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Palaniswamy, S., Hypponen, E., Williams, D., Jokelainen, J., Lowry, E., Keinanen-kankaaniemi, S., Herzig, K-H., Jarvelin, M-R., & Sebert, S. (2017). Potential determinants of vitamin D in Finnish adults: a cross-sectional study from the Northern Finland birth cohort 1966. BMJ Open, 7(3). https://doi.org/10.1136/bmjopen-2016-013161

Published in:
BMJ Open

Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
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Potential determinants of vitamin D in Finnish adults: a cross-sectional study from the Northern Finland birth cohort 1966

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ABSTRACT

Objective: Evidence from randomised controlled trials suggests that vitamin D may reduce multimorbidity, but very few studies have investigated specific determinants of vitamin D2 and D3 (two isoforms of 25-hydroxyvitamin D). The aim of the study was to investigate the determinants of vitamin D2 and D3 and to identify the risk factors associated with hypovitaminosis D.

Design: Cross-sectional study.

Setting: Northern Finland Birth Cohort 1966.

Participants: 2374 male and 2384 female participants with data on serum 25(OH)D2 and 25(OH)D3 concentrations measured at 31 years of age (1997), together with comprehensive measures of daylight, anthropometric, social, lifestyle and contraceptive cofactors.

Methods: We assessed a wide range of potential determinants prior to a nationwide fortification programme introduced in Finland. The determinants of 25(OH)D2, 25(OH)D3 and 25(OH)D concentrations were analysed by linear regression and risk factors for being in lower tertile of 25(OH)D concentration by ordinal logistic regression.

Results: At the time of sampling, 72% of the participants were vitamin D sufficient (≥50 nmol/L). Low sunlight exposure period (vs high) was associated positively with 25(OH)D2 and negatively with 25(OH)D3 concentrations. Use of oral contraceptives (vs non-users) was associated with an increase of 0.17 nmol/L of serum 25(OH)D2 and 0.48 nmol/L (95% CI 0.41 to 0.56) in 25(OH)D2 and 25(OH)D3 concentrations. Sex, season, latitude, alcohol consumption and physical activity were the factors most strongly associated with 25(OH)D concentration. Risk factors for low vitamin D status were low sunlight exposure defined by time of sampling, residing in northern latitudes, obesity, higher waist circumference, low physical activity and unhealthy diet.

Conclusions: We demonstrate some differential associations of environmental and lifestyle factors with 25(OH)D2 and 25(OH)D3 raising important questions related to personalised healthcare. Future strategies could implement lifestyle modification and supplementation to improve vitamin D2 and D3 status, accounting for seasonal, lifestyle, metabolic and endocrine status.

INTRODUCTION

Serum 25-hydroxyvitamin D (25(OH)D), the circulating biomarker of vitamin D status, is found to be associated with multiple pathological conditions. There is growing interest in understanding the causal role of vitamin D in the aetiology of chronic metabolic diseases including obesity, type 2 diabetes and mortality. Vitamin D is classified as a pro-hormone which exists in circulation...
in two major forms of 25(OH)D: 25(OH)D$_2$ (ergocalciferol) and 25(OH)D$_3$ (also known as cholecalciferol). Serum 25(OH)D$_2$ is obtained only from plant-derived dietary sources, fortification or supplementation. In contrast, 25(OH)D$_3$ is predominantly obtained from sunlight exposure and smaller quantities from dietary sources such as fatty fish, fortified milk products and supplements. In Finland, the milk products and spreadable fats are fortified with 25(OH)D$_3$. The current fortification contains 25(OH)D$_3$ due to somewhat lower biopotency of 25(OH)D$_2$ that requests further understanding. Vitamin D status is determined by measuring 25(OH)D$_2$, which reflects the combined intake of vitamins 25(OH)D$_2$ and 25(OH)D$_3$ and subcutaneous synthesis during the past 3–4 weeks. There is limited knowledge about the factors associated with each isoform that may have differential environmental determinants. Total 25(OH)D and the relative proportions of 25(OH)D$_2$ and 25(OH)D$_3$ are suggested to reflect a number of health and lifestyle factors that might be sex specific. In young adults, lifestyle and body composition differ between men and women. As to whether the differential composition of the body between sexes, as well as other endocrine factors, will be reflected by differences in the 25(OH)D concentration and the 25(OH)D$_2$ and 25(OH)D$_3$ components is yet unknown. There are no previous comprehensive studies examining the factors associated with 25(OH)D$_2$ and 25(OH)D$_3$ concentrations in Finland. This limits the availability of inferences that could help to identify people at risk of vitamin D deficiency, and improved fortification policies to meet the requirements of those living at northern latitudes.

We examined here factors associated with 25(OH)D$_2$, 25(OH)D$_3$ and total 25(OH)D concentrations in Finnish adults aged 31 years prior to the implementation of a nationwide supplementation of vitamin D via fortification of milk products and margarine in 2002.

**METHODS**

**Study population**

We analysed data on participants from the Northern Finland Birth Cohort 1966 (NFBC1966) which has previously been described in detail. In brief, all women who were pregnant, residing in Northern Finland (provinces of Oulu and Lapland) with expected dates of delivery between 1 January and 31 December,1966 were targeted for enrolment in the study. Over 96% of eligible women participated. This comprised of 12 055 mothers and 12 058 live born children. The children were followed up at regular intervals from birth onwards. In 1997, when participants were aged 31 years, all cohort participants with known addresses in the provinces of Oulu and Lapland (65°N to 70°N) and in Helsinki (60°N) area were sent a postal questionnaire and invited to a clinical examination which also included, a fasted blood sample. A total of N=4758 individuals of white European origin were included in the study as shown in online supplementary figure S1. All participants gave written informed consent. The procedures follow the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The present study includes individuals with a complete set of data on variables of interest, as detailed below.

**Outcome variables**

**25(OH)D measurement**

Serum 25(OH)D$_2$ and 25(OH)D$_3$ were measured by liquid chromatography tandem mass spectrometry and the detailed assay procedure is published elsewhere. Participants with 25(OH)D$_2$ values under the detectable limit were assigned a value of 1.25 nmol/L. Total 25(OH)D is obtained as the actual sum of D2+D3 without low value assignment. Consequently, in the tables, total 25(OH)D may differ slightly from exact sum of D2 and D3. Vitamin D sufficiency criteria were defined according to the Institute of Medicine (IOM) guidelines as ≥30 nmol/L (risk/deficiency), 30–50 nmol/L (risk/insufficiency) and ≥50 nmol/L (sufficient).

**Explanatory factors**

The season of participant attendance at the clinical assessment was categorised according to the Finnish Meteorological Institute standard as high sunlight (summer (1 June–30 August) autumn (1 September–31 October)) and low sunlight season (winter (1 November–31 March) and spring (1 April–31 May)). This definition aims to assess the impact of natural high and low vitamin D level periods throughout the calendar year. The residence of the participants at age 31 years was collected from the population register office. They were categorised as residing in Helsinki (60°N); the city of Oulu (65°N) and elsewhere in northernmost provinces of Oulu and Lapland (>65°N). In Helsinki, blood samples were collected only during winter in contrast to all year round in other provinces, due to the feasibility of data collection and were excluded in multivariable analyses. Height (cm) and weight (kg) were measured in barefoot and loose clothing by well-trained nurses. Body Mass Index (BMI) (kg/m$^2$) was calculated and categorised according to the WHO 1998. Waist circumference (cm) was categorised as elevated when it was ≥94 cm in men and ≥80 cm in women.

Categorisation of following lifestyle variables was based on the responses in the postal questionnaire. Current smoking was categorised as non-smoker, former/occasional or active smoker. Alcohol consumption during the 6 months prior to the questionnaire was calculated as grams per day (g/day) and has been described elsewhere. It was further categorised according to WHO sex-specific classification as abstainer, low-risk drinker (≤20 and ≤40 g/day for women and men, respectively) or at-risk drinker (>20 and >40 g/day for women and men, respectively). The frequency of computer use
during leisure time was categorised as never, no more than once per week, on 2–5 days per week or on more than 5 days per week. The reported frequency and duration of leisure time and brisk physical activity were used to calculate the metabolic equivalent of task (MET) scores in hours per week, and these were ordered into quartiles. An intensity value of 3 METs is considered as light physical activity, and 5 METs as brisk physical activity. Current use of contraception by women was categorised as no contraception use, other methods of contraception (hormone intrauterine device (IUD), copper IUD, chemical contraception) or oral contraceptive pill (OCP). Socioeconomic position (SEP) was categorised as I and II (professional), III (skilled worker), IV (unskilled worker), V (farmer) and VI (others-pensioner, student, long-term unemployed or not defined). The exclusion criteria consisted of participants with non-fasting blood samples, pregnant women, no consent for use of data and persons whose information was missing on one or more variables of interest.

Statistical analyses

All statistical analyses were performed using SAS V.9.4 (SAS Institute, Cary, NC, USA). The variables were assessed for normality and log transformed where relevant. Mean differences between sexes for continuous variables were measured by independent samples t-test and analysis of variance; and Pearson χ² test for categorical variables. We performed univariable linear regression analysis to explore the association between explanatory variables and serum 25(OH)D₂, 25(OH)D₃ and total 25(OH)D concentrations. We log transformed 25(OH)D₂, 25(OH)D₃ and 25(OH)D, and expressed these on standardised scales (z-scores). To examine the impact of daylight, anthropometric, social and lifestyle risk factors for being in the lower tertiles of 25(OH)D compared with the highest are shown in online supplementary table S3. The mutually adjusted model shows the risk of being in lower tertile of 25(OH)D was increased in individuals whose blood samples were collected during low sunlight months, living in higher latitudes, having elevated waist circumference and unhealthy diet. Figure 1 illustrates the mutually adjusted analyses with OR estimates for the impact of daylight, anthropometric, social and lifestyle factors associated with serum 25(OH)D2, 25(OH)D3 and 25(OH)D concentrations. Univariable and multivariable associations of daylight, anthropometric, social and lifestyle factors with 25(OH)D₂, 25(OH)D₃ and 25(OH)D in the total population are shown in table 3, online supplementary tables S4 and S5.
| Sample size (n) | Total 4758 | Male 2374 | Female 2384 |
|----------------|-----------|-----------|-------------|
|                | n or mean | % or 95% CI | n or mean | % or 95% CI | n or mean | % or 95% CI |
| Daylight       |           |           |            |            |           |            |
| Season of blood sampling† (n %) |   |   |   |   |   |   |
| High sunlight  | 2953      | 62.1      | 1501       | 63.2       | 1452       | 60.9       | 0.09 |
| Low sunlight   | 1805      | 37.9      | 873        | 36.8       | 932        | 39.1       |   |
| Latitude‡ (n %) |           |           |            |            |            |            |   |
| ≥65°N          | 891       | 28.7      | 460        | 29.3       | 431        | 28.1       | 0.58 |
| >65°N          | 3105      | 71.3      | 1571       | 70.7       | 1534       | 71.9       |   |
| Anthropometry  |           |           |            |            |            |            |   |
| BMI (kg/m²) (mean, 95% CI) | 24.7     | 24.6 to 24.8 | 25.2      | 25.1 to 25.3 | 24.1     | 23.9 to 24.3 | <0.01 |
| Waist circumference(cm) (mean, 95% CI) | 83.8     | 83.5 to 84.2 | 88.9      | 88.5 to 89.3 | 78.8     | 78.3 to 79.2 | <0.01 |
| Socioeconomic position: (n %) |   |   |   |   |   |   |
| I+II (Professional) | 1134     | 23.8      | 653        | 27.5       | 481        | 20.2       | <0.01 |
| III (Skilled worker) | 1483     | 31.2      | 433        | 18.2       | 1050       | 44.0       |   |
| IV (Unskilled worker) | 1228     | 25.8      | 856        | 36.1       | 372        | 15.6       |   |
| V (Farmer)     | 165       | 3.5       | 111        | 4.7        | 54         | 2.3        |   |
| VI (Other)     | 748       | 15.7      | 321        | 13.5       | 427        | 17.9       |   |
| Lifestyle      |           |           |            |            |            |            |   |
| Smoking (n %)  |           |           |            |            |            |            |   |
| Non-smoker     | 2128      | 44.7      | 952        | 40.1       | 1176       | 49.4       | <0.01 |
| Former/occasional smoker | 1214     | 25.5      | 600        | 25.3       | 614        | 25.7       |   |
| Active smoker   | 1416      | 29.8      | 822        | 34.6       | 594        | 24.9       |   |
| Alcohol consumption (g/day) (n %) | 426      | 8.95      | 191        | 8.1        | 235        | 9.9        | <0.01 |
| Abstainer       | 4053      | 85.18     | 2026       | 85.3       | 2027       | 85.0       |   |
| Low-risk drinker | 279      | 5.86      | 157        | 6.6        | 122        | 5.1        |   |
| At-risk drinker | 1708      | 35.9      | 852        | 35.9       | 856        | 35.9       | <0.01 |
| Leisure time computer use (n %) |   |   |   |   |   |   |
| Never           | 1461      | 30.71     | 453        | 19.1       | 1008       | 42.3       | <0.01 |
| No more than once per week | 2739     | 57.57     | 1531       | 64.5       | 1208       | 50.6       |   |
| On 2 to 5 days per week | 558      | 11.73     | 390        | 16.4       | 168        | 7.1        |   |
| Physical activity (MET hours/week) (mean, 95% CI) | 15.0     | 14.6 to 15.4 | 14.9      | 14.4 to 15.6 | 15.0     | 14.5 to 15.6 | <0.01 |
| Diet score (n %) |           |           |            |            |            |            |   |
| 0–1             | 1461      | 30.71     | 453        | 19.1       | 1008       | 42.3       | <0.01 |
| 2–3             | 2739      | 57.57     | 1531       | 64.5       | 1208       | 50.6       |   |
| 4–5             | 558       | 11.73     | 390        | 16.4       | 168        | 7.1        |   |
| Contraception status§ (n %) |   |   |   |   |   |   |
| No contraception | 1154     | 49.1      |            |            |            |            |   |
| Other kinds of contraception | 591     | 25.1      |            |            |            |            |   |
| Oral contraceptive pills (OCP) | 607     | 25.8      |            |            |            |            |   |
| Vitamin D status (mean, 95% CI) |   |   |   |   |   |   |
| Serum total 25(OH)D¶ | 68.4     | 67.6 to 69.2 | 68.9      | 67.7 to 70.1 | 67.9     | 66.7 to 68.9 | 0.78 |
| Serum 25(OH)D3 | 64.8     | 63.9 to 65.6 | 65.6      | 64.4 to 66.7 | 64.0     | 62.8 to 65.1 | 0.45 |
| Serum 25(OH)D2 | 4.2      | 3.9 to 4.3  | 3.9        | 3.6 to 4.2  | 4.4      | 4.1 to 4.7  | <0.01 |
| Vitamin D status without OCP** (mean, 95% CI) |   |   |   |   |   |   |
| Serum total 25(OH)D¶ | 67.0     | 66.2 to 67.9 | 68.9      | 67.7 to 70.1 | 64.6     | 63.3 to 65.8 | <0.01 |
| Serum 25(OH)D3 | 63.6     | 62.8 to 64.5 | 65.6      | 64.4 to 66.7 | 60.9     | 59.8 to 62.2 | <0.01 |
| Serum 25(OH)D2 | 4.0      | 3.8 to 4.2  | 3.9        | 3.6 to 4.2  | 4.2      | 3.9 to 4.5  | 0.05 |

Values are presented as mean, 95% CIs or number (%).
*p Value was calculated using independent samples t-test for normally distributed variables and Pearson’s χ² test for categorical variables.
†The season of blood sampling were categorised as high sunlight (summer (1 June–30 August), autumn (1 September–31 October)) and low sunlight (winter (1 November–31 March) and spring (1 April–31 May)).
‡Data included only on samples taken during all seasons from Oulu city and other provinces of Oulu and Lapland. Data not included on N=343 in men and N=419 in women with samples taken during winter months from Helsinki region.
§Data available on N=2352 individuals (N=32 missing with contraception status in women).
¶Serum total 25(OH)D may differ slightly from the actual sum of D2 and D3 because of amendment of undetectable D2 values (see methods).
**Data on N=607 using oral contraceptives excluded.
BMI, body mass index; MET, metabolic equivalent of task of physical activity; 25(OH)D, 25-hydroxyvitamin D; 25(OH)D2, ergocalciferol; 25(OH)D3, cholecalciferol.
| Tertile of serum 25(OH)D† | N | n | or | mean | % or 95% CI | n | or | mean | % or 95% CI | n | or | mean | % or 95% CI | P Value |
|--------------------------|---|---|---|-------|------------|---|---|-------|------------|---|---|-------|------------|--------|
| **Sex**                  |   |    |    |       |            |   |    |       |            |   |    |       |            |        |
| Males                    | 782| 32.9| 800| 33.7  | 792| 33.4 | 792| 33.4  |       |        | 0.75  |
| Females                  | 810| 33.9| 789| 33.2  | 785| 32.9 | 785| 32.9  |       |        |
| **Environmental factors**|   |    |    |       |            |   |    |       |            |   |    |       |            |        |
| Season of blood drawn‡  |   |    |    |       |            |   |    |       |            |   |    |       |            |        |
| High sunlight            | 566| 19.2| 1012|34.3  | 1375|46.5  | <0.0001|
| Low sunlight             | 1026|56.9| 577|31.9  | 202|11.2 |
| Latitude§                 |   |    |    |       |            |   |    |       |            |   |    |       |            |        |
| 65°N                     | 210| 23.6| 305|34.2  | 376|42.2  | 0.0006 |
| >65°N                    | 923| 29.7| 1042|33.6  | 1140|36.7 |
| **Anthropometry**        |   |    |    |       |            |   |    |       |            |   |    |       |            |        |
| Body mass index (kg/m²)  |   |    |    |       |            |   |    |       |            |   |    |       |            |        |
| Mean                     | 24.8|       | 24.6|       | 24.8|       | 24.8|       | 24.6|       | 24.6|       | 24.4|       | 24.2|       | 24.6|       | 0.017|
| Waist circumference (cm) |   |    |    |       |            |   |    |       |            |   |    |       |            |        |
| Mean                     | 84.6|       | 83.9|       | 84.0|       | 83.4|       | 84.6|       | 82.9|       | 82.3|       | 83.4|       | 0.0003|
| **Socioeconomic position**|   |    |    |       |            |   |    |       |            |   |    |       |            |        |
| I+II (Professional)      | 421| 37.2| 374|32.9  | 339|29.9  | 0.0046 |
| III (Skilled worker)     | 501| 33.8| 503|33.9  | 479|32.3  |        |
| IV (Unskilled worker)    | 386| 31.4| 427|34.8  | 415|33.8  |        |
| V (Farmer)               | 60 | 36.4| 49 |29.7  | 56 |33.9  |        |
| VI (Other)               | 224| 29.9| 236|31.6  | 288|38.5  |        |
| **Lifestyle factors**    |   |    |    |       |            |   |    |       |            |   |    |       |            |        |
| Smoking n %              |   |    |    |       |            |   |    |       |            |   |    |       |            |        |
| Non-smoker               | 742| 34.9| 686|32.2  | 700|32.9  |        |
| Former/occasional smoker | 366| 30.2| 438|36.1  | 410|33.7  |        |
| Active smoker            | 484| 34.2| 465|32.9  | 467|32.9  |        |
| Alcohol consumption (g/day) n % |   |    |    |       |            |   |    |       |            |   |    |       |            |        |
| Abstainer                | 165| 38.7| 146|34.3  | 115|27.0  | 0.053  |
| Low risk drinker         | 1335|32.9| 1349|33.3  | 1369|33.8  |        |
| At-risk drinker          | 92 | 32.9| 94 |33.7  | 93 |33.4  |        |
| Leisure time computer use n % |   |    |    |       |            |   |    |       |            |   |    |       |            |        |
| Never                    | 537| 31.4| 599|35.1  | 572|33.5  | 0.0012 |
| No more than once per week | 208 | 30.1| 234|33.9  | 249|36.0  |        |
| On 2 to 5 days per week  | 487| 34.3| 447|31.5  | 485|34.2  |        |
| On more than 5 days per week | 360 | 38.3| 309|32.9  | 271|28.8  |        |
| Quartile of physical activity (MET hours per week) n % |   |    |    |       |            |   |    |       |            |   |    |       |            |        |
| QI: 0.0–3.79             | 444| 36.6| 394|32.5  | 376|30.9  | <0.0001|
| QII: 3.80–11.29          | 403| 33.9| 421|35.4  | 365|30.7  |        |
| QIII: 11.30–21.99        | 415| 34.5| 397|33.0  | 391|32.5  |        |
| QIV: >22.0               | 330| 28.7| 377|32.7  | 445|38.6  |        |
| Diet score n %           |   |    |    |       |            |   |    |       |            |   |    |       |            |        |
| 0–1                      | 478| 32.7| 477|32.7  | 506|34.6  | 0.26   |
| 2–3                      | 912| 33.3| 920|33.6  | 907|33.1  |        |
| 4–5                      | 202| 36.2| 192|34.4  | 164|29.4  |        |
| **Females only**         |   |    |    |       |            |   |    |       |            |   |    |       |            |        |
| Contraception n %        |   |    |    |       |            |   |    |       |            |   |    |       |            |        |
| No contraception         | 441| 38.2| 401|34.8  | 312|27.0  | <0.001 |
| Other kinds of contraception | 216 | 36.6| 187|31.6  | 188|31.8  |        |
| Oral contraceptive pills | 140 | 23.1| 190|31.3  | 277|45.6  |        |

The values are expressed as mean and 95% CIs; numbers and %.
*Differences between males and females were tested with ANOVA for normally distributed variables and Pearson’s χ² test for categorical variables.
†Mean (95% CI) of 25-hydroxyvitamin D tertiles for all were 41.50 (41.11 to 41.89), 63.87 (63.55 to 64.19) and 100.01 (98.81 to 101.22).
‡Serum total 25(OH)D may differ slightly from the actual sum of D2 and D3 because of amendment of undetectable D2 values (see methods).
§Data included only on samples taken during all seasons from Oulu city and other provinces of Oulu and Lapland. Data not included on N=343 in men and N=419 in women with samples taken during winter months from Helsinki region.
MET, metabolic equivalent of task of physical activity; 25(OH)D, 25-hydroxyvitamin D.
The factors associated with 25(OH)D2 and 25(OH)D3 were sex, season of blood sampling, latitude, obesity, waist circumference and physical activity. Unhealthy diet and active smoking were univariably associated with lower 25(OH)D2 concentrations; and SEP was associated univariably with lower 25(OH)D3 concentrations.

In multivariable analyses, sex was associated with serum 25(OH)D2 and 25(OH)D3 concentrations. Men had 0.5 nmol/L lower 25(OH)D2 but 1.6 nmol/L higher 25(OH)D3 than women. When women using oral contraceptives were excluded from the analysis, the association between sex and 25(OH)D2 concentration was attenuated (β=0.06; 95% CI −0.002 to 0.13).

Conversely, the sex difference still persisted for 25(OH)D3 concentrations (β=−0.21; 95% CI −0.26 to −0.15), that is, women having lower concentrations. Low sunlight exposure period (vs high) at sampling associated with higher concentrations of 25(OH)D2 but lower concentrations of 25(OH)D3. Alcohol abstainers were associated with lower 25(OH)D3 concentrations than any other level of drinker. In addition, unhealthy diet score and leisure time computer use were associated with lower 25(OH)D3 concentrations.

In sex-stratified analyses, the associations were in the same direction and of similar magnitude with 25(OH)D2 and 25(OH)D3 concentrations. Female OCP users (vs non-users) had greater serum 25(OH)D2 and 25

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**Figure 1** Forest plots showing the risk factors associated with low vitamin D status based on tertile distribution in the total population and by sex. Associations from mutually adjusted ordinal logistic regression ORs (on log scale) show the risk of being in the lower vitamin D tertile.
### Table 3 Major factors associated with serum 25(OH)D$_2$ (vitamin D2), 25(OH)D$_3$ (vitamin D3) and total 25(OH)D (vitamin D) nmol/L concentrations assessed by univariable and multiple linear regression analysis, total (N=4758)\(^*$

| Explanatory variables | Serum 25(OH)D$_2$, nmol/L \(^†\) | Serum 25(OH)D$_3$, nmol/L \(^†\) | Serum 25(OH)D, nmol/L \(^†\) |
|-----------------------|---------------------------------|---------------------------------|-------------------------------|
|                       | Univariable \(\beta\) | 95% CI | Multivariable\(\beta\) | 95% CI | Univariable\(\beta\) | 95% CI | Multivariable\(\beta\) | 95% CI | Univariable\(\beta\) | 95% CI | Multivariable\(\beta\) | 95% CI |
| **Sex (reference: males)** | | | | | | | | | | | | |
| Females | 0.10 | 0.04 to 0.16 | 0.12 | 0.06 to 0.18 | -0.06 | -0.12 to -0.03 | -0.09 | -0.14 to -0.04 | -0.04 | -0.09 to 0.02 | -0.06 | -0.12 to -0.01 |
| Global p value | 0.0008 | | 0.0001 | | 0.038 | | 0.0005 | | 0.21 | | 0.019 |
| **Daylight** | | | | | | | | | | | | |
| Season of blood sampling § (reference: high sunlight) | | | | | | | | | | | | |
| Low sunlight | 0.57 | 0.51 to 0.63 | 0.29 | 0.21 to 0.36 | -1.03 | -1.08 to -0.98 | -0.43 | -0.49 to -0.36 | -0.92 | -0.97 to -0.87 | -0.36 | -0.42 to -0.29 |
| Global p value | <0.0001 | | <0.0001 | | <0.0001 | | <0.0001 | | <0.0001 | | <0.0001 |
| >65°N | -0.08 | -0.16 to -0.01 | -0.06 | -0.13 to 0.02 | -0.14 | -0.21 to 0.07 | -0.18 | -0.24 to -0.12 | -0.16 | -0.23 to 0.008 | -0.20 | -0.26 to -0.13 |
| Global p value | 0.023 | | 0.12 | | 0.0002 | | <0.0001 | | <0.0001 | | <0.0001 |
| **Anthropometry** | | | | | | | | | | | | |
| BMI (kg/m$^2$) (reference: normal (18.5–24.99)) | | | | | | | | | | | | |
| Underweight | -0.05 | -0.25 to 0.15 | -0.06 | -0.24 to 0.13 | -0.08 | -0.27 to 0.12 | -0.06 | -0.22 to 0.10 | -0.09 | -0.29 to 0.11 | -0.08 | -0.25 to 0.09 |
| Overweight (<18.5) | -0.10 | -0.17 to -0.04 | -0.01 | -0.08 to 0.06 | 0.02 | -0.04 to 0.08 | -0.001 | -0.06 to 0.06 | -0.004 | -0.07 to 0.06 | -0.005 | -0.07 to 0.06 |
| Obese (≥30) | -0.13 | -0.24 to -0.03 | -0.01 | -0.14 to 0.11 | -0.19 | -0.30 to -0.09 | -0.16 | -0.27 to -0.06 | -0.23 | -0.33 to -0.12 | -0.17 | -0.27 to -0.06 |
| Global p value | 0.0035 | | 0.94 | | 0.0008 | | 0.0035 | | 0.0002 | | 0.0057 |
| Waist circumference (cm) (reference: m<94, f<80) | | | | | | | | | | | | |
| M≥94, F≥80 | -0.09 | -0.15 to -0.03 | -0.10 | -0.18 to -0.02 | -0.13 | -0.19 to -0.07 | -0.05 | -0.12 to 0.01 | -0.15 | -0.21 to -0.09 | -0.08 | -0.15 to -0.01 |
| Global p value | 0.003 | | 0.0001 | | 0.11 | | <0.0001 | | 0.030 |
| Socioeconomic position (reference: I+II (professional)) | | | | | | | | | | | | |
| III (Skilled worker) | -0.05 | -0.13 to 0.03 | -0.05 | -0.13 to 0.02 | 0.08 | 0.001 to 0.15 | 0.03 | -0.04 to 0.09 | 0.07 | -0.003 to 0.15 | 0.03 | -0.04 to 0.09 |
| IV (Unskilled worker) | -0.06 | -0.15 to 0.02 | 0.01 | -0.07 to 0.10 | 0.14 | 0.06 to 0.22 | 0.02 | -0.05 to 0.09 | 0.12 | 0.04 to 0.21 | 0.03 | -0.05 to 0.10 |
| V (Farmer) | -0.11 | -0.27 to 0.06 | -0.02 | -0.18 to 0.14 | 0.06 | -0.10 to 0.22 | -0.06 | -0.19 to 0.08 | 0.03 | -0.13 to 0.20 | -0.06 | -0.20 to 0.08 |
| VI (Other) | -0.14 | -0.23 to -0.05 | -0.06 | -0.16 to 0.03 | 0.21 | 0.11 to 0.29 | 0.05 | -0.03 to 0.13 | 0.18 | 0.09 to 0.28 | 0.05 | -0.03 to 0.13 |
| Global p value | 0.056 | | 0.33 | | 0.0002 | | 0.49 | | 0.0012 | | 0.56 |
| Lifestyle | | | | | | | | | | | | |
| Smoking (reference: non-smoker) | | | | | | | | | | | | |
| Former/occasional smoker | -0.03 | -0.10 to 0.04 | -0.01 | -0.08 to 0.06 | 0.05 | -0.02 to 0.12 | 0.02 | -0.03 to 0.08 | 0.04 | -0.03 to 0.11 | 0.02 | -0.04 to 0.08 |
| Active smoker | -0.10 | -0.17 to -0.03 | -0.05 | -0.12 to 0.02 | 0.007 | -0.06 to 0.07 | -0.05 | -0.10 to 0.01 | -0.02 | -0.08 to 0.05 | -0.06 | -0.12 to 0.002 |
| Global p value | 0.014 | | 0.37 | | 0.39 | | 0.071 | | 0.37 | | 0.051 |
| Alcohol consumption (g/day) (reference: abstainer) | | | | | | | | | | | | |
| Low risk drinker | 0.04 | 0.07 to 0.14 | 0.07 | 0.03 to 0.16 | 0.17 | 0.07 to 0.27 | 0.12 | 0.04 to 0.20 | 0.19 | 0.09 to 0.29 | 0.14 | 0.06 to 0.23 |
| At-risk drinker | 0.03 | 0.07 to 0.19 | 0.07 | 0.08 to 0.21 | 0.13 | 0.02 to 0.28 | 0.19 | 0.06 to 0.31 | 0.14 | -0.02 to 0.29 | 0.20 | 0.07 to 0.33 |
| Global p value | 0.71 | | 0.39 | | 0.0043 | | 0.0041 | | 0.0012 | | 0.0019 |

\(^*$\) For minor factors, p values are based on Singleton et al. \(^‡\) \(^†\) P<0.05. Open Access. 

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| Explanatory variables | Serum 25(OH)D₂, nmol/L† | Serum 25(OH)D₃, nmol/L† | Serum 25(OH)D, nmol/L† |
|-----------------------|-------------------------|-------------------------|-------------------------|
|                       | Univariable             | Multivariable‡          | Univariable             | Multivariable‡          | Univariable             | Multivariable‡          |
|                       | β                    | 95% CI                  | β                      | 95% CI                  | β                      | 95% CI                  |
| Leisure time computer use (reference: never) | | | | | | |
| No more than once per week | 0.03 | −0.06 to 0.12 | 0.002 | −0.08 to 0.09 | 0.01 | −0.08 to 0.09 | 0.02 | −0.05 to 0.09 | 0.01 | −0.08 to 0.10 | 0.02 | −0.06 to 0.09 | 0.02 | −0.06 to 0.09 |
| On 2 to 5 days per week | 0.03 | −0.04 to 0.10 | 0.01 | −0.08 to 0.06 | −0.04 | −0.11 to 0.03 | −0.03 | −0.09 to 0.03 | −0.03 | −0.10 to 0.04 | −0.03 | −0.09 to 0.03 | 0.01 | −0.08 to 0.10 | 0.02 | −0.06 to 0.09 |
| On more than 5 days per week | 0.09 | 0.01 to 0.17 | 95% CI                  | 0.02 | −0.07 to 0.10 | −0.20 | −0.28 to −0.12 | −0.09 | −0.16 to −0.02 | −0.17 | −0.25 to −0.10 | −0.08 | −0.15 to −0.01 | 0.01 | −0.08 to 0.10 | 0.02 | −0.06 to 0.09 |
| Global p value | 0.14 | 0.93 | 95% CI                  | 95% CI                  | 95% CI                  | 95% CI                  |
| Quartile of physical activity (MET-hours per week) (reference: QI: 0.0–3.79) | | | | | | |
| QII: 3.80–11.29 | 0.08 | 0.0003 to 0.16 | 0.05 | −0.03 to 0.12 | −0.02 | −0.10 to 0.06 | 0.003 | −0.06 to 0.07 | −0.01 | −0.09 to 0.07 | 0.01 | −0.06 to 0.07 | 0.02 | −0.06 to 0.09 |
| QIII: 11.30–21.99 | 0.10 | 0.02 to 0.18 | 0.05 | −0.03 to 0.12 | 0.02 | −0.06 to 0.10 | 0.05 | −0.01 to 0.12 | 0.04 | −0.04 to 0.12 | 0.07 | −0.02 to 0.13 | 0.01 | −0.08 to 0.10 | 0.02 | −0.06 to 0.09 |
| QIV: >22.0 | 0.11 | 0.03 to 0.20 | 0.08 | −0.002 to 0.16 | 0.15 | 0.07 to 0.23 | 0.14 | 0.07 to 0.20 | 0.18 | 0.10 to 0.26 | 0.16 | 0.09 to 0.23 | 0.01 | −0.08 to 0.10 | 0.02 | −0.06 to 0.09 |
| Global p value | 0.022 | 0.29 | 95% CI                  | 95% CI                  | 95% CI                  | 95% CI                  |
| Diet score (reference: healthy diet) | | | | | | |
| Unhealthy diet | −0.12 | −0.21 to −0.03 | −0.06 | −0.15 to 0.02 | −0.07 | −0.15 to 0.02 | −0.07 | −0.15 to 0.02 | −0.10 | −0.18 to −0.01 | −0.09 | −0.17 to −0.01 | 0.01 | −0.08 to 0.10 | 0.02 | −0.06 to 0.09 |
| Global p value | 0.009 | 0.14 | 95% CI                  | 0.049 | 0.034 | 0.022 |

*The values are standardised regression coefficients (β) and p values from linear regression models by entering each variable separately in univariable analysis and by entering all the variables in multivariable analysis.
†1 SD increase/decrease in 25(OH)D₂, 25(OH)D₃ and 25(OH)D nmol/L per 1 unit or category change in explanatory variable.
‡Analysis performed on N=3996 (total). Blood drawn only in winter on N=343 men and N=419 in women residing in Helsinki were excluded.
§The season of blood sampling were categorised as high sunlight (summer (1 June–30 August), autumn (1 September–31 October)) and low sunlight (winter (1 November–31 March) and spring (1 April–31 May)).
MET, metabolic equivalent of task of physical activity; 25(OH)D, 25-hydroxyvitamin D; 25(OH)D₂, ergocalciferol; 25(OH)D₃, cholecalciferol.
(OH)D₃ concentrations of 0.17 nmol/L and 0.48 nmol/L, respectively.

Total 25(OH)D associations with potential determinants reflect similar associations as reported for 25(OH)D₃ concentrations, with the exception of waist circumference and leisure time computer use (table 3). OCP users (vs non-users) were associated with a 0.50 nmol/L greater serum 25(OH)D concentration.

**DISCUSSION**

According to the present data collected in 1997, 28% of young adults in Northern Finland were exposed to the risk of vitamin D insufficiency defined by IOM. The average vitamin D status observed in our study was higher than those reported by other studies from the same geographical location (ie, Finland), despite these latter samples being collected after 2002, that is, year of the first Finnish fortification campaign for vitamin D. The mean concentration of serum 25(OH)D measured in both precompiled studies of the same geographical location (mean age: approx. 37 and 60 years) were nearly 10 nmol/L lower when compared with our population. Our present sample can be considered as a good representation of the young adult population living in Finland at the time of measurement. In comparison with previous findings, our data may also raise queries about the efficacy of the first wave of fortification introduced in Finland in the year 2002. The fortification levels were since increased in 2010. Careful consideration should be made before speculating a potential causation. We must acknowledge, for instance, the differences in study design such as analysis of wider age groups and determination of vitamin D status by radioimmunoassay as opposed to mass spectrometry.

Adding to previous literature, we observed a strong impact of the duration of sunlight in determining the vitamin D status irrespective of the gender. The latitude of residence also plays an important role in determining vitamin D status. During the six long winter months in northern latitudes (>60°N), the few hours of daylight are incapable of increasing vitamin D naturally. The usage of computers outside working hours and a reduced level of physical activity were negatively associated with vitamin D status, which supports previous reports. It is suspected that the observed association between the characteristics of sedentary behaviour in young adults and a lower vitamin D status is likely to be explained by significant changes in the time spent outdoors. Unfortunately, the current study does not distinguish between indoor and outdoor physical activity that would help to ascertain this hypothesis. In addition, our results supported the negative association between vitamin D status and obesity or higher waist circumference. The current hypotheses linking obesity and reduced vitamin D status consider either an effect due to an increased capacity of storage of vitamin D in the fat tissue or the interplay with autocrine factors produced by the adipose tissues. The experimental evidence from animal and human studies is suggesting a direct biological pathway, although the question of reverse causality has not been fully addressed. Currently, the epidemiological data in adults is supporting a causal inference of increased BMI in the reduction of vitamin D status while the reverse has not been confirmed. In addition, unhealthy diet was negatively associated with vitamin D status. Unfortunately, the food questionnaire used in the present study could not discriminate precisely the consumption of fatty fish or mushrooms to account for a precise dietary quantity of vitamin D₃ and D₂, respectively. Diet score has been previously examined in the same sample as an adequate proxy of a healthy or unhealthy diet, but future research with precise food frequency questionnaire is warranted. This will help understand the role of the natural source of dietary vitamin D to reinforce maintenance of a healthy dietary intake whenever possible.

Many reports and reviews consider vitamin D status as a mere representation of individual lifestyle and health behaviour. The positive association between vitamin D status and the use of OCP is in contrast with the suggestion that vitamin D status merely bio-marks a healthy status. In fact, OCP was linked to 10% higher vitamin D status as consistently reported, Similarly, one study which examined the effect of hormonal contraceptives during vitamin D supplementation in premenopausal women reported that the use of exogenous oestrogen would enhance the response to supplementation. It is not apparent what the underlying mechanism is pertaining to a higher vitamin D status in women using OCP. Two hypotheses are currently being examined to understand such association. These examine whether the mechanisms by which oestrogen increases the 25(OH)D are due to higher activity of vitamin D 25-hydroxylase in the liver, or an increase in circulating concentration of vitamin D binding protein (DBP). According to the IOM classification, OCP users in our study are more likely to be classified as vitamin D sufficient. Previous research using the same data has shown a link between the use of OCP and inflammation. It will therefore be essential to analyse the pathways underpinning the role of OCP in simultaneously increasing inflammation and vitamin D status. Based on evidence from this and other studies reporting consistently higher vitamin D status in women using OCP, it may be important to implement a corrective factor to the IOM criteria to avoid overestimation of vitamin D status in this subgroup of women.

**Importance of considering D₃ and D₂ isomers**

Public health recommendations and clinical diagnostics do not currently distinguish between vitamin D₂ and D₃. However, there is disagreement on whether these two forms should be considered equivalent. Additionally, 25(OH)D₃ accounted for the vast majority (>90%) of the circulating 25(OH)D concentrations in the present population. Our study and the study

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Palaniswamy S, et al. BMJ Open 2017;7:e013161. doi:10.1136/bmjopen-2016-013161

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performed by Tolppanen et al were in agreement on the reported associations between the season of blood sampling and the concentrations in 25(OH)D$_2$ and 25(OH)D$_3$. The determinants associated with the vitamin D status also influenced the serum concentrations of 25(OH)D$_2$ with the highest effect being exerted by the season. Importantly, we replicated the associations of the seasonal variation but not the SEP as first observed in children (mean age 9.8 years) of the Avon Longitudinal Studies of Parents and Children. As expected, 25(OH)D$_3$, known as the main contributor of vitamin D status obtained from sunlight, was positively associated with the season of blood sampling and latitude of residence. Interestingly, we observed a heightened vitamin 25(OH)D$_2$ status during the winter months that has yet to be understood. However, we do not have information on supplement use which hinders the ability to assess the increased vitamin 25(OH)D$_2$ status during winter. As suggested by Tolppanen and colleagues, if serum vitamin D2 is largely associated with dietary and some socioeconomic related factors, this may provide an indication of compensatory behaviour which can be adopted to correct the vitamin D status during the low sunlight months.

CONCLUSIONS AND IMPLICATIONS

Our results have provided information on the potential determinants associated with the vitamin D status prior to the implementation of a nationwide fortification policy. Understanding the associations between sex, season, latitude and multiple lifestyle factors with dual sources of vitamin D (25(OH)D$_2$ and 25(OH)D$_3$) will help better understand the role of vitamin D in research, clinical and public health implications. The data also supported a differential association of 25(OH)D$_2$ and 25(OH)D$_3$ concentrations with sunlight which might have an impact on future strategy for supplementation. These differential results also question current strategies of vitamin D supplementation and IOM cutoffs for vitamin D sufficiency and warrant a personalised approach, accounting for individual and lifestyle characteristics. The fortification of fluid milk products (0.5 μg/100 g) was introduced in Finland in 2002 with limited efficiency in all age groups. More recently, in April 2010, the fortification levels have been raised further (1.0 μg/100 g). In addition, in 2012, the Nordic and Finnish nutritional experts have recommended 10 μg/day for all individuals aged 6 months to 75 years, in addition to dietary intake. Our intended follow-up study from NFBC1966 at 46 years, will be helpful in measuring the efficiency of waves of fortification before (1997) and after (2012), taking into account multiple determinants and personal supplement use in Northern Finland.

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Acknowledgements We thank the entire NFBC1966 study team, including the research staff and all others involved in the data collection and processing and those involved in the oversight and management of the study. We acknowledge late Professor Paula Rantakallio for launch of Northern Finland Birth Cohort 1966 and initial data collection, Sarianna Vaara for data collection, Markku Koiranen for data management and Tuula Ylitalo for administration. The authors thank all the participants of NFBC1966 study.

Contributors SP, MRJ and SS designed the analysis plan. SP conducted the analysis and wrote the manuscript with guidance from SS, JJ, DMW and MRJ. EH and MRJ were responsible for data collection of variables and blood sampling related to this analysis. EL reviewed/edited the manuscript. All authors contributed intellectually to the manuscript and approved the final version.

Funding This work was financially supported by the Academy of Finland (MRJ, grant number 24300796); Medical Research Council, UK (EH, grant number G0601653); Biocenter Oulu Doctoral Programme (SP); European Union’s Horizon 2020 research and innovation programme (MRJ, SS, DMW, grant number 633595) for the DynaHEALTH action.

Disclaimer The funders had no role in the design, analysis or writing of this article.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The study was approved by the ethical committee of University of Oulu and Northern Ostrobotnia Hospital District. The procedures follow the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data are available on request to the NFBC1966 Data Sharing Committee. NFBC1966 data sharing policies and processes meet the requirement and expectations of Northern Ostrobotnia Hospital District policy on sharing of data from population and patient cohorts. Data requests should be submitted to Minna.Mannikko@oulu.fi; further details can be found at http://www.oulu.fi/nfbc/. These policies and processes are in places to ensure the use of data from this prospective birth cohort study is within the bounds of consent given previously by study members, complies with Northern Ostrobotnia Hospital district guidance on ethics and research governance and meets rigorous University of Oulu data security standards.

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