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# Research Submission

## Association Between Headache and Serum 25-Hydroxyvitamin D; the Tromsø Study: Tromsø 6

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**Background.—High prevalence of headache has been associated with high latitude, thus suggesting a relation with vitamin D. However, there are so far no reports on the association between serum 25-hydroxyvitamin D (25[OH]D) and headache.**

**Objective.—To investigate the association between headache and serum 25(OH)D in a general population.**

**Methods.—Cross-sectional study based on questionnaires from 11,614 persons who participated in the sixth survey of the Tromsø Study (Tromsø 6) carried out in 2007-2008. The data were stratified according to smoking status and analyzed with regard to migraine and non-migraine headache. Adjustments were done for age, body mass index (BMI), gender, season, chronic diseases, education, physical exercise, and alcohol consumption.**

**Results.—Headache of non-migraine type was associated with low levels of serum 25(OH)D with an odds ratio (OR) of 1.20 (1.04-1.39) in the lowest quartile as compared to the highest serum 25(OH)D quartile. No significant association was found between migraine and serum 25(OH)D.**

**Conclusion.—Non-migraine headache was associated with low levels of serum 25(OH)D. Although adjustment were done for possible confounders, this finding may still reflect lifestyle rather than causality, and further studies are needed to investigate this. No association was found between serum 25(OH)D and migraine.**

**Key words: headache, migraine, vitamin D, serum 25-hydroxyvitamin D, Norway**

**Abbreviations: 25(OH)D 25-hydroxyvitamin D, BMI body mass index, ICHD-II International Classification of Headache Disorders, OR odds ratio, VDR vitamin D receptor**

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Vitamin D deficiency and its impact on health have been subject to increasing attention for the last decade. There is already a well-established connection between bone health and low levels of vitamin D, and several other conditions, including chronic pain, have also recently been associated with vitamin D deficiency.[1] The mechanism of the association between pain and vitamin D is not yet established, but since the vitamin D receptor (VDR) is widespread in the brain, it has been speculated if there could be an association between headache and low levels of vitamin D. Prakash et al[2] described an increasing

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prevalence of all kinds of headache with increasing latitude, implying that there could be an association with vitamin D levels which is dependent on solar exposure. A few case reports have shown the effect of vitamin D supplementation on headache, but these were very small studies and not placebo controlled.[3-5]

The aim of this cross-sectional study was therefore to investigate if there is any association between serum 25-hydroxyvitamin D (25(OH)D) and headache in a general population using data from the sixth survey in the Tromsø Study, which was carried out in 2007-2008.

## METHODS

**The Tromsø Study.—**The Tromsø Study, initiated in 1974, is an epidemiologic, prospective study of health problems and chronic diseases, and a resource for the surveillance of disease risk factors.[6] The main focus was initially cardiovascular disease, however, several other chronic diseases and conditions have been included through the years, like vitamin D status and chronic pain. The purpose of the sixth survey (Tromsø 6) performed in 2007-2008, was to collect novel and repeated measurement of exposure data and to assess levels of disease-risk factors. The Tromsø Study design and population are described by Jacobsen et al.[7] In the sixth survey 19,762 subjects were invited; 12,982 attended. The age of the participants ranged from 30 to 87 years. The study was conducted by the Department of Community Medicine, University of Tromsø.

**Measurements.—**The participants completed 2 questionnaires on lifestyle variables and health. One was filled in before the first visit and handed in at attendance, the other after the first visit and was either handed in before they left the examination site or returned by mail later. An English translation of the questionnaires is available at http://www.tromsoundersokelsen.no. The answers from the 2 questionnaires were combined for the analyses and used as either dichotomized variables (smoking yes/no and education, tertiary level yes/no [college and/or university] ) or continuous variables (alcohol consumption, physical exercise, and self-reported chronic diseases [asthma, diabetes, stroke, hypertension] ). The physical exercise estimate was calculated in hours/week, giving hard activity double weight and light activity half weight compared to moderate activity. Weekly alcohol consumption was estimated in units/week. Each of the 4 chronic diseases was given equal weight as a confounder in the analyses and was therefore summarized to a continuous score.

**Headache.—**The participants were asked in the questionnaire if they had experienced headache in the last year (yes/no). If the answer was yes, they were asked to specify if it was of migraine or other type of headache (not specified further), average frequency per month (less than 1 day/1-6 days/7-14 days/more than 14 days), average duration (less than 4 hours/4-24 hours/1-3 days/more than 3 days), intensity (mild/moderate/severe), type (pulsating/pressure [tension]/unilateral), and if there were any worsening of symptoms with physical activity. The latter 4 questions were used to evaluate whether the criteria for a diagnosis of migraine was fulfilled according to the International Classification of Headache Disorders (ICHD-II).[8] Migraine was defined as an answer of "yes" to the question on migraine type of headache, combined with 1; headache with a duration of 4-72 hours and 2; at least 2 of the following 4 criteria: intensity moderate or strong, pulsating character, unilateral distribution, and worsening by physical activity. All other types were classified as non-migraine headache. Thus, persons who answered "no" to the migraine question were classified as non-migraine even if they fulfilled the other migraine criteria.

**25(OH)D Analyses.—**Non-fasting blood samples were drawn, and serum 25(OH)$D_3$ was measured by immunometry (electrochemiluminescent immunometric assay) using an automated clinical chemistry analyzer (Modular E170; Roche Diagnostics GmbH, Mannheim, Germany). According to the producer, the assay has, for total analytical precision, a coefficient of variation ≤7.8% as judged in any of 3 different concentrations (48.6-73.8-177.0 nmol/L). The cross-reactivity with 25(OH)$D_2$ was <10%, and the analytical sensitivity was 10 nmol/L. In Norway, all food fortification and ordinary supplements are vitamin $D_3$. Vitamin $D_2$ preparations are only sold by prescription and to highly selected patients. At present, the laboratory has no reference values for 25(OH)D, but the manufacturer provides a

population-based reference range of 27.7-107.0 nmol/L for adults as a guideline. This analysis has been approved by Norwegian Accreditation. After the study was completed, this method was found to overestimate the serum 25(OH)D in smokers.[9] To adjust for this, we chose to divide the study population into current smokers and non-smokers. Serum 25(OH)D values in former smokers are shown to be at the same level as non-smokers, and therefore the former smokers are included in the non-smokers' group. Subjects without information about smoking status or missing serum 25(OH)D values were excluded.

**Statistical Analyses.—**Data were analyzed stratified according to smoking status. Interaction was analyzed by including 25(OH)D*gender in the regression analyses and was not found to be significant. Therefore, men and women were pooled in the analyses, and adjustment was done accordingly. Due to the binary nature of the headache data, logistic regression analyses were used to evaluate the association between serum 25(OH)D using the presence of headache (any type) as a dichotomous variable. Normal distribution of the variables was evaluated with visual inspection of histograms and determination of skewness and kurtosis. Serum 25(OH)D was either used as a continuous variable or divided into quartiles for OR analyses. Adjustment for season was performed by dividing the serum 25(OH)D-values into quartiles for each month individually, thus adjusting for season without use of dummy variables. Age, body mass index (BMI), physical exercise, number of chronic diseases, and alcohol consumption were used as continuous variables, and gender and education as dichotomous variables.

Trend analyses in the logistic regression were performed using serum 25(OH)D quartiles as a continuous variable. *T*-test, Mann-Whitney, and chi-square test were used comparing means, medians, and proportions. The data are shown as mean (SD) unless otherwise indicated. The number of self-reported chronic diseases was not normally distributed but is presented as mean and SD to lessen loss of information since the median value is zero.

All tests were performed 2-sided, and a $P$ value $< .05$ was considered statistically significant. Statistical analyses were performed with PASW (SPSS) version 18.0 software (SPSS Inc., Chicago, IL, USA).

**Ethics.—**All participants gave written consent before participating in the study. The study was approved by the Regional Committee for Medical and Health Research Ethics and The Data Inspectorate of Norway.

## RESULTS

A total of 12,982 participants attended the sixth survey of the Tromsø Study in 2007-2008. Among these, 197 had no record of smoking status, 167 had no serum 25(OH)D measurement, 1011 had not answered the question about headache in the questionnaire, and 455 had missing values of the remaining parameters included in the analyses. Some had more than 1 missing value, and a total of 1368 were excluded. Thus, 11,614 persons were included for analyses, which was 59% of the 19,762 invited in the Tromsø study.

The baseline characteristics, stratified according to smoking status, are shown in Table 1. A total of 725 had filled in the questionnaire that they suffered from migraine, but only 322 of these fulfilled our migraine criteria. Likewise, of the 3336 who reported to have "other type of headache," 1051 fulfilled the supplementary migraine criteria as described in the Methods section.

Table 2 shows unadjusted baseline characteristics of the population divided into subgroups according to headache status. In both headache groups, the persons were younger, they drank less alcohol than persons without headache, and the proportion of women were higher. Furthermore, in the non-smokers group, lower serum 25(OH)D levels were found in both the non-migraine and migraine headache groups. Persons with non-migraine headache exercised less than persons without headache. In the smokers group, persons with non-migraine type of headache reported a higher number of chronic diseases.

The OR for headache across serum 25(OH)D quartiles are presented in Table 3, with the highest serum 25(OH)D quartile as reference. Women had significantly higher rate of headache than men

**Table 1.—Baseline Characteristics of the Study Population. The Tromsø Study: Tromsø 6**

| | Nonsmokers (n = 9275) | Smokers (n = 2339) |
|---|---|---|
| Female/male | 4828/4447 | 1294/1045 |
| Age (years) | 58.0 (12.8) | 55.3 (11.6) |
| BMI (kg/m$^2$) | 27.1 (4.2) | 26.1 (4.3) |
| Serum 25(OH)D (nmol/L) | 55.1 (17.7) | 68.9 (21.1) |
| Headache the last year† | 3151 (34.0%) | 908 (38.8%) |
| Classified as migraine | 248 (2.7%) | 74 (3.2%) |
| Classified as non-migraine headache | 2906 (31.4%) | 833 (35.7%) |
| Intensity‡ | | |
| Mild | 1007 | 257 |
| Moderate | 1282 | 401 |
| Severe | 129 | 55 |
| Frequency‡ | | |
| Less than 1 day | 692 | 178 |
| 1-6 days | 1351 | 416 |
| 7-14 days | 236 | 70 |
| More than 14 days | 143 | 57 |
| Numbers of chronic diseases§ | 0.44 (0.65) | 0.37 (0.61) |
| Physical exercise (hrs/week) | 2.04 (2.33) | 1.25 (1.76) |
| Education > high school level | 3858 (42.0%) | 595 (25.8%) |
| Alcohol consumption (units/week) | 2.5 (3.3) | 2.9 (4.2) |

†Total number is smaller than migraine and non-migraine added, because some did specify headache type but did not state if they had headache the last year.
‡Sum differs from total number with headache, because all persons did not specify strength and/or frequency.
§Self-reported asthma, hypertension, stroke, diabetes.

($P < .005$) in all groups. In model 1 with adjustment for age, gender, BMI, and chronic diseases, the non-smokers had a significantly higher OR for non-migraine type of headache in the lowest quartile. This finding remained significant in model 2 when additional adjustment was done for the possible confounders physical exercise, alcohol consumption, and educational level. No association between headache and serum 25(OH)D was found in the current smokers group. There was no clear trend between serum 25(OH)D levels and migraine, regardless of smoking status.

In the non-migraine headache group, there was no significant differences between serum 25(OH)D levels and severity of headache (data not shown).

## DISCUSSION

To our knowledge, this is the first large cross-sectional study where prevalence of headache has been related to serum 25(OH)D levels. We found that non-migraine headache was associated with low levels of serum 25(OH)D, and the association remained statistically significant after adjusting for possible confounders. However, no significant association was found between migraine and serum 25(OH)D levels.

The literature on vitamin D in relation to headache is sparse. In a meta-analysis on prevalence of

**Table 2.—Baseline Characteristics According to Headache Type. The Tromsø Study: Tromsø 6**

| | Nonsmokers | | | Smokers | | |
|---|---|---|---|---|---|---|
| | No Headache n = 6121 | Migraine n = 248 | Non-Migraine Headache n = 2906 | No Headache n = 1432 | Migraine n = 74 | Non-Migraine Headache n = 833 |
| Gender (female/male) | 2820/3301 | 184/64*** | 1822/1084*** | 686/746 | 54/20*** | 552/281*** |
| Age (years) | 59.8 (12.5) | 50.3(10.9)*** | 54.0 (12.1)*** | 57.1 (11.6) | 48.9 (9.7)*** | 52.4 (10.8)*** |
| BMI (kg/m$^2$) | 27.0 (4.1) | 26.7 (4.6) | 27.1 (4.4) | 26.0 (4.2) | 25.7 (4.4) | 26.2 (4.5) |
| Serum 25(OH)D (nmol/L) | 55.8 (17.9) | 53.0 (16.1)* | 53.5 (17.2)*** | 68.8 (20.4) | 70.1 (27.9) | 68.9 (21.4) |
| Education >high school level (%) | 41.4 | 49.4* | 42.9 | 25.8 | 37.8* | 24.3 |
| Alcohol (units/wk) | 2.6 (3.5) | 1.8 (2.2)*** | 2.1 (2.9)*** | 3.3 (4.4) | 2.1 (2.3)* | 2.6 (4.0)*** |
| Physical exercise (hrs/wk) | 2.1 (2.4) | 2.3 (2.5) | 1.9 (2.2)** | 1.3 (1.9) | 1.3 (1.9) | 1.2 (1.6) |
| Self-reported chronic diseases (number) | 0.44 (0.65) | 0.36 (0.58) | 0.44 (0.65) | 0.34 (0.59) | 0.38 (0.67) | 0.41 (0.64)*** |

Unadjusted analyses on no headache vs headache category, using either Student's *t*-test, Mann-Whitney, or chi-square test.
*$P < .05$, **$P < .01$, ***$P < .005$.

**Table 3.—Odds Ratio for Different Types of Headache Across Serum 25(OH)D Quartiles. The Tromsø Study: Tromsø 6**

| | Non-Smokers | | Smokers | |
|---|---|---|---|---|
| Serum 25(OH)D Quartiles† | Migraine‡ (n = 6122) | Non-Migraine Headache§ (n = 7608) | Migraine‡ (n = 1447) | Non-Migraine Headache§ (n = 1756) |
| Model 1¶ | | | | |
| 1st | 1.14 (0.76-1.71) | 1.31 (1.14-1.49)** | 1.18 (0.59-2.37) | 1.03 (0.80-1.34) |
| 2nd | 1.52 (1.04-2.23)* | 1.18 (1.03-1.35)* | 1.07 (0.53-2.16) | 0.96 (0.74-1.25) |
| 3rd | 1.31 (0.89-1.94) | 1.12 (0.97-1.28) | 1.03 (0.50-2.12) | 1.12 (0.87-1.45) |
| 4th | Ref. | Ref. | Ref. | Ref. |
| Model 2†† | | | | |
| 1st | 1.03 (0.67-1.57) | 1.20 (1.04-1.39)* | 1.21 (0.57-2.55) | 1.03 (0.76-1.36) |
| 2nd | 1.46 (0.98-2.16) | 1.11 (0.97-1.25) | 1.07 (0.50-2.28) | 0.91 (0.69-1.20) |
| 3rd | 1.19 (0.79-1.78) | 1.06 (0.92-1.22) | 0.99 (0.45-2.16) | 1.10 (0.84-1.02) |
| 4th | Ref. | Ref. | Ref. | Ref. |

*$P < .05$. **$P < .005$.
†Serum 25(OH)D quartiles limits in smokers 21.7-71.4, 44.3-83.3, 54.9-96.8, and 67.7-201.2 nmol/L and in nonsmokers 6.7-54.5, 37.1-65.7, 45.9-77.9, and 56.7-182.50 nmol/L. The quartiles overlap due to seasonal differences (see Methods section).
‡Non-migraine headache excluded.
§Migraine excluded.
¶Adjusted for gender, age, body mass index (BMI), and self-reported chronic disease.
††Adjusted for same parameters as model 1 and in addition education level, alcohol consumption, and physical exercise.

headache, Prakash et al[2] found an increasing prevalence with increasing latitude. One possible explanation could be lower levels of vitamin D in the North due to less solar exposure. However, as emphasized by the authors, this is highly speculative as no measurements of serum 25(OH)D were performed, and no adjustments were done for possible confounders. Furthermore, the serum 25(OH)D level in the general population has been shown not to uniformly decrease with latitude, and in some Northern countries, the serum 25(OH)D levels are fairly high due to sun-seeking behavior and nutritional habits.[10] Accordingly, the association between headache and latitude may be due to other factors than vitamin D.

However, some support for a headache-vitamin D association was reported from a small Norwegian study.[11] In a group of 63 subjects selected from a general practice due to suspected hypovitaminosis D, those reporting headache had significantly lower serum 25(OH)D levels than the subjects without headache, even after adjustment for age, gender, and season. Due to the design of the study, the authors wisely inferred caution in the interpretation of the results. Similarly, O'Brien[12] and Wheeler[13] both found migraine patients to have low level of vitamin D, but the results from these studies have not been published in detail and seem to be unadjusted.

To our knowledge, there are only a few case reports on the effect of vitamin D on headache, and no adequate intervention studies have been performed. Thys-Jacobs[4,5] have published 2 case studies, one with 2 women with postmenopausal migraine and another with 2 women with menstrual migraine, where all 4 women were found to have positive effect of high-dose vitamin D on migraine symptoms. Similarly, Prakash et al[3] reported an effect of high-dose vitamin D on chronic tension-type headache in 8 patients, but they also suffered from osteomalacia and bone pain, and the improvement may be related to the bone effect of vitamin D.

Vitamin D deficiency has been associated with chronic pain, including pain due to osteomalacia.[14] The exact mechanism is not known, but vitamin D may be involved in regulating inflammatory cytokine synthesis,[1] which may play a role in chronic pain. If this mechanism also applies to headache is more speculative. However, the VDR and 1-alfa-hydroxylase, which hydroxylates 25(OH)D to the

active metabolite 1,25-dihydroxyvitamin D, are found in areas in the brain which are thought to be involved in the pathophysiology of headache and migraine,[2,15,16] thereby indicating a role of vitamin D in these tissues.

Headache is a complex disease, and our study has some limitations. Some misclassification of headache types is likely to have occurred. Although a diagnosis of migraine is always based on the medical history alone, a classification based on questionnaire data will be less precise than a diagnosis based on interview of the patient by qualified personnel. The category "non-migraine" is thought to represent, for most parts, tension-type headache. Since no further information was available from the questionnaires, this most likely also includes more rare types of headache such as cluster headache. However, the prevalence of these types of headache in a general population is probably too small to have had any effect on the results.[15]

Migraine is defined by at strict set of criteria;[8] however, it is possible that people report that they have migraine, even though they do not fill all the criteria. Our findings confirm this, with many persons that reported they had migraine but did not fill the ICHD-II criteria. Quite surprising, a large number of those who said they suffered from other types of headache filled the criteria for migraine. This may partially be explained by the design of the questionnaires, where no questions about photosensitivity or total number of attacks were included, thus making our definition of migraine less strict than the ICHD-II definition, and thereby possibly overestimating the number of migraineurs. To take this into account, we only included persons in the migraine group, who filled our migraine criteria and had answered in the questionnaire, that they suffered from migraine. This may on the other hand have underestimated the true number of migraineurs, and caution must be taken when interpreting these results.

Confounding is important, especially in studies regarding vitamin D, since serum 25(OH)D reflects lifestyle and nutritional habits, factors that may affect or be affected by headache. Physical exercise, alcohol consumption, educational level, and some chronic diseases (hypertension, asthma, stroke, diabetes) are also found to influence serum 25(OH)D level.[1,17-19] These factors are by some also considered to be associated with headache in some[20,21] but not all studies.[22-24] We found non-migraine headache to be associated with all these factors, whereas migraine was associated with low alcohol consumption and high educational level. We found it important to include all these possible confounders, but as over-adjustment may weaken the results, we chose to present 2 models with different numbers of confounders included.

The strengths of the study include the large number of participants from a general population, with the same prevalence of non-migraine headache as reported from other studies.[20,25,26] The migraine prevalence was lower than found in other studies,[25,26] this is probably due to differences in definition of migraine. As expected, we also found higher prevalence of headache in women and younger persons, and lower alcohol consumption in persons with headache than in those without,[20] giving an indication of the external validity of the study.

In conclusion, we found that low level of serum 25(OH)D were associated with non-migraine type of headache, and the association remained significant after adjustment for possible confounders. Due to the cross-sectional design of the study, no conclusions can be drawn with regard to causality for which intervention studies are needed.

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