



Vitamin D deficiency and suicidal ideation: A cross-sectional study of 157, 211 healthy adults

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ABSTRACT

Objectives: Vitamin D deficiency has been reported to be associated with various neuropsychiatric disorders. However, there are few studies addressing deficient vitamin D levels and suicidal ideation.

Methods: Serum vitamin D of 157,211 Korean adult participants were measured using electrochemiluminescence immunoassay. A self-reported questionnaire was used to assess whether participants experienced suicidal ideation. Logistic regression model was used to estimate the odds ratio (OR) of suicidal ideation according to vitamin D levels. The regression was adjusted for a range of covariates.

Results: Compared with sufficient vitamin D levels (≥ 20 ng/mL), deficient vitamin D levels (< 10 ng/mL) were significantly associated with the risk of suicidal ideation (OR = 1.138, 95% CI = 1.027–1.262). However, the OR of suicidal ideation was not significantly different between the vitamin D insufficient group (10–19.99 ng/mL) and sufficient group (≥ 20 ng/mL) (OR = 0.988, 95% CI = 0.932–1.047).

Conclusion: Deficient vitamin D levels were significantly associated with the risk of suicidal ideation. However, the risk of suicidal ideation was not significantly different between the vitamin D insufficient group and sufficient group.

1. Introduction

Suicide is a public health concern and the leading cause of death worldwide. According to the World Health Organization (WHO), close to 800,000 people die from suicide every year, which is one person every 40 s [1]. In addition, South Korea's suicide rate is the highest in the Organization for Economic Co-operation and Development (OECD) countries [2]. By its very nature, suicide can only be prevented through appropriate interventions; therefore, suicidal ideation is an important upstream factor for determining suicidal behavior [3,4]. It may be possible to determine countermeasures for prevention of suicide by identifying and modifying various risk factors of suicidal ideation.

Recent studies have reported that short durations of sun exposure are associated with the risk of suicide, independent of the season [5];

moreover, suicide rates have been observed to peak during the spring, regardless of a prior history of mood disorders among victims [6,7]. Vitamin D levels have drawn attention as a mediator of the relationship between sun exposure and suicide [8]. Vitamin D is a fat-soluble pro-hormone occurring in two forms. Vitamin D₂ is acquired from food and through supplementation. Vitamin D₃, although available from exogenous supplementation, is produced endogenously in the epidermis when exposed to ultraviolet B (UV-B) rays of sunlight. Therefore, less sun exposure can result in decreased levels of circulating vitamin D₃ [9]. Regarding the potential roles of vitamin D as a neurosteroid, there have been many studies addressing how vitamin D differentiates brain cells, regulates axonal growth and calcium signaling in the brain, modulates the production of brain-derived reactive oxygen species, and stimulates production of neurotrophic factors—which can affect

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neuropsychiatric disorders [9]. According to a systemic review, a low vitamin D status may be associated with various risk factors related to suicide, such as medical illnesses (autoimmune disorder, fibromyalgia and malignancy) and psychiatric disorders (mood and anxiety disorders and schizophrenia) [10]. Additionally, two studies investigated the relationship of low vitamin D status and suicide. Umhau et al. reported that vitamin D deficiency was associated with an increased risk of suicide in active duty military service members [11]. Grudet et al. reported that a vitamin D deficiency in suicidal patients could be responsible for high levels of inflammatory cytokines such as Interleukin (IL)-6 and IL-1 β [12]. However, all these aforementioned studies were limited by various methodological challenges; some did not include suicidal ideation as a dependent variable [11,12], others did not exclude or control critical confounding factors like renal disease, physical activity, or seasonality [12], and still others had too small a sample size [12] and only analyzed certain subgroups [11].

Therefore, using a large sample, this study examined whether vitamin D deficiency was associated with suicidal ideation in healthy adults who did not have a chronic medical illness or psychiatric disease.

2. Methods

2.1. Study population

Our study included 168,561 Korean adults aged 18 years and older, who had visited and undertaken comprehensive health examinations at Kangbuk Samsung Hospital Health Screening Center, between 1 January 2012 and 31 December 2017. South Korea guarantees all employees free annual or biennial health examinations as per the Industrial Safety and Health Law. Therefore, over 80% of our study participants were employees in various companies and their family members. The rest were people who had undergone health examinations voluntarily.

2.1.1. Selection of a “healthy” sample

We used self-report questionnaires in health examinations in order to select healthy adults without physical or psychiatric illness. We excluded individuals who had neurovascular or neurodegenerative diseases (i.e. Alzheimer's or Parkinson's disease), because these diseases can affect suicidal ideation [13–15]. A recent systematic review addressing the relationship between inflammation and vitamin D [16] revealed that chronic inflammation causes low 25(OH)D. Therefore, we excluded participants who had inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), inflammatory bowel disease, chronic obstruction pulmonary disease (COPD), asthma, and/or psoriasis. To initiate vitamin D's metabolic action, both vitamin D₂ and D₃ should be hydroxylated twice in the liver and the kidney [9]. Based on this understanding of vitamin D's metabolism, we also excluded participants who had liver and/or chronic renal disease [17]. Additionally, individuals who had psychiatric disorders (e.g. depressive disorder, panic disorder/claustraphobia, among others) or who took psychiatric medication (e.g. antidepressants, benzodiazepine/sleeping pills among others) were excluded, because psychiatric disorders are risk factors of suicidal ideation [18]. These exclusions resulted in a total of 157,211 eligible participants (Fig. 1).

The study protocol was approved by the Institutional Review Board of Kangbuk Samsung Hospital. The requirement for informed consent was waived because we used anonymized data that were routinely collected during the health screening visits.

2.2. Measurements

2.2.1. Measurement of 25 hydroxy-vitamin D (25(OH)D) levels

In order to function as a hormone, vitamin D should be hydroxylated twice. Vitamin D is transported to the liver where it is 25-hydroxylated to form 25(OH)D, then to the kidneys to be 1- α -

hydroxylated to an active metabolite [1,25(OH)₂D]. However, studies over the past several years have reported that most other tissues, including neurons and glial cells, also possess a 1- α -hydroxylase function. Considering local production of 1,25(OH)₂D fulfills the role of paracrine function, serum 25(OH)D is the appropriate metabolite that indicates vitamin D stores, whilst serum 1,25(OH)₂D levels reveal only renal production and provide no information about actual tissue levels of 1,25(OH)₂D [10].

Blood specimens were collected after a night of fasting and centrifuged to separate sera. Analyses of serum 25(OH)D levels were done by electrochemiluminescence immunoassay (ECLIA) using Modular E170 (Roche diagnostics, Tokyo, Japan). Coefficient of variation (CV) values of low-level and high-level Quality Control (QC) materials were as follows: 3.21%–5.65% and 2.10%–4.03%, respectively. According to recent clinical guidelines [19,20], 25(OH)D levels were categorized into three groups: sufficiency (≥ 20 ng/mL), insufficiency (10–19.99 ng/mL) and deficiency (< 10 ng/mL).

2.2.2. Assessment of suicidal ideation

Self-reported questionnaires, which are a part of the Korea National Health and Nutrition Examination Survey (KNHANES), were used to assess whether participants experienced suicidal ideation [21]. The KNHANES is conducted annually by the South Korean government to analyze the level of public health and to compile relevant statistics for implementing and evaluating public health policies. Participants were asked a yes-or-no question regarding whether they had ever seriously thought of committing suicide in the past year (“Over the last year, have you ever felt that you would be better off dead?”). Answers in the affirmative were taken to indicate suicidal ideation.

2.2.3. Potential confounding variables

Information about age, sex, center (Seoul or Suwon), marital status, education, income, alcohol consumption and smoking status were collected using the self-reported questionnaires. The Korean version of the Alcohol Use Disorders Identification Test (AUDIT) was used to assess participants' alcohol consumption [22]. Since vitamin D levels also depend on the duration of sun exposure, information about the season when the data were acquired, were included as a covariate [8]. Physical inactivity can also decrease opportunities of sunlight exposure, hence we also adjusted for the amount of physical activity [23]. Additionally, current studies have reported a bi-directional relationship between vitamin D deficiency and obesity [24]. Considering obesity as a causal factor, low sun exposure due to a sedentary lifestyle, vitamin D sequestration in adipose tissue, and volumetric dilution of vitamin D levels in the large fat mass, may also result in a low vitamin D status. On the other hand, the expression of both vitamin D receptors and enzymes responsible for vitamin D metabolism in adipocytes depicted a role for the low vitamin D deficiency [24]. Therefore, we controlled for Body Mass Index (BMI). Additionally, depressive and anxiety symptoms were included as covariates, as they can affect suicidal ideation [18]. Lastly, since a current systematic review study has reported that low levels of 25(OH)D are a consequence of chronic inflammation, we also adjusted for C-reactive protein levels [16].

2.3. Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics according to suicidal ideation. The *t*-test and chi-square tests were used to examine differences between participants with suicidal ideation and without suicidal ideation by categorical and continuous vitamin D levels. Logistic regression was used for calculating the odds ratio (OR) for suicidal ideation by categorical and continuous levels of serum vitamin D levels, with adjustments for age, sex, center (Seoul or Suwon), marital status, education, income, alcohol consumption, smoking status, season of data collection, amount of physical activity, BMI, BAI score, CES-D score and CRP levels. The statistical analyses

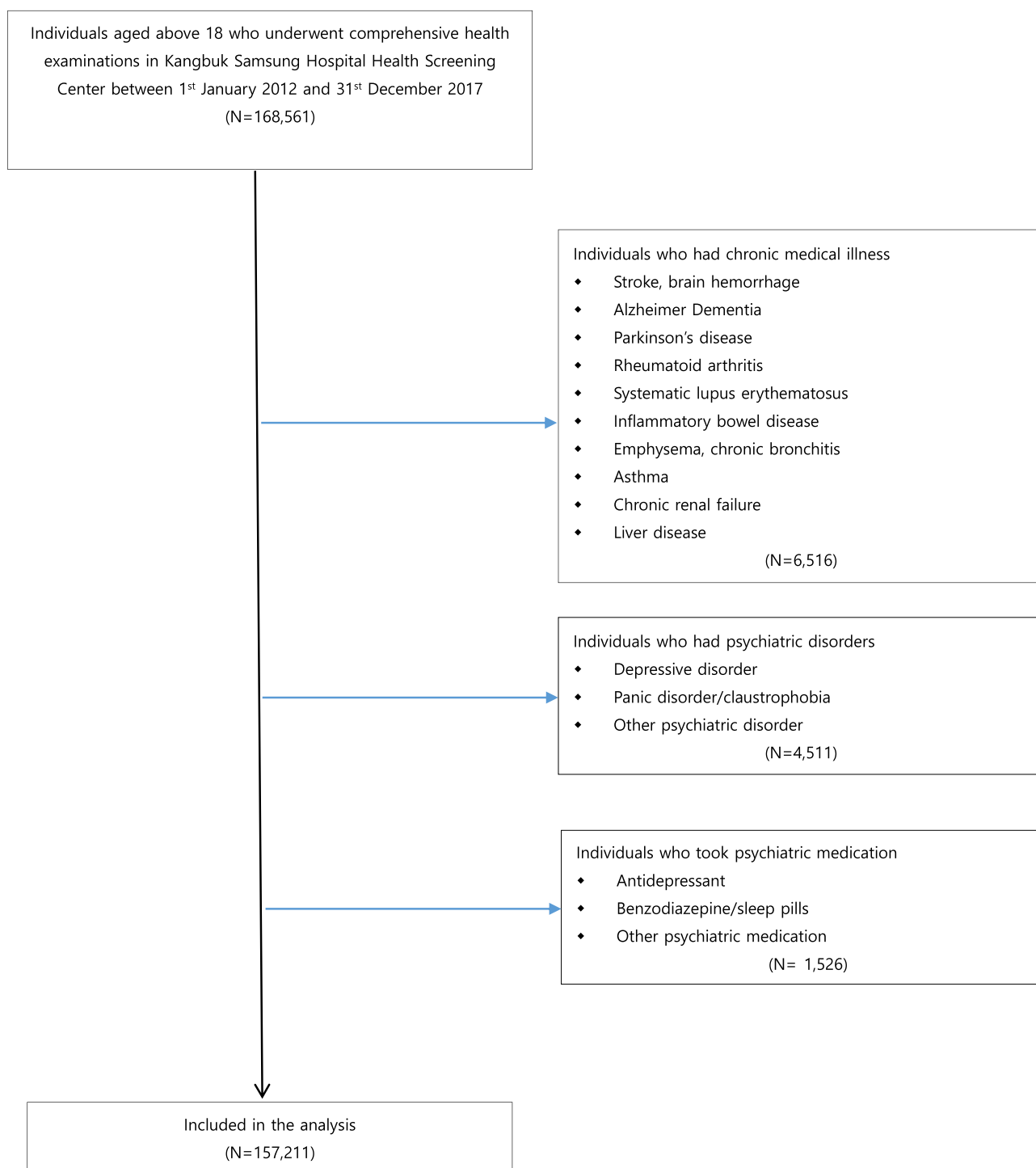


Fig. 1. Overview of the participants.

were performed using STATA version 14.0 (StataCorp LLC, College Station, TX, USA). All *p*-values were two-tailed. The *p*-values of < 0.05 were considered statistically significant.

3. Results

Table 1 summarizes the characteristic of participants. Among 157,211 participants, 6661 (4.2%) experienced suicidal ideation and 150,550 (92.5%) did not. The mean ages were 38.33 ± 7.49 years and 39.43 ± 7.16 years of the participants with suicidal ideation and the control group, respectively. Individuals with suicidal ideation

accounted for 2702 (2.8%) of 96,772 men and 3959 (6.6%) of 60,439 women. Participants with suicidal ideation were more likely to visit a health screening center in Seoul, have a lower education and income level, and higher AUDIT, CES-D and BAI scores. Participants without suicidal ideation were more likely to be married and smokers. As shown in Table 2, the mean level of vitamin D was lower in the suicidal ideation group than in the control group (19.94 ± 8.19 vs. 19.27 ± 8.49 ng/mL, $p < .001$). There were differences in the proportions of individuals with vitamin D sufficiency, insufficiency, and deficiency between suicidal ideation and non-suicidal ideation groups ($p < .001$).

Table 1
Sociodemographic characteristics of participants.

	Without suicidal ideation (n = 150,550)	With suicidal ideation (n = 6661)	P
	mean ± sd or n(%)	mean ± sd or n(%)	
Age (years)	39.43 ± 7.16	38.33 ± 7.49	< 0.001
Sex			
Male	94,070 (62.48)	2702 (40.56)	< 0.001
Female	56,480 (37.52)	3959 (59.44)	
Center			
Seoul	63,044 (41.88)	2888 (43.36)	0.017
Suwon	87,506 (58.12)	3773 (56.64)	
Marital status			
Never married	20,115 (13.36)	1015 (15.24)	< 0.001
Married	128,946 (85.65)	5494 (82.48)	
Others	1489 (0.99)	152 (2.28)	
Education			
Less than middle school degree	656 (0.44)	74 (1.11)	< 0.001
High school degree	21,160 (14.06)	1292 (19.40)	
College degree or higher	128,734 (85.51)	5295 (79.49)	
Income			
< \$4000/month	22,901 (15.21)	1351 (20.28)	< 0.001
≥ \$4000/month	98,845 (65.66)	3826 (57.44)	
Others	28,804 (19.13)	1484 (22.28)	
AUDIT	6.49 ± 5.08	6.99 ± 6.07	< 0.001
Smoking status			
Never smoker	82,229 (54.62)	4349 (65.29)	< 0.001
Former smoker	43,686 (29.02)	1339 (20.10)	
Current smoker	24,635 (16.36)	973 (14.61)	
Season when data acquired			
Spring	43,688 (29.02)	2007 (30.13)	< 0.001
Summer	50,618 (33.62)	2113 (31.72)	
Fall	37,108 (24.65)	1580 (23.72)	
Winter	19,136 (12.71)	961 (14.43)	
Physical activity (MET-min/wk)	1438.56 ± 2453.62	1430.41 ± 2972.22	0.83
BMI	23.92 ± 3.46	23.41 ± 3.74	< 0.001
CES-D	9.54 ± 5.04	17.82 ± 8.86	< 0.001
BAI	4.07 ± 5.13	11.83 ± 8.69	< 0.001
CRP			0.67
Low, ≤ 3 mg/L	150,252 (99.80)	6650 (99.83)	
High, > 3.01-10 mg/L	298 (0.20)	11 (0.17)	

AUDIT: Alcohol Use Disorders Identification Test, BMI: Body Mass Index, CES-D: Center for Epidemiologic Studies Depression Scale, BAI: Beck Anxiety Inventory, CRP: C-reactive protein.

Table 3 shows the association between serum vitamin D levels and the presence of suicidal ideation in general adults. After adjustment for a range of confounding variables, including CRP levels, those who had vitamin D deficiency (25(OH)D, < 10 ng/mL) had a 13.8% (OR = 1.138, 95% CI = 1.027–1.262) increased odds of the risk of suicidal ideation, compared with those who had vitamin D sufficiency (25(OH)D, ≥ 20 ng/mL). However, the OR of suicidal ideation was not significantly different between the vitamin D insufficient group (25(OH)D, 10–19.99 ng/mL) and sufficient group (25(OH)D, ≥ 20 ng/

Table 2
The levels of total vitamin D according to suicidal ideation.

	Without suicidal ideation (n = 150,550)	With suicidal ideation (n = 6661)	P
Total vitamin D			
Categorical level, No.(%)			
Sufficiency, ≥ 20 ng/mL	64,025 (42.53)	2584 (38.79)	< 0.001
Insufficiency, 10–19.99 ng/mL	76,507 (50.82)	3443 (51.69)	
Deficiency, < 10 ng/mL	10,018 (6.65)	634 (9.52)	
Continuous level, mean ± sd, ng/mL	19.94 ± 8.19	19.27 ± 8.49	< 0.001

mL). Additionally, there was no statistically significant relationship between continuous vitamin D levels and the risk of suicidal ideation.

4. Discussion

Results showed that vitamin D deficiency was associated with the risk of suicidal ideation. Compared with the vitamin D sufficiency group, the vitamin D insufficiency group was not significantly associated with the risk of suicidal ideation, and continuous vitamin D levels were also not significantly associated with the risk of suicidal ideation. These results indicate that serum levels of vitamin D do not strongly impact on suicidal ideation when it is at an optimal or sub-optimal status. Additionally, our study included mostly young healthy adults who had undergone health examinations; individuals who had medical illnesses and/or psychiatric disorders, which can affect vitamin D levels and suicidal ideation, were excluded. These findings may explain the relatively weak association between vitamin D levels and suicidal ideation.

Several studies have suggested a set of plausible neurobiological mechanisms explaining the relationship between vitamin D deficiency and suicidal ideation. First, there is the pattern of vitamin D receptors (VDRs) and 1- α -hydroxylase distribution in the human brain, suggesting that D-VDR systems may have autocrine and paracrine functions [25]. The presence of VDRs in the hippocampus, cortex and limbic systems supports the functional role of vitamin D in emotional processing, impulse control, and cognitive functions [26]. Therefore, neuropsychiatric symptoms related to affective, impulsive, and cognitive functions, can increase the risk of suicidal ideation. Second, increased inflammation from vitamin D deficiency may be a risk factor of suicidal ideation. According to a recent systemic review [27], vitamin D and VDR signaling together have a suppressive role on autoimmunity and an anti-inflammatory effect; they promote dendritic cell and regulatory T-cell differentiation while reducing T helper Th17 cell responses and inflammatory cytokines. Meanwhile, there is a growing body of evidence showing that inflammation can contribute to the pathophysiology of suicide by promoting hypothalamic pituitary adrenal (HPA) axis dysregulation and N-Methyl-D-aspartate (NMDA) stimulation, and also depleting serotonin [28]. Therefore, a low vitamin D status can increase inflammation, which negatively impacts suicide. To identify whether inflammatory markers act as mediators between vitamin D deficiency and suicidal ideation or not, this study adjusted for CRP levels. However, in our final model, the OR of suicidal ideation was not virtually changed. On the other hand, since there are a number of inflammatory cytokines, such as interleukin (IL)-2, IL-6, IL-1 β , and tumor necrosis factor (TNF)- α [12,27], future studies should include various inflammation markers as mediators. Third, vitamin D status is associated with various neurotransmitters including dopamine, gamma-aminobutyric acid (GABA) and serotonin [29]. Vitamin D is involved in the release of dopamine and serotonin through the regulation of dopamine-related genes and tryptophan hydroxylase 2 (TPH2), respectively [29–31]. Vitamin D can also augment glutamate decarboxylase (GAD) 65 and GAD 67, enzymes that synthesize GABA from glutamate [29]. These neurotransmitters are related to various neuropsychiatric symptoms such as anxiety, depression, and attention deficit, all of

Table 3
Association between serum vitamin D levels and the presence of suicidal ideation in general adults.

Total vitamin D	Model 1 ^a		Model 2 ^b		Model 3 ^c		Model 4 ^d	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Categorical level								
Sufficiency, ≥ 20 ng/mL	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Insufficiency, 10–19.99 ng/mL	1.000 (0.949–1.054)	1.00	1.008 (0.955–1.064)	0.78	0.988 (0.932–1.047)	0.68	0.988 (0.932–1.047)	0.68
Deficiency, < 10 ng/mL	1.197 (1.093–1.311)	< 0.001	1.207 (1.098–1.327)	< 0.001	1.139 (1.027–1.262)	0.014	1.138 (1.027–1.262)	0.014
Continuous level, ng/mL	0.998 (0.995–1.001)	0.27	0.998 (0.995–1.001)	0.17	0.999 (0.996–1.002)	0.54	0.999 (0.996–1.002)	0.54

CI: confidence interval, AUDIT: Alcohol Use Disorders Identification Test, BMI: body mass index, BAI: Beck Anxiety Inventory, CES-D: Center for Epidemiologic Studies Depression Scale.

^a Model 1 was adjusted for age, sex.

^b Model 2 was adjusted for age, sex, center (Seoul or Suwon), marital status, education, income, AUDIT, smoking status, season when data acquired, amount of physical activity, BMI.

^c Model 3 was adjusted for age, sex, center (Seoul or Suwon), marital status, education, income, AUDIT, smoking status, season when data acquired, amount of physical activity, BMI, CES-D, BAI.

^d Model 4 was adjusted for age, sex, center (Seoul or Suwon), marital status, education, income, AUDIT, smoking status, season when data acquired, amount of physical activity, BMI, CES-D, BAI, CRP levels.

which can contribute to the development of suicidal ideation.

4.1. Strengths and limitations

There are several limitations in our study. First, our study used a cross-sectional design. Therefore, there was no evidence of a temporal relationship between a risk factor and outcome, which can overestimate the association between vitamin D status and the risk of suicidal ideation. Second, since self-reported questionnaires were used to identify whether participants experienced suicidal ideation or not, the results of our study can be affected by response bias. Third, we only measured suicidal ideation as an outcome. Even if suicidal ideation is a distinct risk factor of suicide, information on suicidal behavior or actual suicide may be more desirable in investigating the association between vitamin D status and suicide. Fourth, our study included relatively healthy young adults, which may impede the generalizability of the results. Fifth, certain important covariates were missing from this study, including if participants were taking some food or oral supplements related vitamin D and participants' living region. Our study also has several strengths. First, a large sample was used, making our results more representative of Korean adults. Second, we included many confounding factors related to vitamin D levels and suicidal ideation. Therefore, we attempted to reduce the possibility that an actual association is masked or falsely demonstrated. Third, our study conducted an additional subgroup analysis to identify whether there is any association between vitamin D levels and suicidal ideation in depressed or anxious participants.

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Declaration of Competing Interest

The authors report no conflicts of interest.

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