No improvement of sleep from vitamin D supplementation: insights from a randomized controlled trial

A.U. Larsen a,*, L.A. Hopstock b, R. Jorde a, G. Grimnes a, c

a Department of Clinical Medicine, UiT The Arctic University of Norway, Tromsø, Norway
b Department of Community Medicine, UiT The Arctic University of Norway, Tromsø, Norway
c Division of Internal Medicine, University Hospital of North Norway, Tromsø, Norway

A R T I C L E  I N F O

Article history:
Received 16 June 2021
Received in revised form 11 October 2021
Accepted 13 October 2021
Available online 19 October 2021

Keywords:
Sleep duration
Excessive daytime sleepiness
Insomnia
Vitamin D
RCT

A B S T R A C T

Background: Vitamin D has been linked to sleep health in observational studies. Data from randomized controlled trials (RCTs) with vitamin D is scarce.

Methods: This study presents the results of a secondary analysis of 189 vitamin D insufficient participants (47.1% women) in a previously performed RCT, of which 92 were randomized to vitamin D (100,000 IU (2500 μg) as a bolus dose followed by 20,000 IU (500 μg) per week), and 97 to placebo. At baseline and after 4 months at the end of the study serum 25-hydroxyvitamin D (s-25(OH)D) was measured, and the study questionnaire assessing sleep duration, daytime sleepiness, and symptoms of insomnia, was completed.

Results: At baseline, mean s-25(OH)D was 35.0 ± 11.8 and 35.5 ± 13.3 nmol/L in the vitamin D and placebo groups, respectively. After four months, we found no statistically significant differences between the intervention groups in any of the assessed sleep outcomes, neither when stratified by sex, nor when performed in subgroups based on baseline or end of study s-25(OH)D level or presence of sleep complaints at baseline.

Conclusions: We were not able to demonstrate a significant effect of vitamin D supplementation on sleep in this vitamin D insufficient population.

© 2021 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Sleep is a universal, recurring, and reversible physiological state with restorative and transformative effects, promoting optimal health and well-being [1]. Growing evidence suggest that sleep habits are important, modifiable risk factors for non-communicable diseases [2] which may significantly impact quality of life and overall health status. Specifically, poor sleep health has been associated with metabolic [3], endocrine [4] and psychiatric [5] diseases, as well as all-cause mortality [6]. Combined with high treatment-related costs from increased health care utilization [7], it is therefore concerning that the prevalence of sleep disorders has become epidemic [8].

A growing literature suggest a role of vitamin D in maintaining optimal sleep [9–11], in addition to its well-established role in the preservation of calcium and phosphorus homeostasis [12]. Expression of key enzymes required for vitamin D metabolism, activation and degradation have been demonstrated in brain cells, suggesting local production and regulation of vitamin D for auto- and/or paracrine purposes [13,14]. In particular, this involves the 25-hydroxylases responsible for the conversion of vitamin D to its main circulating metabolite 25-hydroxyvitamin D (25(OH)D), the 1α-hydroxylase responsible for the activating step forming the vitamin D hormone 1,25-dihydroxyvitamin D (1,25(OH)2D), capable of binding the vitamin D receptor (VDR), and the 24-hydroxylase necessary in the first step of inactivation and degradation of vitamin D. Notably, the expression of these enzymes was found to be strongest in the hypothalamus and substantia nigra, areas known to be involved in sleep regulation in humans [13]. Thus, as a fat-soluble, steroid hormone, capable of crossing the blood brain barrier [15], it is plausible that vitamin D could exert

Abbreviations: RCT, randomized controlled trial; s-25(OH)D, serum 25-hydroxyvitamin D; ISD, inadequate sleep duration; ESS, epworth sleepiness scale; EDS, excessive daytime sleepiness; s-Ca, serum calcium; p-PTH, plasma parathyroid hormone; BMI, body mass index; BDI-II, beck depression inventory II.

* Corresponding author. Department of Clinical Medicine, UiT The Arctic University of Norway, 9037 Tromsø, Norway.
E-mail address: anette.uhlving@post.uit.no (A.U. Larsen).
direct effects on brain cells in areas of the brain and brainstem involved in the initiation, maintenance, and timing of sleep through binding of the VDR expressed in these areas [13]. Although not yet fully elucidated, several actions of vitamin D potentially involved in the regulatory mechanism of sleep have been proposed. Experimental studies have indicated that vitamin D might be involved in the regulation of central circadian clock genes [13,16,17], as well as in the transduction of light signals that regulate circadian rhythms [18]. Moreover, vitamin D has been suggested to play a pivotal role in the synthesis of the sleep hormone melatonin [16,11] by regulating the expression of the tryptophan hydroxylase (TPH)-2 [19]. TPH-2 converts tryptophan to 5-hydroxytryptophan, which is further metabolized to serotonin, serving as a main substrate for melatonin synthesis [20]. An emerging literature also highlights an interaction between vitamin D, sleep, and pain [21,22]. Interestingly, in a recent study among U.S. veterans with chronic pain, vitamin D supplementation relieved both pain symptoms and improved sleep [23]. Whether vitamin D represents an indirect role for improved sleep by alleviating pain symptoms or share interrelated pathways in the regulatory mechanisms of both sleep and pain, is currently unknown.

Several observational studies have reported an association between vitamin D deficiency and poor sleep health, including increased risk of short sleep duration [24–26], daytime sleepiness [27,28] and poor sleep quality [29,30]. Nevertheless, a causal link has been difficult to demonstrate, as results from randomized controlled trials (RCTs) are scarce. Previous supplementation trials have shown contrasting results, as some have reported positive effects of vitamin D on both sleep duration and sleep quality [23,31], whereas others have reported deteriorated sleep quality and increased need of sleep medications [32].

In 2015–2016, a large number of individuals with low serum 25(OH)D (s-25(OH)D) living in the municipality of Tromsø, Northern Norway, were invited to participate in an RCT with vitamin D versus placebo. The primary aim of the study was to investigate the effect of vitamin D supplementation on cardiovascular risk factors. A sleep questionnaire was implemented to provide the opportunity to also study the effect of vitamin D supplementation on sleep. Our hypothesis was that supplementation with vitamin D would increase or normalize sleep duration, reduce daytime sleepiness, and increase recovery from inadequate sleep duration (ISD), excessive daytime sleepiness (EDS) and insomnia.

2. Material and methods

2.1. Population and study design

A detailed description of the study design and results of the main vitamin D intervention study (D-COR) have been published elsewhere [33]. In summary, participants were recruited from the seventh survey of the Tromsø Study (Tromsø7 2015–16), a population-based health study conducted in the municipality of Tromsø, Northern Norway [34]. In Tromsø7, all inhabitants aged 40 years and above (n = 32,591) were invited to participate, of which 21,083 men and women aged 40–99 years attended (65% participation). Measurements of height and weight were performed with participants and study personnel were blinded throughout the study. The sleep questionnaire was implemented as part of the first and third visit, about half-way into the inclusion in the main study (from mid-April 2016), with the aim to investigate the effect of vitamin D supplementation on sleep duration and daytime sleepiness, as well as the risk of ISD, EDS and insomnia. In total, 189 participants (92 given vitamin D and 97 given placebo) had both baseline and end of study values for at least one sleep outcome and were included in the present analysis. A flow diagram of the participant inclusion is presented in Fig. 1.

2.2. Measurements

2.2.1. Serum analyses and anthropometric measurements

A detailed description of measurements is published previously [33]. In short, non-fasting serum samples were collected, and measurement of s-25(OH)D (nmol/L) was performed using an in-house liquid chromatography with a tandem mass spectrometry (LC-MS/MS) method detecting both s-25(OH)D1 and s-25(OH)D2 - the sum of which is presented as s-25(OH)D in the results. The LC-MS/MS analysis was accredited by the Norwegian Accreditation Authority, and the laboratory participates in an international quality surveillance programme, namely the vitamin D external quality assurance scheme (DEQAS), to ensure the analytical reliability of the s-25(OH)D assays. Analyses of serum Calcium (s-Ca) (mmol/L) were done using the Hitachi 917 (Roche Diagnostics), with reagents from Boehringer-Mannheim. Plasma parathyroid hormone (p-PTH) (pmol/L) was measured using an Immulite 2000 Intact PTH analyzer (Siemens Healthcare Diagnostics). Measurements of height and weight were performed with participants wearing light clothing without shoes, and body mass index (BMI) was calculated as weight in kilograms (kg) divided by height in meters squared (m²). All measurements were performed by trained technicians.

2.2.2. Sleep measures and covariates

The study sleep questionnaire (Supplemental Fig. 1) was a modified version of the sleep questionnaire used in Tromsø7, which has been described in detail elsewhere [35]. In short, the present questionnaire consisted of 18 items, including items to assess sleep duration, the Epworth Sleepiness Scale (ESS) [36] to assess daytime sleepiness, and central items from the Bergen Insomnia Scale (BIS) [37] to assess symptoms of insomnia. Information regarding shift work and sleep medication use was also registered. In the
following, a detailed description of the sleep items used in the present study is given for each sleep outcome.

To assess sleep duration, the participants were asked to select from pre-specified alternatives which best represented their habitual bedtime, rise time and sleep onset latency (SOL) (ie, the average minutes from bedtime to falling asleep). The participants were asked to report values separately for weekends and weekdays (Supplemental Fig. 1, questions 9–11), in which the latter was used for the present analyses. Sleep duration was calculated by subtracting SOL from time in bed (bedtime subtracted from rise time), and for this purpose the following coding was specified: For participants reporting rise time “before 5 am” or “after 11 am” the value was set to 5 am and 11 am, respectively; bedtime “before 8 pm” or “after 2 am” was set to 8 pm and 2 am, respectively; SOL “more than 60 min” was set to 60 min; and finally, for the SOL alternatives “30–45 min” and “45–60 min”, the median value was chosen (37.5 min and 52.5 min, respectively). Sleep duration was dichotomized into ISD (<7 h)/C21 9 h) and normal sleep duration (7–9 h), in accordance with the recommendations for adults by the National Sleep Foundation [38].

Daytime sleepiness was assessed using the ESS (Supplemental Fig. 1, question 16), which is a validated tool assessing the probability of a person to fall asleep while engaging certain daily activities expressed as the sum of eight items (ESS-score), scored from 0 (no chance of napping) to 3 (great chance of napping) [36,39]. ESS-scores were then categorized in accordance with Johns et al. [40] into normal daytime sleepiness (ESS-score ≤10) and mild (ESS-score of 11–12), moderate (ESS-score 13–15), and severe EDS (ESS score 16–24). For the present analyses, a dichotomous variable (EDS yes/no) was used, in which EDS was defined as an ESS-score of >10 in accordance with Johns et al. [40].

To assess symptoms of insomnia, we used a slightly modified version of the Bergen Insomnia Scale [37], as described in detail by Sivertsen et al. [35]. In short, the original BIS assessed sleep patterns during the last month, whereas according to the Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (DSM-5) [41] and the International Classification of Sleep Disorders, Third Edition (ICSD-3) [42] the minimum symptom duration for chronic insomnia is three months. Also, non-restorative sleep is no longer considered an obligate criterion for chronic insomnia. To accommodate these changes, our modified version of the BIS included a question concerning sleep problem duration (Supplemental Fig. 1, question 7), and the BIS item reflecting symptoms of non-restorative sleep (Supplemental Fig. 1, question 4) was disregarded. Thus, in the present study insomnia was defined as being present if the participants reported: 1) at least one of three nocturnal symptoms (prolonged sleep onset, difficulties maintaining sleep and/or early morning awakening) ≥3 nights/week (Supplemental Fig. 1, question 1–3), and 2) one or both of two daytime symptoms (daytime sleepiness/tiredness and/or dissatisfaction with sleep) ≥3 days/week (Supplemental Fig. 1, question 5–6), and 3) a duration of sleep problems for ≥3 months (Supplemental Fig. 1, question 7).

In addition, antidepressant use (including antidepressant medications, mood-stabilizing drugs, and benzodiazepines) was registered, and symptoms of mental distress were assessed using the Beck Depression Inventory II (BDI-II) [43], as described in a previous publication [44].

2.3. Statistical analyses

Statistical analyses were performed using the SPSS software version 27.0 (IBM Corp, Chicago, IL). Normal distribution was evaluated by visual inspection of histograms and Q–Q plots, in combination with evaluation of kurtosis and skewness. Spearman’s rho was used to evaluate correlations at baseline. Comparisons of baseline values between groups were performed using the Students t-test for continuous variables and the Pearson’s χ²-test for categorical variables. Although some deviations from the normality-assumption of the t-tests were observed, the results did not change with log-transformation or by running the non-parametric Mann–Whitney U-test.
Baseline and end of study values of s-25(OH)D were compared within the vitamin D and placebo groups using a paired samples t-test.

To assess changes in the categorical sleep outcomes (ISD, EDS, and insomnia), the participants changing from having the outcome of interest at baseline to not having it at the final visit were categorized as “recovered”, whereas participants having the outcome at the final visit without having it at the baseline visit were categorized as to have “developed *outcome*”. Thereafter, changes between intervention groups were tested using Fisher’s exact test, as some of the variables tested showed expected cell count less than 5.

Continuous sleep outcomes (sleep duration and ESS-score) were compared between the vitamin D and placebo groups at the end of the study using a linear regression model with the end of study value as the dependent variable, sex and intervention group as fixed factors, and age and baseline values of the sleep outcomes as covariates in accordance with recommendations by Vickers et al. [45].

As previous studies have reported sex-differences in sleep [46], all analyses were performed sex-stratified. Because an effect of vitamin D supplementation was expected to be most likely among participants reporting sleep difficulties (ie, classified with ISD, EDS, and/or insomnia at baseline), we also performed subgroup analyses in these groups. Based on recent recommendations regarding vitamin D deficiency [47], subgroup analyses were also performed according to baseline s-25(OH)D level (above or below 30 nmol/L). Finally, adverse effects on sleep health with repletion of vitamin D were reported during the intervention period [32]. Thus, to allow comparison, we performed subgroup analyses in participants according to s-25(OH)D level at the end of study (above or below 80 nmol/L).

Data are presented as means and standard deviations, unless otherwise specified. Two-sided tests were used for all comparisons, and p-values <0.05 were considered statistically significant.

Power calculations were performed for the main endpoints of the study (ie, cardiovascular risk factors), as previously described [33]. Formal power calculations were not performed for the secondary endpoints regarding sleep.

2.4. Ethics

Written informed consent was obtained from all participants. The D-COR study was approved by the Norwegian Regional Committee for Medical Research Ethics (REK NORD 2013/1464) and by the Norwegian Medicines Agency (2013-003514-40). The study is registered at ClinicalTrials.gov (NCT02750293).

3. Results

In total, 189 participants were included in the primary analysis, having both baseline and end of study values for at least one sleep outcome, as illustrated in Fig. 1. Table 1 shows the baseline characteristics for the included study participants. The 222 participants from the main study who were not included in the present analysis did not significantly differ from the included with regards to age, sex, BMI, or smoking status at baseline (data not shown) but had slightly lower mean s-25(OH)D (32.6 ± 12.2 nmol/L v. 35.2 ± 12.6 nmol/L, p = 0.03).

At baseline, there were no significant differences between the vitamin D and placebo groups (Table 1). Overall, mean age among the participants was 51.5 (range 40–79) years and mean s-25(OH)D was 35.2 (range 12–71) nmol/L. Inclusion in relation to season was similar in the two groups, with most of the participants being included during the winter half-year (Supplemental Fig. 2). There were no significant correlations between sleep duration or ESS-score and age, BMI, s-Ca, p-PTH, or s-25(OH)D at baseline, and neither the risk of ISD, EDS nor insomnia were associated with baseline s-25(OH)D (data not shown).

At the end of the study, after four months, there were no significant differences according to intervention group in sleep duration or ESS-score, nor in the recovery from ISD, EDS or insomnia, both when including all participants, and when analysing men and women separately (Tables 2 and 3).

Subgroup analyses regarding baseline and end of study s-25(OH)D levels and baseline sleep status showed no significant differences between the intervention groups neither in sleep duration, nor in ESS-scores (Supplemental Table 1). Subgroup analyses were not performed for the dichotomous outcomes (ISD, EDS and insomnia) as there were too few events across subgroups.

There was a significant increase in s-25(OH)D at the end of the study of about 51 nmol/L in the vitamin D group (p < 0.001) and a significant decrease in the placebo group of about 7 nmol/L (p < 0.001). At the end of the study, the p-PTH was significantly lower in the vitamin D group than in the placebo group (p < 0.001), whereas there was no difference in s-Ca between the intervention groups (Table 4).

4. Discussion

In the present study we report the results from a secondary analysis of 189 vitamin D insufficient participants in a previously performed RCT. At the end of the study, after four months of treatment, we found no significant effects of vitamin D supplementation on mean sleep duration or mean ESS-score, nor on the recovery from ISD, EDS or insomnia.

Our findings contrast with previous studies on the effect of vitamin D supplementation on sleep health. In a prospective case series from 2013, Huang et al. [23] reported a significant improvement in sleep after 3 months supplementation with vitamin D in 28 US veterans with chronic pain and low s-25(OH)D (<30 ng/mL or <75 nmol/L). In an RCT from 2017, Majid et al. [31] reported that 8 weeks supplementation with 50,000 IU vitamin D significantly increased sleep duration, reduced sleep latency and improved overall subjective sleep quality. However, the sample sizes of these studies were smaller compared to our study, and only one included a proper control group [31]. Nevertheless, the average sleep duration was considerably shorter compared to the present study, in which very few participants reported a sleep duration <5 h. The findings in our study also contrast with another vitamin D intervention study, in which Mason et al. [32] reported that repletion of s-25(OH)D (≥32 ng/mL or 80 nmol/L) among postmenopausal women resulted in an overall worse sleep quality, compared to those who remained insufficient. The results of the present study did not indicate deteriorating effects on sleep duration or ESS-scores, neither from vitamin D supplementation, nor from repletion of s-25(OH)D status (above 80 nmol/L).

The present study has some limitations. The primary aim of the main study was to evaluate the effect of vitamin D supplementation on cardiovascular risk factors. Thus, the inclusion criteria were based on s-25(OH)D measurements in Tromsø7, and not according to specific sleep characteristics. Moreover, the participants were all informed of their vitamin D status through the invitation to participate in the main study, which could potentially have affected their probability of reporting sleep complaints on study visits. Also, most participants were included during winter, which might negatively affect sleep [48,49] and thus could have resulted in higher prevalence of sleep complaints compared to the general population. However, the observed prevalence of sleep complaints in our study was comparable to those previously reported in the Tromsø Study [35] and the importance of seasonal differences in sleep is still a matter of debate [50]. In contrast with previous
intervention studies [23,31,32], our study did not use the Pitts-
burgh Sleep Quality Index (PSQI) [51]. It cannot be excluded that
additional information from the PSQI (eg, affiliations of night sweat
and/or pain) could have changed the results of the present study.
Also, additional medical conditions and/or use of medications
(other than sleep medications and antidepressants) with the po-
tential to affect the sleep/wake cycle were not specifically asked for,
neither was cognitive behavioral therapy or other treatments of
sleep complaints. However, there were no between-groups differ-
ences regarding the assessed covariates at baseline (as shown in
Table 1), indicating a successful randomization procedure. Thus,
potential effects of unmeasured factors were most likely accom-
modated by randomly distributing them between intervention
groups. Also, we cannot exclude that our lack of findings was due to
the choice of sleep variables. In particular, we did not have objec-
tive sleep measures to complement the subjective sleep outcome
analyses. Moreover, the study duration was relatively short.
Because the study enrolled participants with low vitamin D levels,
four months were considered long enough to demonstrate an effect
on the main study endpoints, but also short enough to ethically

### Table 1

Baseline characteristics in participants with both baseline and end of study values for at least 1 sleep outcome, by sex and intervention group.

| Characteristic          | Overall | Vitamin D (n = 92) | Placebo (n = 97) | p-value | Vitamin D (n = 45) | Placebo (n = 44) | p-value |
|-------------------------|---------|-------------------|-----------------|---------|-------------------|-----------------|---------|
| **Age, years**          |         | Mean (SD)         | Mean (SD)       |         | Mean (SD)         | Mean (SD)       |         |
| Male                    | 51.0 (9.0) | 52.0 (8.6)        | 51.2 (9.6)      | 0.475*  | 51.7 (8.4)        | 50.9 (8.4)      | 0.755*  |
| Female                  | 51.5 (47) | 54.6 (53)         | –               | 0.625*  | –                 | –               |         |
| **BMI, kg/m²**          |         | 27.5 (4.2)        | 27.7 (4.3)      | 0.723   | 27.8 (4.0)        | 27.8 (4.1)      | 0.358*  |
| Male                    | 51.0 (37) | 51.6 (35)         | 51.2 (34)       |         | 51.4 (34)         | 51.3 (34)       |         |
| Female                  | 51.5 (44) | 52.1 (44)         | –               |         | –                 | –               |         |
| **Sleep duration, hours** |         | 5.9 (0.9)        | 5.9 (0.9)       | 0.462*  | 5.9 (0.9)        | 5.8 (1.0)       | 0.488*  |
| Male                    | 6.0 (0.7) | 6.1 (0.7)         | –               |         | 6.1 (0.8)         | –               |         |
| Female                  | 5.9 (1.0) | 5.8 (1.0)         | –               |         | –                 | –               |         |
| **ESS-score**           | 5.9 (3.0) | 5.7 (2.9)         | 5.9 (3.0)       | 0.313*  | 5.9 (3.0)         | 5.9 (3.0)       | 0.215*  |
| Male                    | 6.0 (2.0) | 6.1 (2.0)         | –               |         | 6.2 (2.0)         | –               |         |
| Female                  | 5.9 (3.0) | 5.8 (3.0)         | –               |         | –                 | –               |         |
| **Insomnia, %**         |         | 56.0 (51)         | 55.2 (53)       | 0.908*  | 56.1 (51)         | 56.0 (51)       | 0.887*  |
| Male                    | 56.1 (52) | 55.2 (53)         | 56.0 (51)       |         | 56.1 (52)         | 56.0 (51)       |         |
| Female                  | 55.9 (50) | 55.2 (50)         | –               |         | –                 | –               |         |
| **BDI-II score**        | 5.9 (3.0) | 5.7 (2.9)         | 5.9 (3.0)       | 0.311   | 5.9 (3.0)         | 5.9 (3.0)       | 0.645*  |
| Male                    | 6.0 (2.0) | 6.1 (2.0)         | –               |         | 6.1 (2.0)         | –               |         |
| Female                  | 5.9 (3.0) | 5.8 (3.0)         | –               |         | –                 | –               |         |
| **Antidepressant use, %** |         | 5.5 (5)          | 7.2 (7)         | 0.629   | 5.5 (5)           | 7.2 (7)         | 0.311   |
| Male                    | 6.0 (5)  | 7.2 (7)           | –               |         | 6.0 (5)           | –               |         |
| Female                  | 5.5 (5)  | 7.2 (7)           | –               |         | –                 | –               |         |

**Abbreviations:** n = number of participants; SD = standard deviation; BMI = body mass index; s-Ca = serum calcium; p-PTH = plasma parathyroid hormone; s-25(OH)D = serum 25-hydroxyvitamin D; ISD = inadequate sleep duration; ESS = Epworth Sleepiness Scale; EDS = excessive daytime sleepiness; BDI-II = Beck Depression Inventory II.

P-values <0.05 were considered significant.

* Pearson’s χ²-test for categorical variables.

† Student’s t-test for continuous variables.

‡ Baseline values available in (n = 91) participants in the vitamin D group, and (n = 96) in the placebo group.

§ Baseline values available in (n = 91) participants in the vitamin D group, and (n = 97) in the placebo group.

¶ Baseline values available in (n = 89) participants in the vitamin D group, and (n = 96) in the placebo group.

‖ Not eligible for participation in the study.
Abbreviations: n = number of participants; ISD = inadequate sleep duration; EDS = excessive daytime sleepiness. Recovery versus development of each outcome was compared between the vitamin D and the placebo group using Fisher’s exact test. P-values <0.05 were considered significant.

Table 3
Change in sleep duration and ESS-score after four months intervention with vitamin D or placebo.

| Sleep duration (minutes) | Overall | Men | Women |
|--------------------------|---------|-----|-------|
| Daytime sleep onset latency | 89 | 46 | 43 |
| Baseline | 412.1 (47.2) | 420.1 (55.0) | 407.4 (46.8) |
| End of study | 419.8 (57.7) | 419.7 (60.3) | 409.5 (53.8) |
| Difference (95% CI) | 7.5 (229.7, 78) | 0.4 (161.17, 2) | 2.0 (226.18, 16.8) |
| p-value | 0.338 | 0.645 | 0.149 |

| Daytime sleep offset latency | Overall | Men | Women |
|-----------------------------|---------|-----|-------|
| Daytime sleep offset latency | 96 | 53 | 44 |
| Baseline | 436.2 (60.0) | 420.6 (57.7) | 436.2 (60.0) |
| End of study | 343.6 (12.8) | 340.0 (12.6) | 340.0 (12.6) |
| Difference (95% CI) | 0.0 (122.18, 18.8) | 0.0 (122.18, 18.8) | 0.0 (122.18, 18.8) |
| p-value | 0.999 | 0.999 | 0.999 |

| ESS-score | Overall | Men | Women |
|-----------|---------|-----|-------|
| ESS-score | 90 | 62 | 64 |
| Baseline | 5.8 (2.9) | 5.5 (2.9) | 5.7 (3.0) |
| End of study | 6.9 (3.0) | 6.7 (2.9) | 6.9 (3.0) |
| Difference (95% CI) | 0.1 (1.1, 1) | 0.2 (1.1, 1) | 0.0 (1.1, 1) |
| p-value | 0.253 b | 0.421 | 0.071 c |

Abbreviations: n = number of participants; ESS = epworth sleepiness scale; SD = standard deviation; CI = confidence interval; ANCOVA = analysis of covariance.

Values represent means (SD) if not otherwise specified, and the significance level was set to p < 0.05 for all comparisons. Delta values (end of study value – baseline value) were compared between the vitamin D and the placebo group using the Student’s t-test. The ANCOVA analyses were done comparing end of study values in the vitamin D v. placebo group using linear regression.

a Baseline values, age, and sex as covariates.
b Baseline values and age as covariates.
c 185 participants had valid records of both baseline and last visit values and were included in the analyses.
d 186 participants had valid records of both baseline and last visit values and were included in the analyses.

Table 4
Baseline and end of study values in participants with records of both baseline and end of study values for at least 1 sleep outcome, by sex and intervention group.

| Overall | Men (n = 100) | Women (n = 89) |
|---------|---------------|----------------|
| Vitamin D (n = 92) | Placebo (n = 97) | p-value | Vitamin D (n = 47) | Placebo (n = 53) | p-value | Vitamin D (n = 45) | Placebo (n = 44) | p-value |
| BM(basal), kg/m² | 27.5 (4.2) | 27.7 (4.3) | 28.1 (4.3) | 28.2 (3.4) | 26.9 (4.2) | 27.2 (5.1) | 27.2 (4.2) | 27.5 (5.3) | 0.856 |
| BM(end), kg/m² | 27.8 (4.8) | 28.0 (4.4) | 28.3 (4.3) | 28.4 (3.6) | 27.2 (4.3) | 27.5 (5.3) | 27.2 (4.2) | 27.5 (5.3) | 0.856 |
| Δ BMI, kg/m² | 0.3 (0.6) | 0.3 (0.6) | 0.9 (0.6) | 0.9 (0.6) | 27.2 (4.2) | 27.2 (5.1) | 27.2 (4.2) | 27.2 (5.3) |
| s-Ca, mmol/L | 2.28 (0.07) | 2.28 (0.07) | 2.28 (0.07) | 2.28 (0.07) | 2.28 (0.07) | 2.28 (0.07) | 2.28 (0.07) | 2.28 (0.07) | 2.28 (0.07) |
| s-Pth, mmol/L | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) |
| s-PTH, pmol/L | 6.2 (1.8) | 6.2 (1.8) | 6.2 (1.8) | 6.2 (1.8) | 6.4 (1.9) | 6.4 (1.9) | 6.4 (1.9) | 6.4 (1.9) | 0.940 |
| s-25(OH)D, nmol/L | 35.0 (11.8) | 35.5 (12.3) | 36.5 (12.9) | 36.1 (14.3) | 33.4 (10.4) | 34.8 (12.1) | 33.4 (10.4) | 34.8 (12.1) | 0.347 |
| s-25(OH)D, ng/ml | 85.9 (19.8) | 85.2 (19.9) | 85.2 (19.9) | 85.2 (19.9) | 86.5 (17.5) | 28.8 (8.7) | 86.5 (17.5) | 86.5 (19.1) | 0.347 |

Abbreviations: n = number of participants; SD = standard deviation; BL = baseline; END = end of study; BMI = body mass index; s-Ca = serum calcium; s-Pth = plasma parathyroid hormone; s-25(OH)D = serum 25-hydroxyvitamin D. Values represent means (SD) if not otherwise specified. Delta values are presented as Δ and calculated as (end of study value – baseline value). Each characteristic was compared between the vitamin D and the placebo group using Student’s t-test. P-values <0.05 were considered significant and are denoted *.

6
defend postponing vitamin D supplementation of participants with known vitamin D deficiency randomized to placebo. A longer intervention period might have been needed to show an effect of vitamin D, although notably the intervention period was considerably shorter in the study by Majid et al. [31]. Finally, the sample size of the present study was relatively small and separate power calculations regarding the secondary sleep outcomes were not performed.

The present study also has strengths, including the use of a gold-standard RCT-study design with strict inclusion criteria, including only vitamin D insufficient participants at baseline. Moreover, the questionnaire was based on previously validated sleep instruments used in Tromsø77, albeit with minor modifications. Finally, the vitamin D dosing regimen significantly increased s-25(OH)D in the vitamin D group, and both adherence to treatment and compliance were exceptionally high.

5. Conclusion

In conclusion, we were not able to demonstrate any significant effect of vitamin D supplementation on various sleep outcomes in this vitamin D insufficient population.

Funding

The main study was supported by grants from the North Norway Regional Health Authorities (grant number SPP1277-16) and UiT The Arctic University of Norway. AUL received funding through the PhD Program at UiT The Arctic University of Norway. The publication charges for this article were funded through UiT The Arctic University of Norway’s Publishing Agreements. The funding body did not have a role in the design of the study, data collection, analysis, interpretation of data or writing of the manuscript.

Conflict of interest

The authors have no competing interests to declare.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2021.100040

References

[1] National Institute of Mental Health. Arousal and regulatory systems: workshop proceedings. 09.06.2021 from, https://www.nimh.nih.gov/research/research-funded-by-nimh/rdos/ariaular-and-regulatory-systems-workshop-proceedings; 2013.
[2] Dalmas M, Benitez I, Sapina-Betran E, et al. Impact of sleep health on self-perceived health status. Sci Rep 2019;9(1):7284. https://doi.org/10.1038/s41598-019-43873-5.
[3] Cedernaes J, Schioth HB, Benedict C. Determinants of shortened, disrupted, and mistimed sleep and associated metabolic health consequences in healthy humans. Diabetes 2015;64(4):1073–80. https://doi.org/10.23736/s414-1475.
[4] Cappuccio FP, D’Elia L, Strazzullo P, et al. Quantity and quality of sleep and incidence of type 2 diabetes; a systematic review and meta-analysis. Diabetes Care 2010;33(2):414–20. https://doi.org/10.2337/dc09-1124.
[5] Harvey AG. Sleep and circadian functioning: critical mechanisms in the mood disorders? Annu Rev Clin Psychol 2011;7:297–319. https://doi.org/10.1146/annurev-clinpsy-032210-104550.
[6] Huyett P, Siegel N, Bhattacharyya N. Prevalence of sleep disorders and association with mortality: results from the NHANES 2009-2010. Laryngoscope 2016;126(13):2866–9. https://doi.org/10.1002/lary.26590.
[7] Hillman D, Mitchell S, Streafeld J, et al. The economic cost of inadequate sleep. Sleep 2018;41(8). https://doi.org/10.5965/sleep/02878.
[8] Gomina KC, Stumpf WE. The world epidemic of sleep disorders is linked to vitamin D deficiency. Med Hypotheses 2012;79(2):132–5. https://doi.org/10.1016/j.mehy.2012.03.031.
[9] Yan S, Tian Z, Zhao H, et al. A meta-analysis: does vitamin D play a promising role in sleep disorders? Food Sci Nutr 2020;8(10):5696–709. https://doi.org/10.1002/fsn3.1897.
[10] Romano F, Muscogiuri G, Di Benedetto E, et al. Vitamin D and sleep regulation: is there a role for vitamin D? Curr Pharmaceut Des 2020;26(21):2492–6. https://doi.org/10.2174/1381612826666202011041693.
[11] Muscogiuri G, Marica L, Scappaticcio M, et al. The lullaby of the sun: the role of vitamin D in sleep disturbance. Sleep Med 2019;54:262–5. https://doi.org/10.1016/j.sleep.2018.10.033.
[12] Delbaere KF. Overview of general physiologic features and functions of vitamin D. Am J Clin Nutr 2004;80(6 Suppl):169R. https://doi.org/10.1093/ajcn/80.6.169R.
[13] Eyles DW, Smith S, Kivonos R, et al. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. J Chem Neuroanat 2005;29(2):21–30. https://doi.org/10.1016/j.jchneu.2004.08.006.
[14] Garcia E, Wion-Barbot N, Montero-Menei CN, et al. New clues about vitamin D functions in the nervous system. Trends Endocrinol Metabol 2002;13(3):100–4. https://doi.org/10.1016/s1043-2760(01)00547-1.
[15] Partridge WM, Sakiyama R, Coty WA. Restricted transport of vitamin D and A derivatives through the rat blood-brain barrier. J Neurochem 1985;44(4):1138–41. https://doi.org/10.1111/j.1471-4149.1985.tb07335.x.
[16] Gutierrez-Monreal MA, Cueva-Diaz Duran R, Moreno-Cuevas JE, et al. A role for 1α,25-dihydroxyvitamin D3 in the expression of circadian genes. J Biol Rhythm 2014;29(5):384–8. https://doi.org/10.1177/0748734414549239.
[17] Massod T, Kushiwaha RS, Singh R, et al. Circadian rhythm of serum 25 (OH) vitamin D, calcium and phosphorous levels in the treatment and management of type-2 diabetic patients. Drug Discov Ther 2015;9(1):70–4. https://doi.org/10.5582/ddt.2015.01002.
[18] Lucock M, Jones P, Martin C, et al. Vitamin D: beyond metabolism. J Evid Based Complementary Altern Med 2015;20(4):310–22. https://doi.org/10.1177/2165687215580491.
[19] Kaneko I, Sabir MS, Dussik CM, et al. 1,25-Dihydroxyvitamin D regulates expression of the tryptophan hydroxylase 2 and leptin genes: implication for behavioral influences of vitamin D. FASEB J 2015;29(9):4023–33. https://doi.org/10.1096/fj.14-269811.
[20] Amaral FGD, Cipolla-Neto J. A brief review about melatonin, a pineal hormone. Arch Endocrinol Metab 2018;62(2):472–9. https://doi.org/10.20945/2359-3997/0000000666.
[21] Shipton EA, Shipton EE. Vitamin D and pain: vitamin D and its role in the aetiology and maintenance of chronic pain states and associated comorbidities. Pain Res Treat 2015;2015:904967. https://doi.org/10.1155/2015/904967.
[22] de Oliveira DH, Hirotsu C, Tuluf S, et al. The interfaces between vitamin D, sleep and pain. J Endocrinol 2017;234(1):R23–36. https://doi.org/10.1530/JEO-16-0514.
[23] Hana J, Shah S, Long Q, et al. Improvement of pain, sleep, and quality of life in chronic pain patients with vitamin D supplementation. Clin J Pain 2013;29(4):341–7. https://doi.org/10.1097/AJP.0b013e318255655d.
[24] Kim JH, Chang JH, Kim DY, et al. Association between self-reported sleep duration and serum vitamin D level in elderly Korean adults. J Am Geriatr Soc 2014;62(s2):1237–32. https://doi.org/10.1111/jgs.13148.
[25] Massa J, Stone KL, Wei EK, et al. Vitamin D and actigraphic sleep outcomes in older community-dwelling men: the MrOS sleep study. Sleep 2015;38(2):251–7. https://doi.org/10.5665/sleep.4408.
Hirshkowitz M, Whiton K, Albert SM, et al. National Sleep Foundation's updated sleep duration recommendations: final report. Sleep Health 2015;1(4):233–43. https://doi.org/10.1016/j.sleh.2015.10.004.

Lapin BR, Bena JF, Walia HK, et al. The epworth sleepiness scale: validation of one-dimensional factor structure in a large clinical sample. J Clin Sleep Med 2018;14(8):1293–301. https://doi.org/10.5664/jcsm.7258.

Johns MW. Official website of the epworth sleepiness scale (ESS) and the epworth sleepiness scale for children and adolescents (ESS-CHADS). 09.06. 2021 from, http://www.epworthsleepinessscale.com/; 2016.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Publishing; 2013. https://doi.org/10.1176/appi.books.9780890425596.

Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest 2014;146(5):1387–94. https://doi.org/10.1378/chest.14-0970.

Steer RA, Clark DA, Beck AT, et al. Common and specific dimensions of self-reported anxiety and depression: the BDI-II versus the BDI-IA. Behav Res Ther 1999;37(2):183–90. https://doi.org/10.1016/s0005-7967(98)00087-4.

Jorde R, Kubiak J. No improvement in depressive symptoms by vitamin D supplementation: results from a randomised controlled trial. J Nutr Sci 2018;7:e30. https://doi.org/10.1017/jns.2018.19.

Vickers AJ, Altman DG. Statistics notes: analysing controlled trials with baseline and follow up measurements. BMJ 2001;323(7321):1123–4. https://doi.org/10.1136/bmj.323.7321.1123.

Mong JA, Cusmano DM. Sex differences in sleep: impact of biological sex and sex steroids. Philos Trans R Soc Lond B Biol Sci 2016;371(1688):20150110. https://doi.org/10.1098/rstb.2015.0110.

Amrein K, Scherkl M, Hoffmann M, et al. Vitamin D deficiency 2.0: an update on the current status worldwide. Eur J Clin Nutr 2020;74(11):1498–513. https://doi.org/10.1038/s41430-020-0558-4.

Lowden A, Lenos NAM, Gonçalves BSR, et al. Delayed sleep in winter related to natural daylight exposure among arctic day workers. Clocks Sleep Ther 1999;1:105–16. https://doi.org/10.1093/clockssleep/1001010.

Putilov AA. Retrospectively reported month-to-month variation in sleeping problems of people naturally exposed to high-amplitude annual variation in daylength and/or temperature. Sleep Sci 2017;10(3):101–12. https://doi.org/10.5935/1984-0063.20170019.

Sivertsen B, Friberg O, Pallesen S, et al. Sleep in the land of the midnight sun and polar night: the Tromsø study. Chronobiol Int 2020;37(33):334–42. https://doi.org/10.1080/07420584.2020.1845191.

Buysse DJ, Reynolds 3rd CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatr Res 1989;28(2):193–213. https://doi.org/10.1016/0165-1781(89)90047-4.