A SYSTEMATIC REVIEW OF VITAMIN D STATUS AND DIETARY INTAKE IN VARIOUS SLOVENIAN POPULATIONS

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ABSTRACT

Aim: Vitamin D (VitD) is involved in calcium and phosphate homeostasis, bone health, and normal functioning of the immune system. VitD status is monitored using serum 25-hydroxy-vitamin D (25(OH)D) as a biomarker. Serum 25(OH)D concentrations below 30 nmol/L indicate VitD deficiency and below 50 nmol/L indicate insufficiency. VitD can be synthesised endogenously in human skin when exposed to ultraviolet B (UVB) radiation. In the absence of sufficient UVB-light exposure, VitD intake becomes the main source of VitD, with a recommended daily intake of 20 µg. The aim of this study was to conduct a review and meta-analysis on the abovementioned topics, focusing on scientific studies in various Slovenian populations.

Methods: We conducted a systematic review and meta-analysis of published scientific papers, academic theses, or conference contributions reporting serum 25(OH)D status and VitD intake across various Slovenian populations. A search was carried out using Web of Science, Scopus, Medline, and the Slovenian library database.

Results: We identified 43 pertinent studies that addressed 25(OH)D status and 16 that addressed VitD intake. Serum 25(OH)D status was generally low across all populations, and notable seasonal variability was observed. VitD intakes were below 5 µg in all studies.

Conclusions: A general observation is that various population groups across Slovenia are at high risk of vitamin D insufficiency and deficiency, particularly during wintertime. Regarding vitamin D intake, all included studies reported daily intakes below the recommended level. We also identified key research gaps that need to be addressed to support further public health decision-making.

IZVLEČEK

Ključne besede: vitamin D, prehranski vnos, serumski 25-hydroksi-vitamin D, vitamin D deficijenco, sistematični pregled, literature, Slovenija

Namen: Vitamin D (VitD) je vključen v metabolizem kalcija in fosforja, zdravje kosti in normalno delovanje imunskega sistema, hkrati pa je nezadostna preskrbljenost povezana z različnimi skeletnimi in neskeletnimi oboljenji. Splošno uveljavljen biološki kazalnik preskrbljenosti z VitD je serumska koncentracija 25 hidroksi-vitamina D (25(OH)D). Koncentracije 20(OH)D pod 30 nmol/L so definirane kot hudo pomanjkanje, pod 50 nmol/L kot pomanjkanje, optimalna pa je koncentracija nad 75 nmol/L. VitD se endogeno sintetizira v koži ob izpostavitvi ultravijoličnem B (UVB) žarkom. Kadar je izpostavljenost UVB žarkom prenizka, postane VitD vnos s hrano glavni vir VitD. V odsotnosti endogene sinteze je priporočen vnos 20 µg dnevno. Namen raziskave je bil sistematični pregled znanstvene literatur, področju preskrbljenosti z 25(OH)D in prehranskega vnsa VitD pri prebivalcev Slovenije.

Metode: Izvedli smo sistematičen pregled literatur in metaanalizo znanstvenih člankov, zaključnih del in konferenčnih prispevkov, ki so poročali o preskrbljenosti z 25(OH)D in vnosu VitD pri različnih populacijskih skupinah prebivalcev Slovenije. Za iskanje literatur smo uporabili podatkovne baze: Web of Science, Scopus, Medline in Cooperativni online bibliografski sistemi in servisi (COBISS) brez omejevanja leta objave.

Rezultati: O preskrbljenosti s 25(OH)D je poročalo 43 znanstvenih prispevkov, medtem ko je o vnosu VitD poročalo 16 znanstvenih prispevkov. Preskrbljenost s 25(OH)D je bila relativno nizka v vseh zajetih populacijah, opaženo je bilo tudi znatno sezonsko nihanje. Vnos VitD je bil v vseh populacijah pod 5 µg.

Zaključki: Preskrbljenost s 25(OH)D je nizka, zato so mnogi prebivalci izpostavljeni povečanemu tveganju za (hudo) pomanjkanje, posebno v zimskem obdobju. Prav tako opažamo, da je prehranski vnos VitD precej nižji od priporočenega. Identificirane so bile tudi pomembne vzrste, ki jih je treba naslovliti za sprejemanje na dokazih temeljitev javnopravnih ukrepov, ki bodo učinkoviteje podpirali zdravje prebivalcev Slovenije.

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1 INTRODUCTION

Vitamin D (VitD) participates in numerous functions in the human body, including calcium and phosphate homeostasis, bone health, and the normal functioning of the immune system (1, 2). Deficient 25-hydroxy-vitamin D (25(OH)D) status causes rickets and osteomalacia (depending on age) (3, 4), contributes to the development of osteoporosis and myopathy, and has been linked to various non-skeletal disorders, such as acute and chronic respiratory infections, and risks of death due to cardiovascular disease, cancer, and other causes (5, 6). While numerous reports indicate a high prevalence of 25(OH)D deficiency, we should note that different thresholds are used in different studies. VitD status is determined considering the level of serum 25(OH)D, usually reported in both nanomoles per litre (nmol/L) and nanograms per millilitre (ng/mL; 1 ng/mL equals 2.5 nmol/L) (7). Thresholds for risk of 25(OH)D deficiency and insufficiency are typically defined with serum concentrations below 30 and 50 nmol/L, respectively (3, 8, 9), while the Endocrine Society’s guidelines highlight that optimal levels are above 75 nmol/L (3).

VitD can be synthesised endogenously in human skin when exposed to ultraviolet B(UVB) light. Considering the geographical location of Slovenia (latitudes 45-46° north), the intensity of UVB light is sufficient for VitD endogenous synthesis only from April to October, but not during wintertime (10). Therefore, seasonal variation in 25(OH)D status is expected in the population.

In the absence of UVB-induced endogenous synthesis, sufficient dietary intake of VitD is needed. Recommendations for VitD intake are not yet standardised. While the World Health Organization (WHO) recommends 10 µg VitD per day for adults below 65 years and 15 µg for the elderly population (11), the European Food Safety Authority (EFSA) and the nutrition societies of Germany, Austria, and Switzerland (D-A-CH) recommend a VitD intake of 15 and 20 µg per day, respectively for all above the age of 1 year (12). It should be noted that these are recommendations for dietary intake of endogenous UVB-induced VitD synthesis. However, the usual daily dietary VitD intake in adults is below 10 µg in most European countries (13). This is because only a few foods (i.e., fatty fish) are naturally rich in VitD (14), and those are not common in the European diet. Some countries, therefore, have introduced the fortification of particular foods with VitD (15) or prescribed VitD supplementation to certain subpopulation groups.

While several studies have investigated dietary intake or 25(OH)D status in various Slovenian populations, this topic has not yet been systematically reviewed. The aim of this study was thus to conduct a review and meta-analysis on the abovementioned topics, focusing on studies published either as scientific papers, academic thesis, or conference contributions.

2 METHODS

2.1 Search strategy and inclusion/exclusion criteria

We focused on two topics: A) serum 25(OH)D levels as a biomarker for VitD status, and B) VitD intake in various population groups in Slovenia. The main literature search was carried out in September 2020. The following four databases were searched (Box 1):

Box 1. Search strategy.

• Medline, Scopus, and Web of Science (WoS) - with the searching syntax: (TITLE-ABS-KEY ("vitamin D") OR (cholecalciferol)) AND sloven*)
• COBISS - Slovenian library database (Co-operative Online Bibliographic System & Services), with the searching syntax: kw="vitamin d" or cholecalciferol).

For this review, we included original scientific articles, academic thesis (diploma, masters, doctoral, and others), and conference contributions in the Slovene or English language. We included publications which provided data on either serum 25(OH)D levels or dietary VitD intake for the defined population. We included publications with original results, which were available as full texts or comprehensive abstracts, either in digital or hard copy. The literature search was conducted without any time limits, and therefore the identified results correspond to periods covered in the abovementioned databases.

In addition to the described literature search, we also asked members of the national expert working group on guidelines for sufficient vitamin D levels in the Slovenian population to provide information on the references with novel data on dietary VitD intake and 25(OH)D status in Slovenia that they are aware of. These members are experts and researchers in the field, and therefore well informed about nationally available data. The identified relevant publications, which were not already found in the literature search, were counted as additional records identified through other sources.

2.2 Data extraction and study selection process

The methods used in the present review follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (16). After the literature search, we first removed all duplicates; secondly, we removed publications of which title/abstract did not fit the purpose of this review or were not original research. Finally, we removed publications where we could not obtain a full text. We combined publications describing the same data set with the same outcomes, referred to as a ‘research cluster’ (in Supplementary table 1, each presented in a separate row) from here onward. All publications were checked carefully, and the following data were extracted: description of the study period, study group(s), study results (distribution and
mean serum 25(OH)D levels, daily dietary VitD intake). To simplify comparisons, the results of identified studies were re-calculated to internationally accepted units (IU; conversion: 1µg of vitamin D2 or D3=40 IU). Dietary VitD intake is presented in µg per day, while serum 25(OH)D levels are presented in nmol/L. The distribution of serum 25(OH)D levels is presented using the thresholds for VitD deficiency used in the original publication. However, with consideration of the most relevant thresholds (3, 8), we presented the prevalence of serum 25(OH)D levels below 30/50 nmol/L (VitD deficiency/insufficiency) and those above 50/75 nmol/L (sufficient/optimal level) separately.

2.3 Descriptive quantitative synthesis and meta-analysis
Statistical analyses were carried out using Stata Statistical Software, Release 15 (StataCorp LLC, College Station, TX, USA). The proportions of deficiency/optimal vitamin D status were analysed by applying the STATA Metaprop module for pooled meta-analyses of proportions. Analyses were carried out considering studies with healthy individuals, where seasonal proportions of deficiency/optimal 25(OH)D status were provided for a sample of at least 50 subjects.

3 RESULTS
The literature search resulted in 562 records. After the removal of duplicates (n=69) and the addition of records identified through other sources (n=9), a total of 502 records were screened for relevance. After the exclusion of 186 non-relevant records, we started collecting the full texts of 268 publications. Although we made a large effort to obtain full-text access to all of these records (we contacted the authors of publications, searched for records on various internet sources, and ordered the remaining missing publications through the Central Technical Library at the University of Ljubljana), we were unable to obtain full texts for 24 records. Therefore, the literature review was conducted using 58 relevant publications (details provided in Table 1). Altogether, we identified 30 research clusters, the majority referring to the adult population (n=21), one referred to older adults and adults, with an additional two for older adults and two for pregnant women. Two-thirds of the research clusters (n=21) reported data from patients (in- or out-patients), thirteen from the general population, and four reported separately for healthy controls and patient populations. Therefore, we considered these clusters twice, once in the healthy and once in the patient population. Four research clusters referred to children and one additional to newborn infants, giving five in total. In the meta-analyses, we included four studies that reported seasonal proportions of deficiency/optimal 25(OH)D status in a sample of at least 50 subjects.

3.1 Serum 25(OH)D status
The literature review of 25(OH)D included 43 publications (Supplementary table 1), comprising 20 scientific journal articles, 11 conference papers, and 12 academic theses (details provided in Table 1). Altogether, we identified 30 research clusters, the majority referring to the adult population (n=21), one referred to older adults and adults, with an additional two for older adults and two for pregnant women. Two-thirds of the research clusters (n=21) reported data from patients (in- or out-patients), thirteen from the general population, and four reported separately for healthy controls and patient populations. Therefore, we considered these clusters twice, once in the healthy and once in the patient population. Four research clusters referred to children and one additional to newborn infants, giving five in total. In the meta-analyses, we included four studies that reported seasonal proportions of deficiency/optimal 25(OH)D status in a sample of at least 50 subjects.
was only used in one study (20), which was conducted in 2017-2018, and covered all calendar seasons. Serum 25(OH)D in adults (n=125; 18-64 years) was significantly affected by calendar season, sex, and physical activity level. Mean 25(OH)D level was 50.7 nmol/L (95% CI: 45.4-56.0 nmol/L), with 70.4 nmol/L (95% CI: 62.2-78.5) during the extended summer period (May-October), and 36.7 nmol/L (95% CI: 32.5-40.9 nmol/L) during the extended winter period (November-April). The distribution of mean serum 25(OH)D concentrations during the calendar year is presented in Figure 2. The next research cluster (22) included 240 individuals from periodic medical examinations. Blood samples were collected throughout the year, and seasonal variations in serum 25(OH)D levels are evident. Data are reported for every second month, and it is at its lowest in February (61.3 nmol/L) and highest in June (92.8 nmol/L). The third research cluster (21) included a healthy study population mostly from the central Slovenian region (n=238; 18-65 years). Blood samples were collected during winter months (January - March) and mean serum 25(OH)D level was 44.0±17.0 nmol/L.

3.1.1.1 Serum 25(OH)D concentrations in older adults

The population of healthy older adults in our review included three research clusters. The first cluster (28, 29) represented 80 adults aged between 51 and 93 years, living at home or institutionalised; the second cluster (20) included nationally representative data of 155 people aged 65 to 75 years, and the third cluster (30) represented 457 postmenopausal women aged from 55 to 90 years. Average serum concentrations of 25(OH)D were 33.0±27.0 nmol/L, 47.7 nmol/L (95% CI: 43.9-51.5), and 48.2±27.4 nmol/L, respectively. In the nationally representative cluster, seasonal 25(OH)D levels were reported. During the extended summer (May-October) and the extended winter (November-April), mean levels were 60.1 (95% CI: 54.0-66.2) and 39.0 nmol/L (95% CI: 35.0-43.0), respectively. In addition to the influence of seasonal variations, 25(OH)D levels were also significantly negatively affected by the body mass index (BMI). Seasonal variation of 25(OH)D was also observed in the third cluster, where decreasing levels of 25(OH)D concentration with increasing age were also reported (30).

3.1.1.2 Serum 25(OH)D concentrations in pregnant women

The review covered two research clusters of healthy pregnant women. One included data collected in the ‘My Milk’ research project (‘The role of human milk in the development of breastfed child’s intestinal microbiota’) (17, 31, 32). We only included publications with a full study sample (17), as two references refer to a smaller subsample size (31, 32). The second cluster is described in six different publications (33-38). Both research clusters reported serum 25(OH)D levels throughout the year, with mean levels 43.4±23.8 nmol/L and 74.7±27.5 nmol/L for the first and second clusters, respectively.

3.1.1.3 Serum 25(OH)D concentrations in other populations

One research cluster included data on new-born infants (33-38); one was with healthy young athletes (16.9±4.4 years) (39), and three clusters included paediatric patients (3.8-18 years) (40-44); one of these included a healthy control group (40-42). In infants, mean serum 25(OH)D concentrations were 55.2±30.9 nmol/L and varied notably throughout the year. The lowest was observed in March (36.4±22.6 nmol/L), and highest in September (72.9±31.7 nmol/L) and the concentrations were approximately 10 nmol/L higher than in mothers (33-38). In young athletes (39), serum 25(OH)D was measured in samples collected in April (67.6±36.2 nmol/L); there was no significant difference between a group of swimmers and artistic gymnasts.

Eighteen research clusters included data from adult patient populations: five research clusters included chronic kidney disease patients (24, 25, 45-50), three research clusters included type 2 diabetics (26, 51, 52), two clusters included patients with bone metabolism disorder or trauma (53, 54), two clusters included mixed data from University Medical Centre Ljubljana laboratories (55, 56), and single-cluster studies included patients after heart transplant (57), HIV patients (58), chronic intestinal failure patients on long-term home parenteral nutrition (59), and patients treated with antiepileptic drugs (27).
3.1.2 Distribution of serum 25(OH)D concentrations in the healthy population above 18 years

Six clusters reported data for 25(OH)D insufficiency (<50 nmol/L) in eight different (general), populations including pregnant women and newborns (17, 20, 21, 27, 33-39). The prevalence of 25(OH)D insufficiency in year-round samples varied from 14% in pregnant women (17) to 63% in a nationally representative sample of the elderly (20). However, due to notable seasonal differences, we focused on studies that reported seasonal results. Four clusters were included in meta-analyses, since they reported winter- and summertime insufficient serum 25(OH)D levels (<50 nmol/L) in at least 50 healthy subjects (Figure 3). The pooled summertime proportion of 25(OH)D insufficiency is 0.31 (95% CI 0.17, 0.46), where we should note heterogeneity between studies. The pooled wintertime proportion of 25(OH)D insufficiency is 0.77 (95% CI 0.68, 0.58), again with notable heterogeneity between studies. This can be explained by the fact that these analyses included different population groups, for which very different 25(OH)D insufficiency proportions are also presented by studies that used the same design (i.e., adults and elderly in Hribar et al. (20)). Nevertheless, considerable seasonal variation in 25(OH)D insufficiency was observed, with much higher prevalence rates during wintertime (p<0.001; z=5.62).

3.1.3 Non-optimal 25(OH)D status

Seven research clusters (general populations) reported on the prevalence of non-optimal 25(OH)D concentrations using thresholds comparable with the Endocrine Society’s guidelines (75 nmol/L) (3). Four clusters with at least 50 healthy subjects were used for meta-analyses. As seen in Figure 4, very few subjects were in the range of optimal 25(OH)D levels, even during summertime. Analyses showed a significantly different (p<0.001; z=23.3) pooled proportion of non-optimal 25(OH)D status between

![Figure 3. Forest plot of studies with at least 50 healthy subjects evaluating the proportion of insufficient serum 25(OH)D level (<50 nmol/L). Note: In one study (Soltirovska et al. 2015) sampling was carried out across the year, but the majority of the samples were collected during extended summer.](image)

Legend: N: number of participants; ES: test of effect size, p: p-value
Figure 4. Forest plot of studies with at least 50 healthy subjects evaluating the proportion of non-optimal serum 25(OH)D level (<75 nmol/L). *Note: In one study (Dovnik et al. 2015), the non-optimal 25(OH)D level was set at 80 nmol/L.

Legend: N: number of participants; ES: test of effect size, p: p-value.

3.2 Dietary intake of vitamin D

In total, sixteen publications reported dietary VitD intakes (Figure 1); of these, ten were journal articles and six were academic theses (details provided in Supplementary table 2). Most (n=12) publications referred to a healthy population (17, 19, 60-71), while two were on patient populations (72, 73). When considering the age and pregnancy status of the participants, one publication referred to children (<10 years) (60), six to adolescents (10-19 years) (17, 19, 61-65), eight to adults (>19 years) (19, 64-73), and one publication to pregnant women (17). One journal article covered both adolescents and adults (65), and one adolescents, adults, and the elderly (19). Two studies reported VitD intake separately - for food intake, and intake with food and supplements (66, 71). Data on intake of VitD was collected using different methods: a) 24-hour dietary recalls (24h-recall) (n=4), b) different kinds of food frequency questionnaires (FFQ) (n=4), and c) dietary record (DR) ranging from 3 to 7 days (n=6). Two studies investigated VitD intake using both FFQ and 24h-recall (Supplementary table 2).

In the adult population, mean daily VitD intake ranged from 1.1 µg in older adults living in residential home (69, 70), to 14.2 µg in women after dietary intervention, with included food supplements and plant-based meal replacements (n=109; 3DDR) (66). In a teenage population mean VitD intake varied from 1.0 µg in teenage girls (n=180; 2 non-consecutive 24h-recalls) (64) to 4.0 µg in teenage boys (n=1,010; FFQ, portion size-adjusted with 3-day DR) (61). Preschool children had an average intake of 1.1 µg VitD per day (n=129; 3-day DR) (60). Data were available for two adult female patient populations. Celiac patients had an average intake of 2.6 µg VitD per day (n=40; 3-day DR) (72) and osteoporosis patients (n=43) had...
an intake of 1.8 µg (FFQ) or 1.4 µg (24h-recall), depending on the dietary assessment method (73).

The Si.Menu project, conducted on a nationally representative sample, included 468 adolescents (10-17 years), 364 adults (18-64 years), and 416 elderly individuals (65-74 years). VitD intakes were estimated using a combination of two 24h-recalls adjusted with a food propensity questionnaire. Mean daily VitD intakes for adolescents, adults and the elderly were 2.7 µg, 2.9 µg, and 2.5 µg, respectively, and we should also note that the amount of VitD supplements was not recorded. Energy intake was a significant factor across all age groups, sex was determined as a significant factor, affecting VitD intakes in adolescents and adults, with lower VitD intakes observed in females. The most important dietary sources of VitD were eggs, fish, and fish products, and meat and meat products (19).

4 DISCUSSION

Increased interest in VitD research (74) is related to a growing body of evidence that connects sufficient 25(OH)D status with better health outcomes (75-78), while highlighting the high prevalence of VitD deficiency in different populations (13). This topic has recently gained even more attention due to the possible associations of VitD status with health outcomes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected patients (78-82).

In Slovenia, there is currently no official policy on food fortification and supplementation of diets with VitD in the general population. To support further public health decision-making, the Ministry of Health appointed a national expert working group on guidelines for sufficient vitamin D levels in the Slovenian population, under the umbrella of the National Institute of Public Health. To support this activity, this work aimed to review scientific publications, reporting dietary intake and/or 25(OH)D status in various Slovenian population subgroups. We reviewed all available publications with novel research data collected in Slovenia, including original scientific articles, conference papers, and academic theses.

4.1 Vitamin D status

We used reported data on serum 25(OH)D levels as a biomarker of 25(OH)D status across various populations in Slovenia, but due to methodological and analytical differences in different studies, data should be interpreted with caution. For example, in different studies, blood samples were collected in different seasons, or non-evenly distributed across the calendar year. We should also mention that different assays were used for the quantification of 25(OH)D in different studies.

Only one study reported nationally representative data on 25(OH)D concentrations in adults (18-64 years) and the elderly (65-75 years) (20). The prevalence of insufficiency was 58.2% and 62.9% for adults and the elderly, respectively, and 83.3% and 84.4% of adults and the elderly, respectively, had 25(OH)D values below the optimal level. The levels of 25(OH)D were influenced by sex and physical activity, and most importantly by calendar season. In a much smaller cluster (n=22), 59.1% were insufficient; 90.1% were below the optimal status (27), and in a cluster referring to self-paying subjects from the laboratory information system (n=73), 58.9% were below optimal status (23). There were notable differences in the reported prevalence of 25(OH)D insufficiency (<50 nmol/L) and below optimal status (<75 nmol/L) in different studies, as these were conducted on different population groups and in different seasons. In 2016, Cashman et al. made a review of the available European data using the VitD Standardization Program (n=55,844) and reported that, overall, 40% of the European population had insufficient 25(OH)D status (74). In Southern Europe, more than one-third of studies had mean 25(OH)D concentrations below 50 nmol/L (83), and according to recent 2019 European review article, insufficiency occurs in 30-60% of the populations in Western, Southern and Eastern Europe (84). These results are comparable with those reported for various European countries (74, 83, 85).

In the French adult population (18-89 years; population-based cohort), the prevalence of insufficiency was 34.6%, and 80.3% had non-optimal serum 25(OH)D concentrations (86). Similar results were observed in Spain (23-72 years; 43-49°N; nationally representative cohort), where the reported prevalence of insufficiency and non-optimal 25(OH)D status was 34.7% and 88.9%, respectively (87). In Germany (18-79 years) (74), the prevalence of 25(OH)D concentrations below 50 nmol/L was 54.5%, and below 75 nmol/L was 90.9%. Researchers from Portugal (>18 years; 32-42°N; nationally representative cohort) reported serum 25(OH)D insufficiency in 45.4% of the population and below optimal status in 96.4% (88). Even more worrying results came from Ukraine (20-95 years; 44-52°; nationally representative cohort), where the prevalence of insufficiency was 81.8%, with 95.4% below optimal status. Nationally representative data from Europe show that the Slovenian population is among those with a higher prevalence of insufficiency across the year.

We should also note seasonal variations, which were reported in a nationally representative Slovenian study (20). Higher serum 25(OH)D concentrations were observed in the extended summer period from May to October, with insufficient 25(OH)D status in 25.3% of adults and 40.2% of the elderly. A much more concerning situation was reported for an extended winter period from November
to April, when 81.6% of adults and 78.8% of the elderly had insufficient 25(OH)D status. Seasonal variation is also reported in other European countries. In Ukraine, the prevalence of insufficiency varied during the year. In the summer period (May-October) the prevalence for 25(OH)D insufficiency was 79.5%, and 85.8% during the winter period (November-April) (89). Seasonal variation was also noted in Portugal (≥18 years; 32–42°N; nationally representative cohort), where in summer (July-September) the prevalence of insufficiency was 43.2%, rising to 76.0% in winter (January-March) (88). In Southern Italy (40°N; longitudinal) (90), seasonal variation in insufficiency was even more pronounced, and it varied from 4.4% in summer (August) to 70% in winter (February). In the present review, seasonal variation was also noted in pregnant women (17, 33-38) and across other populations (22, 23, 30, 43, 54).

### 4.2 Dietary vitamin D intake

The abovementioned seasonal variability in 25(OH)D status showed that in Slovenia (45-46°-N), endogenous synthesis of VitD is not sufficient during wintertime, as was also observed in other regions (10). In such cases, dietary intake of VitD becomes very important. However, very few foods are rich in VitD (e.g., fatty fish), and these are not common in the Slovenian diet. Achieving adequate VitD intake is therefore challenging without the use of fortified foods and/or VitD dietary supplementation. In a recent Slovenian study (91) it was established that the 33% of population was taking VitD supplements (before the SARS-CoV-2 epidemic), and we should consider this when interpreting the data. In Slovenia, we follow the D-A-CH reference values for VitD intake, which recommend a daily intake of 20 µg VitD, for all above the age of 1 year in the absence of endogenous synthesis (12, 92, 93). Various dietary intake assessment tools have been used (FFQ, DR, and 24h-recall) to estimate dietary intake levels, and we should therefore compare the results with some caution. At the same time, the food database is often incomplete or lacking compositional data regarding VitD content in a certain food/dish, which may result in underestimation of dietary intake of VitD (94).

We reviewed sixteen publications reporting dietary intake of VitD in different Slovenian populations, one of which was nationally representative for adolescents, adults, and the elderly (19). All studies reported VitD intakes well below reference values across all the populations. In the adult and elderly population, daily mean VitD intakes ranged from 1.1 µg to 14.2 µg, the latter with supplements and plant-based meal replacements. A study by Lichthammer et al. (65) (FFQ) included populations from various Central-Eastern European countries (Austria, Poland, Hungary, and Slovenia). The mean daily VitD intake was very low in all countries, and was the lowest in Austria with 2.2 µg and then immediately followed by Slovenia with 2.6 µg.

A similar intake for the Austrian population was found in another study (2.1 µg per day; n=4,972; various dietary intake tools) (95). In a Slovenian nationally representative study, where the amount of supplementation was not included, mean daily VitD intakes were 2.7 µg, 2.9 µg, and 2.5 µg in adolescents, adults, and the elderly, respectively (19). A review of European studies on VitD intake showed a mean VitD intake of 3 to 5 µg per day (13, 96-99), with higher intakes in Northern Europe (up to 11 µg/day) and lower in Southern Europe (13, 84, 97, 99, 100). This can be explained by the high consumption of sea fish and VitD enriched foods in Northern Europe. Our review also covered six children or adolescent populations. In teenage populations, VitD intake varied from 1.0 µg in teenage girls (2x24h-recall) (64) to 4.0 µg in teenage boys (FFQ, portion size-adjusted with 3-day DR) (61). These results are comparable to an Austrian study (95) and other European studies (96, 98, 101, 102). A European nutrition and health report (100) also highlighted that VitD intake in children was generally very low, with the exception of some Nordic countries due to the general vitamin D food fortification policy.

### 4.3 Research gaps

This review has identified several studies reporting dietary intake and/or 25(OH)D status in various Slovenian populations, but the majority were conducted using the convenience sampling method and are therefore not nationally representative. Nevertheless, the reviewed results showed considerable seasonal variability in serum 25(OH)D levels in different populations, with a particularly high prevalence of 25(OH)D deficiency during the wintertime.

Only one study investigated 25(OH)D status in a nationally representative sample of adults and reported insufficient wintertime 25(OH)D levels in about 80% of adults and 25(OH)D deficiency in about 40%. The study sample also included those who reported vitamin D supplementation. The majority of other studies also showed that various population groups in Slovenia are mostly at risk in wintertime with regard to insufficient 25(OH)D status according to the WHO criteria (103). This literature review has also identified some important research gaps. The SARS-CoV-2 pandemic has significantly affected the dietary habits of Slovenians, and increased the consumption of food supplements and medicines with VitD. This might have affected 25(OH)D status in some populations studied in the last year. In addition, some population groups have not been sufficiently investigated. There is very limited data on the 25(OH)D status in healthy children and adolescents, and a lack of data on institutionalised populations, such as those living in elderly care institutions, who are rarely
exposed to sunlight and therefore at an even higher risk of 25(OH)D deficiency. We also reviewed the data on dietary VitD intake in Slovenia. Several studies were identified that estimated VitD intakes in different populations using a variety of study designs and methods. One study reported nationally representative data. All studies reported very low VitD intakes. While the recommended daily intake of VitD in adults is 20 µg in the absence of endogenous synthesis, most studies reported dietary intakes below 5 µg. The majority of the studies did not estimate intakes of VitD with medicines and food supplements or fortified foods, though the latter practice has been negligible in Slovenia. VitD food supplementation practices should be further investigated in the future.

5 CONCLUSION

The general observation of our review is that various population groups across Slovenia are at high risk of 25(OH)D insufficiency and deficiency, particularly during the wintertime. Regarding VitD intake, the majority of included studies reported daily intakes below 5 µg. We also identified key research gaps that need to be addressed to support further public health decision-making.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results. I.P. has led and participated in various other research projects in nutrition, public health, and food technology that were (co)funded by the Slovenian Research Agency, Ministry of Health of the Republic of Slovenia, the Ministry of Agriculture, Forestry, and Food of the Republic of Slovenia, and, for specific applied research projects, also by food businesses. I.P., K.Z., and E.B. are members of a national expert working group on guidelines for sufficient vitamin D levels in the Slovenian population.

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ETHICAL APPROVAL

This is a review article. No ethical approval is needed.

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Supplementary table 1. Review of reports for vitamin D status in the Slovenian population.

| References | Data collection period | Study population | N | Serum 25(OH)D |
|------------|------------------------|------------------|---|--------------|
|            |                        |                  |   | Mean conc.±SD or (95% CI) | Prevalence of conc. < 50 nmol/L | Prevalence of conc. > 50 nmol/L | Publ. type |
| Avberšek-Lužnik 2016 (23) | Jan 2014 - Dec 2015 | Self-paying subjects from laboratory information system in Gorenjska region | 73 | 65.1±33.0 Apr-Sept: 75.3±37.1 Oct-Mar: 55.7±25.7 | <25 nmol/L: 9.6% 25-75 nmol/L: 49.3% >75 nmol/L: 41.1% | B |
| Blazina, Bratanič et al. 2010 (43) | Oct - May (year not provided) | Children and adolescents with celiac disease on strictly compliant to a gluten-free diet (D1) and not strictly compliant to a gluten-free diet (D2): D1: 55 years; 3.8-17.6 years D2: 13.4±4.8 years; 3.8-20.7 years | D1: 55 D2: 19 | 'Common' deficiency between Dec and Apr | D1: 55.1 D2: 53.9 | A |
| References | Data collection period | Study population | N | Serum 25(OH)D |
|------------|------------------------|------------------|---|--------------|
|            |                        |                  |   | Mean conc.±SD | Prevalence of conc. | Prevalence of conc. | Publ. type |
|            |                        |                  |   | or (95% CI)   | < 50 nmol/L          | > 50 nmol/L          |          |
| Dovnik, Mujezinović et al. 2014, Dovnik, Mujezinović et al. 2015, Dovnik, Mujezinović et al. 2015, Dovnik 2016, Dovnik, Mujezinović et al. 2017, Dovnik, Mujezinović et al. 2017 (33-38) | Sept 2013 Dec 2013 Mar 2014 Jun 2014 | Pregnant women and neonates | 398 | Mothers: 43.4±23.8 | Mothers: <25 nmol/L: 23.6% | Mothers: 50-80 nmol/L: 27.9% | A, A, A, B, B, B, C1 |
|            |                        |                  |   |             | Sept: 10.0%           | Sept: 40.0%           | Mar: 12.0% | |
|            |                        |                  |   |             | Dec: 41.4%            | Dec: 16.2%            | Mar: 12.0% | |
|            |                        |                  |   |             | Mar: 34.0%            | Jun: 43.4%            | Jun: 43.4% | |
|            |                        |                  |   |             | Jun: 9.1%             |                     |           | |
| Ekart, Vodošek Hojs et al. 2013 (45) | Mar 2011 - Apr 2012 | Outpatients with chronic kidney disease in predialysis clinic | 72 | 55.75±27.59 | | | B |
| Ferant and Kozar 2012, Šikić Pogačar, Dolinšek et al. 2013, Ferant, Kozar et al. 2014 (40-42) | Feb - Mar 2016 | Pediatrics patients with celiac disease (CD) and inflammatory bowel disease (IBD) | CD: 35 IBD: 35 K: 34 | CD: 32.5 | IR: <7.5 nmol: 14% | IR: <7.5 nmol: 13% | A, B, C4, |
| Gradišnik 2017, Velnar, Gradišnik et al. 2018 (28, 29) | 2006 Jan, Feb, Mar, Aug, Sept, Oct | Participants in the laboratory for analysis of hormones and tumour markers | Jan M: 54 F: 120 | 33.0±27.0 | IR: 27.0 K: 38 K: 39.5 | | A, C3 |
| Gros 2008 (55) | 2006 Jan, Feb, Mar, Aug, Sept, Oct | | Jan M: 54 F: 120 | 55.75±27.59 | | | C3 |
| References | Data collection period | Study population | N | Serum 25(OH)D |
|------------|------------------------|------------------|---|--------------|
|            |                        |                  |   | Mean conc.±SD (or (95% CI)) | Prevalence of conc. < 50 nmol/L | Prevalence of conc. > 50 nmol/L | Publ. type |
| Hribar, Hristov et al. 2020 (20) | 2017 - 2018 | A nationally representative sample of adults and elderly | Adults: 125 | Adults: 50.7 (45.4-56.0) | <30 nmol/L | <75 nmol/L | A |
|            | Summer: May-Oct, Winter: Nov-Apr | Age adults: 18-64 years; mean 46.5±13.2 | Summer: 52 | Adults winter: 70.4 (62.2-78.5) | 24.9% | Adults winter: 83.3% |
|            |                        | Age elderly: 65-75 years; mean 68.6±2.8 | Winter: 73 | Winter: 36.7 (32.5-40.9) | 40.8% | Adults winter: 98.0% |
|            |                        | Elderly: 155 | Winter: 64 | Elderly summer: 47.7 (43.9-51.5) | 2.6% | Elderly summer: 62.6% |
|            |                        | Elderly: 60.1 (54.0-66.2) | Winter: 91 | Elderly winter: 34.6% | 23.5% | Elderly winter: 84.4% |
|            |                        | Elderly summer: 39.0 (35.0-43.0) | | <50 nmol/L | 34.6% | Elderly summer: 92.2% |
| Humar 2015, Osredkar, Humar et al. 2015 (49, 50) | 2000 - 2010 | Patients with IgA nephropathy before and after cholecalciferol supplementation | 18 | Before supplementation: 40.5±17.6 | <12 nmol/L | 40 - 75 nmol/L: 16.8% | B, C3 |
|            |                        | Age: 47.1±10.1 years | After supplementation: 65.0±27.3 | 12 - 37 nmol/L: 51.5% | 40 - 75 nmol/L: 28.7% | |
| Jakopin, Pečovnik-Balon et al. 2011, Jakopin 2013 (46, 47) | May 2008 - May 2010 | Haemodialysis patients | 101 | 28.6±16.7 | <12 nmol/L: 16.8% | 40 - 75 nmol/L: 28.7% | B, C1 |
|            |                        | Age: 63.3±13.5 years | | 12 - 37 nmol/L: 51.5% | 40 - 75 nmol/L: 28.7% | |
| Jakše, Sekulič 2020 (39) | Apr (year not provided) | Indoor female athletes: athletes engaged in weight-bearing (artistic gymnastic (AG)) and non-weight-bearing (swimming (S)) sport | AG: 17 | 67.6±36.2 | <50 nmol/L: 35.5% | 51.75 nmol/L: 32.3% | A |
|            |                        | Age: 16.9±4.4 years | S: 14 | AG: 65.1±36.0 | 35.7% | AG: 35.3% | |
|            |                        | AG: 70.6±37.5 | | S: 35.7% | AG: 41.2% | |
| Krajnc, Čokolič et al. 2018 (54) | 2014 - 2017 | Hospitalised and outpatient patients mostly with osteoporosis and vitamin D risk factors for insufficiency | 2082 | Median: 62.9 | Most individuals lower than 75 nmol/L | B |
| References | Data collection period | Study population | N | Serum 25(OH)D | Mean conc.±SD or (95% CI) | Prevalence of conc. < 50 nmol/L | Prevalence of conc. > 50 nmol/L | Publ. type |
|------------|------------------------|------------------|---|--------------|--------------------------|--------------------------------|---------------------------------|-----------|
| Krajnc, Čokolič et al. 2013 (51) | (year not provided) | Outpatient type II diabetics | 45 | 58.0 ± 35.1 | 29.2 ± 22.8 | 58.0 ± 28.2 | B |
| Kšela and Zavratnik 2013 (52) | Apr 2011 | Ambulatory patients with type II diabetes mellitus | 47 | 33.8 ± 17.1 | 25.0–75.0 nmol/L: 24% | 50.0–74.9 nmol/L: 16.2% | B |
| Marc 1993 (18) | (year not provided) | Haemodialysis patients (DP) and continuous peritoneal dialysis patients (CAPD) | 85 | 68.0 ± 28.4 | 61.3–89.6 nmol/L: 33% | 45.3–61.3 nmol/L: 33% | C2 |
| Osredkar, Marc 1996 (22) | 1994 - 1995 | Individuals from general population included on periodic medical examinations | 240 | 73.1 ± 35.4 | 50-75 nmol/L: 26% | 75-100 nmol/L: 52% | A |
| Pajek, Čuk et al. 2017, Šturm 2017 (24, 25) | 2014 - 2015 | Dialysis patients (DP) from nine haemodialysis outpatient centres and controls (K) | DP: 54 | 48.2 ± 27.4 | 55.6-79.0 years: 42% | 55-79.0 years: 58% | A, C2 |
| Pajk 2011 (30) | Jan 2009 - Dec 2010 | Postmenopausal women from endocrinology and nephrology outpatient centres | 457 | 73.5 (54.7-89.6) | 30.8–50.0 nmol/L: 48% | 50-75 nmol/L: 48% | C3 |
| Pečovnik-Balon, Jakopin et al. 2009 (48) | Sept 2005 - Sept 2007 | Haemodialysis patients treated at the Department of Haemodialysis | 102 | 58 ± 35.6 | 10-25.0 nmol/L: 15% | >25 nmol/L: 52% | A |
| Rakuša, Vrtovec et al. 2020 (57) | 2009 - 2018 | Heart transplantation recipients | 123 | 73.5 (54.7-89.6) | 25-75 nmol/L: 24% | 75-100 nmol/L: 48% | A |
| Rondaij, Rotovnik Kozjek et al. 2021 (59) | Jan 2017 - Dec 2018 | Chronic intestinal failure patients on long-term home parenteral nutrition | 63 | 41.3 | 24% | 50-75 nmol/L: 26% | C3 |
| Salkić 2016 (56) | Summer: Sept - Nov 2015 Winter: Jan - Mar 2015 | Outpatient clinic laboratory | Summer: 776 Winter: 434 | 58.6 | 50-75 nmol/L: 26% | 50-75 nmol/L: 48% | C3 |
| References                                      | Data collection period       | Study population                                      | N   | Serum 25(OH)D                                                                 |
|------------------------------------------------|------------------------------|-------------------------------------------------------|-----|-------------------------------------------------------------------------------|
| Soltirovska Salamon, Benedik et al. 2015 (17) | Dec 2010 - Oct 2012          | Pregnant Women in 3. trimester                        | 132 | Mean conc.±SD or (95% CI) [nmol/L] Prevalence of conc. < 50 nmol/L Prevalence of conc. > 50 nmol/L Publ. type |
| Smaller subsamples of same population          | (31, 32)                    | Age: 30.6±4.4 years                                   |     | 74.7±27.5 <50 nmol/L: 14% 50-75 nmol/L: 41% A                                |
| Tesovnik, Kovac et al. 2015 (44)               | (year not provided)         | Juvenile population with type I diabetes             |     |                                                                               |
| Tomažič, Ul et al. 2007 (58)                   | Jan - Feb 2006               | HIV-infected male population, on three different treatments: T1: antiretroviral treatment naïve; T2: treated with non-protease-inhibitor antiretroviral treatment; T3: treated with protease-inhibitor containing antiretroviral treatment | 96  | T1: 35.8 T2: 26.5 T3: 36.5                                             |
| Trdan 2016 (26)                                | 2014 - 2015                  | DM and controls age: 67.6 years K age: 55.4 years    | 818 | DM: 31.6±17.4 DM: 266 K: 49.2±29.6                                         |
| Troskot and Duhovnik 2013 (27)                 | Autumn 2011 - spring 2013    | Patients treated with antiepileptic drugs carbamazepine and oxcarbazepine (P) and healthy controls (K) | P: 32 | P: 55.6±25.2 P: <50 nmol/L: 46.9% P: 50-70 nmol/L: 31.3% |
| Vindišar, Goličnik et al. 2009 (53)            | (year not provided)         | Patients with hip fracture Age: 58-95 years, mean 79 years | 38  | 39.6±11.9 20-50 nmol/L: 85.8% >50 nmol/L: 13.2% B                             |
| Vujasinović, Kunst et al. 2016 (104)          | (year not provided)         | Patients 1 year after bariatric surgery Age: 42.0±9.2 years | 22  | <65 nmol/L: 95.4% A                                                        |
| Žmitek, Hribar et al. 2020 (21)                 | Jan - Mar 2019               | Healthy adults, mostly from Central Slovenia Age: 18-65 years; mean 37.7±11.4 | 238 | 44.0±17.0 M: 44.3±16.0 F: 43.8±18.0 <30 nmol/L: 21% 30-50 nmol/L: 45% 50-75 nmol/L: 3% |

Notes: Jan - January, Feb - February, Mar - March, Apr - April, Jun - June, Aug - August, Sept - September, Oct - October, Nov - November, Dec - December, K - control group, CD - celiac disease, IR - Institutionalised residents, IBD - inflammatory bowel disease, DP - Dialysis patients, P - Patients treated with antiepileptic drugs carbamazepine and oxcarbazepine, DM - diabetes patients, T1 - antiretroviral treatment naïve; T2: treated with non-protease-inhibitor antiretroviral treatment; T3 - treated with protease-inhibitor containing antiretroviral CAPD - treatment continuous peritoneal dialysis patients, AG - artistic gymnastic, S - swimming, D1 - strictly compliant to a gluten-free diet, D2 - not strictly compliant to a gluten-free diet, M - male, F - female, Publication type (A - scientific paper, B - conference paper, C - academic thesis; 1 - doctoral, 2 - master, 3 - diploma, 4 - other)
Supplementary table 2. Review of reports for vitamin D intake in the Slovenian population.

| Authors | Population | Mean vitamin D intake [µg/day] | Data collection | Publication type |
|---------|------------|--------------------------------|----------------|-----------------|
| Fidler Mis, Kobe et al. 2012 (61) | Teenagers Age 15-16 years M: n=1,010 F: n=1,214 | M: 4±4 F: 4±3 | sq-FFQ (n=2,661) 3DDR for adjustment (n=197) | A |
| Gregorič 2019 (69, 70) | Elderly in residential home n=49 Age: 65-91 years | 2 x 24h-recall: 1.1±0.6 3DDR: 1.3±0.7 | 2 x 24 h-recall 3DDR | A, C3 |
| Gregorič 2015 (62) | Teenagers from 10 primary schools Age 11-15 years n=327 6. grade: age 11-12 years, mean 12.0±0.1 F: n=79 M: n=78 8. grade 13-15 years, mean 14.0±0.2 F: n=84 M: n=86 | All: 1.7 | 2 x 24h recall | C1 |
| Hribar 2021 (19) | Adolescents Age: 10-17 years M: n=238 F: n=230 Adults Age: 18-64 years M: n=173 F: n=191 Elderly Age: 65-74 years M: n=213 F: n=203 | Adolescents All: 2.7 M: 3.0 F: 2.4 Adults All: 2.9 M: 3.4 F: 2.3 Elderly All: 2.5 M: 2.6 F: 2.3 | 2 x 24h recall adjusted with FPQ | A |
| Jakše 2020 (71) | Healthy, active adults after dietary intervention study Age: 18-78 years, mean 39.6 years M: n= 42 F: n=109 | Food, supplements, and plant-based meal replacements: M: 7.1±5.8 F: 14.2±19.4 Food: M: 0.5 ±1.1 F: 0.6 ±1.0 Supplements, and plant-based meal replacements: M: 6.6±5.7 F: 13.6±19.3 | 3DDR | A |
| Jeretina 2019 (66) | Healthy peri- and postmenopausal women Age: 40 - 65 years, mean 57.1±4.7 years n=59 | Food: 1.3±0.93 Food and supplements: 4.1±10.8 | sq-FFQ for fish, milk, and milk products | C2 |
| Juvan 1997 (68) | Students eating vegetarian diets n=14 Semi-vegetarians: 21% Lacto-ovo vegetarians: 58% Lacto vegetarians: 21% | 2.6 Semi-vegetarians: 3.3 Lacto-ovo vegetarians: 2.8 Lacto vegetarians: 1.1 | 7DDR | C3 |
| Koch and Gregorič 2009 (63) | Nationally representative data from secondary school students Age: mean 18 years M: n=216 F: n=237 | Consumed with breakfast M: 0.3±0.5 F: 0.2±0.4 | 24h-recall | A |
| Authors                          | Population                                      | Mean vitamin D intake [µg/day] | Data collection | Publication type |
|---------------------------------|-------------------------------------------------|-----------------------------------------|-----------------|------------------|
| Kocovan Mijatov and Mičetić-Turk 2016 (72) | Adult female coeliac disease patients Age: 23 - 76 years n=40 | 2.6                       | 3DDR            | A                |
| Lichthammer, Nagy et al. 2015 (65)  | Teenage and adult population Age: 15-75 years, mean 38.8 n=81 | All: 2.57 14-18 years: 3.7±3.3 19-29 years: 3.0±2.1 30-69 years: 2.5±1.7 | sq-FFQ          | A                |
| Lopert 2019 (73)                 | Female patients with osteoporosis Age: mean 71.4 years n=43 | >70 years: 1.0±2.4 FFQ: 1.8 24h-recall: 1.4 | FFQ, 24h-recall | C2               |
| Poličnik, Pokorn et al. 2013 (60) | Pre-school children in Central Slovenia Age: 2-6 years, average 4.2 n=129 M: n=68 F: n=61 | All: 1.1±0.7 M: 1.0±0.7 F: 1.1±0.7 | 3DDR            | A                |
| Soltirovska Salamon, Benedik et al. 2015 (17) | Pregnant women in third trimester Age: 30.6±4.4 years n=132 | 2.6                       | 4DDR            | A                |
| Urh, Babnik et al. 2017 (67)     | Elderly in a residential home Age: mean 82.2 years n=48 | 2.6                       | 7DDR            | A                |
| Zdešar-Kotnik 2019 (64)          | Pupils of 1. years of Secondary school M: Age: 13.5 years; n=162 F: Age: 15.4 years; n=180 M: 1.4 (0.8 - 2.5) F: 1.0 (0.6 - 1.7) | 2x24h-recall | 2x24h-recall | C1               |

Notes: M - males, F - females, DDR - day dietary record, FFQ - food frequency questionnaire, FPQ - food propensity questionnaire, sq - semi-quantitative; Publication type (A - scientific paper, B - conference paper, C - academic thesis; 1 - doctoral, 2 - master, 3 - diploma, 4 - other)