Maternal 25-hydroxyvitamin D levels in relation to offspring respiratory symptoms and infections.

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120-character summary: Low late-pregnancy 25(OH)D levels are not associated with offspring parent-reported respiratory symptoms and infections.

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Recently, there has been an increasing interest in immunomodulatory effects of vitamin D. Several studies have suggested detrimental effects of insufficient 25-hydroxyvitamin D (25(OH)D) levels on the innate and acquired immune system which may contribute to the development of infections, and atopic and allergic conditions [1-4] . Children as well as pregnant and lactating women have been identified as groups with a high risk of 25(OH)D insufficiency [5]. Low maternal serum 25(OH)D levels in pregnancy may contribute to increased risk of offspring infections and atopic outcomes. Previous studies demonstrate inconsistency regarding relationships between maternal vitamin D intake, serum 25(OH)D levels and umbilical cord 25(OH)D levels with these outcomes in offspring [6-10]. We aimed to explore relationships between maternal serum 25(OH)D levels during late pregnancy and parent-reported respiratory tract symptoms and doctor-diagnosed lower respiratory tract infections (LRTI) in early childhood in a large cohort study .

The study sample consisted of 2025 mother-child pairs from the Southampton Women's Survey with maternal serum 25(OH)D measurement at 34 weeks' gestation (Diasorin RIA, Diasorin, Stillwater, US) [11]. Follow-up was at children's age 6 months (n=2026), 12 months (n=1946) and 2 years (n=1876). Parents were asked whether the child had suffered from any of the following since the last visit: one or more episodes of chest wheezing/whistling, waking at night coughing three or more nights in a row (prolonged cough), one or more episodes of croup or a croupy cough, bouts of vomiting or diarrhoea lasting 2 days or longer, or a doctor-diagnosed chest infection, bronchitis, bronchiolitis, pneumonia and/or ear infection. Chest infection, bronchitis, bronchiolitis and pneumonia were combined into one variable labelled "lower respiratory tract infection" (LRTI). Binary variables were created for each outcome. Relative risks were calculated by Poisson regression with robust variance with serum 25(OH)D>75 nmol/l as reference category [12]. All analyses were adjusted for child's sex, birthweight and gestational age, and for maternal age at childbirth, educational level, pre-pregnancy BMI, parity, ethnicity, smoking in pregnancy, and breast feeding duration. The study was approved by the Southampton and South West Hampshire Research Ethics Committee (276/97, 307/97, 089/99, 06/Q1702/104). Parental consent was obtained before inclusion of participants.

Median late-pregnancy serum 25(OH)D level was 59.0 [interquartile range 40.6-84.3] nmol/l. Lower late-pregnancy serum 25(OH)D levels were not associated with increased risk of parent-reported respiratory symptoms or infections in children aged 6 months, 12 months or 2 years. On the contrary, mothers with serum 25(OH)D levels below 50 nmol/l reported fewer respiratory symptoms and doctor-diagnosed LRTI in their children aged 0 to 6 months than those with serum 25(OH)D levels above75 nmol/l (Table 1). Additional adjustment for season of blood sampling (April to September versus October to March) did not alter our findings.

Our results do not support an association between low late-pregnancy serum 25(OH)D levels and increased risk of parent-reported offspring respiratory symptoms and infections in early childhood. The positive associations between serum 25(OH)D levels and self-reported respiratory symptoms and LRTI at child's age 0 to 6 months may be attributable to residual confounding. Thus, health conscious women have higher serum 25(OH)D levels and may be more prone to report their children's symptoms and/or have an increased rate of consultation of a doctor at a similar level of symptoms. Other factors which may underlie discrepancies between studies include differences in measurement methods of serum 25(OH)D levels and outcome prevalence, the nature of questions asked and reported behaviour [6-10].The strengths of this study are size and population-based nature. Limitations include the absence of objective outcomes regarding respiratory symptoms and infections and thus the presence of potential recall bias. In addition, awareness about study end-points may have influenced medical behaviour of parents. Furthermore, 25(OH)D has a half-life of a few weeks, and we did not have 25(OH)D in early pregnancy, or postnatally in the offspring. Thus, mediation through 25(OH)D at other times in development remains a possibility, and clearly these observational data do not allow causality to be determined. Finally, wheezing may be a symptom of airway inflammation of either allergic or infectious cause and does not discriminate between these aetiologies. Randomized controlled trials are essential to clarify the role of vitamin D in pregnancy in relation to childhood respiratory symptoms and infections.

Table 1. Relative risks (95% CI) for self-reported respiratory symptoms and infections according to clinical serum 25(OH)D categories.

25(OH)D category		<25 nmol/l	25-49 nmol/l	50-74 nmol/l	>=75 nmol/l	
	N cases/N total	RR (95% CI)	RR (95% CI)	RR (95% CI)		P-value
0-6 months						
N (%)	2025	100 (4.9)	666 (32.9)	572 (28.2)	687 (33.9)	
Wheezing	525/2021	0.64 [0.44-0.95]	0.72 [0.61-0.87]	0.96 [0.81-1.15]	reference	0.000
Prolonged cough	319/2019	0.33 [0.16-0.69]	0.68 [0.53-0.88]	0.80 [0.62-1.02]	reference	0.000
Croupy cough	79/2024	0.13 [0.02-1.01]	0.27 [0.14-0.53]	0.68 [0.41-1.12]	reference	0.000
Diagnosed LRTI	288/2021	0.45 [0.24-0.84]	0.63 [0.49-0.81]	0.76 [0.58-0.99]	reference	0.000
Diagnosed ear infection	123/2024	0.83 [0.41-1.69]	0.64 [0.40-1.01]	0.93 [0.61-1.93]	reference	0.142
Diarrhoea	363/2024	0.99 [0.65-1.50]	0.93 [0.73-1.18]	1.05 [0.83-1.33]	reference	0.484
Vomiting	215/2024	1.04 [0.60-1.81]	0.86 [0.63-1.18]	0.98 [0.71-1.35]	reference	0.733
6-12 months						
N (%)	1946	94 (4.8)	628 (32.3)	552 (28.4)	672 (34.5)	
Wheezing	601/1946	1.10 [0.80-1.52]	1.21 [1.03-1.43]	1.17 [0.98-1.39]	reference	0.163
Prolonged cough	450/1945	1.09 [0.73-1.62]	1.16 [0.95-1.42]	1.09 [0.89-1.35]	reference	0.196
Croupy cough	142/1946	1.62 [0.86-3.04]	0.92 [0.62-1.36]	0.87 [0.58-1.32]	reference	0.773
Diagnosed LRTI	368/1946	1.11 [0.72-1.71]	1.22 [0.97-1.54]	1.12 [0.87-1.42]	reference	0.155
Diagnosed ear infection	386/1945	1.29 [0.87-1.92]	1.13 [0.90-1.42]	1.18 [0.93-1.48]	reference	0.118
Diarrhoea	691/1944	0.91 [0.67-1.25]	0.96 [0.83-1.12]	1.00 [0.86-1.16]	reference	0.670

Vomiting	415/1944	1.26 [0.85-1.88]	1.18 [0.96-1.45]	0.96 [0.76-1.20]	reference	0.046
12-24 months						
N (%)	1876	95 (5.1)	601 (32.0)	537 (28.6)	643 (34.3)	
Wheezing	484/1876	0.85 [0.58-1.25]	1.01 [0.84-1.22]	0.92 [0.75-1.12]	reference	0.991
Prolonged cough	441/1875	0.82 [0.52-1.29]	1.19 [0.97-1.45]	1.07 [0.86-1.33]	reference	0.328
Croupy cough	210/1876	0.79 [0.42-1.48]	0.79 [0.58-1.08]	0.76 [0.55-1.05]	reference	0.288
Diagnosed LRTI	382/1875	0.69 [0.41-1.14]	0.98 [0.79-1.22]	0.92 [0.73-1.16]	reference	0.929
Diagnosed ear infection	506/1875	1.07 [0.77-1.50]	0.95 [0.78-1.14]	1.04 [0.86-1.25]	reference	0.857
Diarrhoea	671/1875	1.23 [0.95-1.57]	1.01 [0.87-1.18]	0.96 [0.82-1.13]	reference	0.680
Vomiting	467/1875	1.13 [0.79-1.61]	1.07 [0.88-1.30]	0.98 [0.80-1.20]	reference	0.636

P-values were derived from Poisson regression analyses with the log-transformed 25(OH)D levels as continuous variable.

All analyses are adjusted for child's sex, birthweight and gestational age, and for maternal age at childbirth, educational level, pre-pregnancy BMI, parity, ethnicity, smoking in pregnancy, and duration of breast feeding.

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Competing interests

The authors declare that they have no conflicts of interest.

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Appendix online supplement

Table. Characteristics of the mothers and children studied

Vitamin D category	<25 nmol/l	25-49 nmol/l	50-74 nmol/l	>=75 nmol/l
N	100	666	572	687
Mothers				
Age at birth of child, years	30.5 (4.0)	30.2 (3.7)	30.5 (3.8)	30.6 (3.8)
Pre-pregnancy BMI	24.3 (22.2-28.4)	24.4 (22.4-28.3)	24.2 (21.9-27.1)	23.7 (21.7-26.8)
Primiparus, n(%)	38 (38.0)	298 (44.7)	295 (51.6)	318 (46.3)
Smoker (in pregnancy), n(%)	23 (23.0)	138 (20.7)	63 (11.0)	86 (12.5)
Educational attainment, n(%)				
None	4 (4.0)	29 (4.4)	9 (1.6)	15 (2.2)
GCSE grade D or below	14 (14.0)	68 (10.2)	59 (10.3)	63 (9.2)
GCSE grade C or above	30 (30.0)	188 (28.2)	170 (29.7)	192 (28.0)
A-level or equivalent	33 (33.0)	206 (30.9)	167 (29.2)	213 (31.0)
HND or equivalent	3 (3.0)	42 (6.3)	38 (6.6)	55 (8.0)
Degree	16 (16.0)	133 (20.0)	129 (22.6)	149 (21.7)
Total vitamin D intake in LP	2.9 (2.2-4.1)	3.5 (2.5-4.7)	3.6 (2.6-5.4)	4.5 (3.2-9.2)
Use of vitamin D supplements in LP, n(%)	6 (1.4)	57 (13.0)	124 (28.3)	251 (57.3)
Season of blood sampling, n (%) April-Sept	22 (22.0)	200 (30)	309 (54)	534 (77.7)
White ethnicity, n (%)	79 (79.0)	624 (93.7)	563 (98.4)	675 (98.3)

Children				
Female, n(%)	48 (48.0)	357 (53.6)	298 (52.1)	353 (51.4)
Birthweight, grams	3437 (503)	3444 (509)	3523 (510)	3501 (464)
Gestational age, weeks	40 (39.0-40.8)	40.1 (39.1-41.0)	40.1 (39.3-41.1)	40.1 (39.1-41.0)
Completed months of breastfeeding, n(%)				
Never tried	25 (25.0)	130 (19.5)	108 (18.9)	106 (15.4)
<1	19 (19.0)	138 (20.7)	121 (21.2)	134 (19.5)
1 to 3	17 (17.0)	157 (23.6)	111 (19.4)	143 (20.8)
4 to 6	15 (15.0)	107 (16.1)	95 (16.6)	127 (18.5)
7 to 11	15 (15.0)	91 (13.7)	95 (16.6)	106 (15.4)
12+	9 (9.0)	43 (6.5)	42 (7.3)	71 (10.3)