Determinants of 25-hydroxyvitamin D in older Irish adults

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Abstract

Background: vitamin D deficiency is prevalent in older adults living in Northern Europe and is influenced by several factors which may vary significantly with age.

Objective: we aimed to investigate the determinants of 25-hydroxyvitamin D [25(OH)D] in older Irish adults and in particular to examine the effect of supplement use and surrogate markers of sun exposure.

Methods: subjects were non-institutionalised community dwelling Irish adults aged over 60 years who were participants of a large cross-sectional study comprising three disease defined cohorts. Serum 25(OH)D was measured by liquid chromatography mass spectroscopy. Associations between 25(OH)D and potential confounders were explored in forward regression models in each cohort.

Results: the three cohorts comprised 1895, 1233 and 1316 participants (respective mean ages 70.1, 71.0 and 80.4 years). Statistical models explained between a fifth to a third of the variation in 25(OH)D. Supplement use and global solar radiation were positive predictors of 25(OH)D in all cohorts whereas the only universal negative predictor was body mass index. Supplement use was associated with a mean increase in 25(OH)D of between 21.4 and 35.4 nmol/l. The other main predictors varied by cohort but included sun holiday travel, enjoyment of sunshine when outside, use of vitamin D fortified milk, smoking, oily fish and egg consumption and physical frailty.

Conclusion: supplement use was the most important determinant of vitamin D status. Vitamin D fortified milk and spending time in the sun, even in the oldest old may also be useful strategies to improve 25(OH)D.

Keywords: vitamin D, older adults, supplements, older people
Introduction

Vitamin D deficiency is prevalent in Northern Europe affecting up to 50% or more of older adults [1, 2]. In locations at high latitude such as Ireland (52°N), little or no cutaneous synthesis occurs during the Winter months [3]. Older adults are at particular risk for deficiency for a number of reasons. Despite similar sun exposure, vitamin D production is reduced by up to 75% due to reduced epidermal concentrations of 7-dehydrocholesterol [4, 5]. Other factors including adiposity, reduced sun exposure and dietary vitamin D intake also negatively affect 25-hydroxyvitamin D [25(OH)D] status [6]. The contribution of these and other biological, dietary and lifestyle factors may vary significantly with age.

A knowledge of determinants of 25(OH)D may help identify those at risk of deficiency and inform strategies aimed at improving vitamin D status. This is important as optimisation of 25(OH)D may reduce falls and fracture risk in older adults [7, 8]. In addition, an increasing body of evidence supports a role for vitamin D in cognition, cardiovascular, neurological and autoimmune disease, as well as cancer and depression [9–11]. We aimed to investigate the determinants of 25(OH)D in the largest study to date of community dwelling older and frail Irish adults, and in particular to examine the effect of supplement use and surrogate markers of sun exposure.

Methods

The study population comprised participants of the TUDA (Trinity, Ulster, Dept. of Agriculture) study (see Figure 1). This is a large cross-sectional study designed to create a phenotype/genotype database for three cohorts of community dwelling non-institutionalised adults aged over 60 years. Recruitment started in Dec 2008 and was completed in Sept 2012. Subjects who were able to provide consent and scored ≥16 in the Mini Mental State Examination (MMSE) were eligible. Those with MMSE scores <24 were excluded in our study as we aimed to examine these relationships in non-dementia subjects.

Two cohorts (cognitive and bone) were recruited from the outpatient services at the Department of Medicine for the Elderly at St. James’ Hospital, Dublin. Subjects in the cognitive cohort were recruited from geriatric clinics and a day hospital service and had cognitive impairment based on testing with the RBANS (Repeatable Battery for the Assessment of Neuropsychological Status) [12]. Subjects in the bone cohort had a diagnosis of osteoporosis or osteopaenia (within 3 years of recruitment) as defined by standard WHO criteria (T score of ≤−2.5 and ≤−1.0 to >−2.5 respectively) and were recruited from a specialist bone health service. The hypertensive cohort comprised subjects who had a current diagnosis of hypertension verified by their GP’s and were recruited from general practices in the catchment area of the Western and

Figure 1. TUDA study population. 1. Recruitment of the Bone cohort was from specialist bone health service at St. James’ Hospital, Dublin. 2. Recruitment of the hypertensive cohort was from GP clinics in Northern Ireland. 3. Recruitment of the cognitive cohort was from St. James’ Hospital, Dublin. *Missing or incomplete data.
Northern Health and Social Care Trusts in Northern Ireland. Subjects were assessed on the day of their outpatient attendance or retrospectively and were contacted by telephone in advance and sent study information by post. All participants provided written consent and ethical approval was obtained from Research Ethnic committees. Trained researchers and doctors did study assessments.

**Overview of assessments**

All participants underwent a single assessment lasting about 70 min which included an interview recording self-reported information (demographic details, medical and psychosocial history, and current medications). All interviews were conducted face to face in the hospital outpatient department with or without the presence of a family member. Biophysical, cognitive assessments and functional scales were also applied.

**Lifestyle factors**

Subjects reported on the current use of vitamin D supplements (defined as prescribed and the over the counter vitamin D or cod liver/fish oil). The frequency of consumption of food sources of vitamin D including oily fish, eggs, vitamin D fortified milk and margarine was recorded. Smoking and alcohol history, sun holiday travel and preference for sunshine exposure and sunscreen use were also recorded.

**Biophysical measures**

Weight was measured with a calibrated scale accurate to 0.01 kg and height with a stadiometer (to the nearest 0.01 m). Body mass index (BMI) was calculated as per standard definition (weight/height$^2$). The Timed Up and Go (TUG) was measured, representing the time it takes to get out of a chair, walk three metres, turn around and walk back to an original seated position [13].

Non-fasting blood samples for 25(OH)D were taken on the day of assessment or within the following week. Bloods were processed on the same day and centrifuged within 3 h. 25(OH)D samples were stored at −70°C and batched for later analysis at the biochemistry laboratory at St James's Hospital, Dublin, a participant of the Vitamin D External Quality Assessment Scheme (DEQAS). 25(OH)D were measured by liquid chromatography mass spectroscopy (LCMS) using a standardised assay (Mass Chrom$^€^$) and National Institute of Standards and Technology (NIST) vitamin D standard reference material. The inter and intra-assay coefficient of variation were 5.7 and 4.5%.

**Statistical analysis**

All parameters were inspected for normality and normal assumptions for linear regression analysis including non-collinearity were observed. All statistical analysis was performed using JMP Edition 11.0 (SAS Institute, 2013). Statistical significance was accepted when $P < 0.05$. The sum of total global solar radiation (GSR) in the month and preceding 2 months of subject recruitment was used as a surrogate marker of UVB exposure. GSR represents the total amount of solar irradiation (direct beam plus the diffuse component on a horizontal surface) received per unit area per month. Data were obtained from the Irish Meteorological Service using weather stations nearest to study sites: Dublin Airport and Malin Head, Donegal.

Differences in cohort characteristics and 25(OH)D were explored with the one-way ANOVA, unpaired $t$ and $\chi^2$ test as appropriate. Cohorts were analysed separately as they had significantly different characteristics that had the potential to alter the influence of factors affecting 25(OH)D. In addition, one was also in a different geographical location. Vitamin D deficiency was defined as a 25(OH)D level below 50 nmol/l as used in other studies [2, 6]. Vitamin D supplement use included using one or more supplements listed in Supplementary data, Table S1, available in Age and Ageing online but excluded the use of 1α-hydroxylated vitamin D. Potential confounders were explored in a stepwise forward regression with a $P$-value to enter of 0.25 and to leave of 0.10. All covariates that were initially included were factors known to or have the potential to affect vitamin D status based on current literature. These included age, gender, GSR, BMI, supplement use (yes/no), sunscreen use classified as no (if rarely or never), and yes (if sometimes, usually or always), sun holiday travel in last 6 months (yes/no), TUG (quintiles), preference for sunshine when outside (enjoy sunshine versus avoid sunshine), education (years), smoking status (current) versus (past or never), alcohol drinking status (yes/no) and consumption of eggs ($\geq$3 versus <3 times per week), oily fish ($\geq$1 versus <1 per week), vitamin D fortified milk (yes/no) and margarine (yes/no). Those variables identified as significant were then included in a final model with fixed covariates (age, gender, GSR, BMI and supplement use) as used in other studies [1, 14, 15]. The relationship between 25(OH)D and GSR was also examined by supplement use.

**Results**

There were 2093, 1699 and 1394 participants recruited into the hypertensive, cognitive and bone cohorts respectively. After applying inclusion criteria and allowing for missing or incomplete data, the final number of available participants for analysis in the hypertensive, cognitive and bone cohort were 1895, 1316 and 1233 (see Figure 1).

There were significant differences between cohorts as outlined in Supplementary data, Table S1 (see Supplementary data). Cognitive cohort subjects were ~10 years older (mean age 80.4) and had more falls, physical, cognitive and functional impairment. Their mean TUG was approximately twice that of the other two cohorts (21.5 s) representing a group who are physically frail.

**Vitamin D deficiency**

The prevalence of vitamin D deficiency ($< 50$ nmol/l) in non-supplemented subjects were 43.4, 66.0 and 75.0% in the
respective bone, hypertensive and cognitive cohorts. Severe
deficiency (<25 nmol/l) was most prevalent (32.8%) in non-
supplemented cognitive cohort participants. The mean
difference in 25(OH)D due to supplementation was between
21.4 and 35.4 nmol/l (P < 0.001) (see Table 1).

The determinants of 25(OH)D in each cohort are shown in
Table 2. Some covariates were eliminated after stepwise regres-
sion or excluded if their proportion in cohorts were too
small. Overall, the models explained 29.0, 17.0 and 36.0% of
the variation in 25(OH)D in the hypertensive, bone and
cognitive cohorts.

Supplement use was the most important and positive pre-
dictor of 25(OH)D in all cohorts (P < 0.0001), whereas BMI
was a negative predictor (P ≤0.0001). GSR predicted higher
vitamin D status in all cohorts (P < 0.05). The relationship
with GSR was significant in supplemented subjects apart from
those in the cognitive cohort. Peak GSR occurred in the month
of July with peak 25(OH)D occurring around August, represent-
ing a lag period of ~1 month (see Figure 2). Sun holiday travel in
the bone and hypertensive cohorts (P < 0.0001) was the second
most important and positive predictor while current smoking in
both was a negative predictor (P < 0.030, P < 0.0001). Those
who enjoyed sunshine when outside were more likely to have
higher 25(OH)D in the hypertensive (P < 0.0001) and cognitive
cohorts (P = 0.0015) as did those who used sunscreen (P <
0.0001, P = 0.023). Consumption of fortified milk predicted
higher 25(OH)D in the bone (P = 0.001) and cognitive cohort
(P < 0.0001). However, no significant relationship was identified
with fortified margarine. The effects of other dietary factors were
inconsistent though eating eggs ≥3 times per week (P = 0.017)
and oily fish at least once per week (P = 0.028) predicted higher
25(OH)D in the respective hypertensive and bone cohorts.

An independent inverse association with TUG was con-
fined to cognitive cohort participants (P < 0.0001). In the
hypertensive cohort female gender predicted lower 25(OH)
D (P = 0.005) whereas increasing age predicted higher status

Table 1. Vitamin D status in different cohorts

<table>
<thead>
<tr>
<th>Vitamin D Status</th>
<th>Hypertensive (n = 1895)</th>
<th>Bone (n = 1233)</th>
<th>Cognitive (n = 1316)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 25(OH)D nmol/l</td>
<td>45.6 ± 23.5a</td>
<td>60.6 ± 32.1a</td>
<td>38.2 ± 22.9a &lt;0.001d</td>
</tr>
<tr>
<td>Difference due to supplement</td>
<td>21.4a</td>
<td>21.9a</td>
<td>35.4a &lt;0.001d</td>
</tr>
<tr>
<td>(&lt;25 nmol/l, %)</td>
<td>17.2b</td>
<td>8.6b</td>
<td>32.8b &lt;0.001b</td>
</tr>
<tr>
<td>3.0b</td>
<td>4.9b</td>
<td>4.4b &lt;0.001b</td>
<td></td>
</tr>
<tr>
<td>(&lt;30 nmol/l, %)</td>
<td>27.3b</td>
<td>13.8b</td>
<td>43.6b &lt;0.001b</td>
</tr>
<tr>
<td>6.4b</td>
<td>3.0b</td>
<td>6.4b &lt;0.001b</td>
<td></td>
</tr>
<tr>
<td>(&lt;50 nmol/l, %)</td>
<td>66.0b</td>
<td>43.4b</td>
<td>75.0b &lt;0.001b</td>
</tr>
<tr>
<td>33.2b</td>
<td>10.5b</td>
<td>22.9b &lt;0.001b</td>
<td></td>
</tr>
<tr>
<td>(50–74.9 nmol/l, %)</td>
<td>22.3b</td>
<td>29.8b</td>
<td>16.8b &lt;0.001b</td>
</tr>
<tr>
<td>35.8b</td>
<td>27.3b</td>
<td>29.6b &lt;0.001b</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Determinants of serum 25(OH)D in cohorts (in multiple linear regression models)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hypertensive (n = 1895)</th>
<th>Bone (n = 1233)</th>
<th>Cognitive (n = 1316)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.22 0.010</td>
<td>0.01 0.91</td>
<td>0.03 0.76</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>-1.86 &lt;0.0005</td>
<td>1.46 0.062</td>
<td>1.66 0.15</td>
</tr>
<tr>
<td>BMI (kg m−2)</td>
<td>-0.71 &lt;0.0001</td>
<td>-0.53 0.0001</td>
<td>-0.81 &lt;0.0001</td>
</tr>
<tr>
<td>GSR (kJ m−2)</td>
<td>1.22 &lt;0.0001</td>
<td>0.59 &lt;0.0001</td>
<td>0.32 0.048</td>
</tr>
<tr>
<td>Supplement use</td>
<td>9.94 &lt;0.0001</td>
<td>16.9 &lt;0.0001</td>
<td>9.8 &lt;0.0001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>-3.34 &lt;0.0001</td>
<td>-3.35 0.030</td>
<td>-3.35 0.030</td>
</tr>
<tr>
<td>Enjoy sunshine</td>
<td>3.38 &lt;0.0001</td>
<td>2.78 0.0015</td>
<td>4.29 &lt;0.0001</td>
</tr>
<tr>
<td>Sun holiday</td>
<td>7.00 &lt;0.0001</td>
<td>-</td>
<td>4.29 &lt;0.0001</td>
</tr>
<tr>
<td>Vitamin D fortified milk</td>
<td>-</td>
<td>-</td>
<td>1.27 0.084</td>
</tr>
<tr>
<td>Vitamin D fortified margarine</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oily fish</td>
<td>-</td>
<td>-</td>
<td>1.7 0.028</td>
</tr>
<tr>
<td>Eggs</td>
<td>1.58 0.017</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Timed up and Go (TUG)</td>
<td>-</td>
<td>-</td>
<td>-2.22 &lt;0.0001</td>
</tr>
<tr>
<td>Education (years)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Current drinker</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*BMI, body mass index; GSR, global solar radiation; TUG, Timed Up and Go; not included in model as proportion of covariate too low or excluded after stepwise regression (P-value to enter 0.25 and to leave 0.10).

*Statistically significant in any cohort (P < 0.05) after adjustment with other covariates in model.

(P = 0.01). Finally, no relationship with drinking or education status was identified.

Discussion

In our analysis of three cohorts of community dwelling older
Irish adults, we identified factors that explained between ap-
proximately one-fifth to one-third of the total variation in 25
(OH)D. Positive predictors of 25(OH)D in all cohorts were
vitamin D supplement use and GSR whilst the only universal
determinant was BMI. The relationship with dietary and oth-
er factors including physical frailty, smoking, gender and
sun exposure habits was inconsistent.

Vitamin D supplement use as expected was the most im-
portant predictor of 25(OH)D. The observed unadjusted effect was +21.4 nmol/l, +21.9 nmol/l and +35.4 nmol/l in the
respective hypertensive, bone and cognitive cohorts. These
differences are similar to a mean difference of 23.8 nmol/l
attributed to supplement use in 546 community dwelling Irish
adults [14]. The greater effect in the bone and cognitive cohort
may be explained by the majority taking prescribed supple-
ments (ideastM™, calcichewTM and osteofosTM™) which may
contain more vitamin D (typically 800 IU per day). The preva-
ance of vitamin D deficiency (<50 nmol/l) was high in unsup-
plemented subjects ranging from 43.4 to 75.0% in the older
and frail cognitive cohort.

GSR was positively associated with 25(OH)D in all cohorts
consistent with a recent study showing a positive correlation
between 25(OH)D and 3 month solar UV-B irradiance [16].
The relationship remained significant in supplemented subjects.
(except in the cognitive cohort) where supplement use may be marker of greater frailty and less sun exposure. A previous study of older Irish adults found no association with monthly GSR in those who were supplemented [14]. However, our sample size was larger and we used GSR data over a 2 to 3-month period. The lack of association with GSR in non-supplemented subjects in the bone cohort might relate to the small sample size. 25(OH)D levels were lowest in the Spring and highest in the Autumn months similar to other studies of older European adults [2, 15].

Similar to other studies, enjoying sunshine when outdoors predicted higher 25(OH)D in the cognitive and hypertensive cohorts as did sun holiday travel where explored [15, 17]. The high level of supplement use in the bone cohort may have diminished the effect of sun exposure. Sunscreen use unexpectedly predicted higher 25(OH)D in the hypertensive and cognitive cohorts but may be a surrogate marker of greater sun exposure as previously suggested [15, 17].

BMI was a universal negative predictor of 25(OH)D in keeping with most previous studies [1, 18]. Sequestration of 25(OH)D in fat cells may account for this finding, though it may also be involved in cell signalling pathways that could lead to an increased risk of obesity through increased lipogenesis [19]. Unexpectedly, increasing age predicted higher 25(OH)D in the hypertensive cohort. However, the lack of an inverse relationship may relate to the relatively narrow age range of participants in all three cohorts. The association with gender was inconsistent in keeping with other studies [20]. Current smoking was a negative predictor of 25(OH)D in both the bone and hypertensive cohorts as previously reported [1, 21]. Alterations in hepatic metabolism of vitamin D or 1-α-hydroxylation due to smoking could be a potential mechanism [22]. Alternatively, smoking may be a surrogate marker for adverse diet and lifestyle factors that diminish 25(OH)D such as lower vitamin D intake [23].

Fortified margarine had no effect on 25(OH)D but this is not surprising given the small amount consumed and its low vitamin D content. Conversely, fortified milk was a positive predictor of 25(OH)D in the bone and cognitive cohort. Fortified milk mainly constituted Supermilk© which contains about 80 IU of vitamin D3 per 200 ml. Few studies have examined the effect of fortified milk in older adults, though a small intervention trial did find a beneficial effect on 25(OH)D in older Irish subjects [24]. Consumption of oily fish at least once per week in the bone cohort and eggs ≥3 times per week in the hypertensive cohort were also predictors of better 25(OH)D status, a result previously reported by other studies [15, 25]. However, these factors may be surrogate markers of better health and compliance with supplement use.

Lower 25(OH)D was also an independent predictor of physical frailty (as measured by TUG) but only in cognitive cohort participants who had a higher prevalence of deficiency and were frailer. Few studies have explored the association between 25(OH)D and TUG, though an inverse relationship has been found in community dwelling adults aged 70 years or older [26, 27]. Other studies in older adults identified no association with physical frailty but used more specific measures [28]. Reduced UVB exposure in those who are frail may account for any relationship. However, low 25(OH)D status might directly lead to frailty as deficiency has been associated with myopathy and supplementation has been found to improve performance in the TUG and other physical measures in older adults [29].

Our study strengths included its large size with subjects from widely varying ages, exclusion of those likely to have dementia and our accurate account of vitamin D supplement use. We also adjusted for a several factors related to UVB exposure and measured 25(OH)D by LCMS. However, we did not have adequate measures of non-supplemental dietary vitamin D intake, outdoor exposure or physical activity. In particular, we were not able to accurately account for meat consumption which is the main contributor to dietary vitamin D intake in Ireland [30]. However, apart from supplements, the overall contribution of diet to vitamin D status is small and unlikely to significantly alter our results.
In summary, supplement use, GSR and sun holiday travel were positive predictors of 25(OH)D while BMI, smoking and other factors negatively influenced status. We identified that those at most risk of deficiency were unsupplemented, oldest and frail in which prevalence was high at 75%. However, even in such a group, fortified milk consumption and spending time outdoors in the sun, might be practical strategies to improve 25(OH)D.

Key points

- Supplement use was the most important determinant of vitamin D status (mean increase in 25(OH)D of between 21.4 and 35.4 nmol/l).
- Physical frailty as assessed by the Timed up and Go was inversely associated with 25(OH)D but only in ‘older’ old adults.
- Vitamin D fortified milk and spending time in the sun, even in the ‘oldest’ old may be useful strategies to improve 25(OH)D.

Conflicts of interest

K.M. received an honorarium for his input on a Vitamin D advisory panel for Consilient Health Ltd, Ireland.

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Supplementary data

Supplementary data mentioned in the text is available to subscribers in Age and Ageing online.

References


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Antibiotic prescribing and associated diarrhoea: a prospective cohort study of care home residents

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Abstract

Background: the risk factors for and frequency of antibiotic prescription and antibiotic-associated diarrhoea (AAD) among care home residents are unknown.
Aim: to prospectively study frequency and risks for antibiotic prescribing and AAD for care home residents.