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Association between serum vitamin D and depressive symptoms in apparently healthy male adults undergoing routine health check-ups at a single centre

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Abstract

Objective: To determine the level of vitamin D and to identify the association between vitamin D and depressive symptoms in apparently healthy Korean male adults.

Design: A retrospective study design. Among 43 513 participants between 1 March and 30 November 2018, after eliminating participants with a history of depression or vitamin D deficiency, 9058 were included. To determine the level of vitamin D, serum 25-hydroxyvitamin D [25(OH)D] was measured. To assess the level of depression, the Korean version of the Center for Epidemiologic Studies Depression Scale (CES-D) was used.

Setting: South Korea.

Participants: Male adults who underwent routine health check-ups.

Results: The average vitamin D level was 22·31 ± 7·09 ng/ml as 25(OH)D, while the number of subjects in the vitamin D insufficiency group with a finding of <20 ng/ml was 3783 (41·8 %). The mean CES-D score in all subjects was 8·31 ± 5·97 points, and the proportion of the depressive symptoms group with a score of ≥16 was 8·71 %. The OR of patients in the depressive symptoms group also being in the insufficiency group was found to be 1·49 (95 % CI 1·12, 2·00).

Conclusions: A total of 41·8 % of apparently healthy male adults had vitamin D levels <20 ng/ml. We identified an association between vitamin D insufficiency and depressive symptoms in apparently healthy Korean male adults.

Keywords
Vitamin D
Depression
Male adult
Routine health check-ups

Vitamin D is well known for its important role in maintaining the balance of calcium and phosphorus for bone and mineral metabolism[1]. It is activated in the skin through sun exposure, promotes the absorption of calcium and phosphorus in the intestine and maintains an adequate concentration of these minerals in the circulation to allow for normal bone mineralisation[1]. Recently, many studies have reported non-skeletal actions on cell proliferation and differentiation[2], immune regulation[3], anti-tumour activity[4] and muscle function[5] associated with vitamin D. Additionally, since it has been suggested that vitamin D deficiency or insufficiency is associated with an increased risk of non-skeletal health conditions, including cardiovascular diseases such as elevated blood pressure[6], diabetes mellitus[7], obesity[8], infections[9] and autoimmune diseases[10], the importance of vitamin D has gained increasing attention. Also, vitamin D insufficiency is known to be associated with sexual dysfunction in apparently healthy women and with erectile dysfunction in men[11].

According to a study performed using the data of the Korea National Health and Nutrition Examination Survey (KNHANES), there was a significant trend towards lower serum hydroxyvitamin D [25(OH)D] levels in male adults by −1·2 nmol/l per year and in female adults by −0·7 nmol/l per year from 2008 to 2014[12]. Furthermore, the overall mean serum level of 25(OH)D decreased from

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53·0 to 43·2 nmol/l in male adults and from 45·7 to 39·2 nmol/l in female adults during the survey. Because of this reduction, a significant increasing trend of vitamin D deficiency, defined as a serum 25(OH)D level <50 nmol/l, was also observed, and the prevalence of vitamin D deficiency rose from 51·8 to 75·2 % in male adults and from 68·2 to 82·5 % in female adults during the survey[12]. At this point, while the attention being paid to the importance of vitamin D is indeed increasing, the problem of vitamin D deficiency among Koreans is clearly severe.

Depression is one of the most prevalent diseases worldwide[13], with the WHO reporting depression to be the single largest contributor to non-fatal health loss worldwide, and the proportion of the global population with depression was estimated to be 4·4 % in 2015[14,15]. According to the Korea Health Statistics in 2017, the overall prevalence of depressive symptoms, defined as feelings of sadness or despair affecting daily activities for two or more consecutive weeks in the past year before the survey, was 11·2 % among participants >19 years of age[16]. Beginning in 2001, epidemiological surveys on mental disorders in Korea have been conducted every 5 years by the Ministry of Health and Welfare, which reported a gradually increasing lifetime prevalence of major depressive disorder (2001, 4·0 %; 2006, 5·6 %; 2011, 6·7 %)[17]. Depression-induced work absenteeism, loss of work productivity, decreases in work competence and increases in health-related expenditures are also serious social problems[18], suggesting that depression is not only a mental burden for one individual but also a public health problem with respect to health promotion and management. Additionally, prior research studies have consistently demonstrated that depression increases the risk for suicidal ideation[19,20]. Although a national suicide prevention programme was implemented in the early 2000s, suicide remains the fifth most common cause of death among Korean adults as of 2017[21]. Based on this, Korea ranks second among the Organisation for Economic Cooperation and Development countries, with a suicide rate of 24·3 per 100 000 people, which is especially higher among male than female adults (34·9 *v.* 13·8 per 100 000 people)[21]. As vitamin D has been reported to be associated with specific cognitive and mood functions, it is also known to be linked with depression[22]. The high prevalence of serum vitamin D deficiency in Korean male adults[23], the increasing prevalence of depressive disorders in Korea[24] and the higher incidence of suicides among male than female adults[21] are all latent problems in the health management of Koreans. Also, few published studies have investigated the association between serum vitamin D and depressive symptoms in Korean subjects. Consequently, the present study aimed to determine the level of serum vitamin D and to identify the association between serum vitamin D and depressive symptoms in apparently healthy Korean male adults using the data from routine health check-ups.

Materials and methods

Study design and population

This cross-sectional study was conducted using the data collected from routine health check-ups under the guidance of the National Health Insurance Service (NHIS) at a single university hospital between 1 March and 30 November 2018. Nowadays, active health management at the prevention level is required for the promotion of health of Koreans, considering the increasing diversification of diseases, falling birth rates and the aging society. Based on this consideration, the NHIS actively promotes adherence to routine health check-ups in an effort to detect diseases early and enhance public health accordingly. Therefore, it is recommended that routine health check-ups be performed biannually for employee subscribers and regional insurance subscribers, and annually for non-office workers. The format of interviews about participants' lifestyles used in routine health check-ups was designed by the NHIS institutional review board (IRB).

General characteristics

The surveys include well-established questionnaires to identify the demographic and socioeconomic characteristics of participants, with questions covering topics such as sex, age, marital and employment status, education level, residential area, past and present medical history, family history regarding any type of cancer, alcohol consumption status (frequency of drinks and total amount per week), smoking status, daily number of cigarettes smoked, level of vigorous exercise, level of stress and sleep satisfaction. Study subjects were classified into a risky drinking group if they consumed ≥5 alcoholic drinks at least twice a week according to the risky drinking classification of KNHANES[25]. Self-reported smoking status was divided into three categories: current, ex-smoker and non-smoker. Respondents who reported having consumed ≥100 cigarettes in their lifetime were regarded as current smokers, based on a 'yes' response to the question 'do you smoke cigarettes now?', while ex-smokers were classified based on a 'no' response to the same question[25]. Respondents who had consumed <100 cigarettes in their lifetime were regarded as non-smokers according to the definition of smoking status by KNHANES[25]. The subjects were divided into a regular exercise group that exercised at least three times a week, regardless of the intensity[25].

Routine laboratory tests

All participants underwent routine evaluations of height, weight and BMI, blood pressure check, visual and auditory acuity tests, chest X-ray, electrocardiography, laboratory tests (i.e. complete blood count and levels of creatinine, glucose, cholesterol, TAG, alanine aminotransferase, aspartate aminotransferase and γ-glutamyl transferase), dental inspection and urinalysis. BMI was categorised into

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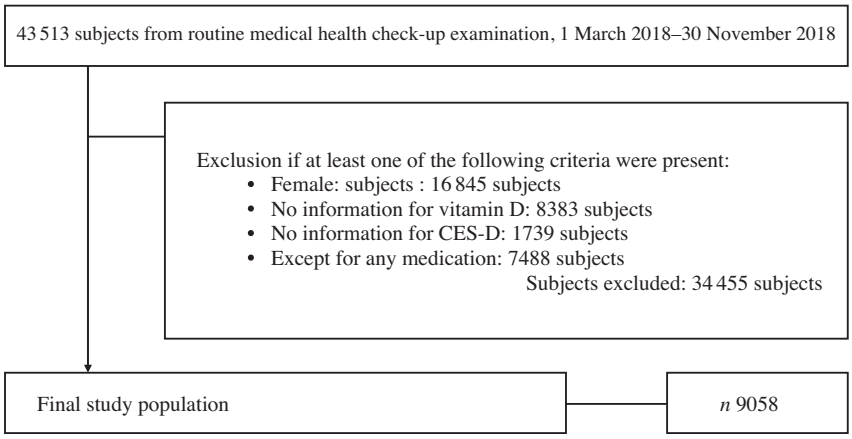

Fig. 1 Flowchart of participants included in this study

four groups: underweight (<18·5 kg/m^2), normal weight (18·5–22·9 kg/m^2), overweight (23–24·9 kg/m^2) and obese (≥25 kg/m^2) according to the WHO criteria for the Asia-Pacific region[24]. Seated BP was measured using a standardised automated oscillometric device after a 5-min rest period and, if initially abnormally high or low, checked again with a mercury sphygmomanometer by a trained nurse. Routine health check-ups were 100 % paid for by the corporation. Additionally, several specific tests, including CT, ultrasonography and echocardiography, were offered to individuals who could pay for it out-of-pocket. This is a unique medical phenomenon of South Korea under the NHIS. We excluded subjects who had been previously diagnosed or treated for any kinds of diseases, including either depressive disorder or vitamin D deficiency (Fig. 1).

Measurement of serum vitamin D

It is widely acknowledged that circulating 25(OH)D is the best indicator of vitamin D status[26]. To determine the level of serum vitamin D, serum 25(OH)D samples were cryopreserved and measured by electrochemiluminescence immunoassay using the Modular E (Hitachi Co.) device. Numerous scientific organisations have developed recommendations for vitamin D supplementation and guidance on optimal serum 25(OH)D concentrations. While the bone-centric guidelines recommend a target 25(OH)D concentration of 20 ng/ml (50 nmol/l), the guidelines focusing on the pleiotropic effects of vitamin D suggest a target 25(OH)D concentration of 30 ng/ml (75 nmol/l)[27]. Upon applying the serum vitamin D criteria used in a previous study[28] (deficiency defined as <10 ng/ml, insufficiency defined as 10–20 ng/ml, and optimal level defined as ≥20 ng/ml), the subjects were classified into lower and higher groups relative to the standards of insufficiency defined as 20 ng/ml in previous studies[27,28].

Level of depression

To assess the level of depression, the Korean version of the Center for Epidemiologic Studies Depression Scale (CES-D) was used. CES-D measures the current level of depressive symptomatology in the general population and boasts excellent sensitivity and reliability as a tool for diagnosing depression; it is, therefore, one of the most frequently used self-report depression scales developed by the US National Institutes of Mental Health[29]. CES-D contains a total of twenty items rated on a four-point Likert scale, ranging from 0 to 3 points according to the frequency of a given depressive symptom experienced during the past week. The Korean version of CES-D has adequate test–retest reliability, internal consistency and concurrent validity, and requires approximately 4–5 min to complete[30]. Total scores range from 0 (lowest) to 60 (highest) points, and patients are categorised into one of the following four groups: not depressed (0–9 points), mildly depressed (10–15 points), moderately depressed (16–24 points) and severely depressed (>25 points). The cut-off values are usually 16 and 25 points, with 16 points suggesting probable depression and 25 points suggesting definite depression[30,31]. Because the standard cut-off point of ≥16 points has been used to classify patients with depressive symptoms[31], in this study, the cut-off value of 16 points was used to divide the subjects into either a group with a score <16 points, or a group with a score ≥16 points.

Data analysis

Clinical data were presented using descriptive statistics, including mean, standard deviation, range, median, minimum and maximum, and percentage. While the independent *t* test was used to determine the average serum vitamin D level according to the variables, the χ^2 test was applied to elucidate the difference in the distribution of serum vitamin D according to the variables. To investigate the influence of the variables associated with a significant difference in the distribution of the depressive symptoms group, univariate logistic regression analysis was conducted. After controlling for variables with significant correlation, a multivariate logistic regression analysis was conducted. Statistical analysis was conducted using the

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Table 1 Serum vitamin D levels as well as percentage of population by categories of general characteristics

	Vitamin D (ng/ml)						
			<20 (*n* 3783)		≥20 (*n* 5275)		
	Mean	SD	*n*	%	*n*	%	*P*-value*
Age							
<30	19·67	6·80	257	61·3	162	38·7	<0·001
30–39	20·96	6·55	1117	49·4	1145	50·6	
40–49	22·59	7·08	1783	40·2	2650	59·8	
50–59	23·59	7·25	607	33·4	1212	66·6	
≥60	26·74	7·94	19	15·2	106	84·8	
Smoking							
Non-smoker	21·73	7·38	1243	45·6	1485	54·4	<0·001
Ex-smoker	22·87	7·03	1155	40·4	1701	59·6	
Current smoker	22·33	6·72	1385	39·9	2089	60·1	
Risky drinking†							
No	21·97	7·23	1996	43·2	2621	56·8	0·004
Yes	22·63	7·18	1787	40·2	2654	59·2	
BMI (kg/m^2)							
<18·5	21·40	7·70	36	48·0	39	52·0	0·036
18·5–22·9	22·67	7·47	1025	40·2	1520	59·8	
23–24·9	22·52	7·31	1050	41·2	1529	58·8	
≥25	21·95	6·60	1672	43·3	2187	56·7	
Marital status							
Married	23·44	6·98	3145	41·2	4486	58·8	<0·001
Unmarried	20·44	6·56	533	59·8	358	40·2	
Others‡	22·91	8·49	105	44·5	131	55·5	
Regular exercise							
No	21·58	6·60	1030	43·6	1332	56·4	0·035
Yes	22·64	7·18	2753	41·1	3943	58·9	

*Calculated by χ^2 test.
†Risky drinking: two or more times per week and seven or more glasses each time.
‡Others: widower, separated, divorced.

Statistical Package for the Social Sciences, version 21.0 (IBM Corp.). For all analyses, *P*-values were two-tailed. A *P*-value <0·05 was considered statistically significant, and the CI was set at 95 %.

Results

Figure 1 reveals the flowchart for persons included in this study. Among the 43 513 participants, considering the exclusion criteria, the total number of subjects deemed apparently healthy was 9085, and their mean age was 43·42 ± 8·03 years. Among the participants, 38·4 % were current smokers, 49·0 % were high-risk drinkers, 12·4 % were single and 73·9 % performed regular exercise (at least three times per week). In terms of BMI, 0·8 % of subjects were underweight, 28·0 % were within the normal range, 28·4 % were overweight and the remaining 42·5 % were obese (Table 1).

Serum vitamin D level of subjects

The average serum vitamin D level of the whole group of subjects was 22·31 ± 7·09 ng/ml. Subjects in the insufficiency group (*n* 3783; 41·8 %) – that is, those with a level <20 ng/ml – constituted a smaller proportion than did those (*n* 5275; 58·2 %) demonstrating a level ≥20 ng/ml. The average serum vitamin D level by age was 19·67 ± 6·80 ng/ml for those aged <30 years and 26·74 ± 7·94 ng/ml for those aged ≥60 years. While the proportion of subjects with vitamin D insufficiency was higher than those with vitamin D sufficiency for subjects <30 years of age, the proportion of subjects with vitamin D sufficiency was not only higher than those with vitamin D insufficiency but also increased as age advanced (Table 1). Current smoking, risky drinking, marital status, regular exercise and BMI also had significant relationships with the distribution of serum vitamin D sufficiency between the groups (Table 1).

Distribution of depressive symptoms according to general characteristics and serum vitamin D level

The mean CES-D score for all the subjects was 8·31 ± 5·97 points, and the proportion of subjects scoring ≥16 points was 8·7 % (*n* 789). The average CES-D score by age was 10·32 ± 6·08 points for those aged <30 years and 6·62 ± 5·03 points for those aged ≥60 years, and the proportion of depressed subjects decreased as age increased (Table 2). Thus, the distribution of subjects showing depressive symptoms was significantly skewed towards those aged <30 years compared with those aged ≥30 years ($P < 0·001$). When we performed a subgroup analysis by

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Table 2 CES-D as well as percentage of population by categories of general characteristics

	CES-D						
			<16 (*n* 8269)		≥16 (*n* 789)		
	Mean	SD	*n*	%	*n*	%	*P*-value*
Age							
<30	10·32	6·08	360	85·9	59	14·1	<0·001
30–39	9·49	5·92	2028	89·7	234	10·3	
40–49	8·03	6·00	4059	91·6	374	8·4	
50–59	7·18	5·60	1702	93·5	117	6·5	
≥60	6·62	5·03	120	96·0	5	4·0	
Smoking							
Non-smoker	8·31	5·72	2512	92·1	216	7·9	0·076
Ex-smoker	8·19	5·64	2611	91·4	245	8·6	
Current smoker	8·56	6·25	3110	90·5	328	9·5	
Risky drinking†							
No	8·13	5·79	4248	92·0	369	8·0	0·013
Yes	8·50	6·03	4021	90·5	420	9·5	
BMI (kg/m^2)							
<18·5	8·00	4·39	68	90·7	7	9·3	0·219
18·5–22·9	8·34	5·98	2342	92·0	203	8·0	
23–24·9	8·31	5·08	2363	91·6	216	8·4	
≥25	8·29	5·87	3496	90·6	363	9·4	
Marital status							
Married	8·16	5·86	7286	92·0	637	8·0	<0·001
Unmarried	9·38	6·21	775	86·2	124	13·8	
Others‡	9·29	7·38	208	88·1	28	11·9	
Regular exercise							
No	8·02	6·44	2146	90·9	216	9·1	0·384
Yes	8·40	5·71	6123	91·4	573	8·6	
Vitamin D (ng/ml)							
<20	8·59	6·24	3413	90·2	370	9·8	0·002
≥20	8·11	5·71	4856	92·1	419	7·9	

CES-D, Center for Epidemiologic Studies Depression Scale.
*Calculated by χ^2 test.
†Risky drinking: two or more times per week and seven or more glasses each time.
‡Others: widower, separated, divorced.

age, except for the group >60 years, there was a significant association between vitamin D levels and depressive symptoms (Table 3). Those in the depressive symptoms group were significantly skewed towards being single rather than married ($P < 0·001$), and risky drinkers over non-risky drinkers ($P = 0·013$). There was no significant difference in the proportion of those with depressive symptoms according to the classification of smoking status, BMI or regular exercise. The depressive symptoms group included 7·9 % of the optimal serum vitamin D group and 9·8 % of the serum vitamin D insufficiency group, which indicates that the depressive symptoms group skewed significantly towards the insufficiency group ($P = 0·002$) (Table 2).

Table 3 Association between vitamin D levels and depressive symptoms according to age

		Vitamin D (ng/ml)		
Age	CES-D	<20 (*n*)	≥20 (*n*)	*P*-value*
<30	<16	213	147	0·030
	≥16	44	15	
30–39	<16	961	1067	<0·001
	≥16	156	78	
40–49	<16	1591	2468	<0·001
	≥16	192	182	
50–59	<16	548	1154	<0·001
	≥16	59	58	
≥60	<16	17	103	0·165
	≥16	2	3	

CES-D, Center for Epidemiologic Studies Depression Scale.
*Calculated by χ^2 test.

Association between serum vitamin D insufficiency and depressive symptoms

To investigate which variables had a significant relationship with depressive symptoms, a logistic regression analysis was conducted. In the univariate logistic regression analysis, vitamin D insufficiency, risky drinking and unmarried state showed significant correlations with depressive symptoms (OR 1·29, 95 % CI 1·02, 1·62; OR 1·38, 95 % CI 1·04, 1·84; and OR 1·56, 95 % CI 1·12, 2·17, respectively; Table 4). Correlations between depressive symptoms and age decreased inversely with increasing age, but there was no statistical significance (OR 3·13, 95 % CI 1·47, 6·20 in those aged <30 years; OR 1·85, 95 % CI 0·44, 3·84 in those aged between 50 and 59 years). In the multivariate logistic regression analysis, after adjusting for variables that showed significance in the univariate logistic regression

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Table 4 Univariate and multivariate logistic regression analyses of factors affecting depressive symptoms

	Crude			Adjusted*		
	OR	95 % CI	*P*-value	OR	95 % CI	*P*-value
Age (years)						
<30	3·13	1·47, 6·20	0·005	2·51	1·32, 4·27	0·019
30–39	2·75	1·36, 5·06	0·012	2·25	1·30, 3·06	0·028
40–49	2·34	1·16, 4·68	0·024	1·45	1·01, 4·68	0·045
50–59	1·85	0·44, 3·84	0·283	1·05	0·57, 2·86	0·381
≥60	Reference			Reference		
Smoking						
Non-smoker	Reference					
Ex-smoker	1·04	0·77, 1·40	0·811			
Current smoker	1·23	0·93, 1·61	0·141			
Risky drinking†						
No	Reference			Reference		
Yes	1·38	1·04, 1·84	0·027	1·40	1·05, 1·87	0·022
BMI (kg/m^2)						
<18·5	Reference					
18·5–22·9	2·72	0·40, 20·18	0·319			
23–24·9	2·57	0·35, 19·75	0·375			
≥25	2·52	0·34, 18·69	0·365			
Marital status						
Married	Reference			Reference		
Unmarried	1·56	1·12, 2·17	0·009	1·16	0·72, 1·86	0·545
Others‡	1·85	0·99, 3·45	0·052	1·53	0·71, 3·29	0·275
Regular exercise						
No	1·22	0·95, 1·56	0·126			
Yes	Reference					
Vitamin D (ng/ml)						
<20	1·29	1·02, 1·62	0·031	1·49	1·12, 2·00	0·007
≥20	Reference			Reference		

*Adjusted for age, risky drinking, marital status, regular exercise and vitamin D level.
†Risky drinking: two or more times per week and seven or more glasses each time.
‡Others: widower, separated, divorced.

analysis, the correlation between the depressive symptoms group and the serum vitamin D insufficiency group remained significant (OR 1·49, 95 % CI 1·12, 2·00).

Discussion

Statement of principal findings

This study suggests significant correlations between serum vitamin D insufficiency and depressive symptoms in apparently healthy male adults. We determined the level of serum vitamin D in apparently healthy male adults when performing routine health check-ups. The average serum vitamin D level in the subjects was 22·31 ± 7·09 ng/ml as 25(OH)D. According to the classifications, the insufficiency and deficiency groups together – that is, those who did not satisfy the optimal level of 20 ng/ml – included 41·8 % of subjects. When comparing the prevalence of vitamin D insufficiency by region, it was 43·8 % among 5276 Hong Kong Chinese adults aged ≥20 years[32].

Interpretation of findings

In this study, the prevalence of serum vitamin D insufficiency (41·8 %) was relatively lower for Korean male adults compared with the data (75·2 %) from KNHANES[12]. Notably, while the proportion of subjects in their thirties was low in this study (*n* 419; 4·63 % of total subjects), a previous study reported that serum vitamin D deficiency is more severe in younger than older age groups[10]. Here, the group aged <30 years showed a lower average serum vitamin D level than did the group aged ≥30 years. Also, while the subjects with vitamin D insufficiency were more prevalent than those with vitamin D sufficiency in the group aged <30 years, the proportion of subjects with vitamin D sufficiency was not only higher than those with deficiency but also increased as age advanced. These results were confirmed by the linear trend test ($P < 0·001$). There are two plausible explanations for this. First, the younger male group may have had fewer opportunities for sun exposure through outdoor activities and a higher rate of sunscreen usage[28,29]. Also, a reverse causation may be possible; elderly people involving in outdoor activity are less likely to be depressive and have more sunlight exposure, and then elderly people have higher vitamin D levels compared to younger people. Second, younger people pursuing employment or trying to adapt to work-life may have fewer chances to participate in outdoor activities compared to older people who are retired and make the effort to promote good health.

In this study, the average CES-D score was 8·31 points, and 8·7 % of subjects fell into the depressive symptoms group. In a study based on the data from KNHNES 2014,

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the prevalence of male adult depression was 4·2 %[33], while, according to the Korea Health Statistics in 2017, the prevalence of depression in male adults (those aged >19 years) was 9·1 %[16]. Further, in a study involving 2531 male subjects between 18 and 92 years following the Korean financial crisis in late 1997, 35·1 % of subjects were in the depressive symptoms group[34]. In this study, the percentage of subjects in the depressive symptoms group was higher than that in the study performed using the data from KNHNES 2014, but slightly lower than that of the Korea Health Statistics and much lower than that of the general male population after the Korean financial crisis in 1997. Nevertheless, considering the characteristics of depressive symptoms, factors such as occupation, age, work patterns, socioeconomic issues, etc. must also be taken into account.

This study suggests significant correlations between serum vitamin D insufficiency and depressive symptoms in apparently healthy male adults. The results were significant even after adjusting for variables showing significant correlations, such as age, risky drinking and marital status, and the OR of the serum vitamin D insufficiency group falling into the depressive symptoms group was also significant, at 1·49 (95 % CI 1·12, 2·00). These findings are similar to the results of previous international studies recently reported. In the European Male Ageing Study involving 3369 middle-aged and older men (mean age 60 ± 11 years), the odds for depression increased by approximately 70 % across decreasing 25(OH)D quartiles[35]. By this result, an inverse association between the levels of 25(OH)D and the degree of depression can be said to be largely independent of several lifestyle and health factors[35]. In a 6-year follow-up study on serum vitamin D levels in 423 Italian male adults aged ≥65 years, men with low vitamin D levels tended to have a higher risk of developing a depressed mood[36]. In a 9-year prospective cohort study of 7358 subjects aged ≥50 years with CVD and no history of depression, even after adjustment, those with very low vitamin D levels (<15 ng/ml) had a nearly threefold increased risk of depression in comparison with those with optimal levels (>50 ng/ml)[37]. Here, vitamin D had a significant graded association with depression, and vitamin D deficiency was a contributing factor to the onset of excess cardiovascular events[37]. To date, although no clear biological mechanisms have been identified to explain the association between vitamin D and the risk of depression, several possible mechanisms have been proposed. First, vitamin D appears to be involved in the modulation of brain neurotransmitters that participate in the regulation of emotional behaviour[38,39]. It is known that there are specific receptors, which are enzymes needed for vitamin D hydroxylation, in the brain and the central nervous system. These receptors can directly affect the activation of neurons and the functioning of the neuroendocrine system by making it biologically plausible for vitamin D. As a result, vitamin D could affect brain development, activity and function and be associated with the development of depression[38,40]. Second, vitamin D can act as a neuroprotective and immunomodulatory factor in suppressing the oxidation and denaturation of neurons by way of its antioxidant activity[38]. Third, another possible mechanism by which vitamin D may contribute to depression is through parathyroid hormone (PTH) levels. Low vitamin D levels cause increased PTH levels through the suppression of calcium, and hyperparathyroidism is accompanied by depressive disorders[41,42]. PTH may have a role in the pathogenesis of depression, and vitamin D may be an intermediating factor with either direct or indirect involvement (i.e. low vitamin D and increased PTH levels increase inflammation, which is a risk factor for depression)[41]. Fourth, although no beneficial effect of higher monthly doses of vitamin D compared with the standard monthly dose is known[43], several studies have evaluated the effects of vitamin D supplementation on depression[44,45]. Finally, although these studies did not support a causal effect on any of the disease outcomes, multiple Mendelian randomisation studies have investigated the putative causal association of vitamin D on multiple health outcomes, especially in preventing or controlling depression and major depressive disorder[46,47].

Strengths and limitations of the present study

This study has several limitations that should be mentioned. Because it boasts a cross-sectional design, this study could identify the association between serum vitamin D and depressive symptoms; however, it cannot explain the exact causal relationship among the variables. Additionally, although a well-structured questionnaire was used, the possibility remains that a degree of response bias may have influenced the results because the study incorporated a self-reported survey. Apparently healthy male adults who underwent routine health check-ups were selected as subjects of this study, but neither their level of outdoor physical activity nor their dietary habits, such as the consumption of vitamin D supplements, were assessed. During this time, reduced exposure to sunlight via urbanisation, industrialisation and health recommendations may have contributed to lower 25(OH)D levels[37]. Also, several physical factors, including clothing, sunscreen, residential location and shielding provided by buildings, may influence the amount of absorbable 25(OH)D. Despite the introduction of schemes/programmes to improve the accuracy of assays to measure 25(OH)D, significant differences might still happen. Although LC-MS/MS has emerged as a gold standard for reliable, accurate and high-throughput quantification of vitamin D metabolites, and the Elecsys concentrations recorded by Modular E analyser were in good overall agreement with those determined with LC-MS/MS[48,49], it is necessary to harmonise the methodologies so they can be decisive in assessing a large number of subjects[49]. Therefore, differences in these factors could

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result in the outcomes being not generalisable to other populations. Finally, given that the proportions of subjects aged <30 years and those aged >60 years were low in this study, if the proportions of all ages were to be distributed evenly, the results might change. Nevertheless, this study is significant considering that: it is a single-institution study that included apparently healthy male adults without a history of vitamin D deficiency or depression; it highlighted that serum vitamin D insufficiency is widespread and thought to be a serious health challenge to the community; it investigated the association between serum vitamin D and depressive symptoms in Korean subjects via routine health check-ups, which is scarcely reported in literature; and it determined the level of serum vitamin D in a large number of Korean male adults and the association with depressive symptoms. Further, because we considered the association between serum vitamin D levels and exposure to sunlight, we reduced the influence of latitude and weather by localising the subjects, and similarly reduced the influence of differences in seasons as well by conducting the examination during 1 March and 30 November 2018, a period characterised by peak daylight.

Unanswered questions and future research

The present study demonstrated the association between serum vitamin D insufficiency and depressive symptoms in apparently healthy male adults via routine health check-ups. Additionally, there is a need for further research on improvement in depressive symptoms in subjects with serum vitamin D insufficiency classified into the depressive symptoms group based on the use of vitamin D supplementation.

Conclusions

This study found a high percentage of Korean male adults with serum vitamin D insufficiency and identified a significant association between serum vitamin D insufficiency and depressive symptoms. Because various factors could be related with depressive symptoms, serum vitamin D insufficiency alone cannot explain the causal relationship with depressive symptoms observed. However, this study provides evidence of an association between serum vitamin D insufficiency and depressive symptoms, which should be further explored.

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