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

To the Editor:

Recently, there has been an increasing interest in the 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 and pregnant and lactating females 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 infections and atopic outcomes in offspring. 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 radioimmunoassay; Diasorin, Stillwater, MN, USA) [11]. Follow-up was at children's age 6 months (n=2025), 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 for three or more nights in a row (prolonged cough), one or more episodes of croup or a croupy cough, bouts of vomiting or diarrhoea $\geqslant$2 days, 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 "LRTI". Binary variables were created for each outcome. Relative risks were calculated using Poisson regression with robust variance with serum 25(OH)D >75 nmol·L^{-1} as the 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 body mass index, parity, ethnicity, smoking in pregnancy and duration of breastfeeding. The study was approved by the Southampton and South West Hampshire Research Ethics Committee (276/97, 307/97, 089/99 and 06/Q1702/104). Consent was obtained before the inclusion of participants.

Median (interquartile range) late-pregnancy serum 25(OH)D level was 59.0 (40.6–84.3) nmol·L^{-1}. 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 <50 nmol·L^{-1} reported fewer respiratory symptoms and doctor-diagnosed LRTI in their children aged 0–6 months than those with serum 25(OH)D levels >75 nmol·L^{-1} (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 0–6 months may be attributable to residual confounding. Thus, health conscious females have higher serum

TABLE 1 Relative risks for self-reported respiratory symptoms and infections according to clinical serum 25-hydroxyvitamin D (25(OH)D) levels

	Subjects n/N	25(OH)D				p-value
		<25 nmol·L^{-1}	25–49 nmol·L^{-1}	50–74 nmol·L^{-1}	⩾75 nmol·L^{-1}	
0–6 months						
Subjects	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						
Subjects	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						
Subjects	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

Data are presented as n, n (%) or relative risk (95% CI), unless otherwise stated. p-values were derived from Poisson regression analyses with the log-transformed 25(OH)D levels as a continuous variable. All analyses were adjusted for child's sex, birthweight and gestational age, and for maternal age at childbirth, educational level, pre-pregnancy body mass index, parity, ethnicity, smoking in pregnancy and duration of breastfeeding. LRTI: lower respiratory tract infection.

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 its 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 the medical behaviour of parents. Furthermore, 25(OH)D has a half-life of a few weeks, and we did not measure 25(OH)D levels in early pregnancy or post-natally 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. Randomised controlled trials are essential to clarify the role of vitamin D in pregnancy in relation to childhood respiratory symptoms and infections.

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Low late-pregnancy 25(OH)D levels not associated with offspring parent-reported respiratory symptoms and infections http://ow.ly/sNzSL

Renate T. de Jongh[1], Sarah R. Crozier[2], Stefania D'Angelo[2], Katharine C. Pike[3,4], Graham Roberts[3,4,5], Jane S.A. Lucas[3,4], Hazel Inskip[2], Keith M. Godfrey[2,4], Cyrus Cooper[2,4,6], Nicholas C. Harvey[2,4] and the Southampton Women's Survey Study Group[7]

[1]Dept of Internal Medicine and Endocrinology, VU University Medical Center, Amsterdam, The Netherlands. [2]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, [3]Clinical and Experimental Sciences Academic Unit, Faculty of Medicine, University of Southampton, Southampton, [4]NIHR Southampton Respiratory Biomedical Research Unit, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, [5]Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, Southampton, and [6]NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Nuffield Orthopaedic Centre, Oxford, UK. [7]A list of the Southampton Women's Survey Study Group members and their affiliations can be found in the Acknowledgements section.

Correspondence: N.C. Harvey, MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Tremona Road, Southampton, SO16 6YD, UK. E-mail: nch@mrc.soton.ac.uk

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A specific DAMP profile identifies susceptibility to smoke-induced airway inflammation

To the Editor:

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality, with a worldwide prevalence of 9–10% [1]. COPD is associated with chronic, neutrophilic inflammation in the lungs, causing destruction of lung parenchyma (emphysema) and/or remodelling of the airways with mucus