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Vitamin D and depressive symptoms in an early adolescent cohort

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Original Article

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Abstract

Background. To explore the cross-sectional and longitudinal association between vitamin D and depressive symptoms across early adolescence.

Methods. This longitudinal study included 1607 early adolescents [mean (S.D.) age, 12.49 years; 972 (60.5%) males] from the Chinese Early Adolescents Cohort, recruited from a middle school in Anhui Province and followed up annually (2019–2021). Serum 25(OH)D levels were measured in both 2019 and 2021. Self-reports on depression were assessed at each of three time points from 2019 to 2021.

Results. In the whole sample, higher baseline serum 25(OH)D levels were linked with a lower risk of cumulative incident depression within two-year follow-ups (adjusted RR = 0.97, 95% CI 0.94–0.99) and the increasing trajectory of depression symptoms across the three waves (adjusted RR = 0.97, 95% CI 0.95–0.99). Baseline vitamin D deficiency (VDD) (adjusted RR = 1.50, 95% CI 1.10–2.05) were associated with an increased risk for the increasing trajectory of depression symptoms across the three waves. Remitted VDD was positively related to one dichotomous depression symptoms across three waves (adjusted OR 2.15, 95% CI 1.15–4.01). The above-mentioned significant association was also found in males. Additionally, baseline VDD (adjusted OR 1.59, 95% CI 1.04–2.44) and persistent VDD (adjusted OR 1.58, 95% CI 1.02–2.60) were linked to an increased risk of having two dichotomous depression symptoms only in males.

Conclusions. Our results highlight a prospective association between baseline vitamin D and depression risk in early adolescents. Additionally, a male-specific association between vitamin D and depression risk was observed. Our findings support a potential beneficial effect of vitamin D supplementation in reducing depression risk in early adolescents.

Introduction

The first onset of depression often occurs in adolescence (Thapar, Eyre, Patel, & Brent, 2022), and early onset relates to negative clinical outcomes such as suicidality (Solano et al., 2016) and poor outcomes in adulthood, highlighting the need for early identification and treatment (Miller & Campo, 2021). Diet has shown promise for depression prevention in adolescents due to its modifiable nature (Marx et al., 2021). Specifically, increasing evidence reveals a potential function of vitamin D in depression development (Berridge, 2017). Biologically, 1,25-dihydroxyvitamin D3 receptors (VDRs) are widespread in different brain regions (Eyles, Smith, Kinobe, Hewison, & McGrath, 2005). Animal studies have supported that vitamin D acts on the pathogenesis of depression-like behaviors (He et al., 2020). Generally, vitamin D status is best characterized by serum total 25(OH)-vitamin D [25(OH)D] levels (Binkley & Wiebe, 2013). Cross-sectional studies have reported a correlation between vitamin D concentrations and depression in children and adolescents (Husmann et al., 2017; Namazi et al., 2021; Robinson et al., 2019; Tolppanen et al., 2012). However, prospective studies regarding this important correlation are limited in this specific population. Longitudinal studies using repeated measurements of both vitamin D status and depressive symptoms are crucial in understanding whether vitamin D is a predictor, correlate or consequence of depression. Only one longitudinal study in a sample of English children found that baseline serum 25(OH)D_3 concentration assessed at age 9.9 years was prospectively linked to self-reported depressive symptoms at age 13.8 years (Tolppanen et al., 2012). Prospective studies in adults have revealed that changes in vitamin D levels are associated with the depressive symptoms (Di Gessa, Biddulph, Zaninotto, & de Oliveira, 2021; Elstgeest et al., 2018). However, this important relationship has not been examined in children and adolescents.

Therefore, we used the Chinese Early Adolescents Cohort (CEAC) to explore the associations of vitamin D with depressive symptoms. Early adolescence (aged 10–14 years) is one of the most critical developmental periods. In this stage, most adolescents reach puberty and experience immense cognitive and emotional changes (Crone & Dahl, 2012; Irwin, 2021). Specifically, early adolescence is a key stage for depression first onset and provides a critical time window for depression prevention (Solmi et al., 2022). We aimed to explore four questions regarding the relationship of vitamin D with depressive symptoms in this cohort: (1) Is vitamin D levels or status cross-sectionally associated with depressive symptoms in early adolescence? (2) Is baseline vitamin D levels or status longitudinally associated with depressive symptoms in early adolescence? (3) Are longitudinal changes in vitamin D levels associated with depressive symptoms in early adolescence? (4) Are longitudinal trajectories of vitamin D status associated with depressive symptoms in early adolescence?

Methods

Participants

The CEAC was conducted in a middle school in Huaibei City, Anhui Province to explore and verify risk factors for adolescent emotional and behavioral problems, which was established in September 2019 by using a random cluster sampling. All 7th grade students in the selected school were invited to participate in the baseline survey (wave 1) after excluding students who had any confirmed organic or chronic diseases that could affect vitamin D metabolism (include inflammatory diseases and liver and/or chronic renal diseases) and history of psychiatric disorders (e.g. depressive disorder, and anxiety). Follow-up survey was conducted in 2020 (wave 2) and 2021 (wave 3) when the COVID-19 occurred. Participants underwent questionnaire survey across three waves, and blood samples were collected for 25(OH)D measurement in wave 1 and wave 3. After excluding participants who did not measure serum 25(OH)D in wave 1 or wave 3, and those who had missing data of analytical variables (i.e. depressive scores and confounding variables), we obtained a total sample of 1607 students for the current analysis. The study flow chart of participants selection is presented in online Supplementary Fig. S1. The study protocol was conducted under the guidelines of the Declaration of Helsinki and approved by the ethical committees of Anhui Medical University (NO. 20180083). Written informed consent was obtained from parents and children.

Measures

Vitamin D levels or status

Fasting blood samples of participants were taken at 8:00 AM at wave 1 and wave 3. After centrifugation, the serum was transferred to an Eppendorf tube and stored at −80 °C until the laboratory test. Serum levels of 25(OH)D were detected by using a direct competitive immunoassay chemiluminescent method with a LIASON 25-OH vitamin D assay TOTAL (DiaSorin, Inc.). Residuals derived from sex-stratified linear regression analysis using the vitamin D levels at wave 3 as the outcome and the vitamin D levels at wave 1 as the predictor were used to index conditional changes in vitamin D levels. Vitamin D deficiency (VDD) was defined by using the cutoff value of serum 25(OH)D levels < 20 ng/mL (Jiang et al., 2021; Patseadou & Haller, 2020). Four vitamin D trajectories were defined: (1) no VDD (reference group): 25(OH)D ⩾ 20 ng/mL at both wave 1 and wave 3; (2) new VDD: baseline 25(OH)D ⩾ 20 ng/mL at wave 1 and 25(OH)D < 20 ng/mL at wave 3; (3) remitted VDD: 25(OH)D < 20 ng/mL at wave 1 and 25(OH)D ⩾ 20 ng/mL at wave 3; and (4) persistent VDD: 25(OH)D < 20 nmol/L at both wave 1 and wave 3.

Depressive symptoms

Self-reports of depressive symptoms across three waves were assessed by using the 20-item Chinese version of the Center for Epidemiological Studies Depression Scale for Children (CES-DC) (Fendrich, Weissman, & Warner, 1990). This scale has been validated and showed desirable reliability, and higher scores indicating greater severity of symptoms (Thapar et al., 2022). The cutoff point of 21 was adopted to indicate a high probability of clinical depression (Chi et al., 2020). Participants who had depression at baseline (CES-DC scores ⩾ 21) were excluded from longitudinal models to enable analysis of incident depression at wave 2 and wave 3. Also, cumulative incident depression was calculated with the sum of the number of new cases of depression within two follow-ups. Specifically, participants who had depression at both wave 2 and wave 3 were only considered as a new case. We also calculated the number of binary depression symptoms across the three waves to roughly reflect the change patterns of depressive symptoms. The changing patterns of depressive symptoms across the three waves are shown in Fig. 1.

Furthermore, we applied group-based trajectory modeling to identify differential developmental trajectories of depressive symptoms across three waves. Four developmental trajectories of depressive symptoms across three waves were identified (see Fig. 2 and online Supplementary Table S1). Specifically, 967 (60.2%) were characterized as having a low risk of depression across three time points, 295 (18.4%) showed decreasing depression scores, 243 (15.1%) showed increasing depression scores, and 6.3% of individuals had persistently high depression scores (i.e. ⩾ 21).

Confounding factors

Based on previous studies (Chi et al., 2020; Husmann et al., 2017; Namazi et al., 2021; Robinson et al., 2019; Weavers et al., 2021), we included sex, age at wave 1, residence area, only child, family structure, self-perceived family economic status, body mass index (BMI) at wave 1, moderate and high-intensity physical activity at wave 1, and self-perceived pubertal timing at wave 1 as potential confounders (see Table 1). The frequency of vigorous-intensity physical activity for 20 min and moderate physical activity for 30 min during the last week were asked at baseline (Hallal et al., 2012; Tan et al., 2020). Response options were coded for 0 days/week, one-two days, and ⩾three days. Height and weight were measured at the baseline survey and were used to calculate BMI. A one-item question was used to assess self-perceived pubertal timing relative to their peers. Responses were coded as earlier, approximately the same and later (Conley & Rudolph, 2009).

Statistical analyses

We summarize the participant characteristics. Group-based trajectory modeling in Stata 12.0 (Traj) was used to identify differential trajectories of depression (Nagin, Jones, Passos, & Tremblay, 2016). A series of sex-adjusted and sex-stratified linear or logistic regression models were performed to examine the

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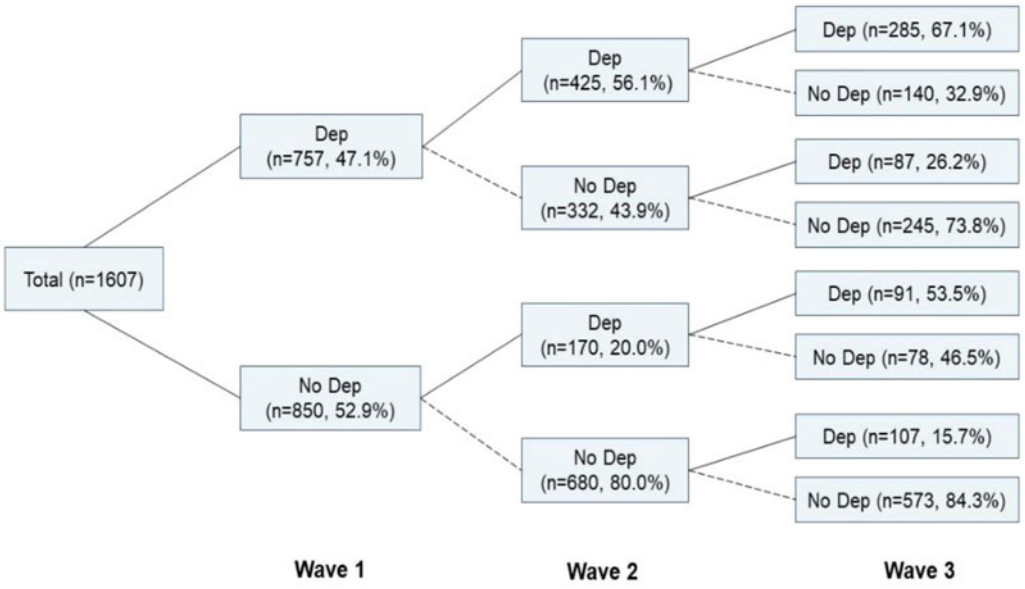

Fig. 1. The changing patterns of depressive symptoms across three waves.

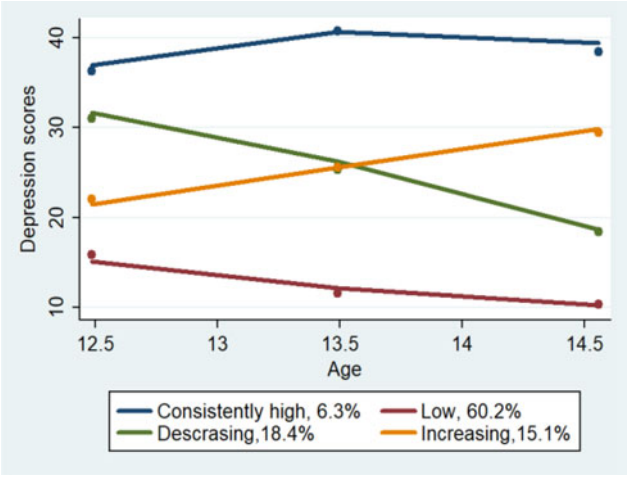

Fig. 2. Developmental trajectory of depression scores across three waves.

associations of vitamin D status with depression risk based on specific research hypotheses by using SPSS 22.0 (see online Supplementary Methods for details). The results were evaluated at a significance level of p value 0.05 (2-tailed).

Results

Sample characteristics

As shown in Table 1, mean serum levels of 25(OH)D at wave 3 were lower than that at wave 1 (19.42 ± 5.79 ng/mL *v.* 23.06 ± 5.69 ng/mL, $p < 0.001$). Correspondingly, the prevalence rate of VDD increased from wave 1 to wave 3 (30.3% *v.* 56.5%, $p < 0.001$). Girls had a higher serum level of 25(OH)D and a higher prevalence of VDD ($p < 0.001$). The depressive scores reduced from wave 1 to wave 3 ($p < 0.001$). Similarly, girls reported higher depression scores and prevalence of depressive symptoms from wave 1 to wave 3 ($p < 0.001$).

Univariate analysis between the relationships of confounding variables with vitamin D levels and depression scores is provided in online Supplementary Table S2. Sex, residence area, family structure and BMI were correlated with vitamin D levels at wave 1. Sex and high-intensity physical activity were linked with vitamin D levels at wave 3. Notably, self-perceived family economic status and frequency of high-intensity physical activity were related to depression scores across the three waves.

RQ1: Vitamin D levels or status was not cross-sectionally associated with depression symptoms in early adolescence

No significant cross-sectional association was found between serum 25(OH)D levels and depression symptoms (continuous and dichotomous) at wave 1 and wave 3 or for the association between VDD and depression symptoms (continuous and dichotomous) at wave 1 and wave 3 (see online Supplementary Tables S3 and S4).

RQ2: Baseline vitamin D levels or status is longitudinally associated with depressive symptoms in early adolescence

No significant association was observed between baseline serum 25(OH)D level and VDD and incident depressive symptoms neither at wave 2 nor wave 3 or for the association between baseline VDD and cumulative incident depression during a two-year follow-up; see online Supplementary Tables S5 for details.

Interestingly, higher baseline serum 25(OH)D levels were associated with a decreased risk of cumulative incident depressive symptoms in the overall sample adjusted for sex (adjusted RR = 0.97, 95% CI 0.94–0.99; See online Supplementary Table S5). Among males, we found that lower serum 25(OH)D level (adjusted RR = 0.97, 95% CI 0.93–0.99; See online Supplementary Table S6) and VDD (adjusted RR = 1.59, 95% CI 1.04–2.44) at wave 1 were linked to an increased risk of having two dichotomous depression symptoms across the three waves. Lower 25(OH)D levels and VDD at baseline were associated with an increased risk for the increasing trajectory of depressive symptoms across three waves in males and the overall sample by using multinomial logistic regression models (Table 2).

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Table 1. Description of the sample characteristics

Characteristic [Mean (s.d.), Median (lower quartile, upper quartile) or *N* (%)]	Overall	Males	Females	*p* value
Age at W1	12.49 ± 0.48	12.52 ± 0.48	12.45 ± 0.48	0.006
Residence area				0.120
Urban	369 (23.0%)	236 (24.3%)	133 (20.9%)	
Rural	1238 (77.0%)	736 (75.7%)	502 (79.1%)	
Only child				<0.001
No	1349 (83.9%)	775 (79.7%)	574 (90.4%)	
Yes	258 (16.1%)	197 (20.3%)	61 (23.6%)	
Family structure				0.363
Nuclear family	739 (46.0%)	451 (46.4%)	288 (45.4%)	
Large family	595 (37.0%)	162 (16.7%)	89 (14.0%)	
Single-parent family	251 (15.6%)	346 (35.6%)	249 (39.2%)	
Other	22 (1.4%)	13 (1.3%)	9 (1.4%)	
Self-perceived family economic status at W1				0.418
Bad	182 (11.3%)	118 (12.1%)	64 (10.1%)	
General	1197 (74.5%)	715 (73.6%)	482 (75.9%)	
Good	228 (14.2%)	139 (14.3%)	89 (14.0%)	
BMI at W1	19.30 ± 4.54	19.75 ± 4.73	18.60 ± 4.15	<0.001
Moderate-intensity Physical activity at W1				<0.001
No	580 (36.1%)	305 (31.4%)	274 (43.3%)	
One-two day	665 (41.4%)	441 (45.4%)	224 (35.3%)	
⩾three days	362 (22.5%)	226 (23.3%)	136 (21.4%)	
High-intensity Physical activity at W1				<0.001
No	637 (39.6%)	316 (32.5%)	321 (50.6%)	
One-two day	658 (40.9%)	423 (43.5%)	235 (37.0%)	
⩾three days	312 (19.4%)	233 (24.0%)	79 (12.4%)	
Depression scores at W1	20.86 ± 10.35	20.03 ± 9.80	22.14 ± 11.02	<0.001
Depression scores at W2	18.42 ± 11.69	17.07 ± 10.86	20.50 ± 12.57	<0.001
Depression scores at W3	17.17 ± 12.03	16.03 ± 11.53	18.90 ± 12.58	<0.001
Depressive symptoms at W1	757 (47.1%)	426 (42.8%)	331 (52.1%)	<0.001
Depressive symptoms at W2	595 (37.0%)	318 (32.7%)	277 (43.6%)	<0.001
Depressive symptoms at W3	570 (35.5%)	302 (31.1%)	268 (42.2%)	<0.001
Trajectory of depression symptoms				<0.001
Low	967 (60.2%)	638 (65.6%)	329 (51.8%)	
Decreasing	295 (18.4%)	161 (16.6%)	134 (12.1%)	
Increasing	243 (15.1%)	125 (12.9%)	118 (18.6%)	
Persistent	102 (6.3%)	48 (4.9%)	54 (8.5%)	
Vitamin D level at W1 (ng/mL)	23.06 ± 5.69	23.74 ± 5.78	22.01 ± 5.39	<0.001
VDD at W1 (<20 ng/mL)	469/1549 (30.3%)	244 (25.9%)	225 (35.1%)	<0.001
Vitamin D level at W3 (ng/mL)	19.42 ± 5.79	19.76 ± 4.73	18.60 ± 4.15	<0.001
VDD at W3 (<20 ng/mL)	888/1572 (56.5%)	464 (48.7%)	424 (68.4%)	<0.001
Conditional change of 25(OH)D	−0.29 (−3.08 to 2.83)	−0.06 (−3.20 to 2.89)	−0.59 (−2.91 to 2.64)	<0.001

(*Continued*)

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Table 1. (*Continued.*)

Characteristic [Mean (s.d.), Median (lower quartile, upper quartile) or *N* (%)]	Overall	Males	Females	*p* value
Trajectory of vitamin D status				<0.001
No VDD	586 (38.7%)	431 (46.7%)	155 (26.2%)	
Remitted VDD	75 (5.0%)	46 (5.0%)	29 (4.9%)	
New VDD	483 (31.9%)	260 (28.2%)	223 (37.7%)	
Persistent VDD	370 (24.4%)	185 (20.1%)	185 (31.3%)	

W, wave; s.d., standard deviation.

RQ3: Longitudinal changes in vitamin D levels were not associated with depressive symptoms in early adolescence

No significant association was detected between conditional changes in vitamin D levels and incident depressive symptoms by using logistic regression models (online Supplementary Table S7). Nevertheless, neither the patterns nor the trajectories of depressive symptoms were related to conditional changes in vitamin D levels in multinomial logistic regression models (online Supplementary Tables S8 and S9).

RQ4: Longitudinal trajectories of vitamin D status were associated with depressive symptoms in early adolescence

Remitted VDD was positively related to cumulative incident depressive symptoms and the risk of one dichotomous depression symptom in males and the overall sample (online Supplementary Tables S10 and S11). Also, persistent VDD was associated with increased odds ratio for the increasing group in males and pooled samples of male and female individuals (Table 3). Notably, persistent VDD was related to a higher risk of being involved in two dichotomous across the three waves only in males (adjusted OR 1.58, 95% CI 1.02–2.60; See online Supplementary Table S11).

Discussion

Longitudinal data from the CEAS cohort revealed that the prevalence rates of VDD increased from 30.3% at wave 1 to 56.5% at wave 3. In particular, the follow-up time of this study was in the post-COVID-19 period. Correspondingly, serum levels of 25(OH)D decreased from wave 1 to wave 3. The prevalence of VDD in this study was comparable to that in a recent meta-analysis in Asia (Jiang et al., 2021), in which the prevalence of VDD, defined as serum 25(OH)D level below < 20 ng/ml, was 52.44% in children and adolescents. This finding confirms that VDD is a serious problem in adolescents, which needs to be particularly considered, especially during the COVID-19 pandemic.

Interestingly, the depression scores of this sample showed a downward trend across the three time points. A cohort study of Chinese adolescents found that depressive symptoms declined from grade 7 to grade 9 (Chi et al., 2020). One explanation for the declining trend was that 7th grade students need to adapt to a new study stage and school environment, and grade 9 students needs to prepare for the admission tests to high school. It is worth mentioned that two follow-ups of this study were conducted in the post-COVID-19 period. However, studies have found a very limited negative effect of COVID-19 on adolescent mental health in the 9 months after the COVID-19 outbreak (van der Velden, van Bakel, & Das, 2022). Although a declining trend of depressive symptoms was observed, the prevalence of depressive symptoms was quite high at the three time points, which suggests that adolescent depression has become a serious problem among early adolescents in China.

Recently, a systematic review was conducted to analyze the association between vitamin D intake or status and mental health in children, including both intervention and observational studies (Głąbska et al., 2021). The finding supports the notion VDD is linked to depression or poor mental health. The authors call for more studies to facilitate comparisons and deepen the observations due to high heterogeneity of the included studies. Thus, we conducted an early adolescent cohort study to explore the relationship between vitamin D and depression. We found that lower baseline serum 25(OH)D levels predicted cumulative incident depression during a two-year follow-up. Prospective studies in adults have reported a prospective association between baseline VDD and incident depression (Ronaldson et al., 2020). Using the repeated measurement of depression across early adolescence, we identified the changing patterns and developmental trajectories of depressive symptoms, aiming to elucidate the role of vitamin D in depression risk and identify subgroups of individuals who might benefit from vitamin D supplementation. Lower serum 25(OH)D levels and VDD at baseline were linked to an increased risk of having two dichotomous depressive symptoms and the increasing group across three waves. This finding suggests that vitamin D status was prospectively associated with recurrent and elevated depressive symptoms. Previously, a prospective cohort study reported that lower serum concentrations of 25(OH)D3 at 9.8 years were linked to higher depressive symptoms at follow-up age of 13.8 years, and a lower risk of decreasing symptoms between the two time points at ages 10.6 and 13.8 years (Tolppanen et al., 2012). In adults, the prospective association between VDD and recent recurrence has been consistently reported (Collin et al., 2017; Ronaldson et al., 2020). Using a repeated measurement of depression from wave 1 to wave 3, this study confirms the prospective link between vitamin D and depression risk. Currently, the biological mechanisms from vitamin D to depression remain unknown; possible mechanisms have been proposed. Vitamin D can regulate serotonin and melatonin metabolism, and neuroinflammation in the brain (Bakhtiari-Dovvombaygi et al., 2021; Berridge, 2017; Huiberts & Smolders, 2021), thus impacting depression risk.

With repeated measures of vitamin D levels, we further explored the relationship between longitudinal changes and trajectories of vitamin D and depression risk during early adolescence. We found that remitted VDD was positively related to cumulative incident depression and one dichotomous depressive symptom in three waves in pooled samples of both sexes. This finding further supports our finding that baseline VDD predicts incident depression and a prospective relationship of vitamin D

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Table 2. RR and 95% CI for the trajectory depressive symptoms according to baseline serum 25(OH) D level and VDD ($n = 1549$)

	Overall sample adjusted for sex		Males		Females	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Serum 25(OH)D level						
Low	Reference	Reference	Reference	Reference	Reference	Reference
Increasing	**0.97 (0.95–1.00)**	**0.97 (0.95–0.99)**	**0.96 (0.93,1.00)**	**0.96 (0.93–0.99)**	0.98 (0.94–1.02)	0.98 (0.94–1.02)
Decreasing	0.99 (0.97–1.01)	0.99 (0.97–1.02)	0.98 (0.95–1.01)	0.98 (0.95–1.01)	1.00 (0.96–1.04)	1.01 (0.96–1.04)
Persistent	1.01 (0.97–1.05)	1.01 (0.97–1.05)	1.02 (0.97–1.08)	1.02 (0.97–1.07)	0.99 (0.94–1.05)	0.99 (0.94–1.05)
VDD						
Low	Reference	Reference	Reference	Reference	Reference	Reference
Increasing	**1.53 (1.13–2.08)**	**1.50 (1.10–2.05)**	**1.58 (1.04–2.40)**	**1.60 (1.04–2.49)**	1.47 (0.95–2.28)	1.42 (0.90–2.24)
Decreasing	1.03 (0.77–1.38)	1.01 (0.75–1.36)	1.20 (0.81–1.78)	1.21 (0.81–1.82)	0.87 (0.57–1.34)	0.89 (0.42–1.88)
Persistent	0.81 (0.51–1.31)	0.80 (0.49–1.30)	0.63 (0.29–1.38)	0.64 (0.29–1.43)	0.93 (0.50–1.73)	0.95 (0.50–1.82)

Adjusted model included covariates: age at wave 1, only child status, family structure, self-perceived family economic status, BMI at wave 1, physical activity at wave 1 and self-perceived puberty timing at wave 1.
Variable levels significant at $p < 0.05$ are in boldface type.

and depression risk. Persistent deficiency was associated with a higher risk for the increasing group in overall samples. Findings from the English Longitudinal Study of Aging reported that adults with persistent VDD were more likely to report elevated depressive symptoms (Di Gessa et al., 2021).

Unexpectedly, we did not find a cross-sectional correlation between vitamin and depression symptoms at wave 1 and wave 3. Consistently, a study also found a lack of cross-sectional association between vitamin D and depressive symptoms in early adolescents (Al-Sabah et al., 2022). Additionally, no significant association between conditional changes in serum vitamin D levels and depression risk was observed. Generally, if vitamin D plays a significant role in the etiology of depression, vitamin D will show a robust cross-sectional and longitudinal association with depression. However, we only detected a limited link between longitudinal association of baseline vitamin D levels or status and depression risk in this early adolescent cohort. This finding might suggest that vitamin D status did not have a causal relationship with depression, which was confirmed by using the Mendelian randomization method (Arathimos et al., 2021; Libuda et al., 2019). Furthermore, randomized controlled trials (RCTs) in depressed adults yield inconsistent findings regarding the positive effect of vitamin D supplementation (Li et al., 2014; Vellekkatt & Menon, 2019). The abovementioned link between vitamin D and depression risk in our study might suggest that the biological pathways linking vitamin D to depression can generate a series of effects that will emerge gradually. Beyond that, other factors such as outdoor physical activities except for vitamin D are possibly accumulated over time, which might explain the association. Finally, vitamin D might function on the depression onset by acting synergistically with other factors (Cui et al., 2015). Taken together, our findings support the potential beneficial effect of vitamin D supplementation in reducing depression risk in adolescence. Currently, RCTs investigating the impact of vitamin D supplementation on depression in adolescents are still lacking (Głąbska et al., 2021); future high-quality RCTs should clarify the role of vitamin D in reducing depression risk in adolescents.

Currently, whether and how vitamin D relates to depression risk in a sex-dependent manner is still an open question. Lower serum vitamin D levels were related to an increased risk for depressive symptoms only in men (Black et al., 2014; Rhee, Lee, & Ahn, 2020). In contrast, studies also reported that vitamin D had a larger association with depression in women (Kjærgaard, Joakimsen, & Jorde, 2011; Milaneschi et al., 2010). However, previous studies have mostly been conducted in adults and used a cross-sectional design. By using a cohort design in a sample of early adolescents, sex-stratified analysis revealed a male-specific link between vitamin D status and depression risk. Additional positive associations between lower baseline serum 25(OH)D levels and persistent VDD and having two dichotomous depressive symptoms were only found in males. One of the main potential explanations for the male-specific relationship is testosterone (Amini, Jafarirad, & Abiri, 2021). Vitamin D can positively impact testosterone levels (Nimptsch, Platz, Willett, & Giovannucci, 2012). Testosterone ameliorates depression in men by acting on serotonin receptors (Walther, Breidenstein, & Miller, 2019). There is a need to confirm our findings and uncover the underlying biological mechanisms.

Strength and limitations

In this study, we used a cohort design with repeated assessments of both vitamin D status and depression symptoms across early

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Table 3. OR and 95% CI for the association between trajectories of vitamin D status and the trajectory of depressive symptoms ($n = 1512$)

	Low	Decreasing	Increasing	Persistent
Overall sample adjusted for sex				
Unadjusted				
No VDD	Reference	Reference	Reference	Reference
New VDD	Reference	1.07 (0.77–1.47)	0.71 (0.48–1.04)	1.02 (0.62–1.69)
Remitted VDD	Reference	1.22 (0.67–2.22)	0.69 (0.31–1.52)	0.59 (0.17–1.99)
Persistent VDD	Reference	0.99 (0.69–1.43)	**1.54 (1.08–2.20)**	0.88 (0.49–1.56)
Adjusted				
No VDD	Reference	Reference	Reference	Reference
New VDD	Reference	1.06 (0.76–1.48)	0.71 (0.48–1.05)	1.04 (0.62–1.74)
Remitted VDD	Reference	1.27 (0.69–2.36)	0.69 (0.31–1.55)	0.60 (0.17–2.10)
Persistent VDD	Reference	0.91 (0.62–1.33)	**1.48 (1.01–2.15)**	0.86 (0.47–1.57)
Males				
Unadjusted				
No VDD	Reference	Reference	Reference	Reference
New VDD	Reference	1.27 (0.84–1.93)	0.81 (0.49–1.35)	0.74 (0.36–1.49)
Remitted VDD	Reference	1.70 (0.81–3.58)	0.75 (0.25–2.21)	0.73 (0.17–3.24)
Persistent VDD	Reference	1.19 (0.73–1.93)	**1.77 (1.11–2.85)**	0.47 (0.18–1.25)
Adjusted				
No VDD	Reference	Reference	Reference	Reference
New VDD	Reference	1.25 (0.81–1.92)	0.87 (0.51–1.49)	0.81 (0.39–1.66)
Remitted VDD	Reference	2.03 (0.93–4.43)	0.84 (0.27–2.58)	0.89 (0.19–4.12)
Persistent VDD	Reference	1.11 (0.66–1.86)	**1.87 (1.12–3.12)**	0.49 (0.18–1.34)
Females				
Unadjusted				
No VDD	Reference	Reference	Reference	Reference
New VDD	Reference	0.78 (0.47–1.31)	0.56 (0.31–1.01)	1.59 (0.70–3.61)
Remitted VDD	Reference	0.68 (0.25–1.84)	0.55 (0.17–1.76)	0.48 (0.06–4.00)
Persistent VDD	Reference	0.74 (0.42–1.28)	1.23 (0.71–2.13)	1.50 (0.63–3.60)
Adjusted				
No VDD	Reference	Reference	Reference	Reference
New VDD	Reference	0.81 (0.48–1.38)	0.55 (0.30–1.01)	1.54 (0.66–3.61)
Remitted VDD	Reference	0.55 (0.19–1.56)	0.45 (0.13–1.49)	0.40 (0.04–3.60)
Persistent VDD	Reference	0.68 (0.38–1.22)	1.13 (0.64–2.00)	1.48 (0.60–3.69)

Adjusted model included covariates: age at wave 1, only child status, family structure, self-perceived family economic status, BMI at wave 1, physical activity at wave 1 and self-perceived puberty timing at wave 1.
Variable levels significant at $p < 0.05$ are in boldface type.

adolescence, which allowed us to explore the longitudinal changes and trajectories of vitamin D and depressive symptoms. Our findings expand the previous studies by showing a male-specific relationship of vitamin D and depression risk. However, limitations should be provided to better understand our results. Firstly, depressive symptoms were measured by self-reported questionnaire; the measure does not constitute a professional diagnosis of a depressive disorder. However, the CES-DC scale has been widely used for measuring depressive symptoms and has shown good validity in children and adolescents (Thapar et al., 2022). In this study, the Cronbach α coefficients of the CES-DC ranged from 0.81 to 0.85 across three waves. Secondly, we did not assess free vitamin D due to financial constraints, which relates to a limitation. Some investigators have proposed that free vitamin D should be measured in studies of the vitamin's health effects (Tsuprykov et al., 2018). Future studies with a detailed measurement of both total and free 25-hydroxyvitamin D will help to better understand the relationship between vitamin D and depression. Thirdly, although we have adjusted for many important confounders, residual confounding owing to unmeasured factors such

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as childhood adversity (Miller & Campo, 2021), and individual personality or affective temperaments (Baldessarini et al., 2017), could not be ruled out. Furthermore, some confounding factors were measured only at the baseline; thus, the changes of confounding factors were not considered. In particular, the COVID-19 suddenly occurred during a two-year follow-up. The pandemic has a great impact on lifestyle behaviors in adolescents, especially for the physical activity (Xiang, Liu, Yamamoto, Mizoue, & Kuwahara, 2022), which might impact on the relationship between vitamin D and depressive symptoms. Fourthly, study participants may not be representativeness as we conducted this study in a secondary school. Lastly, our statistical power was limited due to the size of the groups and the number of cases. This is especially the case with respect to the analyses in which we stratified our models by sex and incident depression.

Conclusion

In this cohort study, we found a prospective association between baseline vitamin D levels or status with depression risk in early adolescents. This study adds new evidence regarding the relationship of vitamin D status with depression in adolescents. Our findings also highlight a male-specific link between vitamin D status and depression risk. These prospective associations support a potential beneficial effect of vitamin D supplementation in reducing depression risk in early adolescents, especially during the period of COVID-19.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291722003117.

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