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Research paper

Maternal vitamin D status during pregnancy and offspring risk of childhood/adolescent depression: Results from the Avon Longitudinal Study of Parents and Children (ALSPAC)

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ABSTRACT

Background: Low maternal vitamin D levels [serum 25-hydroxyvitamin D (25(OH)D)] during pregnancy have been linked to offspring neuropsychiatric outcomes such as schizophrenia and autism, but studies on depression are lacking. We examined the association between maternal vitamin D status during pregnancy and offspring depression during childhood and adolescence and investigated whether any associations were modified by offspring genetic risk for depression.

Methods: Mother-singleton birth offspring pairs in the Avon Longitudinal Study of Parents and Children (ALSPAC) that had maternal 25(OH)D measurements, offspring genetic data, and offspring depression measures collected in childhood (mean age = 10.6 years; n = 2938) and/or adolescence (mean age = 13.8 years; n = 2485) were included in the analyses. Using multivariable logistic regression, we assessed associations between maternal vitamin D status and offspring polygenic risk score (PRS) for depression on childhood/adolescent depression risk.

Results: There was no evidence for an association between maternal vitamin D status during pregnancy and offspring depression in childhood (p = 0.72) or adolescence (p = 0.07). Offspring depression PRS were independently associated with childhood depression (p = 0.003), but did not interact with maternal vitamin D status. These results were robust to adjustments for potential confounders and different cut-offs for vitamin D insufficiency/deficiency.

Limitations: 25(OH)D measurements were only available at a single time point during pregnancy.

Conclusion: These findings suggest that maternal vitamin D status during pregnancy does not affect an offspring's risk for early life depression.

1. Introduction

Vitamin D deficiency among pregnant women is highly prevalent globally, and particularly in geographical regions at higher latitudes, such as Northern Europe and North America (Bodnar et al., 2007; Eggemoen et al., 2016), where it affects up to 80% of dark-skinned women and 47% of light-skinned women (Bodnar et al., 2007; Dror and Allen, 2010; Eggemoen et al., 2016; Holmes et al., 2009). Maintaining sufficient vitamin D levels during pregnancy is important, given that it is the sole source of fetal vitamin D, which may play a crucial role in fetal brain development. Since vitamin D levels can be easily increased by lifestyle modifications and supplementation, understanding the influence of maternal vitamin D levels on offspring brain health is needed to guide the design and implementation of public health efforts aimed at promoting brain health and possibly even prevent brain-related diseases as early on in the lifespan as possible.

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There are several possible mechanisms linking gestational vitamin D exposure to offspring neurodevelopment, including pathways linking vitamin D to neuronal growth and both the signaling and regulation of endocrine functions (D. W. Eyles et al., 2009). Several experimental studies have reported that vitamin D deficiency during pregnancy results in alterations in brain morphology and functioning of rat offspring with long-lasting effects on behavior spanning into adulthood (D. Eyles et al., 2003; D. W. Eyles et al., 2009; O'Loan et al., 2007; Pet and Brouwer-Brolsma, 2016). Observational research in humans has provided some evidence that maternal vitamin D status during gestation, defined by circulating levels of 25-hydroxyvitamin D [25(OH)D], could influence offspring neurocognitive and mental health outcomes (Darling et al., 2017; Keim et al., 2014; Morales et al., 2012; Strom et al., 2014), including increasing risk for schizophrenia, autism, and attention deficit/hyperactivity disorder (ADHD) (Agarwal et al., 2018; D. W. Eyles et al., 2018; Magnusson et al., 2016; Morales et al., 2015; Pet and Brouwer-Brolsma, 2016). Though largely untested, early life vitamin D deficiency in offspring may also be a risk factor for subsequent onset of depression. To our knowledge, only one study has assessed the effect of low gestational vitamin D levels on the risk of offspring depression (Strom et al., 2014). However, the relatively small sample size of 850 mother-child pairs and relatively crude definition for depression rendered findings inconclusive. Studies examining the relationship between maternal 25(OH)D levels during gestation and offspring depression are needed.

Furthermore, because genetic factors are known to contribute to depression risk in both children and young adults (Rice, 2010; Xia and Yao, 2015), efforts to understand the interactions between maternal vitamin D status during pregnancy and polygenic risk scores (PRS) for depression are required. Insights generated from such studies would have potentially important public implications as the presence or absence of gene-environment interactions (GxE) could inform whether preventive strategies adopt a targeted or universal approach (Carey and Crammond, 2017).

In the current study, we used data from the Avon Longitudinal Study of Parents and Children study (ALSPAC) (Boyd et al., 2013), a birth cohort study based in South West England, to examine the prospective association between maternal vitamin D status during pregnancy and offspring depression in childhood and adolescence, and to investigate whether the effects of maternal vitamin D status were modified by offspring genetic risk for depression.

2. Participants and methods

2.1. Study population

ALSPAC is an ongoing population-based birth cohort from South West England. Detailed information about ALSPAC has been described previously (Boyd et al., 2013; Fraser et al., 2013) and is available on the study website (http://www.bristol.ac.uk/alspac), which also includes a searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/). In brief, the study enrolled 14,541 pregnant women with estimated delivery dates between April 1, 1991 and December 31, 1992, which resulted in 14,062 live births (Boyd et al., 2013; Fraser et al., 2013). Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. Consent for biological samples has been collected in accordance with the Human Tissue Act (2004) (Samuels, 2004). From the age of 7 years onwards, children attended annual assessment clinics during which they participated in physical tests and in-person interviews. To address loss to follow-up through attrition, further phases of recruitment were carried out after age 7, resulting in an additional 617 participants enrolling by 16 years of age (Boyd et al., 2013).

The eligible study sample for these analyses included mother-offspring pairs with singleton births and complete data on maternal 25(OH)D levels during pregnancy, offspring genetic data, and offspring depressive symptoms collected during childhood and/or adolescence. Since less than 3% of the ALSPAC cohort were non-European (Matijasevich et al., 2012), only white participants were included. Mothers were excluded if their total 25(OH)D levels were three standard deviations (SD) above or below the study population mean (n = 39). This yielded analytic sample sizes of 2938 (child subsample) and 2485 (adolescent subsample) (Fig. 1).

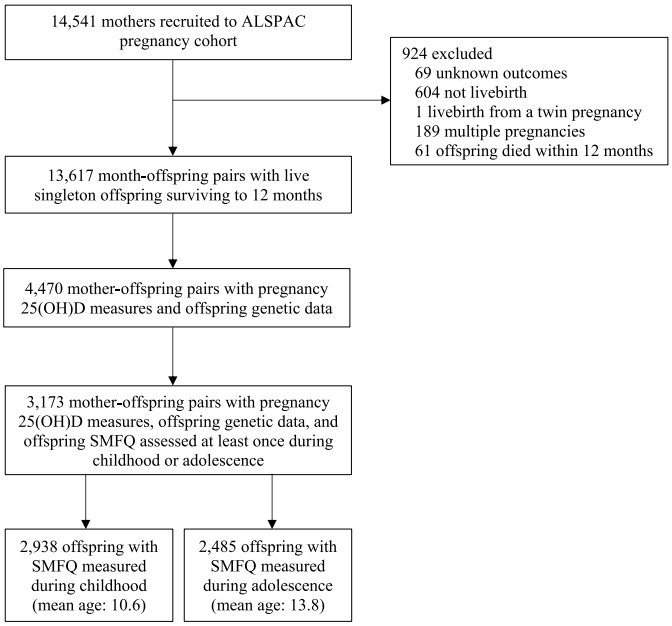

Fig. 1. Flow chart of participants in the Avon Longitudinal Study of Parents and Children (ALSPAC) sample included in the analytic samples. ALSPAC: Avon Longitudinal Study of Parents and Children; SMFQ: Short Moods and Feelings Questionnaire; 25(OH)D: 25-hydroxyvitamin D.

2.2. Offspring depression

Depressive symptoms were measured using the Short Mood and Feelings Questionnaire (SMFQ) by a trained interviewer during childhood (mean: 10.62; SD: 0.25) and adolescence (mean: 13.83; SD: 0.21). The SMFQ consists of 13 items that capture depressive symptoms in the past two weeks. Total SMFQ scores were obtained by summing across all items (possible score range: 0–26), with higher scores corresponding to higher depressive symptoms. The SMFQ has been validated in adolescents (ages 6–18), and correlates highly with both Children's Depression Inventory scores and past-year Diagnostic Interview for Children depression scores (Angold et al., 2002). The SMFQ was dichotomized, with depression defined as SMFQ $\geq$ 11, since the raw SMFQ scores were positively skewed (skewness: 1.36 for childhood subsample, 1.46 for adolescent sample) and the dichotomized score provided greater clinical interpretability. This threshold has been shown to have high sensitivity and specificity for depression defined by the revised Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III-R) (Thapar and McGuffin, 1998), and has been used in prior ALSPAC studies of depression (Joinson et al., 2017; Pearson et al., 2015).

2.3. Serum 25(OH)D measurements

Maternal serum 25(OH)D_2 and 25(OH)D_3 were measured on non-fasting blood samples taken for routine pregnancy tests throughout pregnancy. Blood samples were assayed using high-performance liquid chromatography tandem mass spectrometry (HPLC/MS) in accordance

with Vitamin D External Quality Assessment Scheme requirements. Details about sampling, storage, and processing are described in detail elsewhere (Lawlor et al., 2013). For the few mothers who had multiple measurements taken during pregnancy (4.8%) (Wills et al., 2013), the last result available was used, in line with similar ALSPAC studies that have assessed the influence of maternal 25(OH)D concentrations during pregnancy on child health outcomes (Lawlor et al., 2013; Williams et al., 2013). Total 25(OH)D was calculated by summing $25(OH)D_2$ and $25(OH)D_3$ levels.

As total maternal 25(OH)D levels displayed sinusoidal seasonal variation (**Figure S1**), a seasonality-adjusted 25(OH)D variable was derived to represent annual mean levels of 25(OH)D. Similar trigonometric models have been previously applied to adjust for seasonal variation in 25(OH)D in ALSPAC (Lawlor et al., 2013; Williams et al., 2013), which have been shown to have good validity (Sachs et al., 2013). Further details of the method are described in the **Supplementary Materials**. Briefly, 25(OH)D was modeled in a linear regression against sine and cosine transformations of the month when blood sampling occurred. The annual mean 25(OH)D concentration for each mother was then estimated using the residuals of the model. The seasonality-adjusted and unadjusted 25(OH)D levels were strongly correlated (Spearman's $r = 0.88$).

2.4. Genetic data

9912 children in the ALSPAC cohort were genotyped on the Illumina HumanHap550 Quad chip (Illumina Inc., San Diego, CA). Standard quality control (QC) measures were performed to exclude individuals on the basis of gender mismatch, minimal or excessive heterozygosity, individual genotyping call rates < 97%, cryptic relatedness (IBD > 10%), and non-European ancestry (assessed using multidimensional scaling analysis and compared to HapMap II). Single nucleotide polymorphisms (SNPs) were excluded based on the following criteria: minor allele frequency (MAF) < 1%; missing rate > 5%; and significant deviation from Hardy-Weinberg Equilibrium (HWE) ($p < 5 \times 10^{-7}$). 500,527 directly genotyped SNPs and 8365 children remained after quality control (QC). Imputation was conducted using Impute V2.2.2 (Marchini et al., 2007) against the 1000 genomes reference panel (Phase 1, version 3) (Genomes Project et al., 2012), with 2186 reference haplotypes (including non-Europeans).

2.5. Polygenic risk scores (PRS)

PRS for depression were generated in PLINK v.1.90 using methods described by Purcell et al. (2007). The Psychiatric Genomics Consortium wave 2 (PGC-MDD2) (Wray et al., 2018) was used as the discovery sample (meta-analytic subsample excluding 23andMe: $n = 173{,}005$) and the ALSPAC cohort was used as the training sample. 23andMe data was excluded due to delays in negotiations between our institution and 23andMe for data access. Additional details about the data sources and QC procedures implemented prior to PRS construction are provided in the **Supplementary Materials**. We generated a single PRS for each child based on a threshold of $p < 0.05$, which was the threshold that maximized the variance explained in depression in a previous discovery sample (Howard et al., 2019). PRS was generated by summing the risk alleles (0, 1, or 2) for each SNP, weighted by the natural log-transformed odds ratio (OR) of its association with major depressive disorder in the PGC-MDD2. PRS scores were then standardized using the z-transformation and categorized into three risk groups (*low risk*: quartile 1; *medium risk*: quartiles 2 and 3; *high risk*: quartile 4) (**Figure S2**).

2.6. Missing data

In the analytic samples, a substantial proportion of participants had missing data on one or more of the covariates. For any single covariate, the amount of missingness ranged between 0.3% and 20.9%; 71.2% and 72.9% of participants had complete covariate data for the child and adolescent subsamples, respectively. Missing covariate information was imputed using multiple imputation by chained equations (MICE) in the *mice* (version 2.30) R package (van Buuren and Groothuis-Oudshoorn, 2011) (**Supplementary Materials**). Covariate distribution after imputation was similar to that in the observed data (**Table S1**). All primary analyses were performed in the imputed data sets and effect estimates were pooled across the 20 generated imputed data sets using Rubin's rule (Marshall et al., 2009).

2.7. Statistical analysis

Comparisons of covariate distributions were made across categories of maternal 25(OH)D during pregnancy using the analysis of variance (ANOVA), Kruskal-Wallis rank sum test, or Chi-squared test. Similar comparisons were made to compare characteristics of the eligible sample to the excluded sample (with maternal 25(OH)D and offspring genetic data, but missing offspring depression measures).

25(OH)D was modeled as a categorical variable, consistent with clinical cut-offs defined by the Endocrine Society (i.e., deficient < 20 ng/mL; insufficient 20–29.9 ng/mL; normal ≥ 30 ng/mL) (Dror and Allen, 2010), and also to account for the non-linearity of continuous 25(OH)D levels. PRS was modeled categorically by polygenic risk groups, as described above, with the reference group set as low PRS. Logistic regression models were used to assess: (1) the main effects of PRS and maternal 25(OH)D on offspring depression during childhood and/or adolescence, separately (Models 1–2) and together (Model 3); and (2) the interaction effect between PRS and maternal 25(OH)D on offspring depression (Model 4). All models were adjusted for gestational age at 25(OH)D measurement, maternal age at delivery, maternal pre-pregnancy BMI, maternal education, maternal occupation, parity, smoking during the first trimester, maternal depression during pregnancy, and child sex (**Supplementary Materials**). Models including PRS were additionally adjusted for the top three principal components (PCs); additional details about the population structure analysis are provided in the **Supplementary Materials**. Models with multiplicative interaction terms were further adjusted for all significant covariate*maternal 25(OH)D and covariate*PRS interactions, based on recommendations by Keller et al. (2014). Effect estimates were presented as ORs and 95% confidence intervals (CI). Linear trend tests were performed to evaluate the dose-response relationship between vitamin D status and depression, and results were presented as p for trend (p-trend). Multiplicative interaction terms between maternal 25(OH)D and PRS were tested separately using the Wald test and globally using the likelihood ratio test. Tests for interaction were performed even in absence of significant main effects as there may be crossover interactions (i.e., the effect of maternal vitamin D is dependent on offspring PRS, or vice versa). Statistical significance was set at two-tailed $p < 0.05$ for all analyses. All analyses were performed in R (version 3.3.1).

Based on the power calculations (**Supplementary Materials**), the study had 80% power to detect OR = 1.4–1.7 for the association between vitamin D deficiency and child/adolescent depression, and sufficient power to detect GxE effects of magnitudes greater than $OR_{gxe} = 1.7$.

2.8. Sensitivity and secondary analyses

We conducted several sensitivity analyses to assess the robustness of the findings. First, we fit logistic regression models to further adjust for covariates that may be affected by or affect 25(OH)D levels during pregnancy, including vitamin D intake, calcium intake, vitamin D supplementation, and oily fish intake at 32 weeks of gestation. As the cut-offs for vitamin D deficiency remain controversial, we additionally conducted analyses using more conservative cut-offs for deficiency set

by the Institute of Medicine (i.e., deficient <10 ng/mL; insufficient 10–19.9 ng/mL; normal ≥20 ng/mL) (Ross & Institute of Medicine (US), 2011). Also, given that vitamin D may have different effects on fetal brain development at different stages of gestation, we repeated the analyses stratified by the trimester of 25(OH)D measurement. Finally, we performed a complete case analysis on the subsample of participants with complete observed data on all variables (child subsample: n = 2091, adolescent subsample: n = 1812).

As a secondary analysis, we also examined the prospective association between maternal vitamin D status and the risk of offspring depressive symptoms using negative binomial regression models. Negative binomial regression allows for the modeling of the highly skewed and over-dispersed counts of depressive symptoms and could potentially provide greater statistical power to detect associations (Agresti, 2013). Estimates were presented as rate ratios (RR) and 95% CI, representing the association between maternal vitamin D status, PRS, and the risk for offspring depressive symptoms.

3. Results

Among the eligible mother-offspring pairs (n = 3173), the mean maternal 25(OH)D was 27.38 ng/mL (SD = 11.97), and 63.5% of mothers were vitamin D insufficient or deficient during pregnancy based on clinical cut-offs defined by the Endocrine Society. The proportion of mothers who had their 25(OH)D measurements taken during pregnancy was similar across seasons (Winter: 23.9%; Spring: 28.7%; Summer: 24.6%; Fall: 22.8%). The median gestational week at 25(OH)D measurement was 29.4 weeks (IQR: 12.7, 33.1), with most available measurements collected in the third trimester (58.5%). Table 1 displays the distribution of mother and offspring characteristics by maternal vitamin D status during pregnancy. Higher maternal vitamin D levels was also positively associated with maternal age at delivery, non-manual occupations, having more than one child, non-smoking during the first trimester, vitamin D intake during pregnancy, vitamin D supplementation intake, oily fish intake during pregnancy, and breastfeeding. 6.2% and 12.9% of the offspring were classified as experiencing depression during childhood and adolescence, respectively.

Compared to the excluded participants, the eligible sample was comprised of mothers with higher 25(OH)D levels during pregnancy and offspring with lower PRS (**Table S2**). Further, mothers in the eligible sample also tended to be older when they gave birth, had higher educational attainment, were in non-manual occupations, had no previous pregnancies, were non-smokers during the first trimester, and showed no evidence of depression during pregnancy. However, the absolute differences between maternal 25(OH)D (i.e., 1.3 ng/mL higher in the eligible sample) and offspring PRS (i.e., 0.07 standardized units lower in the eligible sample) in the eligible and excluded samples were small, suggesting that the results are unlikely to be affected by selection bias.

3.1. Maternal vitamin D status and PRS on offspring depression

Associations between maternal 25(OH)D during pregnancy, PRS, and offspring depression are presented in Table 2. There were no associations between maternal 25(OH)D and offspring depression during childhood. However, there was suggestive evidence that offspring exposed to deficient vitamin D levels during gestation had higher odds of depression in adolescence, compared to offspring exposed to normal vitamin D levels (OR = 1.32; 95% CI: 0.98, 1.79; p = 0.07).

Offspring PRS was positively associated with the odds of depression during childhood (p-$trend$ = 0.003), that is, offspring with high PRS had approximately 2-fold higher odds of childhood depression compared with offspring with low PRS (OR = 1.94; 95% CI: 1.24, 3.03; p = 0.0004); higher PRS was associated with non-significantly higher odds of depression during adolescence (p-$trend$ = 0.06) (Model 2). When modeled together (Model 3), the effect estimates for both maternal vitamin D status and PRS were almost identical to those yielded from their separate models, suggesting that they have independent associations with offspring depression. In Model 4, there was no evidence for significant interactions between maternal vitamin D status and PRS on childhood (p = 0.19) or adolescent (p = 0.36) depression.

3.2. Sensitivity and secondary analyses

Further adjustments for nutritional intake at 32 weeks of gestation (Model 5) (**Table S3**) yielded estimates similar to those from the main analyses. Using more conservative cut-offs for vitamin D deficiency created large sample size imbalances across categories, resulting in a small number of mothers classified as vitamin D deficient during pregnancy (n = 55–71). Nonetheless, the direction and magnitude of effects were generally similar to those using higher cut-offs for deficiency (**Table S4**). The results did not change substantially when stratified by trimester of 25(OH)D measurement, although some of the effect directions were reversed in the small subsamples with measurements in the second trimester (n = 381–438) (**Table S5**). Complete case analysis also showed similar trends to those identified from the primary analyses using the imputed data (**Table S6**), but the associations between PRS and childhood/adolescent depression were attenuated to non-significance, likely due to large reductions in sample sizes.

Results from the negative binomial regression models showed similar associational patterns as those produced from the logistic regression models (**Table S7**). There were no significant main effects of maternal 25(OH)D nor interactions with PRS on the risk of offspring depressive symptoms during childhood or adolescence. The only notable difference was the presence of a statistically significant positive association between PRS and the risk of depressive symptoms during adolescence (p-$trend$ = 0.03).

4. Discussion

In this large, prospective birth cohort, we found little evidence for an association between maternal pregnancy vitamin D status (i.e., serum 25(OH)D levels) and offspring depression in childhood or adolescence. In this sample, PRS was positively associated with risk for offspring depression at both time points but did not interact with maternal 25(OH)D. These findings were robust to adjustments for a range of potential confounders and different cut-offs for vitamin D insufficiency/deficiency.

Although several studies have reported the influence of maternal and/or cord blood 25(OH)D on the offspring's risk for neuropsychiatric or neurodevelopmental disorders/traits, including schizophrenia (D. W. Eyles et al., 2018), ADHD (Morales et al., 2015), and autism-related traits (Vinkhuyzen et al., 2018), the same effects do not appear to be present for depression. Results from the current study are consistent with the only existing study, to our knowledge, that assessed the association between maternal 25(OH)D during pregnancy and offspring depression. In this Strom et al. study (Strom et al., 2014), maternal vitamin D deficiency during pregnancy was unassociated with offspring risk for depression over 22 years of follow-up. Other studies that assessed features similar to depression in childhood, such as emotional problems and/or internalizing symptoms, also did not report significant associations with maternal 25(OH)D (Gale et al., 2008; Keim et al., 2014; Whitehouse et al., 2012). Taken together, these findings do not support a role of maternal vitamin D status during pregnancy on offspring depression or related symptoms in childhood or adolescence.

One possible explanation for these lack of findings is that there may be sensitive developmental periods during which the effects of fetal 25(OH)D on neurodevelopment are particularly salient (Pet and Brouwer-Brolsma, 2016). The precise timing of the neurodevelopmental effects of vitamin D is unclear, but may have importance at any

Table 1
Maternal and offspring characteristics by maternal vitamin D status during pregnancy, among eligible mother-offspring pairs (defined by complete data on maternal 25(OH)D, offspring genetic data, and at least one SMFQ measure).

	All (n = 3173)	Maternal 25(OH)D[a]			p[b]
		<20 ng/mL (n = 988)	20–29.9 ng/mL (n = 1027)	≥30 ng/mL (n = 1158)	
Maternal age at delivery, n (%)					
15–19	46 (1.4)	18 (39.1)	18 (39.1)	10 (21.7)	0.02
20–35	2857 (90.0)	906 (31.7)	915 (32.0)	1036 (36.3)	
>35	270 (8.5)	64 (23.7)	94 (34.8)	112 (41.5)	
Maternal BMI (kg/m^2), median [IQR]	22.18 [20.53, 24.38]	22.18 [20.53, 24.52]	22.35 [20.53, 24.51]	22.02 [20.47, 23.88]	
Maternal education, n (%)					
Lower than O-levels	577 (19.3)	203 (52.3)	180 (31.2)	194 (33.8)	0.09
O-levels	1080 (36.1)	331 (30.6)	359 (33.2)	390 (36.1)	
Higher than O-levels	1332 (44.6)	390 (29.3)	428 (32.1)	514 (38.6)	
Maternal occupation, n (%)					
Manual	427 (16.0)	154 (36.1)	131 (30.7)	142 (33.2)	0.03
Non-manual	2237 (84.0)	659 (29.5)	747 (33.4)	831 (37.1)	
Parity, n (%)					
0	1446 (46.8)	482 (33.3)	477 (33.0)	487 (33.7)	0.007
≥1	1647 (53.2)	483 (29.3)	524 (31.8)	640 (38.9)	
Gestational week of 25(OH)D measurement, median [IQR]	29.43 [12.71, 33.14]	28.29 [11.29, 32.86]	28.71 [11.43, 32.86]	31.14 [18.75, 33.29]	<0.001
Season of 25(OH)D measurement, n (%)					
Winter	758 (23.9)	343 (45.3)	256 (33.8)	159 (20.9)	<0.001
Spring	912 (28.7)	412 (45.2)	297 (32.6)	203 (22.3)	
Summer	781 (24.6)	100 (12.8)	218 (27.9)	463 (59.3)	
Fall	722 (22.8)	133 (18.4)	256 (35.5)	333 (46.1)	
Tobacco use during 1st trimester, n (%)					
No	2569 (82.2)	752 (29.3)	831 (32.4)	984 (38.3)	<0.001
Yes	557 (17.8)	221 (39.7)	181 (32.5)	155 (27.8)	
Oily fish intake at 32 weeks, n (%)					
≥1 times/week	813 (26.8)	214 (26.3)	261 (32.1)	338 (41.6)	<0.001
<1 times/week	1045 (34.5)	318 (30.4)	341 (32.6)	386 (37.0)	
Never/rarely	1173 (38.7)	408 (34.8)	379 (32.3)	386 (32.9)	
Vitamin D supplementation at 32 weeks, n (%)					
No	3035 (95.7)	961 (31.7)	985 (32.4)	1089 (35.9)	0.001
Yes	138 (4.3)	27 (19.6)	42 (30.4)	69 (50.0)	
Vitamin D intake at 32 weeks (ug), median [IQR]	3.43 [2.44, 5.40]	3.21 [2.28, 4.84]	3.39 [2.46, 5.46]	3.69 [2.59, 5.72]	<0.001
Calcium intake at 32 weeks (mg), median [IQR]	938.54 [762.25, 1131.15]	935.50 [762.92, 1129.98]	940.01 [763.07, 1129.33]	939.08 [759.17, 1134.02]	0.87
Maternal depression during pregnancy[c], n (%)					
No	2066 (75.6)	637 (30.8)	642 (31.1)	787 (38.1)	0.10
Yes	667 (24.4)	211 (31.6)	231 (34.6)	225 (33.8)	
Breastfeeding, n (%)					
No	1067 (34.9)	366 (34.3)	356 (33.4)	345 (32.3)	0.001
Yes	1994 (65.1)	585 (29.4)	633 (31.7)	776 (38.9)	
Child sex, n (%)					
Male	1592 (50.2)	483 (30.3)	520 (32.7)	589 (37.0)	0.62
Female	1581 (49.8)	505 (31.9)	507 (32.1)	569 (36.0)	

Abbreviations: 25(OH)D: 25-hydroxyvitamin D; BMI: body mass index; IQR: interquartile range; SMFQ: Short Moods and Feelings Questionnaire.
[a] Unadjusted 25(OH)D levels.
[b] P-value calculated using the Chi-squared test for categorical variables and the ANOVA or Kruskal-Wallis rank sum test for normally and non-normally distributed continuous variables, respectively.
[c] Maternal depression at 18 and/or 32 weeks of gestation.

stage of pregnancy: early gestation, when structures important for behavioral regulation and dopaminergic neurons develop (Almqvist et al., 1996; Gale et al., 2008); mid-gestation, which is characterized by neural circuit formation and myelination (Keunen et al., 2017; Kinney et al., 1988); or late gestation, when prolific brain development and growth occurs (Bouyssi-Kobar et al., 2016; Clouchoux et al., 2012; Kostovic and Jovanov-Milosevic, 2006). Yet, when we stratified our analysis by trimester of 25(OH)D measurement, we did not observe any meaningful differences. However, the stratified analyses had limited statistical power given the small sample sizes within certain subgroups. Hence, the possibility for sensitive periods for vitamin D effects remains, and longitudinal studies sampling 25(OH)D in all three trimesters are needed to establish stronger conclusions; the Strom et al. study also did not explore these relationships. Alternatively, the lack of gestational 25(OH)D effects on child depression may be due to critical window(s) of vulnerability to vitamin D exposure occurring postnatally. In the Tolpannen et al. study (Tolppanen et al., 2012), similarly based on children in the ALSPAC cohort, childhood 25(OH)D_3 levels were found to be associated with adolescent depressive symptoms. It is plausible that the protective effects of vitamin D on depression and mental health are exerted through neuroprotective actions, such as moderating inflammatory processes or modulating neurotrophic factors, after birth. Further studies are necessary to characterize the precise mechanisms of vitamin D on the developing brain.

Our study has several strengths. First, this study was conducted in a large, population-based sample that was more than three times larger than the previous study examining the same associations. Second, the longitudinal study design allowed us to prospectively investigate the effects of maternal 25(OH)D on offspring depression measured during both childhood and adolescence, while adjusting for a wide range of potential confounding factors.

The study also has some limitations. First, only one measurement of 25(OH)D, taken at any time during pregnancy, was available for all mothers in the study sample, which may not have been representative

Table 2
Association between maternal vitamin D status during pregnancy, offspring polygenic risk scores (PRS), and offspring depression during childhood or adolescence.

	Childhood depression (n = 2938)			Adolescent depression (n = 2485)		
	OR	95% CI	p	OR	95% CI	p
Model 1: Maternal 25(OH)D only						
Normal (≥30 ng/mL)	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
Insufficient (20–29.9 ng/mL)	1.02	0.71, 1.48	0.90	1.12	0.84, 1.51	0.44
Deficient (<20 ng/mL)	1.07	0.73, 1.58	0.72	1.32	0.98, 1.79	0.07
Model 2: PRS only						
PRS-Low	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
PRS-Intermediate	1.37	0.90, 2.09	0.14	0.99	0.73, 1.34	0.93
PRS-High	1.94	1.24, 3.03	0.004	1.34	0.96, 1.87	0.09
Model 3: PRS and Maternal 25(OH)D (Main effects)						
Normal (≥30 ng/mL)	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
Insufficient (20–30 ng/mL)	1.03	0.71, 1.49	0.87	1.13	0.84, 1.51	0.43
Deficient (<20 ng/mL)	1.08	0.73, 1.59	0.70	1.33	0.98, 1.81	0.06
PRS-Low	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
PRS-Intermediate	1.36	0.90, 2.09	0.15	0.98	0.73, 1.33	0.92
PRS-High	1.94	1.24, 3.03	0.004	1.34	0.96, 1.87	0.09

	Childhood depression (n = 2938)				Adolescent depression (n = 2485)			
	OR	95% CI	p	p-inter.	OR	95% CI	p	p-inter.
Model 4: PRS and Maternal 25(OH)D (Interaction)								
Normal (≥30 ng/mL)	*ref*	*ref*	*ref*	–	*ref*	*ref*	*ref*	–
Insufficient (20–29.9 ng/mL)	0.65	0.29, 1.45	0.29		1.15	0.62, 2.11	0.66	
Deficient (<20 ng/mL)	0.38	0.13, 1.06	0.06		1.45	0.78, 2.69	0.24	
PRS-Low	*ref*	*ref*	*ref*	–	*ref*	*ref*	*ref*	–
PRS-Intermediate	0.74	0.63, 1.46	0.38		1.21	0.71, 2.06	0.49	
PRS-High	1.26	0.37, 2.53	0.52		1.06	0.58, 1.96	0.84	
Insufficient*PRS-Intermediate	1.97	0.74, 5.26	0.18	0.19	0.80	0.38, 1.66	0.54	0.36
Deficient*PRS-Intermediate	4.09	1.26, 13.3	0.02		0.68	0.32, 1.45	0.32	
Insufficient*PRS-High	1.65	0.59, 4.58	0.34		1.38	0.61, 3.15	0.44	
Deficient*PRS-High	2.92	0.86, 10.0	0.09		1.39	0.60, 3.22	0.44	

Abbreviations: 25(OH)D: 25-hydroxyvitamin D; CI: confidence intervals; OR: odds ratio; p-inter.: p for interaction; PC: principle components; PRS: polygenic risk score.
Model 1: Adjusted for gestational age of 25(OH)D measurement, maternal age, maternal pre-pregnancy BMI, maternal education, maternal occupation, parity, smoking during 1st trimester, maternal depression during pregnancy, and child sex.
Model 2: Model 1 confounders + 3 PCs.
Model 3: Model 2 confounders.
Model 4: Model 3 confounders + significant PRS*covariate, maternal 25(OH)D*covariate interactions.

of average 25(OH)D levels for the duration of the pregnancy. However, studies have shown that single measurements may be reasonable proxies for vitamin D status throughout pregnancy, given the strong correlation in 25(OH)D concentrations over time (Hofmann et al., 2010; Major et al., 2013). Second, the SMFQ only captures depressive symptoms in the past two weeks, which may not represent depression over longer periods. This may have led to outcome misclassification, particularly for adolescent depression, which has been shown to be highly episodic in nature (Holsen, 2000); such misclassification may have biased the results towards the null. Third, it is possible that an association between low maternal vitamin D levels and offspring depression is only detectable at very low levels of maternal 25(OH)D, and that the distribution of 25(OH)D levels in this population was not sufficiently wide to capture this. Compared to prior studies that detected significant associations (D. W. Eyles et al., 2018; Vinkhuyzen et al., 2018), mothers in the current study were less diverse ethnically/racially and/or socioeconomically, and on average had higher 25(OH)D levels (27.38 ng/mL compared to 15.3–23.6 ng/mL in other studies) with only a very small proportion having 25(OH)D levels <10 ng/mL (2%). Fourth, as with most longitudinal studies, there was considerable attrition over time, which could introduce bias when both maternal 25(OH)D and offspring depression were associated with loss to follow-up. Since the difference between the average maternal 25(OH)D levels in the excluded and included samples was small in magnitude, we do not expect attrition in this case to substantially influence the results. Fifth, the study was based in a white population, thus the results may not be generalizable to other racial/ethnic groups or populations with different prevalence of vitamin D deficiency and/or depression. Finally, we may have lacked power to detect weaker effects of maternal 25(OH)D on offspring depression and had even lower power to detect GxE. Larger sample sizes are needed to definitively rule out the presence of smaller associations and gene-environment interactions.

In sum, our findings do not support an association between maternal vitamin D status during pregnancy and offspring depression during childhood and adolescence. This suggests that interventions aimed at increasing 25(OH)D levels during pregnancy may not substantially reduce the risk of offspring depression during childhood or adolescence, although such efforts may still be beneficial for other child health outcomes (Wagner and Hollis, 2018). Larger prospective studies in more racially/ethnically diverse populations with lower average values and/or broader ranges of levels of 25(OH)D during pregnancy are needed to confirm the current findings.

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Declaration of interest

J.W.S. is an unpaid member of the Bipolar/Depression Research Community Advisory Panel of 23andMe. All other authors declare no potential conflicts of interest.

CRediT authorship contribution statement

Min-Jung Wang: Conceptualization, Formal analysis, Writing - original draft, Methodology, Writing - review & editing. **Erin C. Dunn:** Conceptualization, Supervision, Writing - review & editing. **Olivia I. Okereke:** Conceptualization, Supervision, Writing - review & editing. **Peter Kraft:** Conceptualization, Supervision, Writing - review & editing. **Yiwen Zhu:** Conceptualization, Formal analysis, Writing - review & editing. **Jordan W. Smoller:** Conceptualization, Supervision, Writing - review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.01.005.

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SUPPLEMENTARY MATERIALS

Supplementary Methods

Supplementary Figures

Supplementary Tables

Supplementary Methods

Derivation of seasonality-adjusted maternal 25(OH)D measurements

The cosinor model is a linear regression model that models 25(OH)D against sine and cosine transformations of time (i.e., months) (Barnett & Dobson, 2010). The transformed model coefficients can be used to derive the amplitude (distance between mean to peak or trough location of the curve) and phase shift (location of peak and trough on time axis) of the sine curve. The coefficient for the model intercept is used to obtain the annual mean 25(OH)D concentration in the study population, and the residuals are used to derive the annual mean 25(OH)D levels for each individual. Full details of this method has been described elsewhere (Barnett & Dobson, 2010).

Polygenic risk score construction

Polygenic risk scores (PRS) for major depressive disorder (MDD) were constructed using summary-level data from the GWAS meta-analysis of MDD from the Psychiatric Genomics Consortium wave 2 (PGC-MDD2; 130,664 cases and 330,470 controls) (Wray et al., 2018). The PGC-MDD2 consisted of 35 cohorts, including the 29 PGC-MDD anchor cohorts (16,823 cases, 25,632 controls) (Wray et al., 2018) and 6 additional cohorts: GERA (7,162 cases, 38,307 controls) (Banda et al., 2015), deCODE (1,980 cases, 9,536 controls) (Wray et al., 2018), GenScotland (997 cases, 6,358 controls) (Fernandez-Pujals et al., 2015; B. H. Smith et al., 2013), iPsych (18,629 cases, 17,841 controls) (Wray et al., 2018), UK Biobank (14,260 cases, 15,480 controls) (D. J. Smith et al., 2013; Sudlow et al., 2015), and 23andMe (75,607 cases, 231,747 controls) (Hyde et al., 2016). Due to delayed negotiations between our institution and 23andMe, full summary statistics were only available for the meta-analytic subsample (n=173,005) excluding the 23andMe cohort. Prior to score construction, SNPs with imputation quality metric score (INFO)<0.8, MAF<1%, call rate<95%, and HWE $p<1x10^{-6}$ were filtered out. SNPs were pruned for linkage disequilibrium (LD) using p-value informed clump-based pruning in PLINK version 1.90 (https://www.cog-genomics.org/plink2) using the following parameters: --clump-p1 1 --clump-p2 1 --clump-r2 0.2 --clump-kb 500). Within a specified window, LD clumping preferentially keeps the most significant SNPs and removes all other SNPs in high LD.

Assessment of covariates

Data on maternal pre-pregnancy body mass index (BMI, kg/m^2), parity, maternal socioeconomic position indicators, tobacco use, nutritional intake, and vitamin D supplementation were provided by mothers through self-administered questionnaires at 18 and/or 32 weeks of pregnancy. Maternal depression during pregnancy was derived using the Edinburgh Postnatal Depression Scale (Cox, Holden,

& Sagovsky, 1987), with depressed mood defined as scores ≥13. Maternal age at delivery, month/season and gestational age at 25(OH)D measurement (weeks) were obtained from obstetric records. Child sex was obtained from birth records, while information on breastfeeding was collected postnatally from mother-completed questionnaires.

Maternal pre-pregnancy BMI and gestational age at 25(OH)D measurement were included in the models as continuous variables. All other variables were included as categorical variables: maternal age at child birth (age 15-19 years, 20-35 years, or >35 years), education (less than O-levels or equivalent, O-levels, or higher than O-levels), occupation (manual or non-manual), parity (0 or ≥1 child), first trimester tobacco use (yes or no), oily fish intake at 32 weeks of gestation (≥once/week, <once/week, or never/rarely), vitamin D supplementation at 32 weeks of gestation (yes or no), vitamin D intake at 32 weeks of gestation (ug), calcium intake at 32 weeks of gestation (mg), maternal depression during pregnancy (yes or no), breastfeeding (yes or no), child sex (male or female). The reference group for all categorical variables were chosen on the basis of sample size and consistency with the literature.

Population structure analysis

Principal components (PCs) reflect a population's genetic structure and can be used to adjust for population stratification (Price et al., 2006). Using genome-wide SNPs in the directly genotyped data, the top 20 PCs were estimated in PLINK using methods described by Price and colleagues (Price et al., 2006). In line with the PGC ricopili pipeline (https://sites.google.com/a/broadinstitute.org/ricopili/pca) the following quality control (QC) procedures were performed: MAF>5%; HWE>1.0E-03; missing rate<2%; no strand ambiguous SNPs (AT/GC); no MHC (6:25-35Mb); no Chromosome 8 inversions (8:7-13Mb). 462,838 SNPs remained after QC and were pruned if their r2>0.2, within a 200 SNP window. After pruning, 90,414 SNPs were available for principal component analysis. 20 PCs were generated from the analysis and the top 3 PCs were included in the analytic models based on examination of the eigenvalues and a scree plot.

Multivariable multiple imputation

All exposure, covariate, and outcome variables that were included in the final analysis were included in the imputation model for imputing covariate data, since failure to do so may result in a biased anlaytic model (White, Royston, & Wood, 2011). Variables that were strongly correlated with the covariates, such as home crowding and home ownership, were also included in the imputation model because this has been shown to reduce bias and improve precision (White et al., 2011). For continuous variables, predictive mean matching was used for imputation, while logistic and polynomial regression

was used to impute dichotomous and categorical variables, respectively. Twenty imputed data sets were generated using this method.

Several diagnostic tests were performed to assess proper imputation. First, convergence plots were inspected to determine whether convergence was achieved. Second, density plots were examined to compare the distribution of the imputed data to observed data. **Table S1** presents the percentage of missing data for each covariate, as well as a comparison of the distribution of the variables in the observed data versus imputed data.

Power analysis

Power calculations were performed for both the main effects of maternal 25(OH)D and GxE on offspring depression. Power analysis for the main effects of maternal 25(OH)D on offspring depression, was implemented in an online power calculator for logistic regression (http://www.dartmouth.edu/~eugened/power-samplesize.php), developed using algorithms derived by Demidenko (Demidenko, 2007, 2008). Power analysis for GxE was performed using the *powerGWASinteraction* package in R. All power calculations assumed α=0.05 and a two-sided test; other parameters were derived from the literature or directly estimated in the study cohort.

Figure S1. Patterns of maternal 25(OH)D levels during pregnancy by month in the study population

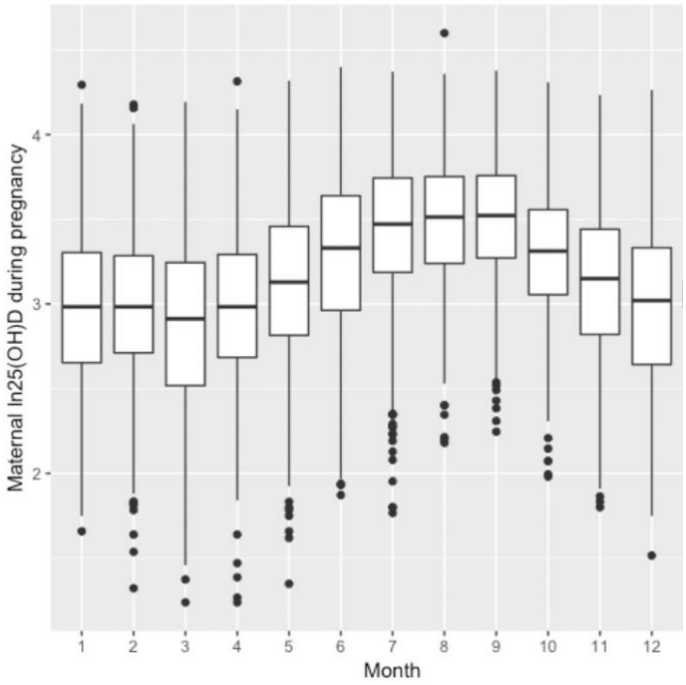

Figure S2. Distribution of offspring MDD PRS and categorizations (low, medium, and high polygenic risk) in the study population

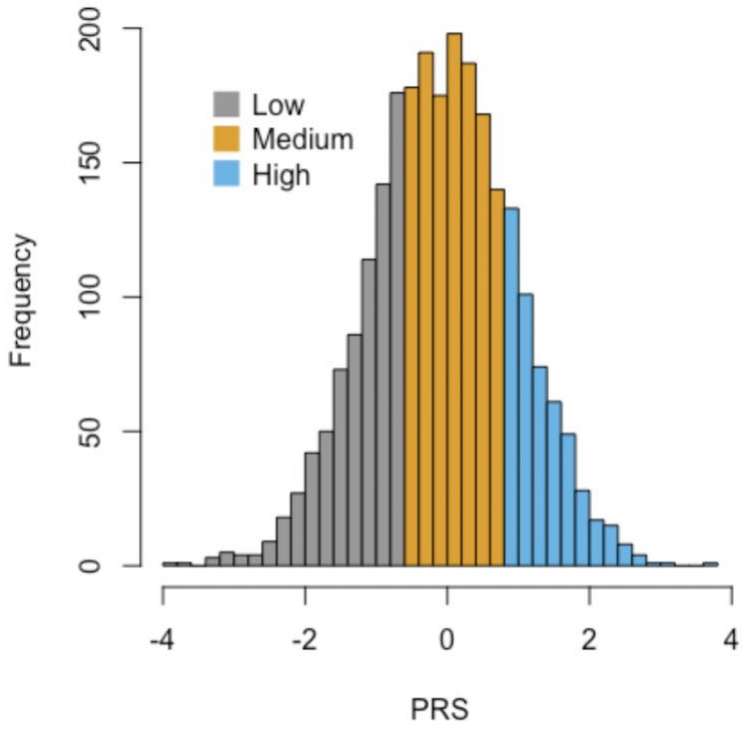

Table S1. Comparison of the distribution of main covariates in the observed data set and the imputed data set, for mother-offspring pairs with (A) SMFQ in childhood; (B) SMFQ in adolescence

(A)

Covariates with missing data	N missing (%)	Mean (SD) or n (%) in sample	
		Observed data	Imputed data
Maternal pre-pregnancy BMI (kg/m2)	264 (5.9)	22.87 (3.63)	22.84 (3.58)
Maternal education			
<O-level	166 (3.7)	534 (19.0)	570 (19.2)
O-level		1016 (36.2)	1077 (36.2)
>O-level		1259 (44.8)	1328 (44.6)
Parity			
0	71 (1.6)	1347 (46.4)	1382 (46.5)
1+		1557 (53.6)	1593 (53.5)
Maternal occupation			
Manual	464 (10.4)	398 (15.9)	504 (16.9)
Non-manual		2113 (84.1)	2471 (83.1)
Tobacco use during the first trimester			
No	40 (0.9)	2434 (82.9)	2466 (82.9)
Yes		501 (17.1)	509 (17.1)
Maternal depression during pregnancy	405 (9.1)		
No		1960 (76.3)	2266 (76.2)
Yes		610 (23.7)	709 (23.8)

(B)

Covariates with missing data	N missing (%)	Mean (SD) or n (%) in sample	
		Observed data	Imputed data
Maternal pre-pregnancy BMI (kg/m2)	191 (7.6)	22.89 (3.74)	22.89 (3.74)
Maternal education			
<O-level	116 (4.6)	417 (17.4)	438 (17.4)
O-level		848 (35.4)	891 (35.5)
>O-level		1130 (47.2)	1182 (47.1)
Parity			
0	57 (2.3)	1200 (48.9)	1226 (48.8)
1+		1254 (51.1)	1285 (51.2)
Maternal occupation			
Manual	353 (14.1)	322 (14.9)	409 (16.3)
Non-manual		1846 (85.1)	2102 (83.7)
Tobacco use during the first trimester			
No	32 (1.3)	2072 (83.6)	2101 (83.7)
Yes		1254 (16.4)	410 (16.3)
Maternal depression during pregnancy	320 (12.7)		
No		1677 (76.5)	1910 (76.1)
Yes		514 (23.5)	601 (23.9)

Table S2. Comparison of covariate distribution among eligible sample and participants excluded due to missing offspring SMFQ

	Excluded sample (n=1297)	Eligible sample (n=3173)	p[1]
Maternal 25(OH)D (ng/mL), median [IQR][2]	24.14 [17.68, 32.82]	25.45 [18.89, 33.42]	**0.003**
Standardized MDD PRS, mean (SD)	0.03 (0.99)	-0.04 (1.01)	**0.04**
Maternal age at birth (years), n (%)			
15-19	77 (5.9)	46 (1.4)	**<0.001**
20-35	1150 (88.7)	2857 (90.0)	
>35	70 (5.4)	270 (8.5)	
Maternal BMI (kg/m2), median [IQR]	22.02 [20.47, 24.51]	22.18 [20.53, 24.38]	0.79
Maternal education, n (%)			
Lower than O-levels	301 (29.7)	577 (19.3)	**<0.001**
O-levels	390 (38.5)	1080 (36.1)	
Higher than O-levels	323 (31.9)	1332 (44.6)	
Maternal occupation, n (%)			
Manual	195 (22.4)	427 (16.0)	**<0.001**
Non-manual	676 (77.6)	2237 (84.0)	
Parity, n (%)			
0	500 (41.9)	1446 (46.8)	**0.005**
≥1	693 (58.1)	1647 (53.2)	
Gestational week of 25(OH)D measurement, median [IQR]	29.71 [13.00, 33.29]	29.43 [12.71, 33.14]	0.26
Season of 25(OH)D measurement, n (%)			
Winter	303 (23.4)	758 (23.9)	0.78
Spring	381 (29.4)	912 (28.7)	
Summer	305 (23.5)	781 (24.6)	
Fall	308 (23.7)	722 (22.8)	
Tobacco use during 1st trimester, n (%)			
No	832 (68.5)	2569 (82.2)	**<0.001**
Yes	383 (31.5)	557 (17.8)	
Maternal depression during pregnancy, n (%)			
No	656 (70.0)	2066 (75.6)	**0.001**
Yes	281 (30.0)	667 (24.4)	

1 P-value calculated using Chi-squared test for categorical variables and the student's t-test or Kruskall-Wallis test for continuous variables

2 Mean annual 25(OH)D levels

Table S3. Association between maternal vitamin D status during pregnancy, PRS, and child/adolescent depression, additionally adjusting for other covariates (Model 5)

	Childhood depression (n=2938)				Adolescent depression (n=2485)			
	OR	**95% CI**	**p**	**p-interaction**	**OR**	**95% CI**	**p**	**p-interaction**
Model 5: PRS and Maternal 25(OH)D								
Normal (≥30 ng/mL)	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
Insufficient (20-29.9 ng/mL)	0.63	0.28, 1.42	0.27	-	1.14	0.62, 2.10	0.66	-
Deficient (<20 ng/mL)	0.35	0.12, 0.99	0.05		1.46	0.79, 2.71	0.23	
PRS-Low	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
PRS-Intermediate	0.74	0.37, 1.48	0.40	-	1.22	0.72, 2.08	0.46	-
PRS-High	1.28	0.64, 2.59	0.48		1.09	0.59, 2.00	0.79	
Insufficient*PRS-Intermediate	1.94	0.73, 5.19	0.19		0.80	0.38, 1.67	0.55	
Insufficient*PRS-High	4.06	1.25, 13.19	0.02	0.20	0.68	0.32, 1.44	0.31	0.37
Deficient*PRS-Intermediate	1.61	0.86, 4.48	0.36		1.38	0.60, 3.15	0.44	
Deficient*PRS-High	2.95	0.58, 10.12	0.08		1.37	0.59, 3.16	0.46	

Abbreviations: CI: confidence intervals; OR: odds ratio; p-inter.: p for interaction; PRS: polygenic risk score
Model 5: Model 4 covariates + oily fish intake + vitamin D supplementation + vitamin D intake + Calcium intake

Table S4. Association between maternal vitamin D status during pregnancy, PRS, and child/adolescent depression, using thresholds of <10, 10-19.99, and ≥20 ng/mL

	Childhood depression (n=2938)					Adolescent depression (n=2485)				
	n	**OR**	**95% CI**	**p**	**p-trend**	**n**	**OR**	**95% CI**	**p**	**p-trend**
Model 1: Maternal 25(OH)D										
Normal (≥20 ng/mL)	2075	*ref*	*ref*	*ref*		1748	*ref*	*ref*	*ref*	
Insufficient (10-19.9 ng/mL)	792	1.08	0.77, 1.51	0.66	0.83	682	1.26	0.97, 1.64	0.09	0.14
Deficient (<10 ng/mL)	71	0.87	0.31, 2.46	0.80		55	1.05	0.46, 2.39	0.92	
Model 2: PRS										
PRS-Low	735	*ref*	*ref*	*ref*		622	*ref*	*ref*	*ref*	
PRS-Intermediate	1471	1.37	0.90, 2.09	0.14	**0.003**	1242	0.99	0.73, 1.34	0.93	0.06
PRS-High	732	**1.94**	**1.24, 3.03**	**0.004**		621	1.34	0.96, 1.87	0.09	
Model 3: PRS and Maternal 25(OH)D (Main effects)										
Normal (≥20 ng/mL)	-	*ref*	*ref*	*ref*		-	*ref*	*ref*	*ref*	
Insufficient (10-19.9 ng/mL)	-	1.08	0.77, 1.51	0.67	0.82	-	1.27	0.97, 1.65	0.08	0.14
Deficient (<10 ng/mL)	-	0.89	0.32, 2.50	0.82		-	1.04	0.45, 2.38	0.93	
PRS-Low	-	*ref*	*ref*	*ref*		-	*ref*	*ref*	*ref*	
PRS-Intermediate	-	1.37	0.90, 2.09	0.15	**0.003**	-	0.99	0.73, 1.34	0.93	0.07
PRS-High	-	**1.93**	**1.23, 3.03**	**0.004**		-	1.34	0.96, 1.87	0.09	

	Childhood depression (n=2938)					Adolescent depression (n=2485)				
	n	**OR**	**95% CI**	**p**	**p-trend**	**n**	**OR**	**95% CI**	**p**	**p-trend**
Model 4: PRS and Maternal 25(OH)D (Interaction)										
Normal (≥20 ng/mL)	-	*ref*	*ref*	*ref*		-	*ref*	*ref*	*ref*	
Insufficient (10-19.9 ng/mL)	-	0.40	0.14, 1.17	0.10	-	-	1.41	0.82, 2.41	0.21	-
Deficient (<10 ng/mL)	-	1.16	0.15, 9.26	0.89		-	0.70	0.09, 5.60	0.74	
PRS-Low	-	*ref*	*ref*	*ref*		-	*ref*	*ref*	*ref*	
PRS-Intermediate	-	1.04	0.64, 1.69	0.86	-	-	1.07	0.74, 1.55	0.71	-
PRS-High	-	1.60	0.96, 2.67	0.07		-	1.27	0.84, 1.92	0.25	
Insufficient*PRS-Intermediate	-	3.46	1.08, 11.07	0.04		-	0.72	0.37, 1.39	0.32	
Deficient*PRS-Intermediate	-	0.71	0.06, 8.97	0.79	0.25	-	2.03	0.20, 20.32	0.55	0.39
Insufficient*PRS-High	-	2.68	0.79, 9.08	0.11		-	1.18	0.58, 2.42	0.64	
Deficient*PRS-High	-	0.72	0.04, 13.52	0.83		-	0.75	0.04, 14.63	0.85	

Abbreviations: CI: confidence intervals; OR: odds ratio; p-inter.: p for interaction; PRS: polygenic risk score
Model 1: Adjusted for gestational age of 25(OH)D measurement, maternal age, maternal pre-pregnancy BMI, maternal education, maternal occupation, parity, smoking during 1st trimester, maternal depression during pregnancy, and child sex
Model 2: Model 1 confounders + 3 PCs
Model 3: Model 2 confounders
Model 4: Model 3 confounders + significant PRS*covariate, maternal 25(OH)D*covariate interactions

Table S5. Association between maternal vitamin D status during pregnancy, PRS, and child/adolescent depression, stratified by trimester of 25(OH)D measurement

	Trimester 1									
	Depression at age 10 (n=781)					Depression at age 13 (n=652)				
	OR	**LCI**	**UCI**	**p**	**p-trend**	**OR**	**LCI**	**UCI**	**p**	**p-trend**
Model 1: Maternal 25(OH)D										
Normal (≥30 ng/ml)	*ref*	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	*ref*	
Insufficient (20-30 ng/ml)	1.56	0.69	3.52	0.28	0.34	1.12	0.61	2.05	0.71	0.09
Deficient (<20 ng/ml)	1.55	0.67	3.56	0.30		1.62	0.90	2.92	0.11	
Model 2: PRS										
PRS-Low	*ref*	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	*ref*	
PRS-Intermediate	1.40	0.64	3.08	0.40	0.72	0.97	0.53	1.77	0.93	0.27
PRS-High	1.19	0.46	3.07	0.72		1.39	0.71	2.70	0.34	
Model 3: PRS and Maternal 25(OH)D (Main effects)										
Normal (≥30 ng/ml)	*ref*	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	*ref*	
Insufficient (20-30 ng/ml)	1.58	0.70	3.57	0.27	0.34	1.14	0.62	2.08	0.68	0.09
Deficient (<20 ng/ml)	1.55	0.68	3.58	0.30		1.64	0.91	2.98	0.10	
PRS-Low	*ref*	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	*ref*	
PRS-Intermediate	1.42	0.64	3.14	0.38	0.70	0.97	0.53	1.77	0.93	0.29
PRS-High	1.22	0.47	3.14	0.69		1.40	0.71	2.73	0.33	
Model 4: PRS and Maternal 25(OH)D (Interaction)	**OR**	**LCI**	**UCI**	**p**	**p-inter.**	**OR**	**LCI**	**UCI**	**p**	**p-inter.**
Normal (≥30 ng/ml)	*ref*	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	*ref*	
Insufficient (20-30 ng/ml)	0.51	0.10	2.71	0.43	-	0.65	0.15	2.84	0.57	-
Deficient (<20 ng/ml)	0.54	0.10	3.03	0.49		2.38	0.65	8.69	0.19	
PRS-Low	*ref*	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	*ref*	
PRS-Intermediate	0.43	0.09	2.08	0.29	-	1.01	0.29	3.49	0.99	-
PRS-High	0.54	0.08	3.51	0.52		1.30	0.33	5.16	0.71	
Insufficient*PRS-Intermediate	5.00	0.65	38.35	0.12		1.69	0.31	9.22	0.54	
Deficient*PRS-Intermediate	4.30	0.53	34.61	0.17	0.62	0.65	0.14	3.01	0.58	0.46
Insufficient*PRS-High	2.90	0.25	33.14	0.39		2.56	0.40	16.29	0.32	
Deficient*PRS-High	3.00	0.25	35.22	0.38		0.56	0.10	3.17	0.51	

	Trimester 2									
	Depression at age 10 (n=438)					Depression at age 13 (n=381)				
	OR	**LCI**	**UCI**	**p**	**p-trend**	**OR**	**LCI**	**UCI**	**p**	**p-trend**
Model 1: Maternal 25(OH)D										
Normal (≥30 ng/ml)	*ref*	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	*ref*	
Insufficient (20-30 ng/ml)	0.78	0.30	2.03	0.61	0.05	1.30	0.63	2.66	0.48	0.91
Deficient (<20 ng/ml)	0.21	0.04	1.03	0.05		1.03	0.48	2.19	0.95	
Model 2: PRS										
PRS-Low	*ref*	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	*ref*	
PRS-Intermediate	1.41	0.36	5.51	0.62	0.14	0.64	0.30	1.36	0.24	0.71
PRS-High	2.60	0.65	10.43	0.18		0.79	0.34	1.84	0.59	
Model 3: PRS and Maternal 25(OH)D (Main effects)										
Normal (≥30 ng/ml)	*ref*	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	*ref*	
Insufficient (20-30 ng/ml)	0.74	0.28	1.98	0.55	0.04	1.33	0.64	2.77	0.44	0.80
Deficient (<20 ng/ml)	0.20	0.04	0.95	0.04		1.10	0.51	2.37	0.81	
PRS-Low	*ref*	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	*ref*	
PRS-Intermediate	1.38	0.34	5.55	0.65	0.12	0.64	0.30	1.36	0.25	0.64
PRS-High	1.76	0.67	11.33	0.16		0.80	0.35	1.87	0.61	
Model 4: PRS and Maternal 25(OH)D (Interaction)*	**OR**	**LCI**	**UCI**	**p**	**p-inter.**	**OR**	**LCI**	**UCI**	**p**	**p-inter.**
Normal (≥30 ng/ml)	*ref*	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	*ref*	
Insufficient (20-30 ng/ml)	-	-	-	-	-	-	-	-	-	-
Deficient (<20 ng/ml)	-	-	-	-		-	-	-	-	
PRS-Low	*ref*	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	*ref*	
PRS-Intermediate	-	-	-	-	-	-	-	-	-	-
PRS-High	-	-	-	-		-	-	-	-	
Insufficient*PRS-Intermediate	-	-	-	-		-	-	-	-	
Deficient*PRS-Intermediate	-	-	-	-		-	-	-	-	
Insufficient*PRS-High	-	-	-	-		-	-	-	-	
Deficient*PRS-High	-	-	-	-		-	-	-	-	

	Trimester 3									
	Childhood depression (n=1719)					Adolescent depression (n=1452)				
	OR	**LCI**	**UCI**	**p**	**p-trend**	**OR**	**LCI**	**UCI**	**p**	**p-trend**
Model 1: Maternal 25(OH)D										
Normal (≥30 ng/ml)	*ref*	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	*ref*	
Insufficient (20-30 ng/ml)	0.91	0.56	1.47	0.71	0.53	1.13	0.76	1.66	0.55	0.19
Deficient (<20 ng/ml)	1.17	0.72	1.92	0.52		1.31	0.87	1.98	0.19	
Model 2: PRS										
PRS-Low	*ref*	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	*ref*	
PRS-Intermediate	1.27	0.73	2.21	0.39	**0.004**	1.12	0.75	1.69	0.58	0.06
PRS-High	**2.15**	**1.22**	**3.78**	**0.008**		1.54	0.98	2.40	0.06	
Model 3: PRS and Maternal 25(OH)D (Main effects)										
Normal (≥30 ng/ml)	*ref*	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	*ref*	
Insufficient (20-30 ng/ml)	0.92	0.57	1.49	0.74	0.50	1.10	0.75	1.63	0.62	0.23
Deficient (<20 ng/ml)	1.20	0.73	1.96	0.47		1.30	0.86	1.96	0.22	
PRS-Low	*ref*	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	*ref*	
PRS-Intermediate	1.27	0.73	2.21	0.40	**0.005**	1.12	0.74	1.69	0.58	0.06
PRS-High	**2.15**	**1.22**	**3.79**	**0.008**		1.54	0.98	2.41	0.06	
Model 4: PRS and Maternal 25(OH)D (Interaction)*	**OR**	**LCI**	**UCI**	**p**	**p-inter.**	**OR**	**LCI**	**UCI**	**p**	**p-inter.**
Normal (≥30 ng/ml)	*ref*	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	*ref*	
Insufficient (20-30 ng/ml)	0.71	0.26	1.95	0.51	-	1.12	0.51	2.45	0.78	-
Deficient (<20 ng/ml)	0.26	0.06	1.22	0.09		1.10	0.48	2.54	0.82	
PRS-Low	*ref*	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	*ref*	
PRS-Intermediate	0.72	0.30	1.72	0.46	-	1.31	0.67	2.56	0.43	-
PRS-High	1.35	0.57	3.17	0.50		1.00	0.45	2.21	0.99	
Insufficient*PRS-Intermediate	1.28	0.36	4.61	0.70		0.78	0.30	2.03	0.61	
Deficient*PRS-Intermediate	7.25	1.31	40.10	0.02	0.10	0.80	0.28	2.24	0.67	0.24
Insufficient*PRS-High	1.61	0.46	5.71	0.46		1.48	0.80	4.39	0.48	
Deficient*PRS-High	4.64	0.81	26.50	0.08		2.47	0.50	7.69	0.12	

Model 1: Adjusted for gestational age of 25(OH)D measurement, maternal age, maternal pre-pregnancy BMI, maternal education, maternal social class, parity, smoking during 1st trimester, maternal psychopathology during pregnancy, child sex
Model 2: Model 1 confounders + 3 PCs
Model 3: Model 2 confounders
Model 4: Model 3 confounders + any significant PRS*covariate and maternal 25(OH)D*covariate interactions

Table S6. Complete case analysis for the association between maternal vitamin D status during pregnancy, PRS, and child/adolescent depression

	Childhood depression (n=2091)				Adolescent depression (n=1812)			
	OR	**95% CI**	**p**	**p-trend**	**OR**	**95% CI**	**p**	**p-trend**
Model 1: Maternal 25(OH)D								
Normal (≥30 ng/mL)	*ref*	*ref*	*ref*		*ref*	*ref* *ref*	*ref*	
Insufficient (20-29.9 ng/mL)	1.19	0.77, 1.84	0.43	0.57	1.01	0.71, 1.43	0.97	0.15
Deficient (<20 ng/mL)	1.14	0.72, 1.80	0.57		1.30	0.91, 1.85	0.14	
Model 2: PRS								
PRS-Low	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
PRS-Intermediate	1.39	0.89, 2.24	0.16	0.12	0.85	0.60, 1.20	0.34	0.10
PRS-High	1.51	0.90, 2.56	0.12		1.36	0.93, 1.99	0.11	
Model 3: PRS and Maternal 25(OH)D (Main effects)								
Normal (≥30 ng/mL)	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
Insufficient (20-29.9 ng/mL)	1.19	0.77, 1.84	0.44	0.55	1.03	0.73, 1.47	0.86	0.15
Deficient (<20 ng/mL)	1.14	0.72, 1.80	0.58		1.32	0.92, 1.88	0.13	
PRS-Low	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
PRS-Intermediate	1.38	0.88, 2.23	0.17	0.12	0.85	0.60, 1.20	0.34	0.10
PRS-High	1.51	0.90, 2.56	0.12		1.36	0.93, 2.00	0.11	
Model 4: PRS and Maternal 25(OH)D (Interaction)	**OR**	**95% CI**	**p**	**p-inter.**	**OR**	**95% CI**	**p**	**p-inter.**
Normal (≥30 ng/mL)	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
Insufficient (20-29.9 ng/mL)	0.49	0.17, 1.32	0.16	-	0.71	0.35, 1.43	0.35	-
Deficient (<20 ng/mL)	0.29	0.09, 0.84	0.03		1.28	0.65, 2.54	0.47	
PRS-Low	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
PRS-Intermediate	0.74	0.36, 1.57	0.43	-	4.50	1.19, 17.7	0.03	-
PRS-High	0.61	0.24, 1.47	0.28		3.73	0.77, 19.3	0.11	
Insufficient*PRS-Intermediate	2.70	0.90, 0.87	0.08		0.85	0.35, 2.05	0.72	
Insufficient*PRS-High	2.89	0.92, 0.99	0.08	0.12	0.72	0.31, 1.66	0.44	0.18
Deficient*PRS-Intermediate	4.70	1.35, 1.78	0.02		2.36	0.90, 6.30	0.08	
Deficient*PRS-High	3.39	0.88, 1.41	0.08		1.47	0.57, 3.86	0.43	

Abbreviations: CI: confidence intervals; OR: odds ratio; p-inter.: p for interaction; PRS: polygenic risk score

Model 1: Adjusted for gestational age of 25(OH)D measurement, maternal age, maternal pre-pregnancy BMI, maternal education, maternal occupation, parity, smoking during 1st trimester, maternal depression during pregnancy, and child sex

Model 2: Model 1 confounders + 3 PCs

Model 3: Model 2 confounders

Model 4: Model 3 confounders + significant PRS*covariate, maternal 25(OH)D*covariate interactions

Table S7. Negative binomial regression results for the association between maternal vitamin D status during pregnancy, PRS, and child/adolescent depressive symptoms

	Childhood depression (n=2938)				Adolescent depression (n=2485)			
	RR	**95% CI**	**p**	**p-trend**	**RR**	**95% CI**	**p**	**p-trend**
Model 1: Maternal 25(OH)D								
Normal (≥30 ng/mL)	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
Insufficient (20-29.9 ng/mL)	1.02	0.94, 1.10	0.68	0.48	1.02	0.94, 1.11	0.63	0.15
Deficient (<20 ng/mL)	1.03	0.95, 1.12	0.48		1.07	0.98, 1.17	0.15	
Model 2: PRS								
PRS-Low	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
PRS-Intermediate	1.10	1.01, 1.18	0.03	**0.002**	1.01	0.93, 1.10	0.86	**0.03**
PRS-High	1.15	1.06, 1.26	0.002		1.11	1.01, 1.23	0.04	
Model 3: PRS and Maternal 25(OH)D (Main effects)								
Normal (≥30 ng/mL)	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
Insufficient (20-29.9 ng/mL)	1.02	0.94, 1.10	0.68	0.49	1.02	0.94, 1.11	0.63	0.15
Deficient (<20 ng/mL)	1.03	0.95, 1.11	0.50		1.07	0.98, 1.17	0.15	
PRS-Low	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
PRS-Intermediate	1.09	1.01, 1.18	0.03	**0.002**	1.01	0.92, 1.10	0.87	**0.04**
PRS-High	1.15	1.06, 1.26	0.002		1.11	1.01, 1.23	0.04	
Model 4: PRS and Maternal 25(OH)D (Interaction)*	**RR**	**95% CI**	**p**	**p-inter.**	**RR**	**95% CI**	**p**	**p-inter.**
Normal (≥30 ng/mL)	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
Insufficient (20-29.9 ng/mL)	0.95	0.82, 1.11	0.52	-	1.06	0.89, 1.26	0.49	-
Deficient (<20 ng/mL)	0.94	0.80, 1.11	0.49		0.99	0.83, 1.19	0.94	
PRS-Low	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
PRS-Intermediate	1.02	0.90, 1.17	0.72	-	1.03	0.88, 1.19	0.72	-
PRS-High	1.08	0.93, 1.26	0.32		1.04	0.88, 1.24	0.63	
Insufficient*PRS-Intermediate	1.09	0.91, 1.32	0.34		0.91	0.74, 1.12	0.39	
Deficient*PRS-Intermediate	1.11	0.91, 1.36	0.28	0.79	1.05	0.84, 1.31	0.66	0.41
Insufficient*PRS-High	1.09	0.88, 1.34	0.43		1.02	0.81, 1.30	0.84	
Deficient*PRS-High	1.13	0.90, 1.42	0.28		1.21	0.94, 1.56	0.14	

Abbreviations: CI: confidence intervals; RR: risk ratio; p-inter.: p for interaction; PRS: polygenic risk score

Model 1: Adjusted for gestational age of 25(OH)D measurement, maternal age, maternal pre-pregnancy BMI, maternal education, maternal occupation, parity, smoking during 1st trimester, maternal depression during pregnancy, and child sex

Model 2: Model 1 confounders + 3 PCs

Model 3: Model 2 confounders

Model 4: Model 3 confounders + significant PRS*covariate, maternal 25(OH)D*covariate interactions

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