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Associations of serum 25-hydroxyvitamin D and subjective sleep measures in an arctic population: Insights from the population-based Tromsø Study

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ABSTRACT

Objective: To investigate the relation between serum 25-hydroxyvitamin D (s-25(OH)D) and subjective sleep measures in an Arctic population (69°N).
Methods: Cross-sectional data was collected from 21,083 individuals (aged ≥40 years) participating in the population based Tromsø Study: Tromsø7 (2015–2016). The present study included 20,438 participants, after having excluded respondents missing data on s-25(OH)D (n = 161) and/or subjective sleep measures (including sleep duration, insomnia, and daytime sleepiness)(n = 490). Based on s-25(OH)D (assessed using LC-MS/MS), participants were grouped as deficient (<30 nmol/L), insufficient (30–49.9 nmol/L), sufficient (50–75 nmol/L), or high (>75 nmol/L). Sleep duration was grouped as inadequate (ISD) if < 7 or ≥9 h. Linear and logistic regression were used to calculate unstandardized β-values and odds ratios [95% confidence intervals]. The analyses were adjusted for season, age, BMI, lifestyle factors and relevant comorbidities.
Results: In both men and women, s-25(OH)D was positively associated with sleep duration, and compared to the sufficient s-25(OH)D group, the insufficient s-25(OH)D group reported significantly shorter sleep duration in both sexes. There was an increased odds of ISD in both men and women but adjusted for confounding factors this was only significant in women (1.16 [1.03, 1.32], $p = .017$). In men, there were no significant associations between s-25(OH)D and the remaining sleep measures. Women in the high s-25(OH)D group had lower ESS-scores (−0.28 [-0.47, −0.08], $p = .006$), but higher odds of insomnia (1.16 [1.01, 1.33], $p = .036$) compared to women in the sufficient group.
Conclusions: In this Arctic population, a tenuous association was found between s-25(OH)D and subjective sleep measures, predominantly in women.

1. Introduction

Sleep is an essential component of human daily routine and function. Adequate duration, timing, regularity, and quality of sleep is required for several critical brain functions and influences many systemic processes [1]. Sleep disturbances have been reported to increase the risk of both mental and somatic diseases, including cardiovascular and cerebrovascular diseases, obesity, diabetes, cancer, and depression [2]. Although sleep-demands show great intra- and inter-individual variability depending on age, sex, and environmental factors, adults are in general recommended 7–9 h of sleep on a daily basis [1,3]. The proportion of adults not reaching this goal is worryingly high [1]. Both environmental and societal factors, such as an increased use of electronic devices and screen time [4], as well as nonstandard working hours [5], may explain some of the discrepancies between the amount of sleep recommended and the amount of sleep obtained. However, additional factors remain to be explored.

Vitamin D is one such factor. Besides its crucial role in

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; ISD, Inadequate sleep duration; EDS, Excessive daytime sleepiness; BMI, Body mass index; OSA, Obstructive sleep apnea; HSCL-10, Hopkins Symptoms Check List 10; DAG, Directed acyclic graph; RCT, Randomized controlled trial.

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maintenance of calcium and phosphorus homeostasis, vitamin D has been increasingly recognized as a steroid prohormone that exerts a variety of functions through its vitamin D receptor (VDR). Over the last decade, emerging evidence have spoken in favour of an association between vitamin D and sleep health [6,7], as vitamin D deficiency is prevalent in populations with sleep complaints [8]. The sleep-wake cycle is regulated by the circadian-clock and hormones produced by the hypothalamus [9]. A number of environmental inputs modulate its functions, and vitamin D may possibly play a role. The link is biologically plausible, as vitamin D metabolites are capable of crossing the blood brain barrier [10]. The VDR has been found in areas of the human brain known to be involved in the regulation of sleep, along with key enzymes required for vitamin D metabolism [11]. Biological mechanisms through which vitamin D may exert its effects on sleep have been suggested, including regulation of circadian clock genes, alterations of melatonin synthesis and through its role as an immune modulator [12,13].

In observational studies, vitamin D has been associated with less difficulty maintaining sleep [14]. Higher concentrations of serum 25-hydroxyvitamin D (s-25(OH)D), the main circulating vitamin D metabolite, have been associated with longer and earlier night sleep [15]. Moreover, vitamin D deficiency has been associated with short sleep duration [16-23], poor self-reported sleep quality [24,25], and an increased risk of daytime sleepiness [26,27]. However, none of these previous studies have been performed in populations living in an Arctic area, in which the prevalence of both insufficient sleep duration and insomnia has been reported as worryingly high [28].

Thus, the aim of the present study was to examine the relation between s-25(OH)D and self-reported sleep measures in a general population living in the Arctic area of Northern Norway, where UVB radiation is beyond the threshold for cutaneous vitamin D production nearly half the year [29].

2. Materials and methods

2.1. The Tromsø Study: population and study design

The Tromsø Study is a longitudinal population-based health study conducted in the municipality of Tromsø in Northern Norway [30]. Tromsø is geographically situated at 69° North, with extreme variations in daylight throughout the year, including two months of polar night during winter and two months of midnight sun during summer. The Tromsø Study consists of seven repeated cross-sectional surveys conducted between 1974 and 2016 (Tromsø 1−Tromsø 7), to which total birth cohorts and random samples have been invited. In Tromsø 7 (2015−2016), all inhabitants aged 40 years and above (N = 32,591) were invited, of which 21,083 women and men aged 40−99 years participated (attendance rate 65%). The participants were included consecutively between March 2015 and November 2016. Data collection included questionnaires, biological sampling, and clinical examinations, as described in detail below.

2.2. Data collection

2.2.1. Vitamin D and anthropometric measurements

Serum sampling was performed non-fasting and s-25(OH)D was measured using the gold standard LC-MS/MS method at the Department of Clinical Biochemistry, University Hospital of North Norway. The analysis was accredited by the Norwegian Accreditation Authority and the laboratory participates in the international quality surveillance programme the vitamin D external quality assurance scheme (DEQAS) to ensure the analytical reliability of the 25(OH)D assays. Subgroup classification of vitamin D status was done according to s-25(OH)D and performed in accordance with recent recommendations [31,32]. Thus, vitamin D deficiency was defined as s-25(OH)D values < 30 nmol/L, and vitamin D insufficiency as values from 30 nmol/L to 50 nmol/L. Values from 50 through 75 nmol/L were defined as sufficient, whereas values > 75 nmol/L were defined as high.

Height and weight were measured with light clothing and without shoes. Body mass index (BMI) was calculated as weight (kilograms) divided by height squared ($meter^2$). All measurements were performed by trained technicians.

2.2.2. Self-reported sleep measures

Each participants completed an extensive questionnaire with questions about habitual sleep traits to assess self-reported sleep measures, including sleep duration, symptoms of insomnia, and daytime sleepiness. The questionnaire was completed online before the study visit or at the examination site, aided by the study personnel as needed. The questionnaire items used to assess self-reported sleep measures are summarized in Supplemental Fig. 1.

Sleep duration was calculated as time in bed (bedtime subtracted from rise time) minus sleep onset latency. Sleep duration was further dichotomized into normal (7−9 h) and inadequate sleep duration (ISD) (<7 h or ≥9 h), in accordance with age-specific recommendations [3].

Insomnia was assessed using a slightly modified version of the Bergen Insomnia Scale (BIS) [33], adjusted to adhere with recent guidelines on diagnosing insomnia, including the Diagnostic and.

Statistical Manual for Mental Disorders, Fifth Edition (DSM-5) DSM-5 [34] and International Classification of Sleep Disorders, Third Edition (ISCD-3) [35]. Insomnia was defined in accordance with *Sivertsen* et al. [28] and categorized as present if the participants reported: 1) at least one of three nocturnal symptoms (prolonged sleep onset latency, difficulties maintaining sleep and/or early morning awakening) ≥3 nights/week, and 2) one or both of two daytime symptoms (daytime sleepiness/tiredness and/or dissatisfaction with sleep) ≥3 days/week, and 3) a duration of sleep problems for ≥3 months.

Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) [36]. The ESS is a 4-point Likert-scale questionnaire composed of 8 items, in which the participant marks the probability of dozing while engaging certain daily activities. The score for each item varies from 0 (no chance of dozing) to 3 (high chance of dozing). The total score ranges from 0 to 24 points. Excessive daytime sleepiness (EDS) was defined as an ESS score of >10, in accordance with *Johns* et al. [37].

2.2.3. Covariates

Covariates were selected based on available empirical evidence, summarized using a directed acyclic graph (DAG) (Supplemental Fig. 2). The following information was obtained: BMI, smoking status (current vs. not current), alcohol consumption (gram/day), leisure time physical activity (sedentary/low vs. moderate/vigorous), marital status (living with spouse yes/no), self-perceived economy (difficult vs. average or good), shift work (yes/no), obstructive sleep apnoea (OSA), cardiovascular disease (myocardial infarction, stroke, atrial fibrillation, angina and/or heart failure), cancer (current vs. not current) and/or presence of constant or constantly reoccurring chronic pain during the last 3 months or more (yes/no), and afflictions of night sweats (not at all/not so much vs. sometimes/definitely), the latter in women only. Symptoms of psychological distress were assessed using the Hopkins Symptoms Check List 10 (HSCL-10), with a HSCL-10-score cut-off of ≥1.85 [38].

2.3. Statistical analyses

Normal distribution was evaluated by visual inspection of histograms and by determination of kurtosis and skewness. Continuous data was presented as means and standard deviations. Proportions were provided as number of participants and percentages. As previous studies have reported sex-differences in sleep [39], all analyses were performed sex-stratified.

The prevalence of each categorical sleep measure (i.e., ISD, insomnia and EDS) was compared between men and women using the Pearson's Chi Square test. Differences across s-25(OH)D groups were tested using the Pearson's Chi-square test for categorical variables and one-way analysis of variance for continuous variables. Mean s-25(OH)D was compared between men and women and within each categorical sleep measure using the Student's t-test.

To identify a valid adjustment set for the statistical analyses, DAGs were constructed using the DAGitty v3.0 software. The final DAG (Supplemental Fig. 2) was selected through evaluation of available empirical evidence. Multivariate binary logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for each categorical sleep measure, using s-25(OH)D as a categorical predictor variable. Each s-25(OH)D group was dichotomized and added to the regression model as an independent variable, except the sufficient s-25(OH)D group which was excluded to serve as a reference. In crude analyses, the ORs were adjusted for month of serum sampling by adding each month as an independent dummy variable (Model 1). In the final model (Model 2), potential confounders were added to the regression, including month of serum sampling, age, BMI, smoking, alcohol intake, leisure time physical activity, living with a spouse or partner, self-perceived economy, shift work, OSA, psychological distress and relevant comorbidities (including cardiovascular disease, cancer and/or chronic pain during the last 3 months or more). In women, the regression models were also adjusted for afflictions of night sweat.

Multiple linear regression was used to model the relationship between s-25(OH)D and the continuous sleep measures (i.e., sleep duration and ESS-score). Using the same models as described for the logistic regression analyses, each of the continuous sleep measures were analysed with s-25(OH)D as a continuous and as a categorical predictor variable in two separate analyses.

Relevant interactions, including [25(OH)D × sex], [25(OH)D × age], [25(OH)D × BMI] and [25(OH)D × depression], were tested by adding the multiplicative term of the two variables in crude analyses. There were no significant interactions with s-25(OH)D, except for sex when applied in the regression models with insomnia as the dependent variable ($p = .012$).

The statistical analyses were performed using SPSS software version 27.0 (IBM Corp, Chicago, IL). All tests were performed two-sided, and p-values < .05 were considered statistically significant.

2.4. Ethics

All of the participants provided written informed consent prior to participating in the Tromsø Study. The present study was approved by the Norwegian Committee for Medical and Health Research Ethics (REC North ref. 2020/7614).

3. Results

3.1. Sample characteristics

Sample characteristics of the study population are shown in Table 1. In the present study, the total sample consisted of 20,438 individuals after having excluded respondents missing s-25(OH)D measurement (n = 161) and/or without data on at least one sleep measure (n = 490). The participant inclusion is shown in Fig. 1. The 645 excluded participants were significantly older and more likely to report comorbidities (including cardiovascular disease, a current cancer diagnosis and/or chronic pain during the last 3 months or more). The mean alcohol consumption was significantly lower among the excluded participants, and they were less likely to report moderate or vigorous physical activity, living with a spouse or partner, and having shift work, compared to the included participants. Characteristics of the excluded participants are also summarized in Table 1.

3.2. Self-reported sleep measures

Included participants with missing data on a specific sleep measure were only excluded from the analyses for which data were missing (sleep duration (n = 1,241), insomnia (n = 901), daytime sleepiness (n = 1,128)).

ISD was the most prevalent categorical sleep measure in both sexes (Table 2), and the prevalence was significantly higher in men compared to women (53.9% vs. 45.8%, $p < .001$). Participants with ISD had significantly lower mean s-25(OH)D compared to those reporting a normal sleep duration, in both men (59.2 ± 20.8 nmol/L vs. 62.4 ± 21.4 nmol/L, $p < .001$) and women (64.6 ± 22.5 nmol/L vs. 66.9 ± 22.1 nmol/L, $p < .001$). In both sexes, a linear trend was observed across s-25(OH)D groups, with a falling prevalence of ISD from the group with the lowest to the highest s-25(OH)D (Table 2, Fig. 2). In both sexes, the logistic regression adjusted for month of serum sampling (Model 1), showed significantly higher odds of ISD in the deficient and insufficient s-25(OH)D groups compared to the sufficient group (Model 1, Table 3). The analysis showed lower odds of ISD in the high s-25(OH)D group compared to the sufficient group, although this finding was only significant in men (Model 1, Table 3). With additional adjustment (Model 2), all estimates were attenuated and remained statistically significant only in women with insufficient s-25(OH)D (Model 2, Table 3). In both sexes, linear regression adjusted for month of serum sampling (Model 1), showed a positive association between the continuous s-25(OH)D variable and sleep duration (unstandardized β for every 10 nmol/L increase: 2.3 min, $p < .001$, and 1.7 min, $p < .001$, in men and women respectively). With additional adjustment for potential confounders (Model 2), the association with remained significant only in women (unstandardized β for every 10 nmol/L increase: 0.6 min, $p = .092$ and .8 min, $p = .013$, in men and women respectively). In both sexes, a positive linear trend in sleep duration was also found across s-25(OH)D groups (Table 4), although when the fully adjusted model was applied the association was only significant for the insufficient s-25(OH)D group, reporting significantly shorter sleep duration compared to the sufficient group (Model 2, Table 4).

The prevalence of insomnia was significantly lower in men compared to women (15.2% vs. 24.7%, $p < .001$). Men with insomnia had significantly lower mean s-25(OH)D compared to men without insomnia (59.8 ± 21.8 nmol/L vs 61.0 ± 21.0 nmol/L, $p = .047$). In contrast, women with insomnia had significantly higher mean s-25(OH)D compared to women without (67.9 ± 23.2 nmol/L vs 65.5 ± 22.0 nmol/L, $p < .001$). In men, the prevalence of insomnia did not differ significantly across s-25(OH)D groups (Table 2, Fig. 3) and there were no significant associations with insomnia in either s-25(OH)D group (Table 3). In women, the highest prevalence of insomnia was seen in the high s-25(OH)D group (Table 2, Fig. 3). Compared to women in the sufficient s-25(OH)D group, the odds of insomnia was significantly higher among women in the high s-25(OH)D group, regardless of the model used (Table 3).

The prevalence of EDS did not differ between men and women (Table 2). Participants with EDS had significantly lower mean s-

Table 1
Participant characteristics. The Tromsø Study (Tromsø7: 2015–2016).

	Overall	Excluded		Serum 25-hydroxyvitamin D (nmol/L)				p-value
	(N = 20,438)	(n = 645)		Deficient	Insufficient	Sufficient	High	for difference
				<30 (2.2–29.9)	30.0–49.9	50.0–75.0	>75 (75.1–243.2)	
				(n = 920)	(n = 4,854)	(n = 8,996)	(n = 5,668)	
Sex, N (%) women	10,713 (52.4)	361 (56.0)		415 (45.1)	2,191 (45.1)	4,671 (51.9)	3,436 (60.6)	.001[a]
Age, years (mean (SD))	57.1 (11.3)	63.6 (13.9)	*	51.1 (9.4)	53.6 (10.3)	57.3 (11.3)	60.7 (11.0)	.001[b]
BMI, kg/m^2 (mean (SD))	27.3 (4.5)	27.7 (4.9)		28.9 (5.8)	28.1 (4.8)	27.3 (4.4)	26.4 (4.1)	.001[b]
BMI-category								.001[a]
<18.5 kg/m^2	111 (0.5)	8 (1.3)		5 (0.5)	22 (0.5)	36 (0.4)	48 (0.8)	
18.5–25 kg/m^2	6,543 (32.1)	185 (29.0)		236 (25.7)	1,272 (26.3)	2,825 (31.5)	2,210 (39.1)	
25–30 kg/m^2	8,899 (43.7)	273 (42.8)		344 (37.5)	2,104 (43.5)	4,046 (45.1)	2,405 (42.5)	
≥30 kg/m^2	4,829 (23.7)	172 (27.0)		332 (36.2)	1,438 (29.7)	2,068 (23.0)	991 (17.5)	
s-25(OH)D, nmol/L (mean (SD))	63.6 (22.0)	62.2 (24.1)		24.5 (4.5)	41.4 (5.5)	62.3 (7.1)	90.8 (14.6)	.001[b]
Season								.001[a]
Winter (October–March)	8,346 (40.8)	210 (43.4)		479 (52.1)	2,165 (44.6)	3,573 (39.7)	2,129 (37.6)	
Summer (April–September)	12,092 (59.2)	274 (56.6)		441 (47.9)	2,689 (55.4)	5,423 (60.3)	3,539 (62.4)	
Living with spouse (yes)	14,893 (77.1)	390 (67.9)	*	567 (66.1)	3,560 (77.2)	6,680 (78.6)	4,086 (76.3)	.001[a]
Self-perceived economy								.001[a]
Average or good	19,652 (96.5)	328 (95.3)		842 (91.7)	4,626 (95.8)	8,707 (97.0)	5,477 (97.0)	
Difficult	721 (3.5)	16 (4.7)		76 (8.3)	202 (4.2)	273 (3.0)	170 (3.0)	
Current smoker (yes)	2,804 (13.8)	100 (15.9)		199 (21.8)	810 (16.8)	1,122 (12.6)	673 (12.0)	.001[a]
Alcohol intake, g/day (mean (SD))	11.4 (13.2)	7.9 (13.1)	*	9.9 (14.2)	10.6 (12.8)	11.3 (13.2)	12.3 (13.4)	.001[b]
Leisure time physical activity								.001[a]
Sedentary or low	14,962 (75.6)	457 (79.8)	*	736 (82.3)	3,662 (77.7)	6,558 (75.2)	4,006 (73.3)	
Moderate or vigorous	4,835 (24.4)	116 (20.2)	*	158 (17.7)	1,051 (22.3)	2,168 (24.8)	1,458 (26.7)	
Shift work (yes)	2,061 (10.4)	17 (6.4)		107 (11.8)	530 (11.2)	936 (10.7)	488 (8.9)	.001[a]
OSA (yes)	751 (3.7)	11 (3.6)		51 (5.6)	233 (4.8)	285 (3.2)	182 (3.2)	.001[a]
CVD (yes)	2,586 (13.2)	138 (23.8)	*	100 (11.3)	544 (11.7)	1,137 (13.1)	805 (14.9)	.001[a]
Current cancer (yes)	375 (1.9)	29 (4.8)	*	12 (1.3)	59 (1.2)	173 (2.0)	131 (2.4)	.001[a]
Chronic pain ≥3 months or more (yes)	6,957 (37.5)	217 (42.0)	*	352 (41.0)	1,648 (37.0)	3,016 (36.9)	1,941 (38.6)	.033[a]
HSCL-10 ≥ 1.85 (yes)	1,705 (8.7)	17 (7.0)		108 (12.3)	448 (9.6)	712 (8.2)	437 (8.1)	.001[a]
Night sweats (sometimes/definitely)	5,040 (48.1)	75 (42.4)		174 (43.1)	932 (43.3)	2,177 (47.5)	1,757 (52.5)	.001[a,c]
Vitamin D supplement (yes)	4,323 (22.0)	75 (26.6)		54 (6.0)	445 (9.4)	1,896 (22.0)	1,928 (35.6)	.001[a]

Abbreviations: SD = standard deviation; BMI = body mass index; s-25(OH)D = serum 25-hydroxyvitamin D; OSA = obstructive sleep apnoea; CVD = cardiovascular disease; HSCL-10 = Hopkins Symptoms Check List 10. Values are number of participants (% of participants in that category) if not otherwise specified. Each characteristic was compared within each vitamin D group using.
Characteristics of excluded participants that were significantly different from the overall sample are denoted *.
[a] Pearson's Chi-square test for categorical variables.
[b] One-way analysis of variance for continuous variables.
[c] Including women only.

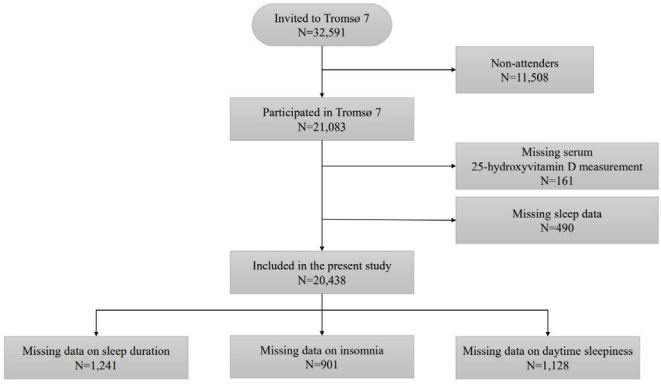

Fig. 1. Flow diagram of participant inclusion.

25(OH)D as compared to participants without EDS, both in in men (59.2 ± 21.2 nmol/L vs. 60.9 ± 21.1 nmol/L, p =.020) and in women (66.2 ± 22.3 nmol/L vs. 64.5 ± 64.5 nmol/L, p = .017). A linear trend was observed across s-25(OH)D groups, with a falling prevalence of EDS from the group with the lowest to the highest s-25(OH)D group, which was more prominent in women compared to men (Table 2, Fig. 4). In men, the logistic regression adjusted for month of serum sampling (Model 1) showed significantly lower odds of EDS in the high s-25(OH)D group compared to the sufficient group (Model 1, Table 3). With additional adjustment (Model 2), the association was attenuated and no longer statistically significant (Model 2, Table 3). The linear regression showed no significant associations between s-25(OH)D and ESS-scores in men, neither adjusted for month of serum sampling (unstandardized β for every 10 nmol/L increase: 0.03 (−0.06, 0.01), p = .137), nor with additional adjustment (unstandardized β for every 10 nmol/L increase: 0.02 (−0.02, 0.06), p = .339). Using the categorical s-25(OH)D variable did not change the results in men (Table 4). In women, logistic regression showed no significant associations between s-25(OH)D group and the odds of EDS (Table 3). The linear regression adjusted for month of serum sampling showed an inverse association between s-25(OH)D and ESS-scores in women (unstandardized β for every 10 nmol/L increase: 0.09 (−0.12, −0.05), p < .001), which was attenuated and no longer significant with additional adjustment (unstandardized β for every 10 nmol/L increase: 0.01 (−0.03, 0.04), p = .777). Adjusted for month of serum sampling (Model 1), women in the high s-25(OH)D group had significantly lower ESS-scores compared to women in the sufficient s-25(OH)D group (Model 1, Table 4), and the difference remained significant with additional adjustment (Model 2, Table 4).

Sensitivity analyses were performed stratifying the study population according to season of serum sampling, including a summer group (April through September), and a winter group (October through March). In men participating during winter, the fully

Table 2
Characteristics of sleep outcomes in men and women. The Tromsø Study (Tromsø7: 2015–2016).

	Missing data	Overall	Serum 25-hydroxyvitamin D (nmol/L)				*p*-value
		(N = 20,438)	Deficient	Insufficient	Sufficient	High	
			<30.0 (2.2–29.9)	30.0–49.9	50.0–75.0	>75.0 (75.1–243.2)	
Men (n = 9,725)			(n = 505)	(n = 2,663)	(n = 4,325)	(n = 2,232)	
Sleep duration, minutes (mean (SD))	(n = 503)	415.8 (64.6)	408.4 (76.3)	410.3 (65.6)	417.5 (62.9)	420.8 (63.1)	<.001[b]
ISD (yes)		4,972 (53.9)	300 (61.1)	1,454 (57.5)	2,174 (53.0)	1,044 (49.7)	<.001[a]
Sleep duration category							<.001[a]
<5 h		324 (3.5)	24 (4.9)	104 (4.1)	132 (3.2)	64 (3.0)	
5–7 h		4,497 (48.8)	263 (53.6)	1,312 (51.9)	1,975 (48.2)	947 (45.1)	
7–9 h		4,250 (46.1)	191 (38.9)	1,075 (42.5)	1,927 (47.0)	1,057 (50.3)	
>9 h		151 (1.6)	13 (2.6)	38 (1.5)	67 (1.6)	33 (1.6)	
Insomnia (yes)	(n = 340)	1,423 (15.2)	89 (18.4)	408 (15.9)	604 (14.4)	322 (14.9)	.071[a]
EDS (yes)	(n = 498)	995 (10.8)	52 (10.8)	298 (11.7)	458 (11.2)	187 (8.9)	.015[a]
Women (n = 10,713)			(n = 415)	(n = 2,191)	(n = 4,671)	(n = 3,436)	
Sleep duration, minutes (mean (SD))	(n = 738)	427.4 (66.2)	417.3 (68.3)	422.4 (61.3)	428.1 (64.9)	430.8 (70.4)	<.001[b]
ISD (yes)		4,568 (45.8)	207 (52.8)	1,021 (49.5)	1,984 (45.3)	1,356 (43.2)	<.001[a]
Sleep duration category							<.001[a]
<5 h		280 (2.8)	15 (3.8)	55 (2.7)	117 (2.7)	93 (3.0)	
5–7 h		3,977 (39.9)	178 (45.4)	912 (44.3)	1,731 (39.5)	1,156 (36.8)	
7–9 h		5,407 (54.2)	185 (47.2)	1,040 (50.5)	2,397 (54.7)	1,785 (56.8)	
>9 h		311 (3.1)	14 (3.6)	54 (2.6)	136 (3.1)	107 (3.4)	
Insomnia (yes)	(n = 561)	2,507 (24.7)	88 (23.0)	493 (23.7)	1,038 (23.3)	888 (27.4)	<.001[a]
EDS (yes)	(n = 630)	1,090 (10.8)	52 (13.2)	231 (11.2)	480 (10.9)	327 (10.2)	.258[a]

Abbreviations: SD = standard deviation; ISD: inadequate sleep duration; EDS = excessive daytime sleepiness. Sleep duration was calculated as time in bed (calculated as self-reported bedtime minus self-reported rise time) minus self-reported sleep onset latency. ISD was defined as sleeping <7 h or ≥9 h. Insomnia was defined as a) having difficulties with initiating sleep, maintaining sleep and/or early morning awakening ≥3 nights per week, b) experiencing daytime sleepiness/tiredness and/or a predominant complaint of dissatisfaction with sleep quantity or quality ≥3 days per week, and c) symptoms being present for ≥3 months. EDS was defined as an ESS-score (Epworth Sleepiness Scale) of ≥10 points.Values are number of participants (% of participants in that category) if not otherwise specified. Each characteristic was compared within each vitamin D group using.
[a] Pearson's Chi-square test for categorical variables.
[b] One-way analysis of variance for continuous variables.

adjusted odds of ISD was significantly higher in both the deficient and insufficient s-25(OH)D groups compared to the sufficient s-25(OH)D group (Model 2, Supplemental Table 1), and both the deficient and the insufficient s-25(OH)D groups reported significantly shorter sleep duration compared to the sufficient group (Model 2, Supplemental Table 2). With full adjustment, the results in men participating during summer did not differ from the main analyses in either sleep measure (Model 2, Supplemental Tables 3–4). In women participating during winter, the results did not differ from the main analyses (Model 2, Supplemental Tables 1–2). In women participating during summer, the fully adjusted odds of ISD was attenuated and no longer significant (Model 2, Supplemental Tables 3–4). The association with insomnia in women was attenuated and no longer significant in either seasonal group when the fully adjusted model was applied (Model 2, Supplemental Tables 1–4).

4. Discussion

To our knowledge, this is one of the largest studies to examine the relation between s-25(OH)D and self-reported sleep measures, and the first study to describe the association in an Arctic population. In this cross-sectional analysis, a tenuous association was found, predominantly in women. The results conflicted across the different sleep measures and most comparisons were non-significant with full adjustment for confounding factors.

Comparison with previous literature is complicated by the substantial variation in methodology, definition of outcomes and covariate adjustment across studies. A positive association between 25(OH)D and sleep duration, as found in some of our analyses, has been reported by others [15,16,18-23], although null findings have also been reported [40,41]. Moreover, a recent meta-analysis by *Gao* et al. [7], summarizing data from nine observational studies on the association between vitamin D and sleep [22–24,27,42–45], reported that vitamin D deficiency was associated with shorter sleep duration. Interestingly, a study by *Bertisch* et al. [17] found that s-25(OH)D was associated with sleep duration when measured objectively, but not when measured using self-report. Whether this may have explained some of the discrepancies in our study is unclear, as the analyses by *Bertisch* et al. [17] were not stratified by sex.

The results regarding insomnia in the present analysis conflicts with previous reports of an inverse association between 25(OH)D and sleep quality [7]. However, there are some important aspects that should be considered when comparing these results: In the meta-analysis by *Gao* et al. [7], only four of the included studies had more than 1000 participants [16,22,24,46]. Only two of these studies included data on sleep quality [24,46] and neither matched the current study population of middle-aged and older (±40 years) men and women. Surprisingly, the present study showed a higher risk of insomnia in women in the high s-25(OH)D group compared to women with sufficient s-25(OH)D. However, our study is not the first observational study to have linked high s-25(OH)D to unfavourable sleep outcomes. *Shiue* et al. [41] found in a cross-sectional study that individuals with higher s-25(OH)D were more likely to report sleep complaints. Moreover, *Mason* et al. [47] found in a double-blind, placebo controlled RCT with vitamin D in 218 post-menopausal women, that women who became vitamin D replete (≥32 ng/ml or 80 nmol/L) reported a deterioration in sleep quality. In contrast, two recent double-blind placebo controlled RCTs [48,49] found a positive effect of vitamin D to improve sleep quality. The mean end-of-study 25(OH)D in the vitamin D groups of these studies were 37.7 ng/ml (~94.2 nmol/L) [48] and 22 ng/ml (~55 nmol/L) [49]. However, both studies had associated limitations such as small sample sizes (<100 participants) and not using the

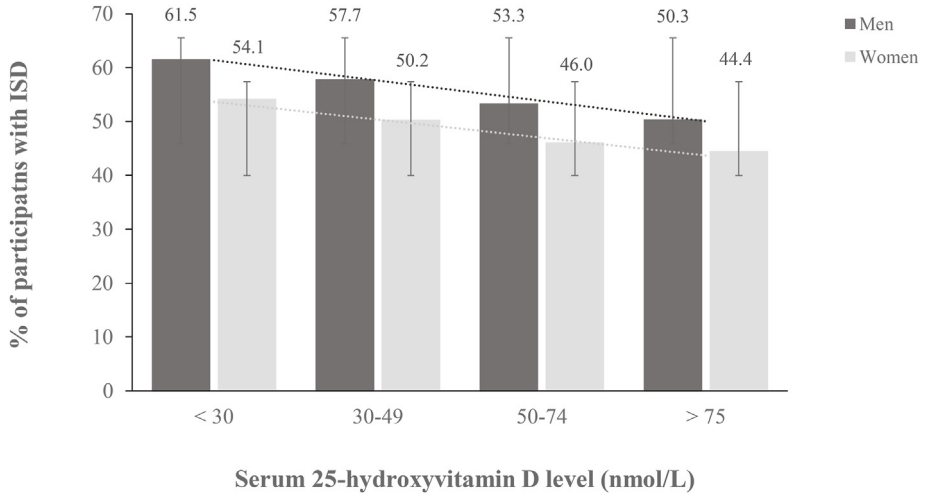

Fig. 2. Prevalence of inadequate sleep duration (ISD) across categories of serum 25-hydroxyvitamin D level in men and women. The Tromsø Study 2015–2016. Error bars represent 2 standard deviations.

Table 3
The odds ratio for having ISD, insomnia or EDS in men and women by serum 25-hydroxyvitamin D levels.

	Serum 25-hydroxyvitamin D (nmol/L)													
	Deficiency				Insufficiency				Sufficient			High		
	<30.0 (2.2–29.9)				30.0–49.9				50.0–75.0			>75.0 (75.1–243.2)		
	n	OR (95% CI)	*p*		n	OR (95% CI)	*p*		n	OR (95% CI)		n	OR (95% CI)	*p*	
Men (n = 9,725)															
ISD															
Model 1[a]	491	1.45 (1.19, 1.76)	<.001	*	2,529	1.22 (1.10, 1.35)	<.001	*	4,101	1.00 (Reference)		2,101	0.88 (0.80, 0.98)	.021	*
Model 2[b]	403	1.16 (0.93, 1.44)	.200		2,043	1.10 (0.98, 1.23)	.122		3,279	1.00 (Reference)	*	1,639	1.01 (0.89, 1.14)	.889	
Insomnia															
Model 1[a]	484	1.28 (0.99, 1.64)	.056		2,558	1.11 (0.97, 1.27)	.145		4,189	1.00 (Reference)		2,154	1.06 (0.91, 1.22)	.466	
Model 2[b]	393	0.99 (0.72, 1.36)	.953		2,045	1.00 (0.84, 1.18)	.951		3,307	1.00 (Reference)		1,665	1.19 (0.99, 1.43)	.062	
EDS															
Model 1[a]	480	1.00 (0.73, 1.36)	.982		2,544	1.07 (0.91, 1.25)	.409		4,105	1.00 (Reference)		2,098	0.78 (0.65, 0.93)	.006	*
Model 2[b]	394	0.93 (0.65, 1.32)	.681		2,057	1.04 (0.87, 1.25)	.647		3,262	1.00 (Reference)		1,635	0.86 (0.70, 1.06)	.148	
Women (n = 10,713)															
ISD															
Model 1[a]	392	1.40 (1.14, 1.73)	.001	*	2,061	1.18 (1.07, 1.32)	.002	*	4,381	1.00 (Reference)		3,139	0.93 (0.85, 1.02)	.124	
Model 2[b,c]	288	1.23 (0.95, 1.57)	.111		1,574	1.16 (1.03, 1.32)	.017	*	3,285	1.00 (Reference)		2,227	1.02 (0.91, 1.14)	.766	
Insomnia															
Model 1[a]	382	0.97 (0.76, 1.24)	.804		2,082	1.01 (0.89, 1.14)	.869		4,448	1.00 (Reference)		3,240	1.25 (1.13, 1.38)	<.001	*
Model 2[b,c]	276	0.84 (0.60, 1.17)	.298		1,557	1.07 (0.92, 1.26)	.388		3,289	1.00 (Reference)		2,256	1.16 (1.01, 1.33)	.036	*
EDS															
Model 1[a]	394	1.27 (0.93, 1.73)	.126		2,063	1.05 (0.89, 1.24)	.597		4,411	1.00 (Reference)		3,215	0.93 (0.80, 1.07)	.306	
Model 2[b,c]	287	1.01 (0.70, 1.45)	.962		1,563	0.91 (0.75, 1.11)	.354		3,274	1.00 (Reference)		2,259	1.05 (0.88, 1.25)	.623	

Abbreviations: OR = odds ratio; CI = confidence interval; ISD = inadequate sleep duration; EDS = excessive daytime sleepiness; HSCL-10 = Hopkins Symptoms Check List 10. Sleep duration was calculated as time in bed (calculated as self-reported bedtime minus self-reported rise time) minus self-reported sleep onset latency. ISD was defined as sleeping <7 h or ≥9 h. Insomnia was defined as a) having difficulties with initiating sleep, maintaining sleep and/or early morning awakening ≥3 nights per week, b) experiencing daytime sleepiness/tiredness and/or a predominant complaint of dissatisfaction with sleep quantity or quality ≥3 days per week, and c) symptoms being present for ≥3 months. EDS was defined as an ESS-score (Epworth Sleepiness Scale) of ≥10 points. OR (95% CI) was calculated for each categorical sleep measure using binary logistic regression with s-25(OH)D level as a categorical predictor variable.
Significant associations are denoted*.
[a] Adjusted for month of serum sampling.
[b] Adjusted for month of serum sampling, age, BMI, smoking, alcohol intake, leisure time physical activity, living with a spouse or partner, self-perceived economy, shift work, obstructive sleep apnoea, psychological distress (HSCL-10 ≥ 1.85) or presence of other comorbidities (cardiovascular disease, current cancer and/or chronic pain during the last 3 months or more).
[c] Adjusted for afflictions of night sweats in women, in addition to other variables.

gold standard method LC-MS/MS to assess 25(OH)D. Also, analyses to explore potential subgroup effects according to achieved 25(OH)D were not performed.

In the present study, subgroup analyses according to season of serum sampling indicated that the association between s-25(OH)D and subjective sleep measures were restricted to men and women participating during winter, except regarding the association between s-25(OH)D and insomnia in women, which was non-significant regardless of seasonal group. In corroboration with the latter finding regarding insomnia, a previous analysis from the Tromsø Study by *Sivertsen* et al. [50] concluded that the extreme seasonal variations in daylight had little influence on self-reported sleep measures.

Due to the considerable attention in mainstream media devoted

Table 4
Associations of serum 25 hydroxyvitamin D level with sleep duration and ESS-score.

	Sleep duration (minutes)					ESS-score			
	n	Unstandardized β	(95% CI)	*p*-value		n	Unstandardized β	(95% CI)	*p*-value
Model 1[a]	9,222					9,227			
Deficient (<30 nmol/L)		−10.05	(-16.15, −3.95)	.001	*		−0.09	(-0.42, 0.25)	.622
Insufficient (30–49 nmol/L)		−7.23	(-10.95, −4.51)	<.001	*		0.07	(-0.11, 0.25)	.431
Sufficient (50–75 nmol/L)		1.00	(Reference)	.			1.00	(Reference)	.
High (>75 nmol/L)		3.50	(0.10, 6.90)	.043	*		−0.16	(-0.35, 0.03)	.095
Model 2[b]	7,376					7,362			
Deficient (<30 nmol/L)		−4.83	(-11.37, 1.72)	.148			−0.06	(-0.43, 0.31)	.739
Insufficient (30–49 nmol/L)		−6.55	(-10.01, −3.08)	<.001	*		0.10	(-0.92, 0.30)	.300
Sufficient (50–75 nmol/L)		1.00	(Reference)	.			1.00	(Reference)	.
High (>75 nmol/L)		2.72	(-0.98, 6.41)	.149			−0.09	(-0.30, 0.11)	.373
Model 1[a]	9,975					10,083			
Deficient (<30 nmol/L)		−9.14	(-16.01, −2.28)	.009	*		0.20	(-0.18, 0.58)	.298
Insufficient (30–49 nmol/L)		−5.77	(-9.24, 2.29)	.001	*		0.20	(0.00, 0.39)	.047
Sufficient (50–75 nmol/L)		1.00	(Reference)	.			1.00	(Reference)	.
High (>75 nmol/L)		2.77	(-0.27, 5.81)	.074			−0.23	(-0.39, −0.06)	.009
Model 2[b,c]	7,391					7,398			
Deficient (<30 nmol/L)		−6.86	(-14.50, 0.78)	0.78			0.23	(-0.22, 0.67)	.317
Insufficient (30–49 nmol/L)		−6.62	(-10.42, −2.83)	<.001	*		0.22	(-0.01, 0.44)	.055
Sufficient (50–75 nmol/L)		1.00	(Reference)	.			1.00	(Reference)	.
High (>75 nmol/L)		2.28	(-1.13, 5.68)	.198			−0.28	(-0.47, −0.08)	.006

Abbreviations: CI = confidence interval; ESS = epworth sleepiness scale; s-25(OH)D = serum 25 hydroxyvitamin D. Sleep duration was calculated as time in bed (calculated as self-reported bedtime minus self-reported rise time) minus self-reported sleep onset latency. ESS-scores were calculated as the sum of 8 items (scored from 0 to 3) assessing the probability of napping in everyday situations. Unstandardized β -values (95% CI) are reported separately for each s-25(OH)D group (deficient, insufficient, sufficient, high) and were calculated using multiple linear regression using the s-25(OH)D sufficient group as the reference category.
Significant associations are denoted*.
[a] Adjusted for month of serum sampling.
[b] Adjusted for month of serum sampling, age, BMI, smoking, alcohol intake, leisure time physical activity, living with a spouse or partner, self-perceived economy, shift work, obstructive sleep apnoea, psychological distress (Hopkins Symptoms Check List (HSCL-10) ≥1.85) or presence of other comorbidities (cardiovascular disease, current cancer and/or chronic pain during the last 3 months or more).
[c] Adjusted for afflictions of night sweats in women, in addition to other variables.

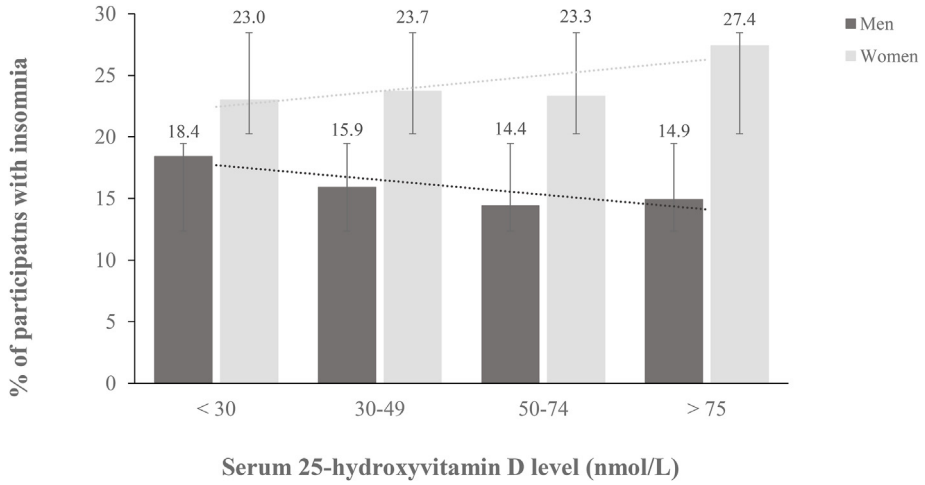

Fig. 3. Prevalence of insomnia across categories of serum 25-hydroxyvitamin D level in men and women. The Tromsø Study 2015–2016. Error bars represent 2 standard deviations.

to extra-skeletal effects of vitamin D, it cannot be excluded that an increased odds of insomnia with higher s-25(OH)D might represent reversed causation. It could be hypothesized that women with insomnia may have been more likely to start taking a vitamin D supplement in an attempt to improve their sleep problems. This was partially seen in our study, as the proportion reporting to use a vitamin D supplement was significantly higher among individuals with insomnia compared to those without, in both sexes. However, as there were more women than men with insomnia, the association may also have been significant in women simply because of the higher prevalence, which increases the probability of finding a statistically significant result. The analyses in the present study were not adjusted for vitamin D supplement use, as the aim was to estimate the association between self-reported sleep measures and s-25(OH)D, regardless of the source.

With the exception of lower ESS-scores among women in the high s-25(OH)D group compared to women in the sufficient s-25(OH)D group, there were no associations between s-25(OH)D and daytime sleepiness in the present study. This contrasts with previous literature suggesting an inverse association between vitamin D and sleepiness [26,27]. Yet, with appropriate covariate adjustment, others have reported null findings [15,17].

The present study has some methodological limitations. First, all sleep measures were assessed using self-report, which has been

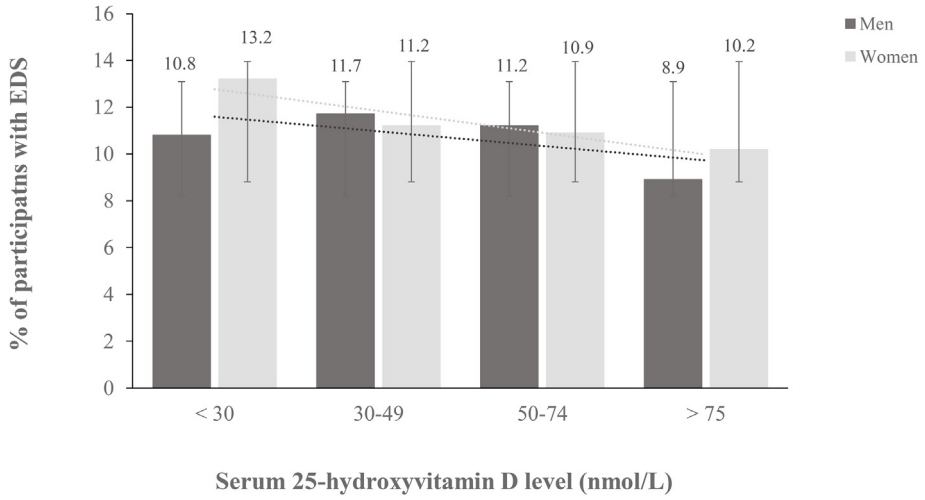

Fig. 4. Prevalence of excessive daytime sleepiness (EDS) across categories of serum 25-hydroxyvitamin D level in men and women. The Tromsø Study 2015–2016. Error bars represent 2 standard deviations.

reported to show less consistent findings than studies using objective sleep measures [15]. Nevertheless, objective sleep measurements may vary depending on the method used (i.e., whether obtained using a gold standard polysomnography or based on more approximate methods such as actigraphy) [51]. Objective sleep recordings are typically performed over a short period of time (usually 1–7 days). Thus, such measurements represents a cross-sectional estimate of an individual's sleep health, whereas the focus of the present study was on habitual sleep traits. Second, information regarding melatonin use was not available. Third, the prevalence of vitamin D deficiency in the present study was low, compromising the power to identify significant associations (especially for subgroup analyses). Fourth, the study population consisted of adults aged 40 years and older, living in an Arctic area of Northern Norway. Extrapolation of the results to younger age-groups or to populations living under different conditions might not be appropriate. Also, data to analyse non-attenders was not available, which could have increased the generalizability. Fifth, DAGs were used to identify relevant confounding factors. However, an important premise of DAGs lies explicitly in the name, emphasizing the existence of an acyclic relationship between the exposure and the outcome. Many of the covariates treated as confounding factors in our study could have been related to s-25(OH)D in an indirect, or even bidirectional manner, for instance through variations in diet, BMI, physical activity, and reduced exposure to sunlight. Finally, a cross-sectional study design as applied in the present study cannot infer causal relationships. The only appropriate way to determine whether the association between s-25(OH)D and sleep health reflects a true causal relationship, rather than confounding or reverse causation, is through well-designed RCTs [52].

This study also has strengths, such as the large sample size of more than 20,000 participants and the high attendance rate (65%), both strengthening generalizability of the results. The categorical sleep measures were adequately prevalent with regards to the study's aim of detecting significant associations between s-25(OH)D and self-reported sleep measures.

5. Conclusion

In conclusion, a tenuous association was found between s-25(OH)D and self-reported sleep measures in this Arctic population. The results conflicted according to sex, s-25(OH)D group and sleep measure. Statistical significance was lost for most of the comparisons when adjusted for confounding factors. Given the cross-sectional design of the study, causal inferences regarding the relationship between vitamin D and self-reported sleep measures could not be drawn, and the effect of vitamin D supplementation on sleep ought to be settled through RCTs.

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CRediT authorship contribution statement

A.U. Larsen: Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization. **L.A. Hopstock:** Methodology, Investigation, Writing – review & editing. **R. Jorde:** Writing – review & editing, Project administration. **G. Grimnes:** Methodology, Writing – review & editing, Supervision.

Declarations of competing interest

The authors have no competing interests to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleepx.2022.100056.

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