Psychiatry Research 190 (2011) 221–225

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Low serum 25-hydroxyvitamin D levels are associated with depression in an adult Norwegian population

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ARTICLE INFO

Article history:
Received 18 February 2011
Received in revised form 24 June 2011
Accepted 29 June 2011

Keywords:
Mental health
Vitamin D
Epidemiology
Cross-sectional studies
Norway

ABSTRACT

Observational and intervention studies have suggested an association between low levels of 25-hydroxyvitamin D (25(OH)D) and depressive symptoms in several subgroups of disease and age. This study tests the hypothesis in a general population. Our data are based on 10,086 persons who participated in the sixth Tromsø study carried out in 2007–2008. Depressive symptoms were evaluated using the Hopkins Symptoms Check List 10 (SCL-10) based on answers from a questionnaire. Results were adjusted for known confounders such as age, gender, body-mass index, physical exercise, alcohol, education, marital status, kidney function and chronic disease. Results are presented for smokers ($N=1966$) and non-smokers ($N=8120$) separately as our immunoassay seems to overestimate 25(OH)D levels for smokers. Low serum 25 (OH)D levels were found to be a significant predictor of depressive symptoms in both smokers and non-smokers. The association seemed to be stronger in women. The odds ratios for depression in the highest 25 (OH)D quartile were 0.59 (0.39–0.89) in smokers and 0.74 (0.58–0.95) in non-smokers compared with the lowest quartile. However, no conclusions with regard to causality can be drawn due to the cross-sectional design of the study.

1. Introduction

Vitamin D deficiency and its association with several health outcomes have received increasing attention over the last decade. The connection between bone health and vitamin D status has been well established for years, and growing evidence now links low levels of circulating vitamin D to cardiovascular disease, hypertension, neurodegenerative diseases, diabetes, metabolic syndrome and cancer (Holick, 2007).

Psychiatric disorders, especially depression, are also speculated to be dependent on vitamin D status because the vitamin D receptor (VDR) is widely distributed in the human brain including areas that are assumed to be involved in the pathophysiology of depression (Berk et al., 2007; Bertone-Johnson, 2009). Several epidemiological studies have investigated the connection between vitamin D and mental health, but most studies have been on specific sub-groups of age or diseases and the results are inconsistent (Schneider et al., 2000; Armstrong et al., 2007; Hoogendijk et al., 2008; Pan et al., 2009; Milaneschi et al., 2010). A recent, large study on the adult US population found no association between serum concentrations of 25-hydoxyvitamin D (25(OH)D) and depression when adjusting for known confounders (Zhao et al., 2010).

Further studies seem to be needed to establish if there is any correlation, and in the present study we investigate the presence of depressive symptoms in relation to serum 25(OH)D levels when adjusting for several confounders in a large cross-sectional population study in Northern Norway.

2. Methods

2.1. The Tromsø Study

The Tromsø Study, conducted by the University of Tromsø in cooperation with the National Health Screening Service, is a longitudinal, population-based, multipurpose study focusing on lifestyle-related diseases. In the sixth survey performed in 2007–2008, 19,762 subjects were invited; 12,984 attended. The age of the participants ranged from 30 to 87 years. The details of the study design and selection of participants are described in detail by Grimnes et al. (2010).

2.2. Variables

The participants completed questionnaires on lifestyle factors, including smoking (no/former/yes), education (above high school no/yes), chronic diseases (admission to hospital last year no/yes and/or consultation at hospital last year no/yes), alcohol consumption (frequency/amount), marital status (living with spouse no/yes), use of antidepressants the last month (none/less than every week/weekly/daily) and physical activity (frequency/time/intensity). A physical activity estimate was calculated in hours/week giving hard activity double weight and light activity half weight compared to moderate activity. With contract contact with health care provider as a proxy, chronic disease was defined as having been admitted to a hospital or been to consultation in a hospital in the last year.

Height and weight were measured with participants wearing light clothing and no shoes. Body mass index (BMI) was defined as weight (kg) divided by height squared (m^2).

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0165-1781/$ – see front matter
doi:10.1016/j.psychres.2011.06.024

Plasma creatinine analyses were performed on the Hitachi Modular model using an enzymatic method that has been standardised against isotope dilution mass spectroscopy (CREA Plus, Roche Diagnostics, GmbH, Mannheim, Germany). Glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) method as defined by Levey et al. (2006).

2.3. Depressive symptoms

The questionnaire also included 10 questions that can be used to evaluate psychological distress (Table 1). The participants were asked if they had any symptoms during the last week. Answers were scored from 1 to 4, where 1 is "no" and 4 is "a lot". From this, the Hopkins Symptoms Check List 10 (SCL-10) score is calculated by dividing the total score with 10 (Strand et al., 2003). Missing values are replaced with the sample mean value for each item. Persons with three or more missing answers were excluded. The score can be further subdivided into an anxiety score and depression score by using the four first questions for anxiety and the last six for depression. SCL-10 scores $\geq$1.85 are considered a sign of significant mental distress and/or depression (Strand et al., 2003).

2.4. 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 $\leq$7.8% as judged in any of three 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.

Because this method has been shown to overestimate serum 25(OH)D in smokers, we chose to divide the study population into current smokers and non-smokers (Grimnes et al., 2010). Serum 25(OH)D values in former smokers are shown to be at the same level as those in non-smokers, and therefore the former smokers are included in the non-smokers' group. Subjects with no record of smoking status and/or with missing 25(OH)D values were excluded.

2.5. Statistics

Normal distribution was evaluated with visual inspection of histograms and determination of skewness and kurtosis. The variable SCL-10 score was found not to follow the normal distribution curve; thus, binary logistic regression was used to test for predictors. The value 1.85 was used as a cut-off point for dividing the cohort into non-depressed and depressed subjects.

To asses interaction 25(OH)D×gender and 25(OH)D×smoking were included in the logistic regression analysis. The data were analysed both stratified by and adjusted for gender (in different analyses), and for smokers and non-smokers separately. BMI, age, physical exercise, alcohol consumption and GFR were used as continuous variables. Marital status, education level and presence of chronic disease were used as dichotomous variables. Adjustment for month of blood sampling was performed with the use of dummy variables when serum 25(OH)D was used as a continuous variable. When serum 25(OH)D quartiles were used in the analyses, each month was divided into quartiles separately, thus adjusting for season without use of dummy variable.

Trend analyses across 25(OH)D quartiles were performed modelling the quartiles as continuous variable in the logistic regression. The trend across SCL-10 quartiles was tested with linear regression on the continuous variables using each individual parameter as a dependent variable. Dichotomous variables were tested with logistic regression. Adjustment was done for the variables as described above. The differences in SCL-10 score between men/women and smokers/non-smokers were tested with the Mann–Whitney *U* test.

Unless otherwise stated, all data are expressed as mean (standard deviation (S.D.)). All tests were performed two-sided, and $P<0.05$ was considered statistically significant. Statistical analyses were performed with SPSS version 16.0 software (SPPS Inc., Chicago, Illinois).

Table 1
The SCL-10 questionnaire.

Participants were asked to respond to the following items according to their experience during the previous week
1. Suddenly scared for no reason
2. Feeling fearful
3. Faintness, dizziness, or weakness
4. Feeling tense or keyed up
5. Blaming yourself for things
6. Difficulty in falling asleep or staying asleep
7. Feeling blue
8. Feeling of worthlessness
9. Feeling everything is an effort
10. Feeling hopeless about future

Out of the 10 items described above, the first 4 items were related to anxiety and the remaining to depression. Each item was scored on a scale from 1 (not at all) to 4 (a lot).

2.6. Ethics

The study was approved by the Regional Committee for Medical Research Ethics. All participants gave written informed consent prior to the study.

3. Results

A total of 12,984 attended the Tromsø Study in 2007–2008. Of these 197 had no record of smoking status, 167 had no serum 25(OH)D measurement, 684 had answered less than eight questions regarding mental distress and 924 had no valid values for the remaining variables. Excluding these, a total of 10,086 subjects, 51% of the 19,762 invited, remained for the present analyses. The excluded subjects had significantly higher SCL-10 score, age and BMI, there were a higher proportion of females and they had lower serum 25(OH)D ($P<0.05$). The baseline characteristics for the study population are shown in Table 2. As expected from UV radiation on latitude 69.6° N, the mean serum 25(OH)D level showed a characteristic variation throughout the year with highest levels in August (Fig. 1). Fig. 1 also illustrates the difference in 25(OH)D levels between smokers and non-smokers due to the analytical method by Roche.

The mean SCL-10 score was significantly different between males and females ($P<0.001$) but showed a similar distribution with a positive skew and the majority having a score of 1. Smokers had significantly higher SCL-10 scores than non-smokers ($P<0.001$). Neither the interaction gender×25(OH)D ($P=0.35$) nor smoking status×25(OH)D ($P=0.40$) was found to be significant, but due to the analytical differences we chose to present the results stratified according to smoking status. Regarding gender, the results are presented both adjusted and stratified to investigate earlier reported differences between men and women (Milaneschi et al., 2010).

As expected, with a decrease in physical activity, an increase in alcohol intake, a decrease in percentage of subjects with education higher than high school, a decrease in percentage of subjects living with spouse, and an increase in frequency of subjects with chronic diseases, there was increasing SCL-10 score (Lee et al., 2010) (Table 2). A significant positive association ($P<0.001$) between use of anti-depressants and SCL-10 score was found in all four population sub-groups (data not shown).

With the use of logistic regression and SCL-10 score with cut-off point at 1.85 (to separate non-depressed and depressed subjects) as a dichotomous dependent variable, serum 25(OH)D was a significant predictor of depression in crude analyses (adjusted for month of sampling) in both smokers ($P=0.002$) and non-smokers ($P=0.001$). This finding remained significant when, in addition to season, adjustments were done for age, BMI, GFR, chronic disease, physical activity, education, alcohol consumption and marital status (smokers $P=0.002$ and non-smokers $P=0.009$). When stratified according to gender and adjusting for the factors listed above, 25(OH)D was a significant predictor of depression in women regardless of smoking status (smokers $P=0.015$ and non smokers $P=0.003$), and in smoking ($P=0.023$) but not in non-smoking men ($P=0.912$). When dividing the SCL-10 score into anxiety and depression sub-scores, there was a non-significant relation between low serum 25(OH)D levels and anxiety, whereas the relation to depression remained significant (data not shown).

The same analyses were performed including persons in the "depressed" group who did not have SCL-10 score above 1.85 but were using anti-depressants. The results became weaker but remained significant in the mixed gender analyses and in women,