

Asthma

PATHOPHYSIOLOGY

Paracetamol in Pregnancy and the Risk of Wheezing in Offspring: A Systematic Review and Meta-analysis

Eyers S, Weatherall M, Jefferies S, Beasley R. *Clin Exp Allergy*. 2011;41(4):482–489

PURPOSE OF THE STUDY. To review the evidence from studies that investigated the association between paracetamol (acetaminophen) use in pregnancy and childhood asthma.

STUDY POPULATION. The meta-analysis included randomized controlled trials (RCTs) and observational studies published before October 2010 that compared women who used paracetamol during pregnancy with a placebo (RCT) or control (observational) group and evaluated the effect of paracetamol use during pregnancy on offspring using wheeze or asthma as a primary outcome. Only studies that presented raw data, or from which raw data were available from the authors on request, were used.

METHODS. Articles were searched for in health research databases, in previous meta-analyses, and in the reference lists of relevant studies. Articles were examined, and raw data were extracted. If appropriate data were not included in the studies, the lead author was contacted in an attempt to obtain the raw data. The primary outcome variable was wheeze in the 12 months before the last interview, defined as “current wheeze.” For tabulated raw data, not adjusted for confounders, random-effects odds ratios were pooled by the inverse variance weighted method.

RESULTS. Six studies were included: 5 prospective cohort studies and 1 cross-sectional study. The age range of the children in these studies was 30 to 84 months. The pooled random-effects odds ratio for the risk of current wheeze in the children of women who were exposed to any paracetamol during any stage of pregnancy was 1.21 (95% confidence interval: 1.02–1.44).

CONCLUSIONS. The use of paracetamol during pregnancy is associated with an increased risk of childhood asthma.

REVIEWER COMMENTS. The results of this meta-analysis confirm the association seen in individual studies over recent years between early paracetamol (acetaminophen) exposure and wheeze. In contrast with studies of the association between paracetamol use in early postnatal life and wheeze, studying paracetamol exposure in utero vastly decreases the potential for confounding by indication. The authors’ decision to use the unadjusted odds ratio is well justified but leaves open the possibility that the effect seen might be a result of confounding to some

extent. Given the almost ubiquitous use of paracetamol, and the recent increase in rates of atopy, untangling the true association between paracetamol and atopy is a topic that should, and undoubtedly will, have significant attention devoted to it in the coming years.

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Cord-Blood 25-Hydroxyvitamin D Levels and Risk of Respiratory Infection, Wheezing, and Asthma

Camargo CA Jr, Ingham T, Wickens K, et al; New Zealand Asthma and Allergy Cohort Study Group. *Pediatrics*. 2011;127(1). Available at: www.pediatrics.org/cgi/content/full/127/1/e180

PURPOSE OF THE STUDY. Previous studies have provided support for the role of low vitamin D levels in the increasing prevalence of asthma. This study examined the relationship between cord-blood levels of vitamin D and respiratory infection, wheezing, and asthma.

STUDY POPULATION. Cord blood from study participants ($N = 922$) was collected as part of a prospective birth cohort of 1105 children recruited by a random sample of midwives in the New Zealand Asthma and Allergy Cohort Study. Questionnaires were administered by study nurses at birth, 3 months, and 15 months and then annually between the ages of 2 and 5 years.

METHODS. Cord-blood 25-hydroxyvitamin D (25[OH]D) levels were measured and categorized as ≥ 75 , 25 to 75, or < 25 nmol/L. The primary outcomes were the incidence of respiratory infection, cumulative wheeze, and incidence of asthma by 5 years of age based on answers to the questionnaires. Multiple confounding covariates were accounted for, including season of birth, ethnicity, and environmental tobacco smoke exposure. The linear regression or the Kruskal-Wallis test for continuous variables and the Wilcoxon-Mann-Whitney test for categorical variables were used to test for trend across vitamin D levels. Multivariable logistic regression models were used to test the association between cord-blood 25(OH)D levels and infection outcomes at 3 months of age.

RESULTS. Data were available for 882 (96%) children at 3 months of age and 823 (89%) children at 5 years of age. The median 25(OH)D cord-blood level was 44 nmol/L. An inverse association was found between cord-blood 25(OH)D levels and risk of respiratory infection by 3 months of age. Newborns with 25(OH)D levels of < 25 nmol/L had an increased risk of respiratory infections (odds ratio [OR]: 2.04) and other viral infections (OR: 2.36) compared with those with levels of

≥75 nmol/L. There was an inverse linear association between vitamin D level and cumulative wheezing by 5 years of age but no association with asthma incidence. Every 10 nmol/L increase in cord-blood 25(OH)D level lowered the cumulative risk of wheezing by the age of 5 years (adjusted OR: 0.95).

CONCLUSIONS. This birth-cohort study revealed an inverse association between 25(OH)D cord-blood levels and the risk of respiratory and other viral infections by the age of 3 months and cumulative risk of wheezing by the age of 5 years. The 25(OH)D cord-blood levels were not associated with the risk of incident asthma.

REVIEWER COMMENTS. The measurement of vitamin D in cord blood, but not at follow-up visits, is a major limitation of this study. Recall bias that resulted from the use of parent questionnaires to detect the outcomes of interest is another limitation. It remains unclear whether low vitamin D levels in utero cause increased respiratory infections and wheezing or if this low level is a marker for likely low vitamin D levels in the future. Further studies are needed to clarify this issue. This study adds to the body of evidence that suggests that low vitamin D levels might play a role in wheezing and respiratory infections in infants and children.

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Dairy Food, Calcium and Vitamin D Intake in Pregnancy, and Wheeze and Eczema in Infants

Miyake Y, Sasaki S, Tanaka K, Hirota Y. *Eur Respir J*. 2010;35(6):1228-1234

PURPOSE OF THE STUDY. Previous studies have provided mixed results regarding a relationship of intake of dairy products with allergic disorders. This study examined the association between maternal consumption of dairy products, calcium, and vitamin D during pregnancy and risk of wheeze and eczema in Japanese children at 16 to 24 months of age.

STUDY POPULATION. A total of 763 mother-child pairs in the Osaka Maternal and Child Health Study (OMCHS) were included.

METHODS. The OMCHS is a prospective cohort study. Participants mailed each of 3 questionnaires to the data center. The first survey was performed on pregnant women between the 5th and 39th weeks of gestation, and the second and third surveys were collected from 2 to 9 and 16 to 24 months after delivery, respectively.

Symptoms of wheeze and eczema were based on the criteria of the International Study of Asthma and Allergies in Childhood.

RESULTS. Higher maternal intake of total dairy products, milk, cheese, and calcium during pregnancy was significantly related to a decreased risk of infantile wheeze but not eczema (adjusted odds ratios [ORs] between extreme quartiles were 0.45 [95% confidence interval (CI): 0.25-0.79], 0.5 [95% CI: 0.28-0.87], 0.51 [95% CI: 0.31-0.85], and 0.57 [95% CI: 0.32-0.99], respectively). Children whose mother had consumed ≥4.3 μg/day of vitamin D, using a cutoff point at the 25th percentile, had a significantly reduced risk of wheeze and eczema (adjusted ORs were 0.64 [95% CI: 0.43-0.97] and 0.63 [95% CI: 0.41-0.98], respectively). However, the inverse associations between maternal intake of calcium in the highest quartile and ≥4.3 μg/day of vitamin D and infantile wheeze were not statistically significant after further control for maternal intake of docosahexaenoic acid or vitamin E.

CONCLUSIONS. Higher consumption of total dairy product, milk, cheese, calcium, and vitamin D during pregnancy might reduce the risk of infantile wheeze. Also, higher maternal vitamin D intake during pregnancy might be protective against eczema.

REVIEWER COMMENTS. The role of vitamin D in atopy and other immune disorders is a hot area of research. The results of this study help to place the importance of diet in pregnancy for atopy in a non-Westernized society. However, the need for long-term follow-up and questionnaire-based definitions for wheeze and eczema were a limitation of this cohort study. Confounders include undisclosed sources of vitamin D and calcium. The relationship between actual vitamin D levels and supplement use during pregnancy is still not conclusive. Additional studies to clarify the multifactorial causes of allergic disorders are desirable, and current randomized double-blind placebo-controlled trials that evaluate vitamin D supplements during pregnancy and wheeze/asthma outcomes are ongoing.

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Vitamin D Serum Levels and Markers of Asthma Control in Italian Children

Chinellato I, Piazza M, Sandri M, Peroni D, Piacentini G, Boner AL. *J Pediatr*. 2011;158(3):437-441

PURPOSE OF THE STUDY. Recent data indicate that increased serum concentrations of 25-hydroxyvitamin D are asso-

**Cord-Blood 25-Hydroxyvitamin D Levels and Risk of Respiratory Infection,
Wheezing, and Asthma**

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