Psychiatr. Pol. ONLINE FIRST Nr 205: 1–18
Published ahead of print 30 December 2020
www.psychiatriapolska.pl
ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
DOI: https://doi.org/10.12740/PP/OnlineFirst/130992

Vitamin D deficiency and depressive symptoms: Meta-analysis of studies

Krzysztof M. Wilczynski[1,2], Katarzyna Checinska[3], Krzysztof Kulczyk[3], Małgorzata Janas-Kozik[1,2]

[1] Department of Psychiatry and Psychotherapy of Developmental Age, Medical University of Silesia, Katowice, Poland

[2] Pediatric Centre of John Paul II in Sosnowiec Sp. z o.o., Sosnowiec, Poland

[3] Kozminski University, Warsaw, Poland

Summary

Aim. The aim of this study was the identification and summarization of studies examining the relationship between vitamin D levels and the risk of depression and depressive symptoms severity, published between January 2008 and January 2019.

Methods. A systematic review of literature published within the last 10 years and accessible in PubMed database was conducted by each author separately based on predetermined inclusion criteria.

Results. Out of the 823 studies qualified to the initial abstract analysis, 24 were included into the full-text review and 18 into the meta-analysis. Statistically significant odds ratio was obtained for risk of depression in the course of vitamin D deficiency (OR = 1.51; 95% CI: 1.4–1.62; $p < 0.01$).

Conclusions. The analysis of available literature seems to indicate that there is an association between risk of depression and vitamin D deficiency. However, current literature does not give the possibility to state explicitly what is the exact mechanism and direction of this dependency.

Key words: vitamin D, calcitriol, depression

Introduction

Depression is currently the most common mental disorder in the world. It is estimated that it affects from about 350-840 million people worldwide [1-3]. This is particularly important for people over 60 years of age, among whom, according to literature, symptoms can be observed in about 15% of the population, whereas depression together with diabetes and ischemic heart disease are the main causes of

disability [4]. According to the DSM-5 classification, the essential elements of the clinical picture of a major depressive episode are: (1) depressed mood, (2) lowered perception of pleasure – anhedonia, (3) significant weight loss and change in appetite, (4) psychomotor retardation, (5) fatigue, (6) feelings of worthlessness or inappropriate sense of guilt, (7) impaired concentration and difficulties with decision-making, and (8) recurrent thoughts of death, suicidal ideation, or suicide attempts [5]. The third point is particularly noteworthy because in this type of disorder there is a reduction or increase in appetite as well as food avoidance, irregular eating and a preference for sweet foods [6]. It is estimated that depression is associated with a 1.5 to 6-fold increase in the risk of cardiovascular disorders, diabetes, obesity and metabolic syndrome [7]. The pattern of nutrition observed in the course of depression may be associated with the risk of many nutritional deficiencies, which is observed in available literature. The most frequently indicated deficits are: (1) omega-3 fatty acids, (2) B vitamins, (3) microelements and (4) amino acids, precursors of neurotransmitters (e.g. tryptophan – a serotonin precursor) [6]. These types of nutritional disturbances may lead to the intensification of symptoms of affective disorders, reduce the effectiveness of treatment and worsen the prognosis. For this reason, the issues of eating disorders and nutritional deficits in the course of depression have been of great interest in recent years.

Vitamin D is a group of steroidal fat-soluble hormones, whose unique feature is photoisomerization, constituting a key element in the biosynthesis of the active compound. This process takes place in the epidermis and provides up to 100% of the body's need for vitamin D; however, for this to take place, exposure to the sun (UV radiation) is necessary [8]. Nonetheless, despite such a seemingly "easily" available source, vitamin D deficiency has become a major problem around the world. This also applies to countries with a significant exposure to the sun, such as Australia, where as much as a third of the population has a reduced concentration of vitamin D [3] (Australian average sun exposure > 3,000 h annually; Poland: 1,200-1,600 h). Currently, vitamin D deficiency is defined as a decrease in its concentration below 20 ng/ml (50 nmol/L), and besides endogenous production, the main source of this vitamin is through the exogenous supply of plant (ergocalciferol) and animal (cholecalcitriol) products (for example, fatty fish are a rich source of vitamin D [3, 9]). Deficiency of Vitamin D can have serious consequences for the wide range of tasks this vitamin performs in the human body. The classic perception of the function of this group of compounds includes the control of calcium-phosphate homeostasis and bone resorption and reconstruction by regulating the absorption of calcium in the gastrointestinal tract and its secretion in the kidneys, as well as modulation of osteoclast function. This paradigm changed with the discovery of nuclear receptors for vitamin D (VDR) in about 50 different kinds of tissues [9-11]. One of the locations where the presence of VDR was discovered are neurons and glial cells, which led to further discoveries in the field of vitamin D function in the central nervous system (CNS). Research indicates that Vitamin D may participate, among others, in regulating the synthesis of neurotransmitters, increasing the concentration of dopamine and serotonin in the CNS [3], in the biosynthesis of neurotrophic factors and in exerting neuroprotective effects by inhibiting the synthesis of free oxygen radicals and inducing glutathione synthesis [9, 11].

In the context of the growing interest of researchers regarding the issue of nutritional deficiencies in the course of depression, along with a systematically growing literature database that has increased significantly in the last 15 years regarding the main functions of Vitamin D, unsurprisingly, there has been an observed increase in the number of publications linking Vitamin D deficit with depression.

The aim of the study

The aim of the study was the identification and summarization of studies examining the relationship between vitamin D levels and the risk of depression, published between January 2008 and January 2019.

Materials and methods

This literature review focused on publications from the last 10 years obtained through the MEDLINE/PubMed database. During the search, the following keywords were used: *"vitamin D", "cholecalciferol", "24,25-dihydroxyvitamin D3", "ergocalciferol", "calcitriol", "calcifeldiol", "D3", "25-hydroxyvitamin D2",* "*depression"*, "*depressive disorder"*, "*depress"*, *"depressed"*, *"depressive"*. The review included Polish – and English-language original studies published in recognized local and international journals, with the exception of those involving animal testing. The review was performed by two authors separately in three phases, based on 6 inclusion criteria:

1. Published between January 2008 and January 2019.
2. Published in English or Polish.
3. Published as part of journals (excerpts from books were excluded).
4. The studies directly analyzed the relationship between vitamin D concentration and symptoms of depression,
    a. Meta-analysis included studies that expressed this relationship using an odds ratio with a 95% confidence interval or presented data enabling its calculation.
5. The work presented the methodology in a clear and comprehensive manner (e.g. inclusion and exclusion criteria, demographic data about participants, and the methodology of confirmation and exclusion of depressive symptoms).
6. The study used a good methodology (including reliable research tools validated for the target population, clearly defined research hypotheses, a satisfactory description of the statistical methods used).

The first phase of the review included searching for publications and analyzing their compliance with the subject of the review based on the title of the work. In the second stage, the abstract was analyzed for compliance with the inclusion criteria for the study. The research studies that were qualified by each of the authors for further analysis were compared with each other and, after the deletion of duplicates, subjected to a preliminary full-text analysis aimed at assessing compliance with the previously assumed inclusion criteria. An analysis of the bibliography of the works included was also carried out. Finally, 21 works were identified that were included in the meta-

analysis. The scheme for the selection of publications for review and meta-analysis is presented in Figure 1.

The quality of the publications, qualified for the last stage of the analysis during literature review, was assessed utilizing *The Newcastle-Ottawa Quality Assessment Scale* (NOQAS). It is a structured questionnaire designed to evaluate the quality of studies from the viewpoint of the group selection and verification of the diagnosis ("exposition"), in which each publication is granted points (in the form of stars) for fulfilling specific criteria. Each study can obtain a maximum of 5 stars for group selection and 3 stars for verification of exposition (diagnosis). In the presented paper, interpretation of the NOQAS outcome was based on the following scheme (group selection/exposition): good quality (5* or 4*/3* or 2*); average quality (3* or 2*/1*); weak quality (0 or 1*/0*).

The PQstat program, version 1.6.6 was used to compile the results using the odds ratio with 95% confidence interval, Egger's *b*-coefficient, heterogeneity (I^2) and the number of "fail-safe" publications using the Rosenthal method.

A significant difficulty in the compilation of the analyzed publications was the differences in the units used and the standards of measuring vitamin D. Most of the publications used "ng/ml"; however, some presented the results in "nmol/L". Therefore, in the following analysis, in order to maintain data consistency, it was decided to use "ng/ml", while the results in "nmol/L" were converted by dividing the result by 2.496 [12]. Another issue was the standards used in the publications. The vast majority of authors based the calculation of the odds ratio on the norm of 20 ng/ml (50 nmol/L); however, in several works, instead of this method the authors based the calculations on their own division of concentrations, usually in quartiles. Therefore, the analysis was based on the odds ratio of the group with the highest and lowest levels of vitamin D. The basic formula for calculating odds ratios in the analyzed publications was as follows (symbols in accordance with Table1):

$$OR = (A/B) / (A'/B')$$

However, some authors alternatively used the formula:

$$OR' = (A'/B') / (A/B)$$

And in such cases, in order to maintain data consistency, the result was calculated according to the following formula:

$$OR = 1/OR'$$

Finally, not all of the analyzed works included the odds ratio, so in cases where the data provided enabled this type of calculation, it was made using the PQstat program in version 1.6.6.

Table 1. **Symbols utilized in the calculations of odds ratio for meta-analysis**

	Lowest concentration of vit D	Highest concentration of vit D
Depression (+)	A	A'
Depression (-)	B	B'

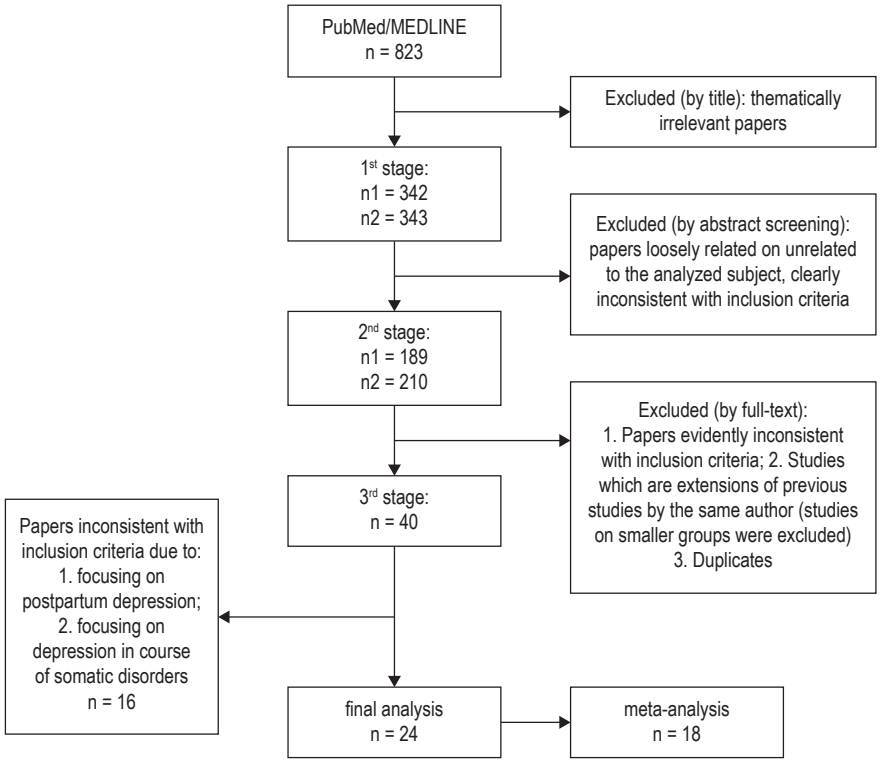

Figure 1. **The scheme of the literature review procedure**

n1, n2: works obtained by author 1 and author 2

Results

Initially, 823 publications were selected based on the key words previously chosen, from which, after the first stage, 342 and 343 works were qualified for further review by the respective authors. In the second stage, the authors respectively identified 152 and 133 publications as inconsistent with the inclusion criteria. After a full-text analysis, a comparison of the results of the review between the authors and the removal of duplicates, a total of 40 publications were qualified for the third stage. Of these, another 16 publications were removed because of non-compliance with the inclusion criteria due to (1) analysis of depression in the course of somatic diseases and (2) analysis of postpartum depression. Ultimately, the review included 24 works, of which 18 were included in the meta-analysis. The characteristics of the works included in the review are described in Table 2.

Table 2. **Overview of literature**

Publication	No.	Diagnosis	Age of participants M(SD) or min/max	Conclusions and results	Confirmation of hypothesis of relation	NOQAS
Hoogendijk et al. (2008) [12]	1282	CES-D	76.6	Significant ↓ vitamin D concentrations in patients with depression; Average CvitD (depr): 19 ng/ml Average CvitD (cont): 22 ng/ml, p < 0.001 OR: 1.34 (95% CI: 0.92-1.94), p < 0.05	+	Good quality (4*/2*)
Johnson et al. (2008) [13]	158	GDS	77 (8)	No significant difference in the severity of GDS depression symptoms between vitamin D concentration <20 ng/ml and >20 ng/ml	-	Average quality (4*/2*)
Nanri et al. (2009) [14]	527	CES-D	43	(n/s) relation of ↓ vitamin D concentration with risk of depression closer to statistical significance in months with lower sun exposure Study conducted in July: OR: 0.63 (95% CI: 0.09-4.60), p = 0.62 Study conducted in November: OR: 0.4 (95% CI: 0.16-1.03), p = 0.12	-	Average quality (3*/2*)
Stewart and Hirani (2010)[15]	3151	GDS	73.7	Significant ↓ vitamin D concentrations in patients with depression; OR: 1.46 (95% CI: 1.17 – 1.82), p < 0.001	+	Average quality (3*/2*)

table continued on the next page

Zhao et al. (2010) [16]	3916	PHQ	n/a	(n/s) ↓ vitamin D concentration in patients with depression; Average CvitD (depr): 19.6 ng/ml Average CvitD (cont): 22.0 ng/ml p < 0.01 OR: 0.92 (95% CI: 0.6-1.41) The decreased concentration of vitamin D is not related to symptoms of depression.	-	Average quality (3*/2*)
Milaneschi et al. (2010) [17]	531	CES-D	74.4 (6.9)	A significant relationship of ↓ vitamin D concentration in women at risk of depression; HR(F): 2.0 (95% CI: 1.2-3.2), p = 0.005 (n/s) relationship of ↓ vitamin D concentration in men at risk of depression; HR(M): 1.6 (95% CI: 0.9-2.8), p = 0.1	+/-	Good quality (4*/2*)
Ganji et al. (2010) [18]	7970	DIS	27.5 (0.2)	(n/s) relationship of ↓ vitamin D concentration with the risk of depression Average CvitD (depr): 32 (SD: ± 0.8) ng/ml Average CvitD (cont): 31.2 (SD: ± 0.4) ng/ml, p < 0.01 OR: 1.85 (95% CI: 0.9-3.81), p = 0.021 (unadjusted) OR: 2.01 (95% CI: 1.25-3.24), p < 0.001	+	Average quality (3*/2*)
Chan et al. (2011) [19]	939	GDS	72.4 (5.1)	Significant ↓ vitamin D concentrations in patients with depression; Average CvitD (depr): 29.2 (SD: ± 7.33) ng/ml Average CvitD (cont): 31.4 (SD: ± 8.33) ng/ml, p < 0.023 OR: 2.17 (95% CI: 1.02-4.54), p = 0.004	+	Average quality (3*/2*)

table continued on the next page

Lee et al. (2011) [20]	3151	BDI	59.7 (11)	Significant ↓ vitamin D concentrations in patients with depression; Average CvitD (depr): 20.95 (SD: ± 10.1) ng/ml Average CvitD (cont): 25.4 (SD: ± 12.66) ng/ml, p < 0.01 OR: 1.74 (95% CI: 1.00-3.00), p = 0.04	+	Average quality (3*/2*)
Brouwer-Brolsma et al. (2012) [21]	118	GDS	70/75	(n/s) ↓ vitamin D concentration in patients with depression; RR: 0.74 (0.53-1.06), p = 0.41	-	Average quality (3*/2*)
Kwasky and Groh (2012) [22]	139	BDI	20.3 (1.8)	No significant relationship between depression and vitamin D levels Average CvitD (depr): 28.0 (SD: 17.9) ng/ml Average CvitD (cont): 23.8 (SD: 11.2) ng/ml, p = 0.212	-	Average quality (2*/2*)
Black et al. (2014) [23]	735	DASS	19.95 (0.5)	Significant ↓ vitamin D concentrations in men with depression; RR(F): 0.99 (95% CI: 0.95-1.03), p = 0.5 RR(M): 0.92 (95% CI: 0.87-0.96), p = 0.001	+	Good quality (4*/2*)
Maddock et al. (2013) [24]	7401	CIS-R	45	Significant ↓ vitamin D concentrations in men with depression; OR: 2.32 (95% CI: 1.36 – 3.84), p = 0.001	+	Average quality (3*/1*)
Lapid et al. (2013) [25]	1618	HICDA	73.8 (8.48)	Significant ↓ vitamin D concentrations in patients with depression; Average CvitD (depr): 32.7 (SD: ± 13.5) ng/ml Average CvitD (cont): 35.0 (SD: ± 15.4) ng/ml, p = 0.002 OR: 2.093 (95% CI: 1.092-4.011), p = 0.026	+	Average quality (3*/2*)

table continued on the next page

Almeida et al. (2015) [4]	3105	GDS	77 (3.6)	Significant ↓ vitamin D concentrations in patients with depression; Median CvitD (depr): 24.31 (IQR: 18.99-30.4) ng/ml Median CvitD (cont): 27.36 (IQR: 21.5-33.3) ng/ml, p = 0.001 OR: 2.70 (1.39-5.25), p < 0.05	+	Average quality (3*/1*)
Jääskeläinen et al. (2015) [26]	5371	BDI	50.4 (12.7)	Significant ↓ vitamin D concentrations in patients with depression; OR: 0.65 (95% CI: 0.46-0.93), p = 0.006	+	Good quality (4*/2*)
Von Känel et al. (2015) [27]	380	HADS; BDI	47 (12)	Significant ↓ vitamin D concentrations in men with depression; G1 <50 nmol/L (n = 211; 55.5%): HADS-D av = 13.12 ± 0.29; BDI-II total av = 31.67 ± 0.77; G2 (50-75 nmol/L) (n = 121, 31.8%): HADS-D av = 12 ± 0.38; BDI-II total av = 29.9 ± 1.01; G3 >75 nmol/L (n = 48, 12.6%): HADS-D av = 11.28 ± 0.61; BDI-II total av = 26.7 ± 1.62; p-value: (HADS): 0.01; (BDI): 0.023	+	Weak quality (2*/0*)
Krysiak et al. (2016) [28]	14	BDI	30 (5)	Statistically significant relationship between depression symptoms and vitamin D levels: Group of patients with vitamin D deficiency CvitD = 12 ± 4 ng/d L (G1) Group of patients with the correct level of vitamin D CvitD = 46 ± 8 ng/dL (G2) BDI: G1 vs. G2: 12.5 (SD: 4.5) vs. 7.6 (SD: 3), p <0.01	+	Average quality (2*/2*)

table continued on the next page

Moy et al. (2017) [29]	770	DASS	41.15 (95% CI: 40.5-41,78)	Significant ↓ vitamin D concentrations in patients with depression; OR: 1.88 (95% CI: 1.27-2.79), p < 0.05	+	Average quality (2*/2*)
Lee et al. (2017) [30]	7198	S/R	39	Significant ↓ vitamin D concentrations in patients with depression; Average CvitD (depr): 15.8 (95% CI: ± 5.84) ng/ml Average CvitD (cont): 17.14 (95% CI: ± 5.76) ng/ml, p < 0.0 5 OR: 1.54 (95% CI: 1.20-1.98), p < 0.001	+	Average quality (2*/1*)
Jovanova et al. (2017) [31]	3251	CES-D	71 (6.6)	A significant relationship of ↓ vitamin D concentration with the severity of depressive symptoms; β = (– 0.27); 95% CI: (-0.51) – (– 0.04) p = 0.023 Persons with CvitD <20 ng/ml: N/total CES-D > 16 points: 129/1843 Persons with CvitD >20 ng/ml: N/total CES-D > 16 points: 75/1408 OR: 1.33 (95% CI: 0.99-1.79), p = 0.03	+	Good quality (4*/2*)
Collin et al. (2017) [32]	1196	CES-D	51.3 (6)	Significant ↓ vitamin D concentrations in patients with depression; Average CvitD (depr): 19.75 ng/ml Average CvitD (cont): 20.9 ng/ml	+	Good quality (4*/2*)

table continued on the next page

Sherchand et al. (2018) [33]	300	BDI	38.3 (10.2)	Significant ↓ vitamin D concentrations in patients with depression; Average CvitD (depr): 16.89 (95% CI: ± 7.14) ng/ml Average CvitD (cont): 21.28 (95% CI: ± 7.13) ng/ml, $p < 0.0001$ OR: 3.5 (95% CI: 1.1-11.9), $p < 0.05$	+	Average quality (2*/1*)
Yao et al. (2018) [34]	940	GDS	102.5 (2.7)	Significant ↓ vitamin D concentrations in patients with depression; Average CvitD (depr): 20.8 (95% CI: ± 8.7) ng/ml Average CvitD (cont): 23.7 (95% CI: ± 9.7) ng/ml, $p < 0.0001$ OR: 1.47 (95% CI: 1.08-2.00), $p < 0.05$	+	Average quality (3*/2*)
Cumulative	54,161	n/a	45.17 years		16 (+); 5 (-); 1 (+/-)	Average quality (2.91*/1.75*)

PHQ: Patient Health Questionnaire; GDS: Geriatric Depression Scale; BDI: Beck's Depression Inventory; CES-D: Center for Epidemiologic Studies Depression scale; S/R: a subjective evaluation of mood; DIS: Diagnostic Interview Schedule; CIS-R: Clinical Interview Schedule Revised; HICDA: Hospital International Classification of Disease Adaptation

NOQAS: The Newcastle-Ottawa Quality Assessment Scale – Group selection / exposition: quality: good (5 or 4*/3 or 2*); average (3* or 2*/1*); weak (0 or 1*/0*)

OR: odds ratio; RR: relative risk; HR: hazard ratio; CvitD: concentration of vitamin D; (depr): group of patients with symptoms of depression or with depression; (cont): group of patients without symptoms of depression or without depression ; (n/s): non-significant; (F): females; (M): males; cg: control group; gt: group tested ; β: beta coefficient – regression

From the works qualified for the meta-analysis, the values of the odds ratio with 95% confidence interval, the size of the groups and the age of the respondents were distinguished. The total population from all analyzed publications was 52,130 persons. The odds ratio obtained was $OR = 1.51$ (95% CI: 1.4-1.62) and was statistically significant ($p < 0.000001$). Among the analyzed works, negligible heterogeneity was observed (statistics $Q = 16.08$; I^2: 0% (95% CI: 0-47.11), $p = 0.51$). Egger's coefficient b (asymmetry) was 0.46 (95% CI: (-0.53-1.477), $p = 0.33$) and the number of fail-safe publications using Rosenthal's method was $N(fs) = 625$. The results of the meta-analysis are presented in Figure 2.

Author	OR	-95% CI	+95% CI	C/P
Hoogendijk et al. (2008)	1.34	0.92	1.94	2.66%
Nanri et al. (2009)	2.5	0.98	6.40	-2.80E-03%
Ganji et al. (2010)	1.17	0.72	1.91	1.85%
Zhao et al. (2010)	1.08	0.76	1.53	4.08%
Stewart i Hirani (2010)	1.46	1.17	1.82	6.88%
Chan et al. (2011)	2.17	1.03	4.57	0.14%
Lee et al. (2011)	1.52	1.17	1.97	5.13%
Maddock et al. (2013)	2.32	1.37	3.94	0.14%
Lapid et al. (2013)	2.093	1.09	4.00	0.24%
Almeida et al. (2015)	1.65	1.13	2.41	1.69%
Von Känel et al. (2015)	1.09	0.56	2.12	1.08%
Jääskeläinen et al. (2015)	1.56	1.36	1.79	18.20%
Moy et al. (2017)	1.88	1.27	2.78	1.06%
Lee et al. (2017)	1.54	1.20	1.98	5.26%
Collin et al. (2017)	1.35	0.79	2.31	1.24%
Jovanova et al. (2017)	1.33	1.00	1.77	4.63%
Sherchand et al. (2018)	3.5	1.10	11.14	-0.15%
Yao et al. (2018)	1.47	1.08	2.00	3.77%
TOTAL	1.51	1.40	1.62	n/a
$p < 0.0000001$; Q: 16.08; I^2: 0% (0–47) [p = 0.51]; bEgger = 0.46; p = 0.33; N(fs) = 625				

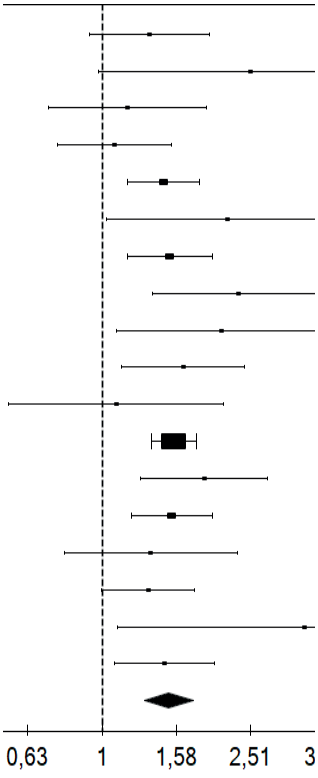

Figure 2. **Forest plot for studies included in the meta-analysis**

C/P: change in precision;

n/a: not applicable

Discussion

The works selected in the presented study seem to be rather consistent with regards to the existence of a connection between vitamin D deficiency and symptoms of depression in the general population. This is also confirmed by the results of the meta-analysis, both in terms of the homogeneity of the presented data in the analyzed publications and the final result itself, where the obtained odds ratio was statistically significant and amounted to *OR* = 1.51 (95% CI: 1.4-1.62; $p > 0.05$). However, the actual nature and direction of this dependence remain unclear at this moment. On one hand, taking into account the numerous central functions that vitamin D [9] fulfills, its role in the pathophysiology seems to be likely. On the other hand, it should be remembered that the clinical picture of depression itself creates a predisposition to vitamin D deficiency, both in terms of lower exposure

to the sun associated with reduced activity as well as an improper diet and decrease in appetite, which consequently leads to a reduced supply of exogenous vitamin D [5].

The hypothesis of a deficiency of vitamin D being primary in relation to depression symptoms has become the basis for numerous studies on the effectiveness of supplementation as a treatment of mild forms of depression or an adjuvant to the treatment of more severe forms. Among others, their effectiveness was assessed by Stefanowski et al. in 2017, showing that supplementation of 3-6 thousand IU/d, combined with monitoring of serum vitamin D, may have a significant antidepressant effect [9]. However, in the works of other authors the results are less homogeneous and often show ineffectiveness of this type of intervention. In 2014, a meta-analysis by Shaffer et al., which included 7 studies (3,191 participants), showed that vitamin D supplementation is effective in patients with severe intensity of depression symptoms (standardized mean difference SMD = (– 0.6); 95% CI: (-1.19) – (– 0.01), $p = 0.046$) but not in the low-intensity group (SMD = (-0.04); 95% CI: (-0.2) – 0.12, $p = 0, 61$) [35]. In a meta-analysis by Gowda et al. from 2015, involving 9 papers with a total of 4,923 participants, no difference was observed in the intensity of depressive symptoms between patients with supplementation and the placebo group (SMD = 0.28 (95% CI: (-0.14) – 0.69), $p = 0.19$) [36]. Such a large discrepancy in results is most likely due to significant non-uniformity of the studies, which were often based on different populations, vitamin D levels at the beginning of treatment were not checked, or disparate and often subtherapeutic doses were used. These limitations were attempted to be addressed in a meta-analysis from 2014 by Spedding [3]. After selecting the works in which there were no significant methodological errors, he showed that supplementation with a dose of >800 IU per day of vitamin D showed some anti-depressant effect (SMD = 0.78 (95% CI: 0.24-1.27), $p < 0.05$). The latest meta-analysis from 2019, carried out by Vellekkatt et al. [37], included 4 works (948 participants) and also showed significant superiority of supplementation over placebo (Cohen's effect size $d = 0.58$ (95% CI: 0.45-0.72)). A separate issue is the use of nutraceuticals as supportive therapy for traditional anti-depressant drug treatment. This type of combination was analyzed by Khoraminya et al. in 2012 on a group of 42 patients, showing a significantly higher efficacy of 20 mg fluoxetine in combination with supplementation of 1500 IU of vitamin D in comparison with monotherapy with fluoxetine [38].

Thus, current reports on the effectiveness of vitamin D supplementation remain ambiguous as far as the potential benefit of this type of therapeutic intervention. There are several potential mechanisms through which vitamin D can affect the intensity of depressive symptoms. First, it has a significant impact on the regulation of neurotransmitter metabolism in the CNS. In the publication by Patrick et al. from 2014 [39], the authors indicate that vitamin D can activate gene transcription of tryptophan hydroxylase 2 (*TPH2*) in the CNS and inhibit its activity outside the brain. As this enzyme is a key element of the serotonin biosynthesis pathway, this type of interaction can significantly increase its concentration in the CNS – and therefore act synergistically with, e.g. serotonin reuptake inhibitors. Another issue is the postulated, among others, by Kesby et al. [38] in their 2010 publication, effect of vitamin D on the concentration and function of dopamine in the CNS [40] as well as for norepinephrine [41]. No less important is the modulation function of vitamin D in the field of brain neuroplasticity and neuroprotection. It was

observed that it significantly increases the concentration of neurotropic growth factors (e.g. NGF or GDNF) [9] whose blood level concentrations are reduced in people suffering from depression. This type of action is again synergistic with antidepressants, which also significantly increase the concentration of these compounds [42]. The neuroprotective effect of vitamin D may also be exerted through the intensification of antioxidative processes in the CNS due to induction of glutathione synthesis [9]. In a study conducted in a population of patients with schizophrenia (never treated with neuroleptic drugs), it was also shown that the concentration of vitamin D is strongly related to the volume of gray matter of the hippocampus [43]. In animal studies, it was additionally indicated that vitamin D deficiency led to an increase in the volume of the brain ventricles, as well as disturbances of the mitochondrial function in the entire CNS [44]. Thus, vitamin D exerts a wide range of varied activities within the brain. The dysfunction of such activities may have serious consequences for the functioning, mood and well-being of the person affected.

However, currently available literature does not allow to clearly determine the direction of the relationship between vitamin D and symptoms of depression. Lowering of its concentration may be secondary to depressive symptoms and result from nutritional deficiencies and low exposure to the sun, to which the representatives of this group of patients are significantly predisposed. This type of secondary deficiency of vitamin D can of course lead to intensified symptoms of depression, which would explain the efficacy of supplements in clinical trials. This hypothesis is supported by the results of some prospective studies. In the publication by Almeida et al. [4] from 2015, the authors showed a significant relationship between vitamin D concentration and symptoms of depression at the time of the study (OR: 2.70; (95% CI: 1.39-5.25), $p < 0.05$). However, further observation of people with low vitamin D concentrations and without depressive symptoms showed that over 6 years of the study, the relative risk of a depressive episode was statistically insignificant and amounted to HR = 1.03 (95% CI: 0.59-1.79), pointing to the rather secondary nature of Vitamin D deficiency in patients with depression [4]. Similarly, in the Jovanova et al. [31] study from 2017, although the concentration of vitamin D at the time of the study was significantly associated with symptoms of depression (OR: 1.33, (95% CI: 1.00-1.77), $p < 0.05$), no significant association was observed in the follow-up between decreased vitamin D and depression, after both 5 years (B = 0.01, (95% CI: (-0.28) – 0.29), $p = 0.95$) and after 12 years (B = 0.05 (95 % CI: (-0.31-0.4)), $p = 0.8$). The concentration of vitamin D also did not allow prediction of the risk of diagnosis of a major depressive episode over 12 years after the study (HR = 0.95 (95% CI: 0.86-1.05), $p = 0.61$).

Among prospective research on this subject, an interesting perspective can also be provided by studies analyzing the risk of postpartum depression in women with low levels of vitamin D during pregnancy. During the described literature review, 5 such works were identified, of which four were prospective. These studies were not qualified for the review due to non-compliance with the inclusion criteria. The first of these was a publication by Nielsen et al. [45] from 2013, including 1,480 pregnant women whose vitamin D levels were measured at 23-25 weeks of pregnancy. The median concentration found for patients diagnosed with postpartum depression was 55.62 nmol/L (5.3-127.0 nmol/L; IQL: 36.9-74.6 nmol/L) and 55.6 nmol/L (5.9-227.8 nmol/L; IQL: 37.5-72.4 nmol/L) for patients

with no postpartum depression. The odds ratio of depression during the follow-up was OR = 1.12 (95% CI: 0.91 – 1.34; $p = 0.27$) for the group of patients with a concentration of <50 nmol/L (<20 ng/ml), indicating, similarly to the aforementioned studies, the lack of connection between vitamin D concentration and depression in prospective analysis. Similar results were also obtained by the team of Huang et al. [46] in 2014 on a group of 498 women whose vitamin D levels were measured at 15 weeks of pregnancy and then observation was conducted in the direction of prenatal depression. The odds ratio in this group was OR = 1.08 (95% CI: 0.56-1.43; $p > 0.05$) and was statistically insignificant, also indicating a lack of association. Interestingly, the following studies present opposite conclusions. In the analysis by Robinson et al. [47] from 2014, including 706 women, the level of vitamin D at 18 weeks of pregnancy was a predictive factor of depression appearing in the first days after delivery, with odds ratio equal to OR = 2.19 (95% CI: 1.26, 3.78; $p < 0.05$) for the group with a concentration of <20 ng/ml. Similarly, in the study of Gur et al. from 2014 for a group of 179 pregnant women, vitamin D levels below 20 ng/ml during 24-28 weeks of pregnancy were a strong predictive factor of postpartum depression during the first 7 days (OR = 2.61 (95% CI: 1.24 – 3.85), $p < 0.05$) as well as 6 months after delivery (OR = 4.35 (95% CI: 2.01-6.8), $p < 0.05$) [48].

Another aspect worthy of attention is the connection between vitamin D deficiency and occurrence of depression in the elderly population, where the risk of deficiency of this vitamin is significantly higher than in the general population [49]. Among the 24 publications qualified for this literature review, in the case of 10 of these publications the average age of patients was above 70 years. Seven of these publications presented a statistically significant link between depression and vitamin D deficiency in the elderly (n=14,404), two denied its existence (n= 276) and in the case of one publication there was a significant link in females and a lack of it in males (n=531).

Conclusions

The publications included in this review were relatively homogeneous as far as research protocols and results. Therefore, the odds ratio obtained based on these studies seems to be reliable, which in turn seems to confirm the existence of a relationship between vitamin D concentration and depression symptoms in the population without underlying somatic illness. However, current literature does not give the possibility to state explicitly what is the exact mechanism and direction of this dependency. On one hand, through acting centrally, deficiency of vitamin D may be primary and potentially play a role in the pathogenesis of depression. On the other hand, the clinical picture of mood disorders may predispose to their secondary occurrence, which of course, does not exclude the possibility that they may intensify depressive symptoms, worsening the patient's condition. In both cases, especially in the context of current studies on supplementation, the use of nutraceuticals in this group of patients under controlled vitamin D levels may show some clinical utility, both to support antidepressant treatment and to avoid possible peripheral complications of vitamin D deficiency. However, evaluation of the actual usefulness of this type of therapy requires a better understanding of the mechanisms that it can be based on. For this, further prospective studies are needed to analyze the risk of depression as-

sociated with low vitamin D levels as well as clinical trials assessing the effectiveness of supplementation versus placebo.

Bibliography

1. Poniatowska-Leszczyńska K, Małyszczak K. *Depresja a patologia osobowości w ujęciu psychodynamicznym.* Postepy Psychiatr. i Neurol. 2013; 22(3): 201–209.
2. Anglin RES, Samaan Z, Walter SD, Sarah DM. *Vitamin D deficiency and depression in adults: Systematic review and meta-analysis.* Br. J. Psychiatry. 2013; 202(2): 100–107.
3. Spedding S. *Vitamin D and depression: A systematic review and meta-analysis comparing studies with and without biological flaws.* Nutrients. 2014; 6(4): 1501–1518.
4. Almeida OP, Hankey GJ, Yeap BB, Golledge J, Flicker L. *Vitamin D concentration and its association with past, current and future depression in older men: The Health in Men Study.* Maturitas. 2015; 81(1): 36–41.
5. American Psychiatric Association: *Statistical Manual of Mental Disorders, 5th ed.* Washington, DC: American Psychiatric Association; 2013.
6. Sathyanarayana Rao T, Asha M, Ramesh B, Jagannatha Rao K. *Understanding nutrition, depression and mental illnesses.* Indian J. Psychiatry. 2008; 50(2): 77.
7. Lang UE, Beglinger C, Schweinfurth N, Walter M, Borgwardt S. *Nutritional aspects of depression.* Cell Physiol. Biochem. 2015; 37(3): 1029–1043.
8. Holick MF. *Photosynthesis of vitamin D in the skin: Effect of environmental and life-style variables.* Fed. Proc. 1987; 46(5): 1876–1882.
9. Stefanowski B, Antosik-Wójcińska A, Święcicki Ł. *Wpływ niedoboru witaminy D3 na poziom nasilenia objawów depresyjnych.* Przegląd aktualnych badań. Psychiatr. Pol. 2017; 51(3): 437–354.
10. Józefowicz O, Rabe-Jabłońska J, Bogaczewicz J, Woźniacka A. *Rola witaminy D3 w patogenezie zaburzeń psychicznych.* Psychiatr. i Psychol. Klin. 2009; 9(3): 200–206.
11. Garcion E, Wion-Barbot N, Montero-Menei CN, Berger F, Wion D. *New clues about vitamin D functions in the nervous system.* Trends Endocrinol. Metab. 2002; 13(3): 100–105.
12. Hoogendijk WJG, Lips P, Dik MG, Deeg DJH, Beekman ATF, Penninx BWJH. *Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults.* Arch. Gen. Psychiatry. 2008; 65(5): 508.
13. Johnson MA, Fischer JG, Park S. *Vitamin D deficiency and insufficiency in the Georgia Older Americans Nutrition Program.* J. Nutr. Elder. 2008; 27(1–2): 29–46.
14. Nanri A, Mizoue T, Matsushita Y, Poudel-Tandukar K, Sato M, Ohta M et al. *Association between serum 25-hydroxyvitamin D and depressive symptoms in Japanese: Analysis by survey season.* Eur. J. Clin. Nutr. 2009; 63(12): 1444–1447.
15. Stewart R, Hirani V. *Relationship between vitamin D levels and depressive symptoms in older residents from a national survey population.* Psychosom. Med. 2010; 72(7): 608–612.
16. Zhao G, Ford ES, Li C, Balluz LS. *No associations between serum concentrations of 25-hydroxyvitamin D and parathyroid hormone and depression among US adults.* Br. J. Nutr. 2010; 104(11): 1696–1702.
17. Milaneschi Y, Shardell M, Maria Corsi A, Vazzana R, Bandinelli S, Guralnik JM et al. *Serum 25-hydroxyvitamin D and depressive symptoms in older women and men.* J. Clin. Endocrinol. Metab. 2010; 95(7): 3225–3233.

18. Ganji V, Milone C, Cody MM, McCarty F, Wang YT. *Serum vitamin D concentrations are related to depression in young adult US population: The third National Health and Nutrition Examination Survey.* Int. Arch. Med. 2010; 3(1): 29.
19. Chan R, Chan D, Woo J, Ohlsson C, Mellström D, Kwok T et al. *Association between serum 25-hydroxyvitamin D and psychological health in older Chinese men in a cohort study.* J. Affect. Disord. 2011; 130(1–2): 251–259.
20. Lee DM, Tajar A, O'Neill TW, O'Connor DB, Bartfai G, Boonen S et al. *Lower vitamin D levels are associated with depression among community-dwelling European men.* J. Psychopharmacol. 2011; 25(10): 1320–1308.
21. Brouwer-Brolsma EM, Feskens EJM, Steegenga WT, De Groot LCPGM. *Associations of 25-hydroxyvitamin D with fasting glucose, fasting insulin, dementia and depression in European elderly: The SENECA study.* Eur. J. Nutr. 2013; 52(3): 917–925.
22. Kwasky AN, Groh CJ. *Vitamin D and depression: Is there a relationship in young women?* J. Am. Psychiatr. Nurses Assoc. 2012; 18(4): 236–243.
23. Black LJ, Jacoby P, Allen KL, Trapp GS, Hart PH, Byrne SM et al. *Low vitamin D levels are associated with symptoms of depression in young adult males.* Aust. N Z J. Psychiatry. 2014; 48(5): 464–471.
24. Maddock J, Berry DJ, Geoffroy MC, Power C, Hyppönen E. *Vitamin D and common mental disorders in mid-life: Cross-sectional and prospective findings.* Clin. Nutr. 2013; 32(5): 758–764.
25. Lapid MI, Cha SS, Takahashi PY. *Vitamin D and depression in geriatric primary care patients.* Clin. Interv. Aging. 2013; 8: 509–514.
26. Jääskeläinen T, Knekt P, Suvisaari J, Männistö S, Partonen T, Sääksjärvi K et al. *Higher serum 25-hydroxyvitamin D concentrations are related to a reduced risk of depression.* Br. J. Nutr. 2015; 113(09): 1418–1426.
27. Von Känel R, Fardad N, Steurer N, Horak N, Hindermann E, Fischer F et al. *Vitamin D deficiency and depressive symptomatology in psychiatric patients hospitalized with a current depressive episode: A factor analytic study.* PLoS One. 2015; 10(9): 1–15.
28. Krysiak R, Gilowska M, Okopień B. *Sexual function and depressive symptoms in young women with low vitamin D status: A pilot study.* Eur. J. Obstet. Gynecol. Reprod. Biol. 2016; 204: 108–112.
29. Moy FM, Hoe VCW, Hairi NN, Vethakkan SR, Bulgiba A. *Vitamin D deficiency and depression among women from an urban community in a tropical country.* Public Health Nutr. 2017; 20(10): 1844–1850.
30. Lee SH, Suh E, Park KC, Haam JH, Kim K, Koo HS et al. *Association of serum 25-hydroxyvitamin D and serum total cholesterol with depressive symptoms in Korean adults: The Fifth Korean National Health and Nutrition Examination Survey (KNHANES V, 2010–2012).* Public Health Nutr. 2017; 20(10): 1836–1843.
31. Jovanova O, Aarts N, Noordam R, Carola-Zillikens M, Hofman A, Tiemeier H. *Vitamin D serum levels are cross-sectionally but not prospectively associated with late-life depression.* Acta Psychiatr. Scand. 2017; 135(3): 185–194.
32. Collin C, Assmann KE, Deschasaux M, Andreeva VA, Lemogne C, Charnaux N et al. *Plasma vitamin D status and recurrent depressive symptoms in the French SU.VI.MAX cohort.* Eur. J. Nutr. 2017; 56(7): 2289–2298.
33. Sherchand O, Sapkota N, Chaudhari RK, Khan SA, Baranwal JK, Pokhrel T et al. *Association between vitamin D deficiency and depression in Nepalese population.* Psychiatry Res. 2018; 267(March): 266–271.

34. Yao Y, Fu S, Zhang H, Li N, Zhu Q, Zhang F et al. *The prevalence of depressive symptoms in Chinese longevous persons and its correlation with vitamin D status.* BMC Geriatr. 2018; 18(1): 198.
35. Shaffer JA, Edmondson D, Wasson LT, Falzon L, Homma K, Ezekoli N et al. *Vitamin D supplementation for depressive symptoms*. Psychom Med. 2014; 76(3): 190-196.
36. Gowda U, Mutowo MP, Smith BJ, Wluka AE, Renzaho AMN. *Vitamin D supplementation to reduce depression in adults: Meta-analysis of randomized controlled trials.* Nutrition. 2015; 31(3): 421–429.
37. Vellekkatt F, Menon V. *Efficacy of vitamin D supplementation in major depression: A meta-analysis of randomized controlled trials.* J. Postgrad. Med. 2019; 65(2): 74–80.
38. Khoraminya N, Tehrani-Doost M, Jazayeri S, Hosseini A, Djazayery A. *Therapeutic effects of vitamin D as adjunctive therapy to fluoxetine in patients with major depressive disorder.* Aust N Z J Psychiatry. 2013;47(3):271–5.
39. Patrick RP, Ames BN. *Vitamin D hormone regulates serotonin synthesis. Part 1: Relevance for autism.* FASEB J. 2014; 28(6): 2398–2413.
40. Kesby JP, Cui X, O'Loan J, McGrath JJ, Burne THJ, Eyles DW. *Developmental vitamin D deficiency alters dopamine-mediated behaviors and dopamine transporter function in adult female rats.* Psychopharmacology (Berl). 2010; 208(1): 159–168.
41. Eyles DW, Burne THJ, McGrath JJ. *Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease.* Front. Neuroendocrinol. 2013; 34(1): 47–64.
42. Brunoni AR, Lopes M, Fregni F. *A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: Implications for the role of neuroplasticity in depression.* Int. J. Neuropsychopharmacol. 2008; 11(8): 1169–1180.
43. Shivakumar V, Kalmady SV, Amaresha AC, Jose D, Narayanaswamy JC, Mahavir S et al. *Serum vitamin D and hippocampal gray matter volume in schizophrenia.* Psychiatry Res. 2015; 233(2): 175–179.
44. McCann JC, Ames BN. *Is there convincing biological or behavioral evidence linking vitamin D deficiency to brain dysfunction?* FASEB J. 2008; 22(4): 982–1001.
45. Nielsen NO, Strøm M, Boyd HA, Andersen EW, Wohlfahrt J, Lundqvist M et al. *Vitamin D status during pregnancy and the risk of subsequent postpartum depression: A case-control study.* PLoS One. 2013; 8(11): e80686.
46. Huang JY, Arnold D, Qiu C, Miller RS, Williams MA, Enquobahrie DA. *Association of serum vitamin D with symptoms of depression and anxiety in early pregnancy.* J. Women's Heal. 2014; 23(7): 588–595.
47. Robinson M, Whitehouse AJO, Newnham JP, Gorman S, Jacoby P, Holt BJ et al. *Low maternal serum vitamin D during pregnancy and the risk for postpartum depression symptoms.* Arch Womens Ment Health. 2014; 17(3): 213–219.
48. Gur EB, Gokduman A, Turan GA, Tatar S, Hepyilmaz I, Zengin EB et al. *Mid-pregnancy vitamin D levels and postpartum depression.* Eur. J. Obstet. Gynecol. Reprod. Biol. 2014; 179: 110–6.
49. Mosekilde L. *Vitamin D and the elderly.* Clin. Endocrinol (Oxf). 2005; 62(3): 265–281.

Address: Krzysztof Maria Wilczyński
Department of Psychiatry and Psychotherapy of Developmental Age
Medical University of Silesia in Katowice
41-218 Sosnowiec, Gabrieli Zapolskiej Street 3
e-mail: wilczynskimed@gmail.com