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Review Article

Association of Vitamin D with Suicide Behaviors: A Systematic Review and Meta-Analysis

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Abstract

Objective: Research findings on the relationship between vitamin D and suicide are not consistent; therefore, the objective of the present paper is to assess the relationship between vitamin D and suicide behaviors using a systematic review and meta-analysis.
Method: A search strategy was developed using keywords including “Vitamin D”, “Vitamin D deficiency”, “suicide” "attempted suicide", "completed suicide”, “Suicide, Attempted”, “Suicidal Ideation.” We searched databases including Scopus, Medline, Web of Science, and Google Scholar by July 7, 2022. We examined the titles, abstracts, and full texts of the articles to select eligible ones. To pool the results of the selected studies, we used the random-effect method and mean difference as the effect size. The quality of the articles was evaluated by the Newcastle-Ottawa Scale (NOS). Moreover, heterogeneity and bias of reporting were evaluated by the I^2 statistic and Egger's and Begg's tests, respectively.
Results: Out of 149 studies retrieved in the databases, 11 studies were included in the final phase. Among these, the pooled findings of seven studies included in the meta-analysis phase showed that low levels of vitamin D are related to increased probability for suicide behaviors ($P < 0.05$). Moreover, subgroup analysis showed a significant relationship between vitamin D and suicide ideation and suicide attempt ($P < 0.05$). In addition, the I^2 statistic indicated moderate heterogeneity (58%) and Egger's and Begg's tests did not show any evidence of publication bias ($P > 0.05$).
Conclusion: This study provides evidence in favor of the relationship between vitamin D and suicide behaviors. It suggests that insufficient levels of vitamin D play a role in suicidal behaviors. However, it should be noted that further and stronger evidence is needed to establish this role. Finally, incorporating vitamin D-rich foods into the diet or taking vitamin D supplements is recommended to reduce the risk of suicide.

Key words: *Mortality from Suicide; Suicide Attempt; Suicide Ideation; Systematic Review; Vitamin D*

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Suicide is a global phenomenon and an anti-social act that may cause the intentional death of a person. It poses a worldwide challenge, which accounts for approximately 1.5% of all deaths, making it one of the main causes of death (1, 2). According to the latest report, about 800000 people decease due to suicide annually (3). The evidence reveals that despite all strategies developed to reduce the suicide statistics, the rate of suicide has increased by 4% in the latest decade (3-6). Therefore, suicide and suicide attempts have remained as a health concern worldwide. Thus, it is imperative to develop novel and comprehensive strategies for effective suicide prevention in the world.

One critical step in preventing the growing frequency of suicide in the world is to identify the risk factors and causes of this phenomenon. Results of studies have indicated that suicide is an intricate behavior with various causes such as family history (7, 8), early-life adversity (9), and symptoms of psychopathology (10, 11). Other factors including drug abuse, mental disorders (particularly depression), familiarity with someone having committed suicide, social isolation, chronic diseases, and disability may remarkably increase the risk of suicide (12-14). According to a previous study, Milner *et al*. (2013) inferred that mental problems existed in most people deceased from suicide (15). Such mental problems which have led to suicide are associated with many organic pathologies (16), such as vitamin D deficiency (17).

One of the factors that its potential role in suicide has been investigated by researchers is vitamin D, which plays a main role in bodily well-being as well (17-19). Furthermore, the results of several studies have indicated that vitamin D affects brain function (20-22). It controls the transcription of more than 1,000 genes which could influence suicidal behaviors by promoting neurotrophic and neuroprotective effects (20). However, some research findings regarding the relationship between vitamin D and suicide are not completely consistent. Some inquiries have supported the association between Vitamin D and psychological disorders such as suicide. Atik *et al*. (2020) reported a relationship between prior suicide attempts, levels of vitamin D, and the presence of psychiatric diseases (17). Fond *et al.* (2019) indicated the relationship between hypovitaminosis D and the risk of suicide in schizophrenia (23). Gokalp (2020) examined the association between suicidal behaviors and vitamin D in adolescents and considered the shortage of vitamin D as one of the determinants of suicidal behavior among them (24). However, some studies do not confirm the association between vitamin D and suicide. For example, Park *et al*. (2016) did not show a relation between low vitamin D levels and suicidal ideation (25). Kim *et al*. (2020) also did not demonstrate a significant relationship between suicidal ideation and vitamin D in two groups with and without vitamin D deficiency, despite the fact that the risk of suicidal ideation can be linked to vitamin D levels (26).

The inconsistency in research findings on the relationship between suicide and vitamin D prompted us to conduct a systematic review and meta-analysis to determine the relationship between them and the sources of heterogeneity and possible publication bias.

Materials and Methods

Databases and Search Strategy

This paper was provided using PRISMA guideline. In the first step, international databases include Scopus, Medline, WOS, as well as Google Scholar were used to retrieve eligible articles. Using Mesh thesaurus, “Vitamin D”, “Vitamin D deficiency”, “suicide” "attempted suicide", "completed suicide”, “Suicide, attempted”, “Suicidal Ideation” were extracted to use in search strategy. The appropriate search strategy for each database were used as follows on July 7, 2022:

Medline: ("Vitamin D" [MeSH Major Topic] OR "Vitamin D deficiency" [MeSH Major Topic] OR "Vitamin D" [MeSH] OR "Vitamin D deficiency" [MeSH] OR "Vitamin D" [tiab] OR "Vitamin D deficiency" [tiab]) AND (suicide [MeSH Major Topic] OR suicide [MeSH] OR suicide [tiab] OR "Suicide, attempted"[Mesh] OR "Suicide, Completed"[Mesh] OR "Suicidal Ideation" [Mesh]).

Scopus: ((TITLE-ABS-KEY ("Vitamin D") OR TITLE-ABS-KEY ("Vitamin D deficiency") OR INDEXTERMS ("Vitamin D") OR INDEXTERMS ("Vitamin D deficiency") OR AUTHKEY ("Vitamin D") OR AUTHKEY ("Vitamin D deficiency")) AND (TITLE-ABS-KEY (suicide OR "attempted suicide" OR "completed suicide") OR INDEXTERMS (suicide OR "Suicide, attempted" OR "Suicide, completed") OR AUTHKEY (suicide OR "attempted suicide" OR "completed suicide") OR INDEXTERMS ("Suicidal Ideation").

Web of Science: (TS = "Vitamin D" OR TS = "Vitamin D deficiency" OR TI = "Vitamin D" OR TI = "Vitamin D deficiency") AND (TS = suicide OR TI = suicide OR TS = "attempted suicide" OR T S = "completed suicide" OR TI = "attempted suicide" OR TI = "completed suicide" OR TS = "Suicidal Ideation").

Then to find gray literature, including unpublished studies such as conference proceedings, theses and desperations, governmental reports etc., we searched Google and Google Scholar. Moreover, to increase the sensitivity of our search, we explored the reference list of the final studies which had eligibility criteria. Additionally, we did not impose any language and time limitations.

Inclusion and Exclusion Criteria

The PICOTS tool (Population, Intervention, Comparison, Outcome, Time and Study type) was used in this research, with a focus on I and O. Therefore, the inclusion criteria for our work encompassed all types of studies (including cross-sectional, cohort, and case-control) that explored the association between Vitamin D (as Intervention, in observational study is called predictor) and suicide behaviors, which include suicidal ideation, suicide

attempt, and completed suicide (as Outcome) in general population, without geographical and time limitations. Moreover, the common effect size should be the mean difference (MD). The titles and abstracts of all identified documents were evaluated by the researchers, and unrelated items were excluded. The abstracts and full texts of the remaining documents were examined to find related studies meeting the inclusion criteria.

Data Extraction

After retrieving the documents from the mentioned databases using appropriate search strategies, the selected documents were exported to Endnote. Subsequently, the title and abstract of each remaining document were independently examined by two investigators, and any unrelated documents were excluded at this step. Afterward, the full texts of the related documents were examined to extract the required data and evaluate the quality of the papers with the aim of conducting a meta-analysis. To resolve the disagreement between reviewers, a discussion was held to reach a consensus. In the next step, we made a datasheet to include the information of the selected studies. This information encompassed details such as authors' names, journal name, country of the study, sample size, type of effective size, and results obtained for each study.

Evaluation of Study Quality

The Newcastle Ottawa Statement (NOS), which includes three sections, namely selection, comparability, and outcome, was utilized to assess and allocate each article a score. Depending on the study type (cross-sectional, cohort, and case-control) a related checklist was employed. Regarding previous studies (27, 28), those studies with score 7 or higher were considered to be of high quality, while those with a score lower than 7 were regarded as low quality.

Summary Measures

In this study, we chose MD summary measure.

Synthesis of Results

To combine the results of the selected studies, we used the random-effect method. Moreover, the heterogeneity of results across studies was quantified by the I^2 statistic. This statistic categorizes heterogeneity as follows: "less than 25% = low heterogeneity", "25% to 75% = moderate heterogeneity", and "greater than 75% = high heterogeneity."

Assessing Reporting Bias

To assess the likelihood of publication bias across the studies, we used Egger's and Begg's tests. A P-value of less than 0.05 indicates the presence of reporting bias.

Ethical Considerations

The study authorized by Ethics Committee of Hamadan University of Medical Sciences (No: IR.UMSHA.REC.1400.147).

Results

The initial search in the mentioned databases using the appropriate search strategy and reference list of relevant articles led to the retrieval of 211 studies. After removing duplicate records in the Endnote software, 166 studies remained for the next phase. After screening these 166 articles by studying their titles, abstracts, and full texts, finally 11 studies were found to have the eligibility criteria. However, only seven papers were chosen for the meta-analysis. Figure 1 demonstrates the process of choosing the documents.

The descriptive characteristics of the 11 studies are presented in Table 1. Examining the type of study showed that six studies were cross-sectional and five were case-control in design. In terms of the geographical distribution of the studies, the majority of research (four studies) conducted in the USA, Turkey (two studies), and South Korea (two studies). The total sample size across all studies was 175314, with Kim *et al.*'s study (26) having the largest sample size of 157211 participants, and Postolache *et al.*'s study (29) having the smallest sample size of 30 participants. Finally, in terms of participants' sex, all studies included both men and women in their studies.

In the following, we present the output of the meta-analysis for the relationship between vitamin D and suicide behaviors.

Relationship between Vitamin D and Suicide Behaviors

As can be seen in Figure 2, seven articles that examined the relationship between vitamin D and suicide behaviors (ideation, attempts, and mortality from suicide) were included for the meta-analysis. The findings demonstrate that the level of vitamin D in persons with suicidal behavior is 0.421 ng/ml lower than that of healthy people, and this difference is statistically significant (P-value < 0.001).

Relationship between Vitamin D and Suicide Ideation

Out of seven studies, three studies investigated the average vitamin D level in individuals with and without suicide ideation. The results of the meta-analysis indicate that the average level of vitamin D in people with suicide ideation is less than those without suicide ideation (effect size = -0.06, P-value < 0.001) (Figure 3).

Regarding suicide ideation, two studies (23, 30) were not incorporated in the final phase of the meta-analysis due to the use of effect sizes other than the ones of our interest; they also included odds ratio and correlation. However, both studies found a negative relationship between vitamin D and suicide ideation.

Relationship between Vitamin D and Suicide Attempt

Three studies investigated the relationship between suicide attempts and vitamin D levels. However, the result of the meta-analysis revealed that the mean level of vitamin D among people with suicide attempts was lower than those without suicide attempts, which was statistically significant (effect size = -0.84, P-value < 0.001) (Figure 4).

Association of Vitamin D with Completed Suicide

Two studies (2, 29) investigated the association between vitamin D and completed suicide. However, due to the lack of homogeneity in effect sizes and differences in methodology, a meta-analysis was not conducted. A study by Umhau *et al*. (2013) showed that the risk of death from suicide in human's increases with a decrease in vitamin D levels (2). In another study, Postolache *et al*. (2020) reported that increased vitamin D receptor (VDR) is accompanied by reduced cathelicidin-related antimicrobial peptide (CRAMP) expression, a finding that is consistent with other studies regarding the relation between vitamin D and suicidal behaviors (29).

Quality Assessment

The results of the quality assessment based on NOS scores is presented in Table 1, indicating that the highest score belongs to Grudet *et al*.'s study (31) (score 9 out of 9) and the studies by Atik *et al*. (17) and Postolache *et al*. (29) received the lowest scores (score 6 out of 9).

Reporting Bias

The P-values for both Egger's and Begg's tests were greater than 0.05. Therefore, we may hope that no bias existed in terms of reporting in the results.

Heterogeneity

Our analysis showed that the I^2 statistic for heterogeneity was 58%, indicating a moderate degree of heterogeneity between the studies.

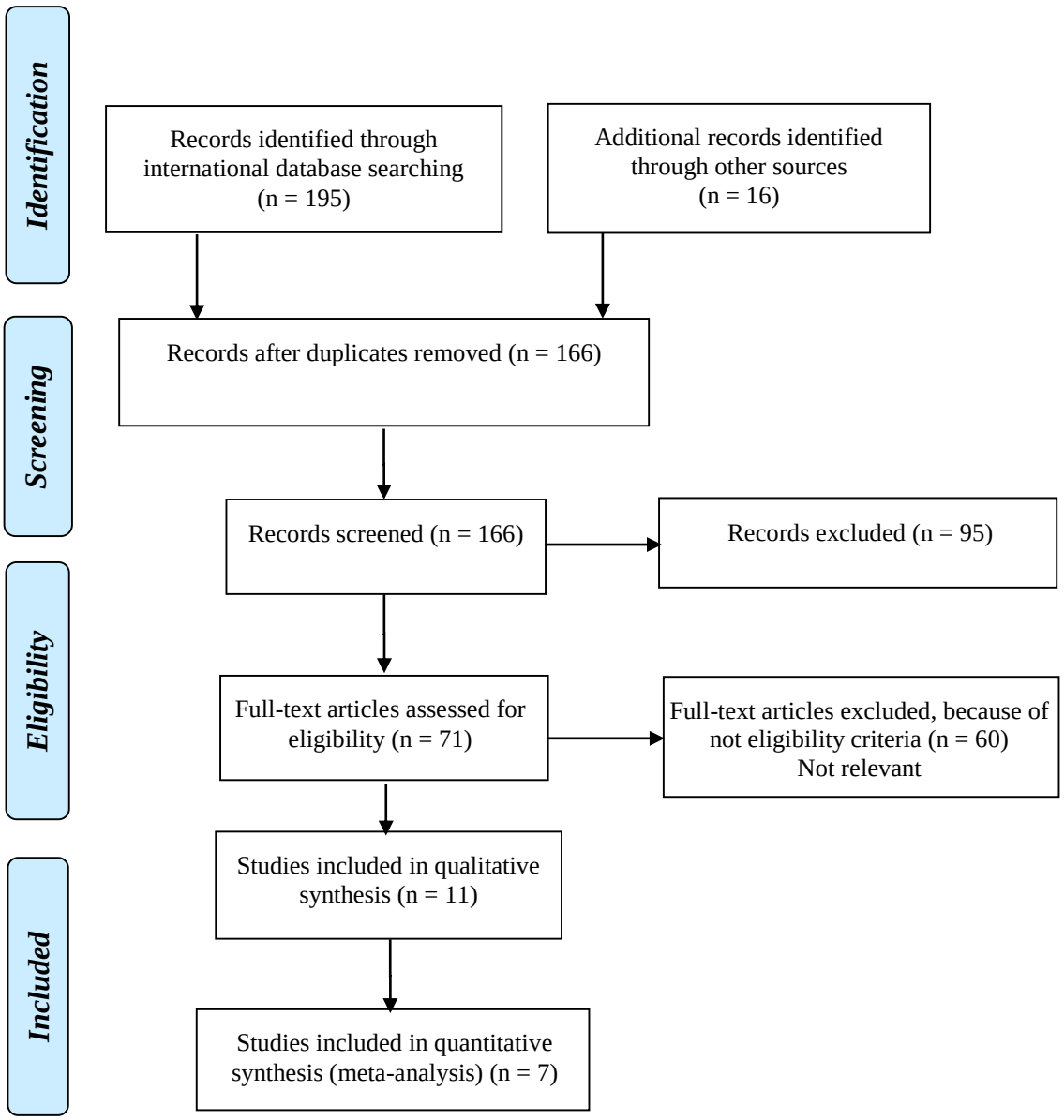

Figure 1. PRISMA Flowchart of the Search Steps to Choose Studies on Association of Vitamin D with Suicide Behaviors

Table 1. General Characteristics of the Studies that Were Eligible for Meta-Analysis

Author	Journal	Study Type	Suicidal Behavior	Country	Sex of Case Group (Percentage of Males)	Sex of Control Group (Percentage of Males)	Age of Case Group (Mean ± Standard Deviation)	Age of Control Group (Mean ± Standard Deviation)	Sample Size	Type of Effect Size	Result	Quality Score (Out of 9)
Kim *et al.* (2020) (26)	Journal of Psychosomatic Research	cross-sectional	suicidal ideation	Turkey	40.5%	62.5%	38.33 ± 7.49	39.43 ± 7.16	157,211	Mean Difference	Negative association	8 (High quality)
Grudet *et al*.(2020) (31)	Journal of Affective Disorders	cross-sectional	suicidal ideation	Sweden	47%	39%	42.1 ± 14.3	42.1 ± 14.3	102	Mean Difference	No association	9 (High quality)
Hashash *et al*. (2019) (32)	Journal of Clinical Gastroenterology	cross-sectional	suicidal ideation	Turkey	54.9%	-	42.91 ± 15.34	-	71	Mean Difference	Negative association	7 (High quality)
Nerhus *et al.* (2016) (30)	Schizophrenia Research	cross-sectional	suicidal ideation	Turkey	60.6%	-	30. ± 9.1	-	358	Correlation	Negative association	8 (High quality)
Park *et al.* (2016) (25)	The International Journal of Psychiatry in Medicine	cross-sectional	suicidal ideation	Sweden	34.8%	51.9%	49.24 ± 0.522	45.11 ± 0.249	15,695	Mean Difference	No association	8 (High quality)
Fond *et al.* (2019) (23)	European archives of psychiatry and clinical neuroscience	cross-sectional	suicidal ideation	Turkey	24.2%	37.7%	36.11 ± 10.80	35.17 ± 11.44	251	Odds Ratio	Negative association	8 (High quality)
Atik *et al.* (2020) (17)	Journal of Surgery and Medicine	case-control	suicide attempt	Turkey	35%	36.6%	30.9 ± 10.7	30.5 ± 7.84	101	Mean Difference	Negative association	6 (Low quality)
Grudet *et al.* (2014) (33)	Psychoneuroendocrinology	case-control	suicide attempt	Sweden	-	-	38 ± 14	-	90	Mean Difference	Negative association	7 (High quality)

Gokalp, G (2020) (24)	Annals of clinical psychiatry	case-control	suicide attempt	Turkey	-	-	-	-	415	Mean Difference	Negative association	7 (High quality)
Postolache *et al.* (2020) (29)	Journal of Psychiatric Research	case-control	completed suicide	USA	100%	87%	39.00 ± 3.80	36.66 ± 3.28	30	Correlation	Negative association	6 (Low quality)
Umhau *et al.* (2013) (2)	PLoS ONE	case-control	completed suicide	USA	94%	94%	28.5 ± 0.3	-	990	Mean Difference	Negative association	8 (High quality)

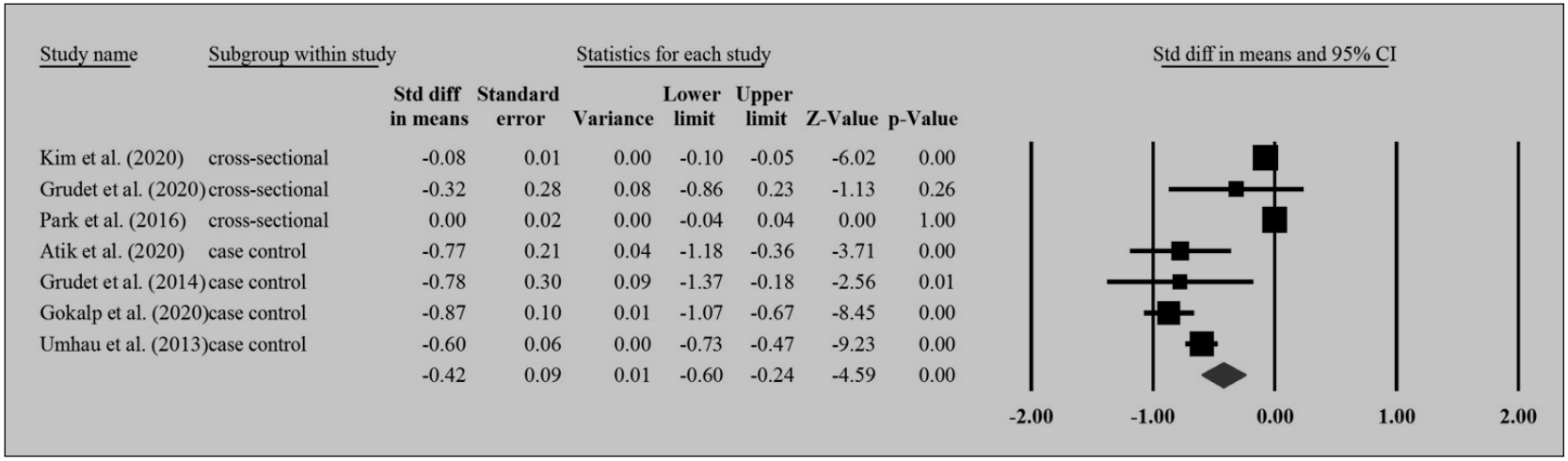

Figure 2. Forest Plot for Association of Vitamin D with Suicide Behaviors

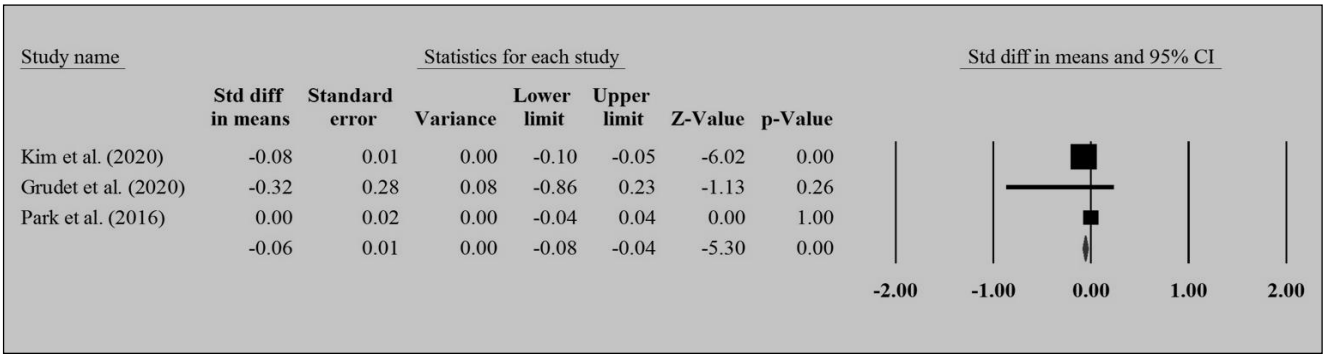

Figure 3. Forest Plot for Association of Vitamin D with Suicide Ideation

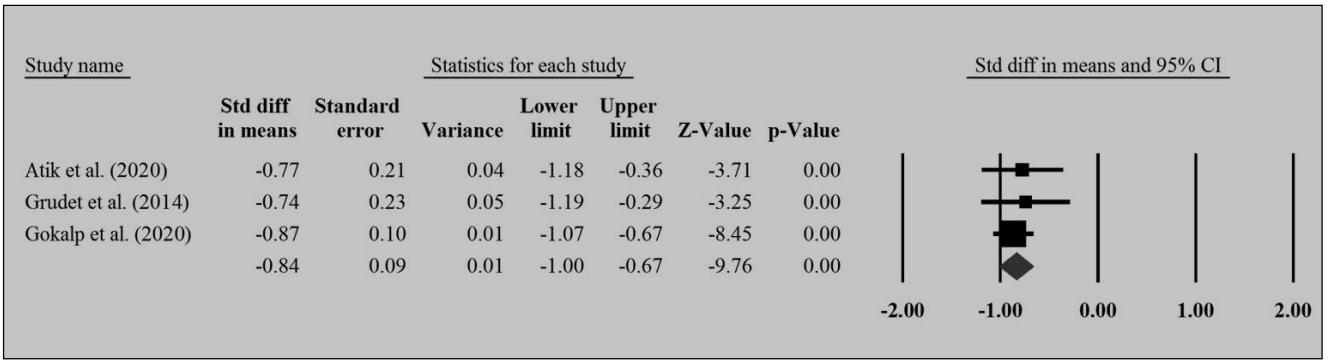

Figure 4. Forest Plot for Association of Vitamin D with Suicide Attempt

Discussion

Suicidal behavior is a growing phenomenon in many countries, and identifying risk factors among patients with suicidal behaviors is essential for managing this problem. In this meta-analysis, seven studies explored the impact of vitamin D on suicide behaviors. The results of the current research indicate that the average level of vitamin D in individuals with suicidal behavior is less than others. In other words, this study demonstrates the existence of a relationship between suicidal behavior and vitamin D, a finding that is consistent with the study by Umhau *et al*. (2013) which found that the low levels of vitamin D in active duty service members were associated with an amplified risk of suicide (2). In another study conducted by Postolache *et al*. (2020), it was found that there are associations between high amounts of VDR and reduced CRAMP expression with low vitamin D levels and suicidal behaviors (29). Another research reported that low vitamin D is related to suicide (23).

Three of the seven reviewed articles examined the relationship between suicidal ideation and vitamin D levels. Suicidal ideation happens unexpectedly, and suicide attempts often follow 10 minutes after that (17). In their research, Park *et al*. (2016) did not identify vitamin D as a determinant for suicidal ideation (25), which is consistent with our study. Shah and Gurbani (2019) indicated that vitamin D levels were lower in suicidal people compared to their control group (20).

The meta-analysis of other three studies on the relationship between suicide attempts and vitamin D indicated that those who attempted suicide had lower levels of vitamin D. Atik *et al*. (2020) concluded in their study that lower vitamin D levels were significantly related to suicide attempts. In addition, vitamin D is a fundamental element in the etiology of neuropsychiatric disorders. The risk of suicide varies among various mental disorders, with a higher risk in major depression (17). In his research, Grudet (2014) showed that the mean level of vitamin D in individuals who had attempted suicide was significantly lower than healthy individuals and non-suicidal depressed people. The prevalence of vitamin D deficiency in those individuals who attempted suicide, according to clinical standards, was 58 % (33). Recently, in a study by Gokalp (2020), the mean levels of vitamin D and calcium among adolescent participants with suicide attempts were lower compared to healthy controls (24).

Different mechanisms are proposed to explain the incidence of suicidal behavior. Some important risk factors for suicidal behaviors including stress, some infections, autoimmune disorders, anxiety (34), depression (22, 35-40) cognitive performance, psychotic-like symptoms (2), and mood disorders (20) are related to vitamin D deficiency (41). The impact of vitamin D receptor in the brain on the performance of central nervous system, as well as its influence on the size, shape,

and structure of the neonatal brain (like enlarged ventricles and cortical thinning), the expression of growth factor, and cell proliferation in animal models (17), together with the imbalance of the immune system as a risk factor for depression and specially suicidal inclinations (20) are suggested as other proposed mechanisms for the association between vitamin D and suicide behaviors. Another possible mechanism for the impact of vitamin D on suicide is related to its immune-modulatory functions. It is hypothesized that vitamin D may induce immune system attenuation by repressing the impacts of IL-2 and IFN-γ, thereby preventing the stimulation of T-cell population (42). Additionally, vitamin D probably reduces suicidal behaviors by impelling the release of corticotropin-releasing factor (CRF), vascular endothelial growth factor (VEGF), osteopontin, and anti-inflammatory pathways and hindering the release of IL-6 and TNF-α from monocytes as well as inhibiting the proinflammatory pathways, thereby controlling inflammation (43). A reduction in vitamin D causes a decrease in the expression of the CRAMP which encodes the cathelicidin antimicrobial peptide and regulates the immune system; this can increase vulnerability to infections and ultimately contribute to suicidal behaviors (29). Additionally, the reduction of vitamin D, triggered by an increase in brain inflammatory cytokines, can lead to a reduction of serotonergic activity, which may explain the increased risk of suicide, especially in the spring (2).

Limitations

We had some limitations in this study. First, we included only English language studies, which may have resulted in excluding some relevant non-English studies. Second, the number of eligible studies included in the meta-analysis was limited; thus, the statistical power could have been affected.

Conclusion

The existing evidence strongly supports the relationship between vitamin D deficiency and suicide behavior. Insufficient levels of vitamin D can contribute to the development of depressive symptoms and increase the risk of suicidal behaviors. Understanding the role of vitamin D in mental health is crucial for developing effective prevention and intervention strategies for suicide. Further research is needed to explore the underlying mechanisms and establish clear guidelines for vitamin D supplementation in individuals at risk of suicide.

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Conflict of Interest

None.

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