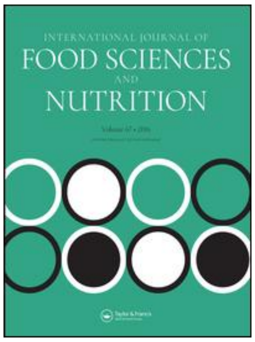


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RESEARCH ARTICLE

# Adherence to the Mediterranean diet is an independent predictor of circulating vitamin D levels in normal weight and non-smoker adults: an observational cross-sectional study

Maria Dalamaga[a], Giovanna Muscogiuri[b], Georgia Paganitsa[c], Georgeta Parvouleskou[c], Vassiliki Syriou[c], Panagiotis Karagkoynis[c], Theodora Stratigou[d], Natalia Vallianou[d], Gerasimos Socrates Christodoulatos[a], Irene Karampela[a] and Konstantina Daskalopoulou[c]

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**ABSTRACT**

We explored the association between circulating 25OHD and adherence to the Mediterranean Diet (MedDiet) in 402 Greek (21–65 years, 188 men and 214 women), normal weight, non-smoker, healthy volunteers in the Athens metropolitan area during summer and autumn, taking into account skin phototype, anthropometric, and lifestyle variables. Circulating 25OHD, parathormone, creatinine, calcium, and phosphate were determined. A vitamin D status of $\leq$25, $\leq$50, and $\leq$75 nmol/L was observed in 4.5, 37.3, and 74.1% of the subjects, respectively. The independent predictors of 25OHD deficiency were autumn, darker skin phototype, BMI, or waist circumference (WC), sunscreen use, less physical outdoor activity, and less adherence to the MedDiet. Higher intake of fish and olive oil was a positive independent predictor of elevated circulating 25OHD levels. In conclusion, higher adherence to the MedDiet, fish and olive oil consumption, were positively associated with circulating 25OHD independently from BMI or WC, skin phototype, season, and physical activity.

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**KEYWORDS**
Body mass index; fish; Mediterranean diet; olive oil; phototype; vitamin D; 25OHD

## Introduction

Vitamin D is a secosteroid playing a pivotal role in the calcium-phosphate metabolism. Adequate vitamin D status, as expressed by serum 25-hydroxyvitamin D (25OHD) concentration, is critical for optimal bone mineral density and neuromuscular activities, presenting also anti-inflammatory, anti-neoplastic, immune-modulatory and microbicidal properties (Mason et al. 2011). Hence, low circulating vitamin D has been associated in many observational studies with a plethora of diseases such as osteoporosis, diabetes mellitus (DM), cardiovascular disease (CVD), autoimmune disorders, and certain types of cancer. However, causality has not been demonstrated yet and conflicting data have been reported regarding the extraskeletal effects of vitamin D (Holick 2007; Bouillon et al. 2019). A serum level of 25OHD $\geq$50 nmol/L is considered an optimal vitamin D status for the general population by the US Institute of Medicine while a concentration above 75 nmol/L is recommended by the US Endocrine Society for optimal health benefit, particularly in elderly subjects with augmented risk of fractures as well as osseous, renal, and digestive disorders (Holick et al. 2011; Ross et al. 2011).

Vitamin D deficiency (<50 nmol/L) has been described as pandemic across diverse age groups and countries with a high prevalence rate in Europe (40%), particularly in Mediterranean countries despite a high exposure to sunlight (Kassi et al. 2014; Cashman et al. 2016; Souberbielle et al. 2016; Grigoriou et al. 2018). Although the major natural source of vitamin D is its endogenous production through exposure of the skin to sun UVB radiation, circulating 25OHD levels may depend on biologic, environmental and cultural determinants, including age, gender, race/ethnicity, season, smoking, body mass index (BMI), vitamin D dietary intake, medication use, etc. (Fayet-Moore et al. 2019; Marquina et al. 2019).

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The Mediterranean Diet (MedDiet) constitutes the gold standard dietary pattern in preventive medicine, presenting anti-inflammatory, anti-neoplastic, anti-obesogenic and anti-oxidant properties, attributed mainly to the synergy of its food items. Based on systematic reviews, randomised controlled trials (RCTs) and prospective studies, the Mediterranean Diet (MedDiet) is considered a highly beneficial dietary pattern showing a favourable impact on the prevention of CVD, t2DM, obesity, metabolic syndrome, hypertension, colorectal cancer, and postmenopausal breast cancer as well as the reduction of CVD and cancer mortality (Martinez-Gonzalez et al. 2009; De Pergola and D'Alessandro 2018; Hidalgo-Mora et al. 2020; Mirabelli et al. 2020; Sánchez-Sánchez et al. 2020). Pooled analyses of individual components of the MedDiet have shown that the protective effects against CVD appear to be associated with olive oil, fruits, vegetables, and legumes (Grosso et al, 2017). Overall, the beneficial properties associated with the MedDiet are attributed to the higher consumption of complex carbohydrates, fibres, monounsaturated fatty acids (MUFA), and anti-oxidants, particularly polyphenols derived from olive oil (Bonaccio et al. 2020). Although its protective effects on bone mineral density and the risk of fracture (Malmir et al. 2018), the MedDiet is not particularly rich in vitamin D, which is considered one of the most important dietary parameters in the prevention of osteoporosis, rickets, and osteomalacia (Holick et al. 2011; Ross et al. 2011).

Although several studies have reported that higher adherence to the MedDiet is associated with elevated dietary vitamin D intake (Grosso et al. 2013; Marventano et al. 2018; Aparicio-Ugarriza et al. 2019), there is very limited data on the influence of the MedDiet in serum 25OHD levels (Jennings et al. 2018; Aparicio-Ugarriza et al. 2019; Simunovic et al. 2019; Barrea et al. 2020; Zupo et al. 2020). Interestingly, only one study has investigated the association between adherence to the MedDiet and circulating vitamin D levels in overweight and obese subjects (Zupo et al. 2020). No study has examined the previous association in healthy normal weight adults. Therefore, our aim was to investigate the prevalence and the independent predictors of vitamin D deficiency as well as the independent association of the MedDiet and its food items with circulating vitamin D in a large, well-defined sample of Greek, normal weight, and non-smoker adults of Athens metropolitan area during sunnier seasons, taking into account skin phototype, anthropometric, and lifestyle variables.

## Material and methods

In a cross-sectional study which was conducted in the Athens metropolitan area between July and November 2019, a total of 402 Greek (aged 21–65 years, 188 men and 214 women), Caucasian, normal weight ($18.5 \leq \text{BMI} < 25\,\text{kg/m}^2$), non-smoker, healthy volunteers recruited consecutively at the Outpatient Laboratory Department of ELPIS General Hospital was included in the analysis. This sample population is representative of the regional population of the Athens metropolitan area.

Main exclusion criteria included age less than 18 years old; overweight, and obesity; any current acute or chronic illness; intestinal malabsorption; impaired hepatic or renal function; endocrinopathy (diabetes mellitus, hyper- or hypothyroidism, hypopituitarism, etc.); malignancy; autoimmune disorders; cardiovascular, pulmonary or neuropsychiatric disorders; pregnancy or lactation; medication influencing bone metabolism, including vitamin D and/or calcium supplements for the last 12 months; smoking; family history of hypocalcaemia or vitamin D disorders; history of immobility. The flow chart of the study is shown in Figure 1. The study protocol was approved by the Ethics Committee of ELPIS Hospital (#18236/15-10-2019). A written informed consent was obtained from each study participant in accordance with the Helsinki Declaration of 1964 and successive revisions.

Subjects participating in the study were examined by means of the medical history, anthropometric, routine hematobiochemical parameters, and a clinical check-up. Anthropometric measurements (weight, height, waist circumference/WC) were performed by the same resident early in the morning as previously described (Sotiropoulos et al. 2018). BMI was calculated based on the formula body weight (kg)/height$^2$(m$^2$). A validated 11-item questionnaire, the MedDietScore, was used to evaluate the adherence to the MedDiet (Panagiotakos et al. 2007). This questionnaire includes 11 closed questions exploring the frequency of intake of foods that characterise the MedDiet, such as fish, poultry, red meat, legumes, vegetables, fruits, olive oil, dairy products, potatoes, alcohol, and unprocessed cereals (wholemeal bread, pasta, rice, etc.) (Panagiotakos et al. 2007; Korovesi et al. 2019). The score (from 0 to 55) of each individual indicates the level of the adherence to the MedDiet; a score from 0 to 20 is considered low adherence, a score of 21–35 is considered medium adherence while a score of 36–55 is considered high adherence (Panagiotakos et al. 2007). Moreover, to evaluate calcium intake, we recorded the consumption

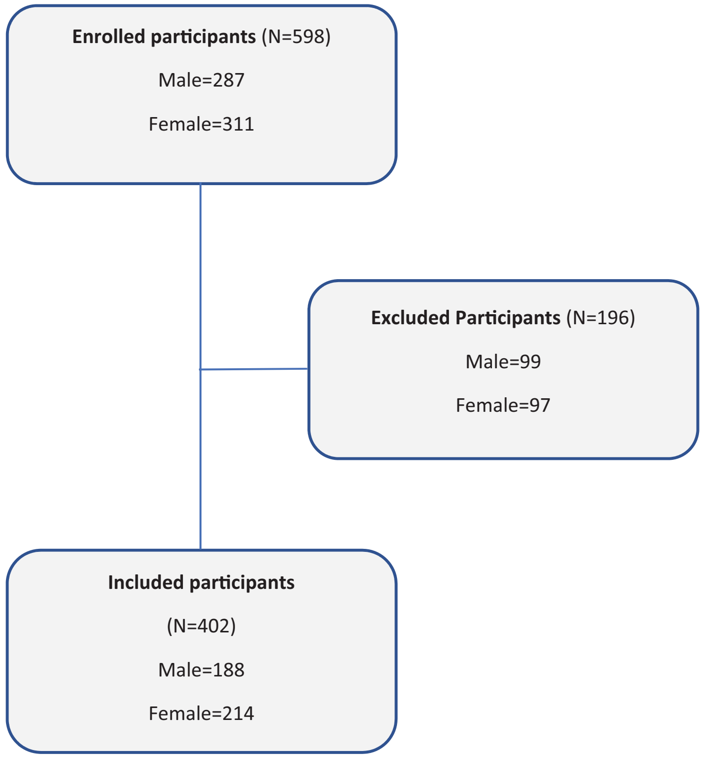


Figure 1. The flowchart of study participants.

of food items which represent the major sources of daily calcium intake, such as milk, yogurt, and cheese, including Greek cheeses (feta and kasseri). Calcium intake per week was estimated and expressed in mg of calcium per week. Skin phototype was categorised according to the Fitzpatrick skin type classification (Kochevar et al. 1999). The Fitzpatrick skin phototype describes a scale to classify the skin by its reaction to exposure to sunlight. Based on this classification, skin phototype I always burns and never tans; skin phototype II usually burns and tans minimally; skin phototype III sometimes presents mild burn and tans uniformly; skin phototype IV burns minimally and always tans well; skin phototype V rarely burns and tans very easily; and skin phototype VI never burns and always tans darkly (Kochevar et al. 1999). Finally, information on physical outdoor activity, sunscreen use including number of applications per day and sun protection factor, and educational level were recorded.

### Laboratory methods

All interviews and determinations were performed under similar conditions at the same time in the morning (8:00 to 9.30 am). An overnight fasting morning sample was obtained from all participants. Serum calcium, albumin, creatinine, and phosphate were measured using Dimension® Siemens clinical chemistry autoanalyzer. Serum calcium levels were adjusted for serum albumin. Estimated Glomerular Filtration Rate (eGFR) was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation which gives the best estimation of GFR based on serum creatinine, age, gender and race (Michels et al. 2010; Matsushita et al. 2012). Serum intact parathormone (iPTH) and 25OHD were determined using an automated Chemiluminescent Microparticle immunoassay (Architect Abbott Diagnostics, Germany). For 25OHD, the intra-and inter-assay coefficients of variation were <5.1 and <7.1%, respectively. For iPTH, the total assay variability was <6.4%.

### Statistical analysis

Primarily, data were assessed through simple cross-tabulations and $\chi^2$ test for categorical variables, *t*-test for normally distributed continuous variables, and Mann–Whitney *U* for not normally distributed continuous variables. In order to compare means of cases amongst different subgroups, one-way ANOVA test for normally distributed variables or Kruskal–Wallis test for not normally distributed variables were conducted. For descriptive purposes, data were presented as mean ± standard deviation, and median and interquartile range (IQR) for continuous normally and not normally distributed variables, respectively, as well as frequency/proportion for categorical and ordinal variables. Spearman correlation coefficient was used as a measurement of correlation for continuous and ordinal variables. Subsequently, analysis was undertaken through multivariable logistic regression models in order to evaluate independent determinants/predictors of vitamin D deficiency. Variables significantly associated with vitamin D deficiency were included in the model. For logistic regression, the 25OHD cut-off level was set at 50 nmol/L as values less than 50 nmol/L reflect inadequate (26–50 nmol/L) or deficient (≤25 nmol/L) levels for bone and overall health in healthy subjects (Institute of Medicine (US) 2011). Moreover, a multiple stepwise linear regression analysis was used to identify in a final model only significant independent predictors affecting circulating 25OHD levels as a dependent variable (stepwise criteria of entry in the model ≤0.05 and removal from the model ≥0.1) (Cook 2000). In linear regression models, apart from the adherence to the MedDiet, we analysed in a separate model food items that are included in the MedDietScore along with other variables. As BMI and WC are similar and collinear predictors, two separate models were conducted for BMI and WC as independent variables in both logistic and linear regression models. For all statistical tests, a two-sided $p$ value of less than 0.05 was considered significant. The statistical package IBM-SPSS® version 24 for Windows was used for the analysis. From our earlier clinical studies (Hroussalas et al. 2008; Kassi E et al. 2009), we calculated that we required a total sample size of at least 400 patients to achieve 87% statistical power at the 0.05 level of significance in order to detect a 6% difference in the MedDietScore between groups.

## Results

The entire sample included 402 consecutive, normal weight, and non-smoker healthy subjects with a mean age ± standard deviation of 43.9 ± 12.6 years (range: 21–65). Characteristics of the study population based on serum 25OHD status are depicted in Table 1. All individuals had normal calcium, albumin, phosphate, and eGFR values. In univariate analyses, lower serum 25OHD levels were associated with higher iPTH, BMI, WC, and lower MedDiet score as well as with autumn season (compared to summer), darker skin phototype, less physical outdoor activity, less fish and olive oil intake, more alcohol intake and sunscreen applications per day ($p < 0.05$).

A vitamin D status of ≤25, ≤50, and ≤75 nmol/L was observed in 4.5, 37.3, and 74.1% of subjects, respectively while 25.9% of subjects presented 25OHD levels above 75 nmol/L. Overall, mean serum 25OHD was 59.8 ± 23.9 nmol/L. Mean serum iPTH concentration was 6.03 ± 2.68 pmol/L. The majority of the subjects (341 subjects, 84.8%) presented a medium adherence to the MedDiet (21–35 points). In the whole sample, the median value and IQR of the MedDietScore was 30 (27–33). Females tended to present a higher MedDietScore (median, IQR: 30, 27–33) than males (median, IQR: 29, 27–33; $p = 0.08$), though not statistically significant at 0.05 level of significance.

Table 2 depicts a correlation matrix of main study variables in the study population. Notably, serum 25OHD negatively correlated with serum iPTH ($r=-0.17$, $p = 0.001$), BMI ($r=-0.59$, $p < 0.001$), WC ($r=-0.26$, $p < 0.001$) and skin phototype ($r=-0.17$, $p = 0.001$) while it positively correlated with serum calcium ($r = 0.21$, $p < 0.001$) and phosphate ($r = 0.15$, $p = 0.002$; data not shown).

Interestingly, MedDietScore was negatively associated with BMI ($r=-0.12$, $p = 0.013$), WC ($r=-0.11$, $p = 0.03$) and iPTH ($r=-0.14$, $p = 0.006$), and positively associated with serum 25OHD ($r = 0.21$, $p < 0.001$).

Figure 2 depicts the relationship curve between iPTH and 25OHD levels, which showed an inflexion point at a 25OHD serum concentration of approximately 43 nmol/L, below which the slope becomes steeper.

In Table 3, multiple logistic regression analysis showed that the independent predictors of vitamin D deficiency (≤50 nmol/L) were autumn (versus summer, $p = 0.001$ and $p < 0.001$), darker skin phototype ($p < 0.001$, in the model with WC), sunscreen use ($p = 0.04$ and $p = 0.003$), BMI ($p < 0.001$) or WC ($p = 0.007$), less physical outdoor activity ($p < 0.001$) and lower adherence to the MedDiet ($p = 0.04$ and $p = 0.01$). Figure 3 depicts the significant determinants of vitamin D deficiency.

As portrayed in Table 4, the final models of multiple stepwise linear regression depict only the significant independent predictors of circulating 25OHD levels taking into account the adherence to the MedDiet or its food items. In both models, BMI ($p < 0.001$) and darker skin phototype ($p = 0.02$ and $p = 0.005$) were negative independent predictors of serum 25OHD while adherence to the MedDiet ($p = 0.02$) or more fish ($p < 0.001$) and olive oil ($p < 0.001$) consumption as well as summer season ($p < 0.001$) and physical outdoor activity ($p < 0.001$ and $p = 0.004$) were positive independent predictors of serum 25OHD levels. WC was a negative

**Table 1.** Characteristics of the study population ($N = 402$) based on circulating 25OHD concentrations.

| Variables<br>Continuous | 25OHD ≤25 nmol/L (N = 18)<br>Mean ± SD or median (IQR) | 25 < 25OHD ≤50 nmol/L (N = 132)<br>Mean ± SD or Median (IQR) | 25OHD >50 nmol/L (N = 252)<br>Mean ± SD or Median (IQR) | p Value |
|---|---|---|---|---|
| Age (years) | 46.8 ± 14.5 | 43.1 ± 13.2 | 44.3 ± 12.5 | 0.46 |
| 25OHD (nmol/L) | 19.33 ± 3.60 | 39.55 ± 6.84 | 73.35 ± 19.23 | **<0.001** |
| Albumin (g/L) | 43 ± 5 | 43.4 ± 4.9 | 43.8 ± 5.5 | 0.65 |
| Corrected Calcium (mmol/L) | 2.32 ± 0.14 | 2.33 ± 0.12 | 2.35 ± 0.10 | 0.41 |
| Phosphate (mmol/L) | 1.08 ± 0.6 | 1.09 ± 0.99 | 1.11 ± 0.97 | 0.07 |
| intact PTH (pmol/L) | 5.60 ± 1.24 | 6.77 ± 3.19 | 5.68 ± 2.38 | **<0.001** |
| Creatinine (μmol/L) | 70.72 ± 7.28 | 73.37 ± 15.99 | 72.31 ± 14.69 | 0.69 |
| eGFR (mL/min)† | 99.44 ± 15.05 | 99.01 ± 18.94 | 98.48 ± 15.35 | 0.94 |
| WC (cm) | 86.6 ± 10.7 | 85.9 ± 9.1 | 82.5 ± 11.2 | **0.006** |
| BMI (kg/m$^2$) | 24.67 ± 0.32 | 24.31 ± 0.78 | 22.5 ± 1.85 | **<0.001** |
| Calcium intake per week (mg/week) | 3900 (3800–4275) | 3900 (2700–5400) | 3900 (2700–5400) | 0.29 |
| MedDiet score | 28 (25–31) | 29 (26–32) | 31 (28–34) | **<0.001** |
| Categorical variables | *N* (%) | *N* (%) | *N* (%) | |
| Gender | | | | 0.62 |
| Male | 10 (55.6) | 64 (48.5) | 138 (54.8) | |
| Female | 8 (44.4) | 68 (51.5) | 114 (45.2) | |
| Month/Season of blood draw | | | | **<0.001** |
| June–August (summer) | 12 (66.7) | 96 (72.7) | 230 (91.3) | |
| September–November (fall) | 6 (33.3) | 36 (27.3) | 22 (8.7) | |
| Educational level (years) | | | | 0.75 |
| <6 | 0 (0) | 3 (2.3) | 4 (1.6) | |
| 6 (Primary) | 7 (38.9) | 49 (37.1) | 88 (35) | |
| 9 | 3 (16.7) | 17 (12.9) | 20 (7.9) | |
| 12 (Secondary) | 4 (22.2) | 27 (20.4) | 59 (23.4) | |
| >12 (Superior) | 4 (22.2) | 36 (27.3) | 81 (32.1) | |
| Fitzpatrick skin phototype∂ | | | | **<0.001** |
| Type I | 0 (0) | 2 (1.5) | 4 (1.6) | |
| Type II | 2 (11.1) | 12 (9.1) | 54 (21.4) | |
| Type III | 4 (22.2) | 86 (65.2) | 154 (61.1) | |
| Type IV | 12 (66.7) | 32 (24.2) | 40 (15.9) | |
| Adherence to the Mediterranean diet (0–55) | | | | 0.05 |
| Low (0–20) | 2 (11.1) | 6 (4.5) | 6 (2.4) | |
| Medium (21–35) | 16 (88.9) | 114 (86.4) | 211 (83.7) | |
| High (36–55) | 0 (0) | 12 (9.1) | 35 (13.9) | |
| Food items of MedDietScore | | | | |
| Consumption of poultry (servings per week) | | | | 0.79 |
| ≤3 | 13 (72.3) | 87 (65.9) | 158 (62.7) | |
| 4–5 | 3 (16.7) | 22 (16.7) | 45 (17.9) | |
| 5–6 | 1 (5.5) | 6 (4.5) | 21 (8.3) | |
| 7–8 | 0 (0) | 10 (7.6) | 12 (4.8) | |
| 9–10 | 1 (5.5) | 7 (5.3) | 16 (6.3) | |
| Consumption of red meat (servings per week) | | | | 0.47 |
| ≤1 | 8 (44.4) | 58 (43.9) | 115 (45.6) | |
| 2–3 | 8 (44.4) | 47 (35.6) | 73 (28.9) | |
| 4–5 | 1 (5.6) | 20 (15.2) | 44 (17.5) | |
| 6–7 | 0 (0) | 3 (2.3) | 8 (3.2) | |
| 8–10 | 1 (5.6) | 0 (0) | 4 (1.6) | |
| >10 | 0 (0) | 4 (3) | 8 (3.2) | |
| Consumption of legumes (servings per week) | | | | 0.97 |
| Never | 3 (16.7) | 22 (16.7) | 35 (13.9) | |
| <1 | 2 (11.1) | 23 (17.4) | 46 (18.3) | |
| 1–2 | 11 (61.1) | 73 (55.3) | 147 (58.3) | |
| 3–4 | 2 (11.1) | 10 (7.6) | 16 (6.3) | |
| 5–6 | 0 (0) | 4 (3) | 8 (3.2) | |
| Consumption of vegetables (servings per week) | | | | 0.53 |
| 1–6 | 4 (22.2) | 38 (28.8) | 57 (22.6) | |
| 7–12 | 5 (27.7) | 44 (33.3) | 109 (43.3) | |
| 13–20 | 7 (38.9) | 31 (23.5) | 54 (21.4) | |
| 21–32 | 1 (5.6) | 12 (9.1) | 22 (8.7) | |
| >33 | 1 (5.6) | 7 (5.3) | 10 (4) | |
| Consumption of fruits (servings per week) | | | | 0.31 |
| 1–4 | 2 (11.1) | 14 (10.6) | 25 (9.9) | |
| 5–8 | 14 (77.8) | 98 (74.2) | 180 (71.4) | |
| 9–15 | 0 (0) | 14 (10.6) | 39 (15.5) | |
| 16–21 | 2 (11.1) | 6 (4.6) | 8 (3.2) | |

(*continued*)

**Table 1.** Continued.

| Variables<br>Continuous | 25OHD ≤25 nmol/L (*N* = 18)<br>Mean ± SD or median (IQR) | 25 < 25OHD ≤50 nmol/L (*N* = 132)<br>Mean ± SD or Median (IQR) | 25OHD >50 nmol/L (*N* = 252)<br>Mean ± SD or Median (IQR) | *p* Value |
|---|---|---|---|---|
| Consumption of potatoes (servings per week) | | | | 0.53 |
| Never | 1 (5.6) | 2 (1.5) | 3 (1.2) | |
| 1–4 | 3 (16.7) | 16 (12.1) | 40 (15.9) | |
| 5–8 | 4 (22.2) | 37 (28) | 91 (36.1) | |
| 9–12 | 2 (11.1) | 24 (18.2) | 39 (15.5) | |
| 13–18 | 4 (22.2) | 23 (17.5) | 31 (12.3) | |
| >18 | 4 (22.2) | 30 (22.7) | 48 (19) | |
| Consumption of unprocessed cereals (wholemeal bread, pasta, rice, etc.) | | | | 0.39 |
| Never | 14 (77.7) | 87 (65.9) | 162 (64.3) | |
| 1–6 | 1 (5.6) | 10 (7.6) | 23 (9.1) | |
| 7–12 | 0 (0) | 14 (10.6) | 33 (13.1) | |
| 13–18 | 1 (5.6) | 10 (7.6) | 24 (9.5) | |
| 19–31 | 2 (11.1) | 9 (6.8) | 6 (2.4) | |
| >32 | 0 (0) | 2 (1.5) | 4 (1.6) | |
| Consumption of olive oil in cooking (times per week) | | | | **<0.001** |
| Never | 1 (5.6) | 1 (0.8) | 4 (1.6) | |
| Rarely | 2 (11.1) | 2 (1.5) | 3 (1.2) | |
| <1 | 2 (11.1) | 8 (6.1) | 9 (3.6) | |
| 1–3 | 4 (22.2) | 46 (34.8) | 18 (7.1) | |
| 3–5 | 2 (11.1) | 39 (29.5) | 69 (27.4) | |
| Daily | 7 (38.9) | 36 (27.3) | 149 (59.1) | |
| Alcohol intake (mL per week, 100 ml = 12 g ethanol) | | | | **<0.001** |
| <300 mL | 4 (22.2) | 26 (19.7) | 70 (27.8) | |
| 300–400 mL | 2 (11.1) | 30 (22.7) | 76 (30.2) | |
| 401–500 mL | 2 (11.1) | 26 (19.7) | 44 (17.5) | |
| 501–600 mL | 0 (0) | 4 (3) | 30 (11.9) | |
| 601–700 mL | 0 (0) | 8 (6.1) | 20 (7.9) | |
| ≥700 mL | 10 (55.6) | 38 (28.8) | 12 (4.7) | |
| Consumption of dairy products (servings per week) | | | | 0.05 |
| ≤10 portions | 4 (22.2) | 38 (28.8) | 74 (29.4) | |
| 11–15 portions | 10 (55.6) | 38 (28.8) | 106 (42.1) | |
| 16–20 portions | 4 (22.2) | 40 (30.3) | 42 (16.7) | |
| 21–28 portions | 0 (0) | 8 (6.1) | 14 (5.6) | |
| 29–30 portions | 0 (0) | 2 (1.5) | 10 (3.9) | |
| >30 portions | 0 (0) | 6 (4.5) | 6 (2.3) | |
| Fish consumption (times per week) | | | | **<0.001** |
| 0 | 12 (66.7) | 42 (31.8) | 10 (3.9) | |
| <1 | 6 (33.3) | 70 (53) | 32 (12.7) | |
| 1–2 | 0 (0) | 6 (4.5) | 186 (73.8) | |
| 3–4 | 0 (0) | 14 (10.6) | 24 (9.6) | |
| Physical outdoor activity per week | | | | **<0.001** |
| <2h | 10 (55.6) | 70 (53) | 86 (34.1) | |
| ≥2h | 8 (44.4) | 62 (47) | 166 (65.9) | |
| Sunscreen use | | | | 0.95 |
| Always | 6 (33.3) | 32 (24.2) | 62 (24.6) | |
| Often | 6 (33.3) | 38 (28.8) | 78 (30.9) | |
| Occasionally (summer) | 4 (22.3) | 40 (30.3) | 76 (30.2) | |
| Never | 2 (11.1) | 22 (16.7) | 36 (14.3) | |
| SPF for sunscreen users (*N* = 342) | *N* = 16 | *N* = 110 | *N* = 216 | 0.66 |
| ≤30 | 6 (37.5) | 52 (47.3) | 106 (49.1) | |
| >30 | 10 (62.5) | 58 (52.7) | 110 (50.9) | |
| Sunscreen applications per day for sunscreen users (*N* = 342) | *N* = 16 | *N* = 110 | *N* = 216 | **0.04** |
| <2 | 6 (37.5) | 74 (67.3) | 152 (70.4) | |
| ≥2 | 10 (62.5) | 36 (32.7) | 64 (29.6) | |

In bold, statistically significant results.

BMI: body mass index; eGFR: estimated glomerular filtration rate; PTH: parathormone; SD: standard deviation; SPF: sun protection factor; WC: waist circumference; 25OHD: 25-hydroxyvitamin D.

[∂]Fitzpatrick skin phototype: Type I: always burns, never tans, Type II: usually burns, tans minimally, Type III: sometimes mild burn, tans uniformly; Type IV: burns minimally, always tans well.

**Table 2.** Spearman Correlation coefficients of main study variables among 402 Greek, Caucasian, normal weight and non-smoker healthy participants.

| Variable | BMI | WC | 25OHD | PTH | Education | MedDiet score | Skin Phototype |
|---|---|---|---|---|---|---|---|
| Age | 0.04 | 0.2*** | 0.06 | 0.36*** | 0.13* | −0.02 | −0.07 |
| BMI | – | 0.45*** | −0.59*** | 0.17** | −0.03 | −0.12** | 0.16** |
| WC | – | – | −0.26*** | −0.11** | 0.03 | −0.11* | 0.02 |
| Vitamin D | – | – | – | −0.17** | 0.04 | 0.21*** | −0.17** |
| PTH | – | – | – | – | 0.06 | −0.14** | −0.09 |
| education | – | – | – | – | – | −0.002 | −0.02 |
| MedDiet score | – | – | – | – | – | – | 0.05 |

$^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

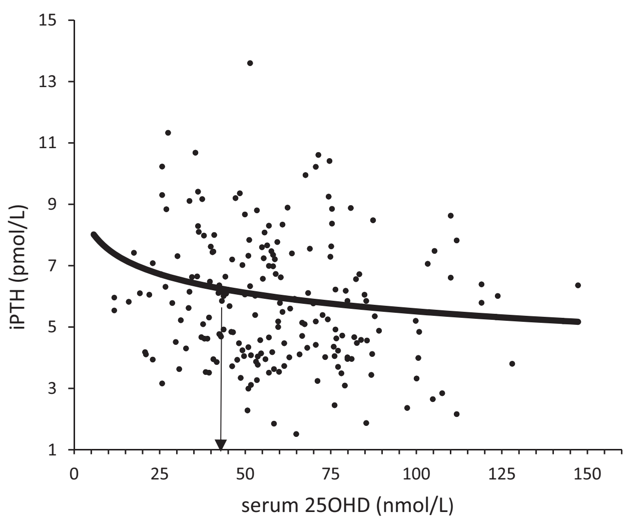


**Figure 2.** The relationship curve between iPTH and 25OHD levels, showing an inflexion point at a 25OHD serum concentration of approximately 43 nmol/L, below which the slope becomes steeper.

independent predictor of serum 25OHD ($p < 0.001$) when WC was introduced in the model instead of BMI.

## Discussion

To date, very few studies have focussed on the association between adherence to the MedDiet and circulating 25OHD levels with only one study exploring this association in overweight/obese subjects (Jennings et al. 2018; Aparicio-Ugarriza et al. 2019; Simunovic et al. 2019; Barrea et al. 2020; Zupo et al. 2020). In our study, we investigated a broad range of potential determinants of hypovitaminosis D and circulating 25OHD levels, including the MedDiet, as well as the prevalence of hypovitaminosis D in non-smoker, normal weight, and healthy adults of the metropolitan area of Athens during sunnier seasons. Overall, we have found that lower adherence to the MedDiet may be a significant independent determinant of hypovitaminosis D and an independent predictor of circulating 25OHD levels in line with previous studies including those on obese children, adolescents, and adults (Aparicio-Ugarriza et al. 2019; Simunovic et al. 2019; Barrea et al. 2020; Zupo et al. 2020). These results are in accordance with observational studies reporting a protective action of the MedDiet in bone mineral density and a reduced risk of fractures, particularly amid premenopausal women (Malmir et al. 2018; Pérez-Rey et al. 2019). Paradoxically, food enriched in vitamin D, such as egg yolks, beef liver, cheese, milk, salmon, mackerel, and tuma are not representative of the MedDiet. Interestingly, scores of adherence to the MedDiet "penalize" food items containing smaller amounts of vitamin D such as meat and egg (Panagiotakos et al. 2007). Indeed, MedDiet without vitamin D supplementation/fortification did not influence 25OHD levels in one study (Jennings et al. 2018). Nevertheless, other food items such as fish, olive oil, dried fruits, nuts, and less alcohol may enhance vitamin D levels. Our study confirmed the positive association between certain food items of the MedDiet, such as fish and olive oil, with circulating 25OHD levels as observed in a previous study (Zupo et al. 2020). Noteworthy, it must be highlighted that each component of a specific dietary pattern may influence the inter-individual variability of circulating vitamin D levels (Hollander 1981). In addition to fortified foods, some vitamin D can be obtained from fish, and in lower quantities from eggs and meat (Fayet-Moore et al. 2019). Fish consumption, even that of non-oily fish, was negatively associated with vitamin D deficiency (Fayet-Moore et al. 2019). Moreover, greater consumption of olive oil was a significantly positive predictor of serum 25OHD in line with the previous study (Zupo et al. 2020) and the PREDIMED study which showed a correlation of minor risk of osteoporosis-associated fractures with olive oil consumption (García-Gavilán et al. 2018). Olive oil, which is characterised by the rich presence of MUFA, may ameliorate the bioavailability of vitamin D affecting its intestinal absorption (Niramitmahapanya et al. 2011). Dietary fats could also modulate gut microbiota which may impact on higher vitamin D absorption and circulating 25OHD

**Table 3.** Association of season, skin phototype, body mass index (model A) or waist circumference (model B), physical outdoor activity, sunscreen use, and adherence to the Mediterranean diet with vitamin D deficiency occurrence in 402 Greek, Caucasian, normal weight, and non-smoker healthy volunteers; odds ratios (OR)‡ and their 95% confidence intervals (95% C.I.).

| Model A with body mass index | | | | | Model B with waist circumference | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Category or increment | *p* Value | OR‡ | 95% C.I. | Variable | Category or increment | *p* Value | OR‡ | 95% C.I. |
| Season | Summer versus Autumn | **0.001** | 0.13 | 0.06–0.29 | Season | Summer versus Autumn | **<0.001** | 0.14 | 0.07–0.31 |
| Fitzpatrick skin phototype<br>Type I<br>Type II<br>Type III<br>Type IV | Darker skin phototype | 0.15 | 1.35 | 0.89–2.03 | Fitzpatrick skin phototype<br>Type I<br>Type II<br>Type III<br>Type IV | Darker skin phototype | **<0.001** | 2.08 | 1.43–3.04 |
| Sunscreen use<br>Never<br>Occasionally (summer)<br>Often<br>Always | More use | **0.04** | 1.36 | 1.01–1.85 | Sunscreen use<br>Never<br>Occasionally (summer)<br>Often<br>Always | More use | **0.03** | 1.37 | 1.04–1.81 |
| Body mass index ($kg/m^2$) | 1 $kg/m^2$ more | **<0.001** | 2.86 | 2.17–3.76 | Waist circumference (cm) | 1 cm more | **0.007** | 1.04 | 1.01–1.06 |
| Physical outdoor activity per week<br>$<2$ h<br>$\geq 2$ h | More than 2h per week versus less than 2h per week | **<0.001** | 0.28 | 0.16–0.50 | Physical outdoor activity per week<br>$<2$ h<br>$\geq 2$ h | More than 2 h per week versus less than 2 h per week | **<0.001** | 0.20 | 0.12–0.34 |
| Adherence to the MedDiet<br>Low (0–20)<br>Medium (21–35)<br>High (36–55) | Higher Adherence to the MedDiet | **0.04** | 0.48 | 0.24–0.97 | Adherence to the MedDiet<br>Low (0–20)<br>Medium (21–35)<br>High (36–55) | Higher adherence to the MedDiet | **0.01** | 0.43 | 0.22–0.83 |

Bold values suggest statistically significant if $p<0.05$.

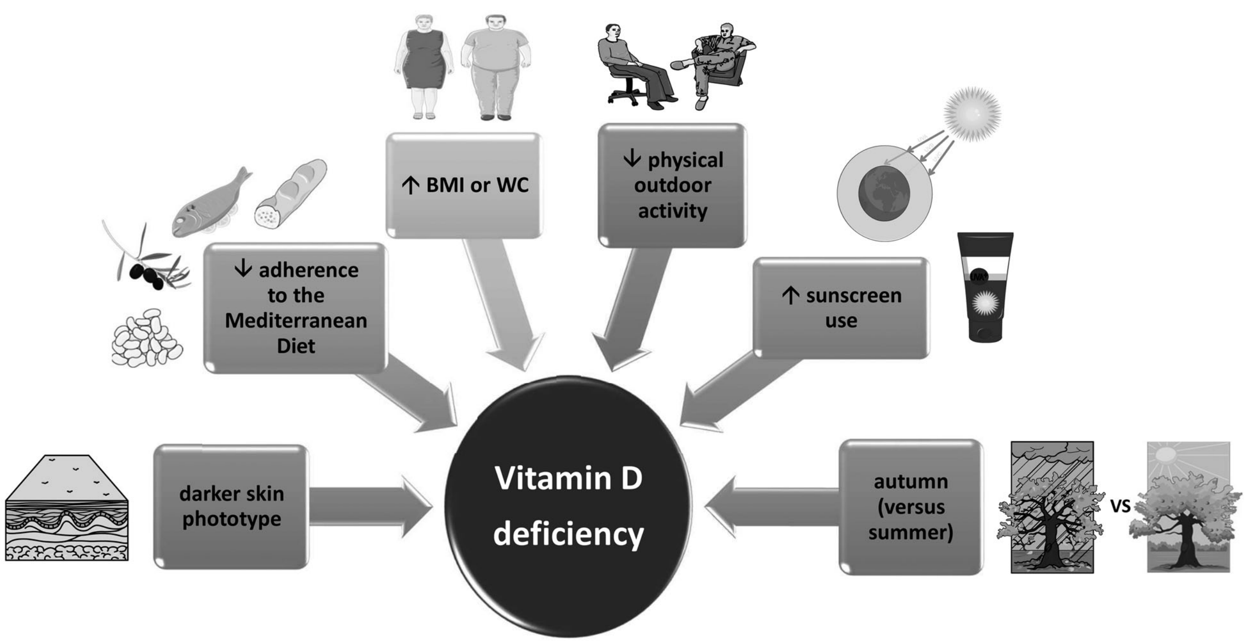


**Figure 3.** Independent predictors of vitamin D deficiency. All images are derived from the free medical site http://smart.servier.com/ by Servier licenced under a Creative Commons Attribution 3.0 Unported License).

levels (Vallianou et al. 2019; Vallianou et al. 2020). Adherence to the MedDiet may promote beneficial gut bacteria such as *Lactobacilli* and *Bifidobacteria* decreasing the ratio of *Firmicutes* to *Bacteroidetes* and increasing the production of short chain fatty acids with beneficial metabolic properties (Nagpal et al. 2018; Vallianou et al. 2019). Alcohol intake, another component of the MedDiet, was not independently associated with vitamin D levels as observed in some but not all studies (Tardelli et al. 2017).

**Table 4.** Multiple linear regression analysis (stepwise method) depicting independent predictors (with adherence to the MedDiet/model A or its food items/model B) of circulating 25OHD levels (as dependent logarithmically transformed variable) in 402 Greek, Caucasian, normal weight and non-smoker healthy volunteers; regression coefficients (b), standard error of b ($SE_b$) and $t$ statistic with corresponding $p$-value.

| Model A with adherence to the MedDiet as predictor | | | | | Model B with food items of the MedDiet as predictors | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Independent variables | *b* | $SE_b$ | *t* Statistic | *p* Value | Independent variables | *b* | $SE_b$ | *t* Statistic | *p* Value |
| Body mass index ($kg/m^2$) | −0.05 | 0.004 | −11.72 | **<0.001** | Body Mass Index ($kg/m^2$) | −0.04 | 0.004 | −9.92 | **<0.001** |
| Season (summer versus autumn) | 0.10 | 0.02 | 4.75 | **<0.001** | Season (summer versus autumn) | 0.09 | 0.02 | 4.63 | **<0.001** |
| Fitzpatrick skin phototype<br>Type I<br>Type II<br>Type III<br>Type IV | −0.03 | 0.01 | −2.36 | **0.02** | Fitzpatrick skin phototype<br>Type I<br>Type II<br>Type III<br>Type IV | −0.03 | 0.01 | −2.94 | **0.005** |
| Physical outdoor activity per week<br><2 h<br>≥2 h | 0.06 | 0.02 | 3.72 | **<0.001** | Physical outdoor activity per week<br><2 h<br>≥2 h | 0.04 | 0.01 | 2.91 | **0.004** |
| Adherence to the MedDiet<br>Low (0–20)<br>Medium (21–35)<br>High (36–55) | 0.05 | 0.02 | 2.42 | **0.02** | Fish consumption (times per week; 0; <1; 1–2; 3–4) | 0.07 | 0.008 | 7.96 | **<0.001** |
| | | | | | Olive oil consumption (times per week; never; rarely; <1; 1–3; 3–5; daily) | 0.02 | 0.006 | 3.74 | **<0.001** |

Bold values suggest statistically significant if $p<0.05$.

Low vitamin D synthesis in the skin appears to be the major determinant of vitamin D status. Environmental conditions such as air pollution, sunscreen use, and darker skin phototype, which is frequent in Mediterranean countries, have also been proposed as determinants of low vitamin D production in the skin (Sayed-Hassan et al. 2014; Dimakopoulos et al. 2019). In our study, all participants reside in the urban metropolitan area of Athens, which is considered one of the most polluted towns in the world. In agreement with other studies, we have found that darker skin phototype was associated with hypovitaminosis D (Kochevar et al. 1999; Kassi et al. 2014; Dimakopoulos et al. 2019). Higher pigmentation of the skin as reflected by higher melanin expression may absorb UV radiation leading to reduced 25OHD levels after UV exposure or may demand more UV exposure to synthesise the same concentration of vitamin D (Kassi et al. 2014). Consistent with previous literature, outdoor physical activity which is related to sun exposure was associated with increased 25OHD levels (Grigoriou et al. 2018; Fayet-Moore et al. 2019). Even indoor moderate or vigorous physical activity may have beneficial effects on serum 25OHD levels (Grigoriou et al. 2018; Dimakopoulos et al. 2019). Not surprisingly, autumn season versus summer was found a significant predictor of vitamin D deficiency, as 25OHD levels reach their zenith at the end of the summer (Piirainen et al. 2016; Dimakopoulos et al. 2019). Serum 25OHD concentration starts diminishing over September, since adults follow their usual work schedule, spending less time outdoors under sun exposure (Dimakopoulos et al. 2019).

Although our subjects were normal weight, we found an independent negative association between 25OHD status and BMI or WC, as observed in many studies (Cashman et al. 2016; Dimakopoulos et al. 2019; Barrea et al. 2020; Zupo et al. 2020). In particular, a recent meta-analysis of RCTs reported an overall inverse association between BMI and circulating 25OHD levels in non-diabetic individuals as observed in our study (Rafiq and Jeppesen 2018). Despite the fact that the exact mechanism is obscure, this may be due to the lipophilic nature of the adipose tissue which acts as an isolator of vitamin D, rather than a depot (Dimakopoulos et al. 2019). Other mechanisms linking lower 25OHD to higher BMI include the lesser skin exposure to sunlight, the diminished outdoor physical activity, the lower vitamin D intake, and the reduced intestinal absorption of vitamin D (Barrea et al. 2017). Noteworthy, MedDiet in combination with physical activity was effective in reducing weight with results lasting longer than 6 months (Mancini et al. 2016). Due to its polyphenol content, MedDiet may present favourable anti-obesogenic and anti-orexigenic actions including prebiotic modulation of the gut microbiome, stimulation of β-oxidation, and regulation of white and brown adipose tissues (Castro-Barquero et al. 2018). In accordance with other studies (Sai et al. 2011; Souberbielle et al. 2016; Dimakopoulos et al. 2019), our chemistry data have also indicated the negative correlation between 25OHD levels and serum iPTH (Figure 2), which was adjusted for in the models to reduce confounding and bias from hormonal regulation (Dimakopoulos et al. 2019).

Despite the sunnier weather, a significant percentage (37.3%) of non-smoker, normal weight, Greek adults from the urban metropolitan area of Athens presented vitamin D deficiency during summer and autumn, and only 25.9% had levels above 75 nmol/L, which is the optimal vitamin D status proposed by the US Endocrine Society (Holick 2007). Similar results were yielded from other European studies including countries at a similar latitude to Greece despite sunnier weather (Kassi et al. 2014; Cashman et al. 2016; Souberbielle et al. 2016; Grigoriou et al. 2018; Manios et al. 2018; Dimakopoulos et al. 2019). In Canada, a significant percentage of the population (40.8%) is reported to present 25OHD levels more than 75 nmol/L (Greene-Finestone et al. 2011). This is attributed to the fortification of food with vitamin D. Interestingly, the fortification of dairy products such as cheese, milk, and yoghurt at 270 IU per serving doubled vitamin D intake throughout all age and gender groups with a parallel decrease of dietary insufficiency from more than 80% to less than 50% (Shakur et al. 2014). In Greece, very few foods, particularly some dairy products for children, are fortified with vitamin D. The recommended dietary intake of calcium intake in our study and in other Greek studies is lower than the 1,000 mg/day proposed by the Institute of Medicine (Ross et al. 2011). However, the percentage of vitamin D deficiency in our study population was much lower than that observed in smoker healthy Greek adult males (50.3%) (Kassi et al. 2014). In the majority of studies, smoking is associated with vitamin D deficiency due to its association with worse dietary habits, lower physical activity and alcohol consumption, and the suppression of CYP27A1 activity (Kassi et al. 2014).

The findings of our study must be interpreted in relation to its limitations and strengths, and the study population. The limitations include its cross-sectional design which cannot infer causal relationships, the non-study of polymorphisms of the genes affecting vitamin D status and the immune-assay methodology for the 25OHD determination. However, this laboratory methodology is a widely used automated chemiluminescent immunoassay. Furthermore, although the MedDiet score consists of an 11-item questionnaire and cannot assess dietary vitamin D intake, in particular, it is a simple, less time-demanding, straightforward, and validated questionnaire (Panagiotakos et al. 2007). Our study presents considerable strengths including its large sample size and the investigation of healthy, non-smoker, and normal weight Greek adults during sunnier seasons offering data on an array of biologic, lifestyle, and behavioural determinants.

## Conclusion

In conclusion, our study shows that higher adherence to the MedDiet, particularly fish and olive oil consumption, is positively associated with higher circulating vitamin D levels independently from BMI or WC, skin phototype, season, and physical activity in healthy, normal weight, and non-smoker adults. Besides its favourable effects on cardiovascular and metabolic risk factors, adherence to the MedDiet may positively affect vitamin D levels, which are critical for optimal bone mineral density and neuromuscular activities. Important translational potentials of our study include the implementation of the anti-inflammatory, anti-obesogenic, and anti-oxidant MedDiet in the management of individuals with higher BMI or WC and low 25OHD levels as well as in the prevention and treatment of many disorders associated with inflammation and/or oxidative stress (Koloverou et al. 2016). In particular, the joint effect of increased physical activity with higher adherence to the MedDiet has been shown to enhance anti-oxidant defences (Kavouras et al. 2011) and vitamin D levels, playing a key role in the maintenance and optimal functioning of immune cells, which is absolutely essential for the prevention of severe COVID-19 (Belanger et al. 2020; Dalamaga et al. 2020a, 2020b). Amid the components of the MedDiet, the key food items that could be found universally at reasonable prices include dried fruits/nuts and olive oil, which display anti-oxidative, anti-inflammatory, and cardio-protective properties (Urpi-Sarda et al. 2012; Kanellos et al. 2014).

Future well-designed dietary intervention trials on larger population samples are needed to define specific dietary guidelines for the prevention of hypovitaminosis D. Further large RCTs are necessary to explore the beneficial effects of the MedDiet in subjects with obesity and hypovitaminosis D.

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## Disclosure statement

No potential conflict of interest was reported by the author(s).

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