $P < 0.05$ within group differences on the pre- versus post-test.

** $P < 0.05$ between group differences on the post-test. Planning time data were log transformed.

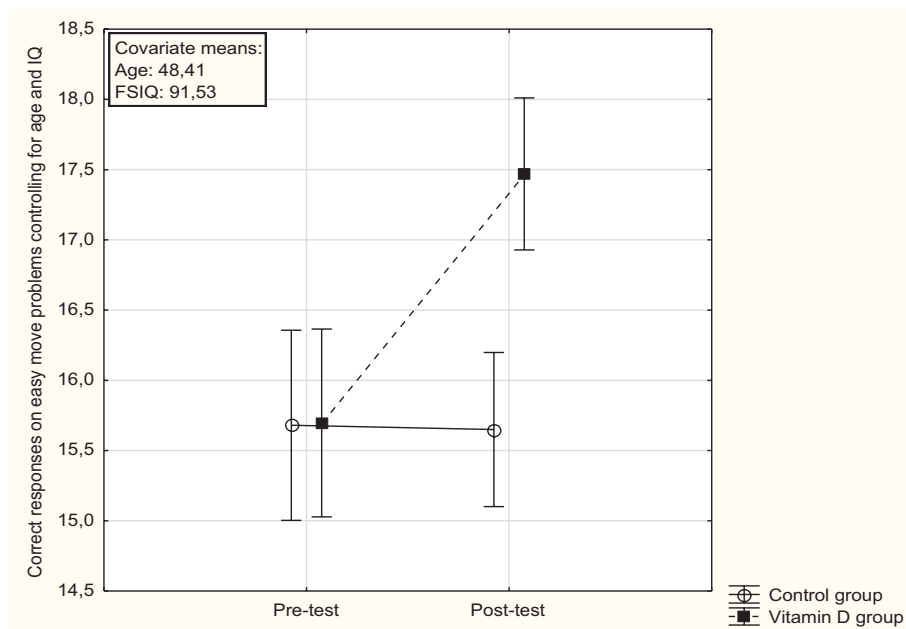


Fig. 2 Number of correct responses (estimated means) to easy move problems (1–2) on the Tower of London task controlling for age and IQ. Vertical bars denote \pm standard errors.

$\eta^2 = 0.207$. No significant effect of IQ was found, $F(1,73) = 1.53$, $P = 0.220$, $\eta^2 = 0.021$. A significant effect of the intervention period, $F(1,73) = 19.07$, $P < 0.001$, $\eta^2 = 0.073$, showing that, overall, there was a significant decrease in planning time from pre- to post-test ($P < 0.001$) was found. Controlling for age and IQ, there was no significant interaction effect between the intervention period and groups; in a follow-up test with Bonferroni correction, the results revealed both the Control and the Vitamin D groups had a significant decrease in planning time to correct responses ($P < 0.001$ and $P = 0.001$, respectively).

There was a significant effect of age looking at planning time to the easier tasks (1–2), $F(1,73) = 20.76$, $P < 0.001$, $\eta^2 = 0.221$, but no effect of IQ was found, $F(1,73) = 3.24$, $P < 0.076$, $\eta^2 = 0.042$. Controlling for age and IQ, there was also a significant effect of the intervention period, $F(1,73) = 5.487$, $P < 0.022$, $\eta^2 = 0.070$, and there was an overall decrease in planning time from pre- to post-test ($P < 0.001$). There was no significant interaction effect between the intervention period and groups, $F(1,73) = 0.103$, $P = 0.749$, $\eta^2 = 0.001$. Follow-up tests with Bonferroni correction revealed both the Control and the Vitamin D groups had a significant decrease in planning time from pre- to post-test ($P = 0.019$ and $P = 0.003$, respectively).

Controlling for age and IQ, there was a significant effect of age looking at planning time to the more difficult 3–5 move problems, $F(1,73) = 15.08$, $P < 0.001$, $\eta^2 = 0.171$. There was no effect of IQ, $F(1,73) = 0.404$, $P = 0.527$, $\eta^2 = 0.006$. The interaction between the intervention period and groups was not significant, $F(1,73) = 2.928$, $P = 0.091$,

$\eta^2 = 0.039$. Follow-up of this non-significant interaction with Bonferroni correction revealed both groups had a significantly faster planning time at post-test compared to pre-test ($P < 0.001$ for the Control group and $P = 0.012$ for the Vitamin D group) (Table 3).

Discussion

The results from this study showed that vitamin D supplementation improved performance on the easier, but not the more demanding, problem-solving and planning tasks during stress. This was also true when we controlled for age and IQ. For the more demanding problem-solving tasks, there were effects of both age and IQ, but IQ explained most of the variance for accuracy, and age seemed to explain most of the variance for planning time.

Looking at the overall sum score of correct responses on the ToL, the results revealed a positive effect of vitamin D supplementation. These results correspond with a study conducted by van den Eynde et al. (15) who found that 12 weeks of treatment with quetiapine (an antipsychotics medication) increased the total number of correct responses on the ToL. But our study also expanded on that study in several ways. First, we distinguished between easy and difficult move-problems or sub-tasks. Second, we included a Control group for comparison purposes. van den Eynde et al. (15) did not include a Control group, and the improved performance can also reflect a learning effect. Results from pre-post-tests should be interpreted with caution without a control group. Third, we investigated performance on ToL during stress. Fourth, we investigated the effects of vitamin D supplementation,

without side effects, rather than a medical drug. Quetiapine that was investigated in the study conducted by van den Eynde et al. is associated with side effects, such as sleepiness, headache, and increased weight, and the medication is not suitable for people with other underlying diseases (e.g., heart conditions or blood vessel diseases) (see [32] for more information). Importantly, regular medicinal use has also been associated with shorter life-expectancy (33). Thus, there is an urgent need for development and identification of resilience enhancing strategies without side effects that are safe to use for people with different conditions.

A closer look at the accuracy performance of the easy tasks during stress showed the Vitamin D group improved significantly from pre- to post-test. At post-test, the Vitamin D group also had significantly better performance than the Control group. The improved performance observed in the Vitamin D group is also interesting due to the long test–retest period of more than three months. The test–retest reliability of the ToL has been debated (e.g., [34]), but studies have also found that the reliability of the test is adequate (e.g., [35]). Due to the variety of ToL task versions across different studies, reported findings should always be interpreted with caution. This RCT study is interesting in this regard, adding new insights to understanding effects of vitamin D on dealing with stress. The improved performance in the Vitamin D group appears attributable to the elevated vitamin D status (see Table 1), as the Control group did not change their number of correct responses pre- to post-test.

Another interesting finding in this study is that the improved number of correct responses in the Vitamin D group was not related to a speed-accuracy trade-off effect (i.e., participants in the Vitamin D group showed fast responses with high accuracy). Both groups showed a significant *decrease* in planning time from pre- to post-test, but the Control group did not improve in accuracy. Thus, vitamin D seems to be important for processing of information. It should be mentioned that other studies have found a relationship between vitamin D and myelination – which is important for effective communications between nerve cells (36). In this regard, it should also be mentioned that relationship between slower information processing speed and low content of vitamin D has also been found (37). Controlling for age and IQ, the results reveal that both age and IQ explained some of the variance, but vitamin D still improved accuracy on the easy problems relative to Controls (Fig. 2). Importantly, the different move problems (1– 5) were presented in a randomized order to prevent possible expectations related to task difficulties and fatigue during presentation of the most difficult move-problems.

This study supports and expands the results from Hansen et al. (8). As the participants were exposed to

acute stress during task performance, physiological stress responses increased (see [8]). This study clearly demonstrated that vitamin D supplementation influenced the participant’s problem-solving and planning abilities during stress. This improved resilience observed in the Vitamin D group might be due to the greater physiological variability compared to the Control group (6). Higher resting HRV has been associated with generally good health, flexibility, and resilience, as well as improved executive functioning (9, 10, 38, 39). As increased HR is caused by noradrenaline and adrenaline, and HRV is mediated by acetylcholine (40), a question for future research is to investigate whether vitamin D affects HR and HRV directly or indirectly through these neurotransmitters.

An interesting question in this regard is whether the effects of vitamin D supplementation on stress are comparable to the effects of physical activity, another resilience enhancing strategy (41). Acute stress and physical activity elicit similar physiological responses such as increased sympathetic and hypothalamic-pituitary adrenal activity, as well as decreased parasympathetic activity. Over time, however, regular physical activity results in physiological adaptations, such as decreased sympathetic activity and increased parasympathetic activity, resulting in lower HR and higher HRV (42, 11). Some studies investigating the acute physiological effects of physical activity have shown that regular physical activity over time not only attenuates physiological responses to psychological stress but also influences physiological resting *recovery* (see [11] for an overview) as the vitamin D supplementation did in Hansen et al. (8). Thus, the question is whether the Vitamin D group showed better performance on ToL during stress because vitamin D supplementation is a buffer for stress, like physical activity has been shown to be (42, 11). It should be noted that we also found a relationship between vitamin D status and physical activity in Hansen et al. (23). Another interesting question for future research will be to find out whether there is a direct relationship between vitamin D and improved stress resilience, or whether the positive effect of vitamin D on stress resilience is caused by positive repercussions of vitamin D (e.g., increased physical activity).

Vitamin D supplementation did not benefit the more difficult problem-solving and planning abilities during stress. To our knowledge, the effects of vitamin D supplementation on performance of ToL during stress/noise in inpatients with stress-related disorders have not been investigated before. Alimohammadi et al. (18) studied the effects of noise on ToL in workers from the industry and found that noise significantly increased the number of errors. However, they did not distinguish between easy and difficult move problems. The more demanding subtasks on the ToL (e.g., 3–5) (26) put higher demands on executive functioning such as working memory (12).

Importantly, the ToL task used in the current study asks the participants to *imagine* how many moves would be necessary to match the target configuration. No moves were actually performed – the cognitive operation must be completed in the participant's mind before a response is given. Thus, the present results might be explained in terms of Baddeley's model of working memory.

Successful performance of the ToL task required the participant to make use of a 'visuo-spatial sketchpad' (VSSP) to *hold* and *manipulate* visual information (43, 44). The participant had to imagine or construct mental images of *each move* and *hold each move in mind while planning the next move*. For more difficult move tasks, the participant had to hold many elements in mind simultaneously while planning the next step. The VSSP is one of two slave systems coordinated by the central executive, which provides attentional control of the working memory. The other slave system is the phonological loop, which manages auditory/speech-based information. Both slave systems have limited capacity. Research has shown that due to this limited capacity, both systems are very vulnerable to distraction, as attention can be captured by irrelevant stimuli, such as sounds. The current results align with investigations, studying the effects of distracting sound on cognitive functions and concentration in real work-type settings. Within this field, numerous studies have demonstrated that, even in healthy participants, distracting sounds or noise can influence cognitive performance. This is particularly pertinent for short-term and working memory storage functions because the changing nature of acoustic signals draws our attention (e.g. [45, 46]). These findings provide reason to believe that the nature of the acoustic stressor used in this study makes it extremely difficult to improve performance on the more demanding ToL move problems. Controlling for age and IQ, the current results show that age accounted for some of the variance, but most of the performance accuracy variance for the difficult move problems was accounted for by IQ.

There was no effect of vitamin D supplementation on the planning time to the difficult move problems. Again, both groups had significantly faster planning times on post-test compared to pre-test. This faster planning time on post-test might be due to a learning effect of the first exposure to the task (pre-test). Another explanation might be the distracting sound, and the participants increased their speed to finish the task. Thus, the faster planning time for both groups combined with the fact that there was no significant increase in correct responses on these sub-tasks for any of the groups may point to a speed-accuracy trade-off for the difficult move-problems (i.e., fast responses with low accuracy). It should be mentioned that the Vitamin D group had a slight, but not significant, increase in correct responses on the more demanding

sub-tasks ($d = 0.19$). In addition, the Vitamin D group also showed higher number of correct responses, but still not significant, compared to the Control group at post-test ($d = 0.38$). However, controlling for age and IQ, the results showed that age seemed to explain most of the variance with regard to speed.

Overall, these results correspond with other studies, showing that executive functioning is related to both IQ and age (30, 31), but the study in its whole adds to the literature that vitamin D supplementation can improve performance on easy problem-solving tasks during stress, but not difficult tasks with high working memory load. The present study may also add something to animal models investigating the effects of adult vitamin D deficiency in relation to hippocampal-dependent learning and memory formation (e.g., 47). Regardless of the reliability of the ToL task (cf. [34]), the present results show that vitamin D can reduce the effect of stress on easy cognitive tasks. If the improved performance observed in the Vitamin D group is due to a learning effect, the Control group with a classic nadir in vitamin D during spring failed to learn from the pre-test, even on easy tasks.

Strengths and limitations

One may question the ecological validity of the present study, as resilience to stress was investigated using a contrived experimental task in a highly secure treatment facility. Many cognitive laboratory experimental studies have been criticized for having low ecological validity (48). However, the present results appear to align with the results of studies investigating the effect of irrelevant sound on cognitive performance in real office landscapes (45, 46). Future studies should investigate the effects of other stressors such as heat or threat. Investigations of other types of stressors might expand the current results, but noise seems to be a common, intrusive stressor with regard to taxing executive functioning during task performance (45, 46). Since distracting sound automatically interferes with concentration, it may not be possible to improve performance on tasks with high working memory load during exposure to noise. Another concern is the fact that many versions of the ToL task exist, making it difficult to compare results with other studies using a ToL task to assess executive functioning. Thus, comparison of the present results with other studies should be done with caution. Moreover, a recent systematic review of RCT's investigating the effects of vitamin D on cognition revealed mixed results. Beauchet et al. (49) suggest this could be due to methodological factors, such as sample population characteristics (e.g., number of participants and ethnicity) and the use of different cognitive tests.

Despite the limitations, the present RCT has important strengths to acknowledge. These include high compliance

(8, 23), the homogeneity of the sample (i.e., male inpatient with stress-related mental health disorders from the same institution), and the use of a computerized version of the ToL task to measure executive functioning. We also distinguished between easy and difficult move problems. Unfortunately, it was not possible to achieve the sample size required based on the power calculation (50 participants in each group). However, we included as many as we could, and this study was carried out under unusually controlled conditions. A particularly important strength with this study was that all participants were on the same diet before, during, and after the testing procedures. In food or supplement intervention studies, it is usually very difficult, or often impossible, to control what people are eating during the intervention period. Since all participants in this study were from the same institution, we know that their habitual diet was low in fatty fish – one of the main food sources of vitamin D. This knowledge together with the timing of this study (carried out during winter) makes our study unique.

Conclusion

This study showed that vitamin D supplementation throughout the winter improved problem-solving and planning abilities in participants with stress-related disorders when exposed to stressful circumstances, but the improvement was limited to accuracy performance of easier tasks. Controlling for age and IQ, the same pattern of result was found for the easy tasks. For the more difficult move problems, both age and IQ seemed to be of importance for accuracy, but IQ explained more of the variance than age. For planning time, age seemed to explain most of the variance. As stress, in general, both early stress (e.g., childhood trauma) and everyday life stress (acute or chronic), is related to negative psychological (e.g., impairment in cognitive functioning and mental health problems) and physical (e.g., cardiovascular diseases and dysregulation of the immune system) health outcomes (50, 41, 17, 51), there is a need for effective resilience enhancing strategies. This study helps to add knowledge, but more investigation of the effects of vitamin D status on mechanisms of stress resilience is needed.

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Conflict of interest and funding

The authors declare no potential conflicts of interest. Pharma Nord provided the placebo and vitamin D pearls, but Pharma Nord had no role in the design of the study;

in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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