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Association between serum 25-hydroxyvitamin D concentration and symptoms of respiratory tract infection in a Norwegian population: the Tromsø Study

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Abstract

Objective: Previous studies have suggested anti-infection effects of vitamin D, although the associations reported between vitamin D (serum 25-hydroxyvitamin D (25(OH)D) concentration) and respiratory tract infection (RTI) are conflicting. The main aim of the present study was to explore this association in a Norwegian population.

Design: We examined the association between serum 25(OH)D and recent RTI symptoms in 6350 middle-aged and elderly participants in the Tromsø Study 6. The main outcome measurement was self-reported RTI symptoms in the previous week.

Setting: Tromsø, Norway, 69°N.

Subjects: Six thousand three hundred and fifty middle-aged and elderly residents of Tromsø.

Results: Of the 6350 included, 791 (12·5 %) reported RTI symptoms in the previous week. We classified serum 25(OH)D concentrations into quartiles and adjusted the data for current smoking habit and month of attendance. The prevalence of RTI symptoms did not increase with decreasing serum 25(OH)D level, was highest in quartile 3 (15·0 %) followed by quartile 4 (12·4 %), and was lowest in quartiles 1 and 2 (11·1 % and 11·4 %). There was no trend for increasing duration of illness with decreasing serum 25(OH)D. The prevalence of RTI symptoms was not significantly associated with the intake of fish, *n*-3 capsules or vitamin and/or mineral supplements, or sun exposure. Only use of cod-liver oil or fish oil capsules daily or sometimes was significantly associated with fewer RTI symptoms during the preceding 7 d ($P = 0{\cdot}04$).

Conclusions: Low serum 25(OH)D was not associated with increased prevalence of recent RTI symptoms. Our findings do not support the idea that vitamin D supplementation can reduce the incidence of RTI in Norway.

Keywords
Respiratory tract infection
Vitamin D
Norway

Symptoms of respiratory tract infection (RTI) are a frequent reason for visiting a doctor[1,2], although most people with symptoms of a common cold do not seek health care[3]. RTI represent a major economic burden because of the need for hospitalization in severe cases and because of disruption of work caused by RTI symptoms[4,5].

Vitamin D plays an important role in bone mineralization and skeletal health[6]. Vitamin D is formed in the skin from 7-dehydrocholesterol after activation by UV-B radiation (290–315 nm)[7]. Dietary products are the most important source of vitamin D at northern latitudes during the wintertime because sunlight exposure during this time is inadequate for inducing sufficient endogenous production of vitamin D[8,9]. Foods that contribute the most to dietary intake of vitamin D vary between countries and habitual dietary patterns. In Norway, fish and cod-liver oil are the predominant food sources[9,10] and intake of fresh cod liver is important in northern Norway[11]. The presence of the vitamin D receptor and enzymes needed to hydroxylate 25-hydroxyvitamin D (25(OH)D) to its active form 1,25-dihydroxyvitamin D is found in the intestines and in tissues throughout the body[12]; this widespread distribution suggests that vitamin D is important for more than skeletal health. Low circulating levels of 25(OH)D have been associated with a number of extraskeletal diseases such as cancer, diabetes and CVD[13–16], and 25(OH)D plays a key role in immunity[17].

Previous studies have reported associations between low serum 25(OH)D concentration and increased occurrence of RTI[2,18,19]. However, other studies performed in selected

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populations have not found a significant association[20,21]. The evidence for a favourable effect of vitamin D on resistance to RTI is inconsistent and is not based on randomized controlled trials[17]. The main aim of the present study was to determine whether vitamin D level is associated with symptoms of RTI in the Norwegian population.

Experimental methods

The Tromsø Study is a repeated, multi-purpose, population-based study in the municipality of Tromsø, Norway[22]. Tromsø is a city in the northern part of Norway, 69°N, with 69 000 inhabitants. The sixth survey (Tromsø 6) took place between October 2007 and December 2008, with a break in July 2008. The Department of Community Medicine, University of Tromsø, provides scientific leadership and administration of the Tromsø Study.

Persons invited to participate in Tromsø 6 included all residents aged 40–42 years or 60–87 years, a 10 % random sample of individuals aged 30–39 years, a 40 % random sample of individuals aged 43–59 years, and persons who had attended the second visit of Tromsø 4 if not already included in the three groups above. The Population Registry of Norway, which maintains the unique national identity number given to all citizens, was the source of the invitations.

The attendance rate was 65·7 %, giving 12 984 individuals who attended the first visit. About two-thirds of the participants who attended the first visit were invited to a second visit, which included an extended medical examination, if they fulfilled one of the following criteria: all persons aged 50–62 years or 75–84 years, a 20 % random sample of men and women aged 63–74 years, or persons, if not already included in the two groups above, who had attended the second visit of Tromsø 4.

A total of 7958 persons who attended the first visit were invited to the second visit, of which our study was a part, and 7307 attended (91·8 %).

Examinations

Information was obtained from questionnaires, clinical examinations and blood samples collected by specially trained health-care workers using standardized procedures.

The primary outcome was recent symptoms of RTI based on the response to the following question asked during the second visit: 'Have you had symptoms of the common cold, acute bronchitis or other airway infection in the last 7 days?' Those answering 'yes' were asked how many days had passed since the illness started. The participants also answered questions about smoking, self-reported health, CVD, asthma and chronic obstructive pulmonary disease (COPD), sunlight exposure, eating fish, and use of fish oil, *n*-3 (omega-3) and vitamin and/or mineral supplements. Height and weight were measured in all individuals.

Non-fasting blood samples were drawn from an antecubital vein at the first visit. Serum 25(OH)D concentration was measured using an electrochemiluminescence immunoassay on an automated clinical chemistry analyser (Modular E170; Roche Diagnostics GmbH, Mannheim, Germany)[23]. The total analytical CV was 7·3 %. At the second visit, blood was also drawn for measurement of C-reactive protein (CRP) concentration[24].

Spirometry was performed using a SensorMedics Vmax Encore 20 spirometer, following American Thoracic Society/European Respiratory Society criteria[25]. Norwegian reference values were used[26].

Statistical analysis

The percentages of persons reporting symptoms of recent RTI were analysed in relation to the characteristics of the participants such as smoking habit, self-reported diseases, sun exposure, intake of fatty fish and vitamins, BMI, spirometry results and serum 25(OH)D concentration. Information about CRP concentration was also included in the analyses to increase the validity of the RTI questions.

The spirometry results were dichotomized, and the ratio between forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) $<0{\cdot}7$ was regarded as indicating bronchial obstruction. The FEV_1:FVC ratio is used as a diagnostic criterion of COPD in the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[27].

The immunometric method used to measure serum 25(OH)D concentration yields systematically higher values in smokers than in non-smokers[28]. Serum 25(OH)D level varies by season. Because the serum 25(OH)D threshold needed for an adequate immune response is not known, we divided serum 25(OH)D concentrations into four quartiles and adjusted these data for current smoking status and month of participation by allocating smokers and non-smokers into quartiles for each month.

The main outcome measure was recent RTI symptoms. Patient characteristics, sun exposure, intake of fatty fish and vitamins, BMI, lung function and pre-questionnaire serum 25(OH)D concentration were analysed as possible predictors of RTI. The serum 25(OH)D quartile was used as a secondary outcome with the same explanatory variables.

Three sensitivity analyses were performed. Because the time difference between the first and second visit varied considerably, we narrowed the analyses to participants who attended the second visit within 28 d after the first visit. Recent RTI symptoms are associated with increased CRP values[24], and the variation in the prevalence of RTI symptoms supported by a CRP level ≥ 5 mg/l was analysed. In the third sensitivity analysis, smokers and non-smokers were analysed separately, using 25(OH)D quartiles adjusted only for the month of attendance.

A two-sided Pearson χ^2 test was used for dichotomous variables. Tests for linear trends of frequencies were performed using the Wald χ^2 test. The statistical software package SPSS 19·0·0 for Windows was used in the statistical analyses. A P value $<0{\cdot}05$ was considered significant. The Tromsø Study complies with the Declaration of Helsinki,

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Table 1 Characteristics, including intake of fish and dietary supplements, of 6350 middle-aged and elderly participants in the Tromsø Study 6, Norway (October 2007 to December 2008)

	n	%
Sex		
Men	2735	43·1
Women	3615	56·9
Age		
<65 years	3684	58·0
≥65 years	2666	42·0
Smoking		
Current smoker	1147	18·1
Ex-smoker	2926	46·1
Never smoker	2187	34·4
Missing data	90	1·4
Solarium or any form of light therapy during the previous 7 d		
Yes	41	0·6
No	1646	25·9
Missing data	4663	73·4
Travelling to the south during the past 4 weeks		
Yes	118	1·9
No	1565	24·6
Missing data	4663	73·4
Consumption of lean fish		
1–2 times/d	150	2·4
4–6 times/week	701	11·0
1–3 times/week	3894	61·3
2–3 times/month	1038	16·3
0–1 times/month	258	4·1
Missing data	309	4·9
Consumption of fatty fish (e.g. salmon, trout, mackerel, herring, halibut, redfish)		
1–2 times/d	155	2·4
4–6 times/week	306	4·8
1–3 times/week	2533	39·9
2–3 times/month	2098	33·0
0–1 times/month	926	14·6
Missing data	332	5·2
Cod liver and roe for dinner		
≥13 times/year	267	4·2
7–12 times/year	588	9·3
4–6 times/year	1486	23·4
1–3 times/year	2819	44·4
Rarely/never	1102	17·4
Missing data	88	1·4
Intake of cod-liver oil or fish oil capsules		
Yes, daily	1492	23·5
Sometimes	802	12·6
No	3057	48·1
Missing data	999	15·7
Intake of *n*-3 capsules (fish oil, seal oil)		
Yes, daily	2522	39·7
Sometimes	885	13·9
No	2399	37·8
Missing data	544	8·6
Intake of vitamin and/or mineral supplements		
Yes, daily	605	9·5
Sometimes	320	5·0
No	4169	65·7
Missing data	1256	19·8

and each individual gave written informed consent prior to participation. The Regional Committee of Medical and Health Research Ethics approved the study.

Results

A total of 6350 persons, 86·9 % of those who attended the second examination, provided a serum 25(OH)D measurement and answered the main question 'Have you had symptoms of the common cold, acute bronchitis, or other airway infection in the last 7 days?', and were thus included in the study. The mean age was 63·7 years, 56·9 % were women and the average BMI was 27·1 kg/m^2. Of the 6350 individuals, 791 (12·5 %) answered 'yes' to the main question. Characteristics of the participants are presented in Table 1.

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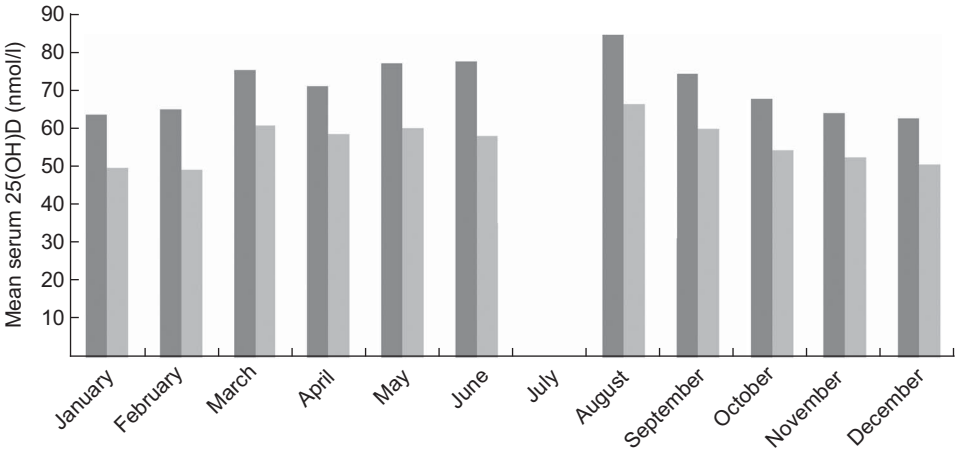

Fig. 1 Seasonal variation in serum 25-hydroxyvitamin D (25(OH)D) concentration according to smoking status (■, smokers; ■, non-smokers) among 6350 middle-aged and elderly participants in the Tromsø Study 6, Norway (October 2007 to December 2008, with a break in July 2008)

Table 2 Frequency of recent symptoms of RTI (*n* 791) analysed by quartile of serum 25(OH)D concentration and patient characteristics, adjusted for smoking and date of attendance, among 6350 middle-aged and elderly participants in the Tromsø Study 6, Norway (October 2007 to December 2008)

	Recent RTI symptoms (%)				
	Serum 25(OH)D quartile adjusted for smoking and date of attendance				
	Quartile 1 (*n* 1563)	Quartile 2 (*n* 1623)	Quartile 3 (*n* 1598)	Quartile 4 (*n* 1566)	Total (*n* 6350)
All participants*	11·1	11·4	15·0	12·4	12·5
Sex					
Male (*n* 2735)	13·0	11·9	14·6	11·6	12·8
Female (*n* 3615)†	9·8	11·0	15·2	13·0	12·2
Age					
≥65 years (*n* 2666)	8·5	12·2	13·9	10·9	11·3
<65 years (*n* 3684)	13·4	10·8	15·6	13·3	13·3
Smoking					
Current smoker (*n* 1147)	16·4	14·5	24·0	18·8	18·5
Never or ex-smoker (*n* 5113)	10·0	10·7	12·8	11·1	11·1
Self-rated health					
Bad or neither good nor bad (*n* 2369)	13·6	13·8	16·9	13·2	14·3
Good or excellent (*n* 3921)‡	9·3	9·6	13·9	12·0	11·3
Spirometry					
FEV_1:FVC < 0·7 (*n* 1440)§	11·4	13·5	17·3	17·3	14·9
FEV_1:FVC ≥ 0·7 (*n* 4898)	11·0	10·8	14·1	10·9	11·7
BMI					
<30 kg/m^2 (*n* 5017)‖	10·9	11·2	15·1	12·8	12·6
≥30 kg/m^2 (*n* 1326)	11·6	12·3	14·2	10·2	12·1

RTI, respiratory tract infection; 25(OH)D, 25-hydroxyvitamin D; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.
*Linear-by-linear association: $P = 0·042$.
†Linear-by-linear association: $P = 0·004$.
‡Linear-by-linear association: $P = 0·008$.
§Linear-by-linear association: $P = 0·011$.
‖Linear-by-linear association: $P = 0·022$.

Current smokers had 20–25 % higher serum 25(OH)D concentrations. A similar pattern of seasonal variation in serum 25(OH)D concentration was found among smokers and non-smokers (Fig. 1).

There was no significant association between the prevalence of RTI symptoms and reduced serum 25(OH)D concentration (Table 2). The prevalence of RTI symptoms was highest in quartile 3 (15·0 %), followed by quartile 4 (12·4 %), and lowest in quartiles 1 and 2 (11·1 % and 11·4 %, respectively). This yielded a significant linear-by-linear association ($P = 0·042$) between increasing serum 25(OH)D level and recent RTI symptoms. This relationship was strongest in women, participants with good or excellent self-rated health, those without COPD according to the GOLD criteria and those with a BMI of <30·0 kg/m^2 (Table 2).

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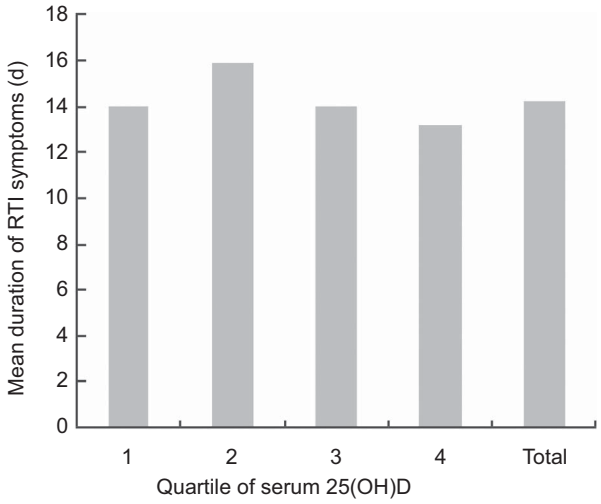

Fig. 2 Mean duration of symptoms of respiratory tract infection (RTI) according to quartile of serum 25-hydroxyvitamin D (25(OH)D) concentration and in total among 6350 middle-aged and elderly participants in the Tromsø Study 6, Norway (October 2007 to December 2008)

The participants who answered 'yes' to the main question were also asked how many days had passed since the symptoms started. The average was 14·2 d, but there was no trend for increasing duration of illness according to serum 25(OH)D concentration (Fig. 2).

There were no associations between the prevalence of RTI symptoms and the frequency of eating lean fish, fatty fish or cod liver and roe, or use of *n*-3 capsules or vitamin and/or mineral supplements. Of those who reported taking cod-liver oil or fish oil capsules daily or sometimes, 10·9 % and 10·3 %, respectively, reported RTI symptoms in the previous 7 d compared with 12·9 % of those not taking cod-liver oil or fish oil capsules ($P = 0·04$; Table 3). There was no association between sun exposure and RTI symptoms (Table 3).

A significantly lower frequency of 25(OH)D concentration within the lowest quartile was found by higher intake of fatty fish, cod liver and roe, capsules of cod-liver oil or fish oil, and vitamin and/or mineral supplements (Table 3).

Sensitivity analyses

Non-fasting blood samples were drawn at the first visit and the participants answered the main question on RTI symptoms at the second visit. There was variability in the time difference between the first and second visit; e.g. for 37·7 % of participants the time difference was 4–8 weeks, and for 17·4 % it was ≥8 weeks. We thus narrowed the analyses to participants with a time difference <28 d. This included 2850 (44·9 %) of the participants. The main result was unchanged. That is, there was still no significant association between the prevalence of RTI symptoms and reduced serum 25(OH)D concentration, and the highest frequency of RTI symptoms was found in the third quartile (Table 4).

Among the 791 participants reporting RTI symptoms, 167 (2·6 % of the total study sample) also had a CRP value of ≥5 mg/l. The frequency of RTI symptoms in combination with CRP ≥5 mg/l in the four vitamin D quartiles showed the same pattern of distribution as for RTI symptoms alone (Table 4).

Of 5113 non-smokers and 1147 smokers, 569 (11·1 %) and 212 (18·5 %) respectively reported RTI symptoms (Table 2). Analysis of the serum 25(OH)D quartiles, adjusted only for month of participation, produced no significant association between serum 25(OH)D concentration and RTI symptoms among either non-smokers or smokers. However, there was an unexpected association between increasing serum 25(OH)D and RTI symptoms only in smokers with COPD, the group with good or excellent self-reported health and those with BMI < 30·0 kg/m^2 ($P = 0·020$, 0·017 and 0·045, respectively).

Discussion

In the present large population-based study, we could not confirm an association between vitamin D level and recent RTI reported by Ginde *et al.*[2] and Berry *et al.*[19]. Serum 25(OH)D concentration was not inversely associated with recent RTI symptoms. This finding seemed to be robust after controlling for date of attendance and smoking habit.

Laaksi *et al.*[18] found that people with a serum 25(OH)D concentration <40 nmol/l had significantly more days of absence from work because of respiratory infection. We found no association between serum 25(OH)D level and duration of RTI symptoms.

The findings are consistent with the results from an intervention study by Jorde *et al.*[29], which concluded that the role of vitamin D in the prevention of influenza and upper respiratory infections remains unresolved.

A strength of our study is that it was a population-based survey with a high attendance rate that included information on recent symptoms obtained directly from the participants. Serum 25(OH)D concentrations were measured before the RTI symptoms were recorded and hence were not a consequence of infection. Another strength is that we measured CRP concentration to confirm that an RTI had occurred[24]. A limitation of our study is the time difference between the blood sample obtained to measure vitamin D level and the questionnaire. 25(OH)D, the major circulating form of vitamin D, has a half-life of about 2 weeks in the blood[30] and we assumed that the serum 25(OH)D level is stable in most of the participants because of the relatively consistent intake of vitamin D and sun exposure. We reanalysed the data by including only those data for participants with <4 weeks difference between the time of blood sample and questionnaire and found the same results.

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Table 3 Frequency of serum 25(OH)D concentration in the lowest quartile and of RTI symptoms according to dietary factors and sun exposure among 6350 middle-aged and elderly participants in the Tromsø Study 6, Norway (October 2007 to December 2008)

		Participants in quartile 1 of serum 25(OH)D		% with RTI (of total)
	n	*n*	%	
Intake of lean fish				
≥4 times/week	851	211	24·8	12·5
1–3 times/week	3894	920	23·6	12·3
2–3 times/month	1038	272	26·2	13·1
0–1 times/month	258	67	26·0	10·9
Intake of fatty fish (e.g. salmon, trout, mackerel, herring, halibut, redfish)				
≥4 times/week	491	109	22·3*	13·4
1–3 times/week	2602	594	22·8	12·6
2–3 times/month	2127	523	24·6	11·7
0–1 times/month	934	274	29·3	12·7
Intake of cod liver and roe				
≥13 times/year	267	50	18·7*	15·4
7–12 times/year	588	119	20·2	12·1
4–6 times/year	1486	315	21·2	12·4
1–3 times/year	2819	729	25·9	12·7
Rarely/never	1102	325	29·5	11·3
Intake of cod-liver oil or fish oil capsules				
Yes, daily	1492	241	16·2*	10·9‡
Sometimes	802	223	27·8	10·3
No	3057	850	27·8	12·9
Intake of *n*-3 capsules (fish oil, seal oil)				
Yes, daily	2522	609	24·1	13·4
Sometimes	885	213	24·1	12·9
No	2399	626	26·1	11·9
Intake of vitamin and/or mineral supplements				
Yes, daily	605	87	14·4*	12·7
Sometimes	320	82	25·6	11·9
No	4169	1079	25·9	12·3
Solarium or any form of light therapy during the previous 7 d				
Yes	42	5	25·3†	11·9
No	1868	473	11·9	11·9
Missing data	4663			
Travelling to the south during the past 4 weeks				
Yes	160	13	8·1*	13·8
No	1747	464	26·6	11·8
Missing data	4663			

25(OH)D, 25-hydroxyvitamin D; RTI, respiratory tract infection.
*χ^2 test for linear trend: $P < 0{\cdot}001$.
†χ^2 test: $P = 0{\cdot}007$.
‡χ^2 test for linear trend: $P = 0{\cdot}030$.

Table 4 Sensitivity analyses: frequency of RTI symptoms in the previous week in subgroups and of RTI symptoms in combination with elevated CRP level by quartile of serum 25(OH)D concentration among 6350 middle-aged and elderly participants in the Tromsø Study 6, Norway (October 2007 to December 2008)

	Serum 25(OH)D quartile				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Total
Recent symptoms of RTI (% of total)	11·1	11·4	15·0	12·4	12·5
Time between measurement of serum 25(OH)D and RTI question (% of total)					
0–4 weeks (*n* 2850)	12·0	13·2	15·7	12·9	13·4
>4 weeks–8 weeks (*n* 2449)	10·0	9·5	16·1	11·5	11·8
>8 weeks (*n* 1051)	10·8	10·7	10·4	13·4	11·3
RTI symptoms in combination with CRP ≥5 mg/l	2·5	2·1	3·5	2·4	2·6

RTI, respiratory tract infection; 25(OH)D, 25-hydroxyvitamin D; CRP, C-reactive protein.

We also adjusted for current smoking status. When smokers and non-smokers were analysed separately, we found no associations between decreasing levels of vitamin D and RTI symptoms. We found a significantly higher vitamin D level in participants with a high intake of lean fish, fatty fish, cod liver and roe, and in those who took cod-liver oil, fish oil capsules or vitamin and/or mineral supplements, as one might expect[10]. Only use

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of cod-liver oil or fish oil capsules daily or sometimes was significantly associated with fewer RTI during the previous 7 d. However, the difference between users and non-users of cod-liver oil or fish oil capsules was small and may have occurred by chance. If the difference is real, we cannot conclude that this is related to an effect on the serum 25(OH)D concentration. It is possible that regular ingestion of cod-liver oil, a strong tradition as a preventive measure against RTI in Norway, may be related to an unknown factor.

In conclusion, low serum 25(OH)D concentration was not associated with recent RTI symptoms. Our findings do not indicate that vitamin D supplementation reduces the incidence of RTI in Norway.

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