Association Between Paracetamol Use in Infancy and Childhood, and Risk of Asthma, Rhinoconjunctivitis, and Eczema in Children Aged 6–7 Years: Analysis From Phase Three of the ISAAC Programme


PURPOSE OF THE STUDY. The authors evaluated the associations between exposure to paracetamol (acetaminophen) in infancy and childhood and development of asthma and other atopic conditions in early school-aged children.

STUDY POPULATION. The study included 205,487 children 6 to 7 years of age from 73 centers in 31 countries.

METHODS. Parents or guardians completed written questionnaires regarding the presence of asthma, rhinoconjunctivitis, and eczema symptoms; child and family demographic information; and exposure to environmental risk factors including medications, breastfeeding, diet, home exposures, and traffic pollution. Acetaminophen administration for fever in the child’s first year of life and the frequency of acetaminophen use in the previous 12 months (none; medium, once per year or more; or high, once per month or more) were determined.

RESULTS. Acetaminophen use for fever in the first year of life was associated with symptoms of asthma (odds ratio [OR]: 1.46 [95% confidence interval [CI]: 1.36–1.56]), rhinoconjunctivitis (OR: 1.48 [95% CI: 1.38–1.60]), and eczema (OR: 1.35 [95% CI: 1.26–1.45]) for children 6 to 7 years of age and was associated with severe asthma symptoms and with rhinoconjunctivitis and eczema after exclusion of children with wheeze. The overall population attributable risk of asthma was 21% to 40%. The association between asthma and current acetaminophen use was dose dependent (medium frequency OR: 1.61 [95% CI: 1.46–1.77]; high frequency OR: 3.23 [95% CI: 2.91–3.60]); dose-response relationships were also seen for rhinoconjunctivitis and eczema.

CONCLUSIONS. Acetaminophen use in infancy and childhood was associated with the development of asthma, rhinoconjunctivitis, and eczema in 6- to 7-year-old children, and the associations seemed to be dose-responsive for childhood acetaminophen exposure.

REVIEWER COMMENTS. This large, multinational, retrospective study demonstrated an association between previous and current acetaminophen use and childhood atopic conditions that persisted across populations with different lifestyles, medical access and practices, and types of febrile childhood illnesses. Prospective studies of acetaminophen use during pregnancy and a randomized controlled trial that compared acetaminophen with another antipyretic medication also suggested associations between acetaminophen and childhood asthma, although an association between decreased aspirin use and asthma development has also been hypothesized. Before these findings can be interpreted as causal, additional prospective observational or randomized studies should be performed and should include information on covariates such as parental atopy and asthma, types of febrile illnesses, and use of other antipyretic agents.

Allergic Disease and Atopic Sensitization in Children in Relation to Measles Vaccination and Measles Infection


PURPOSE OF THE STUDY. To determine the role of measles vaccination and infection in the outcome of allergic disease and atopic sensitization.
STUDY POPULATION. A total of 14,893 children 5 to 13 years of age were included from the cross-sectional, multicenter, Prevention of Allergy–Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Lifestyle (PARSIFAL) study, conducted in 5 European countries.

METHODS. Four groups of children were compared, those in farming communities, those attending Steiner schools (which are known for avoidance of immunizations), and nonfarming and non-Steiner reference groups. By using parental questionnaires based on previously validated questionnaires (including the International Study of Asthma and Allergies in Children), 14,893 children (69% response rate) were evaluated for environmental exposures, history of vaccinations and infections, lifestyle factors, and symptoms and diagnoses of allergic diseases. Atopic sensitization was defined as ≥1 allergen-specific immunoglobulin E level of ≥0.35 kU/L against inhalant allergens and/or foods. A sample of children with complete information on measles vaccination and infection was invited to undergo an additional blood test, and 4,049 children (83% response rate) did so, with parental consent.

RESULTS. In reviewing the entire group of children, atopic sensitization was inversely related to measles infection and vaccination. After exclusion of children who confirmed symptoms of wheezing and/or eczema in the first year of life, an inverse relationship was noted between measles infection but not vaccination and “any allergic disease. Atopic sensitization was inversely related to measles infection and vaccination and “any allergic disease. Atopic sensitization was inversely related to measles infection and vaccination and “any allergic disease.

CONCLUSIONS. The authors concluded that measles infection may be protective against allergic conditions in children.

REVIEWER COMMENTS. The literature is inconsistent on the relationship between measles infection and allergic disease or atopic sensitization. The predominant confounder in these studies is determining and controlling for whether the exposure precedes the disease, which is a problem in this study as well. The strengths of the study are its size and international design, with a high prevalence of measles infection. However, there was a low prevalence of allergic disease and sensitization in the reference group. The authors also cannot exclude other vaccinations included in the measles-mumps-rubella vaccine or other aspects of the anthroposophic lifestyle that may affect the observed relationship. Additional prospective cohort studies are needed to establish causality.

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Relevance of the Hygiene Hypothesis to Early vs. Late Onset Allergic Rhinitis


PURPOSE OF THE STUDY. To compare the effects of siblings, infections, and rural environment on the development of allergic rhinitis before and after 7 years of age.

STUDY POPULATION. The population-based cohort of participants in the Tasmanian Longitudinal Health Study (TAHS) was studied. Initial data were collected on 8,583 children 7 years of age, comprising 99% of the schoolchildren in Tasmania born in 1961. The most recent follow-up evaluation occurred in 2004 and captured 5,729 of the original participants at the age of 44 years, with the balance either lost to follow-up monitoring or deceased.

METHODS. Subjects were categorized according to outcome, as those with early-onset allergic rhinitis (developed before the age of 7 years), those with late-onset allergic rhinitis (developed after the age of 7 years), and a reference group of those who did not report allergic rhinitis. The exposures considered were siblings, infections, tonsillectomy, and farm residence during childhood. Potential confounders considered were gender, maternal and paternal atopy, mother’s age at participant’s birth, paternal socioeconomic status in 1968, and personal socioeconomic status in 2004. Univariate associations were evaluated by using χ² tests. Multinomial logistic regression was used to examine independent effects of different exposures on outcome with adjustment for confounders. The main analysis included 3,429 subjects.

RESULTS. Subjects with sibling exposure before the age of 2 had less early-onset allergic rhinitis than did those with no siblings (<1-year sibling exposure, odds ratio [OR]: 0.6 [95% confidence interval [CI]: 0.3–1.0]; 1- to 3-year sibling exposure, OR: 0.6 [95% CI: 0.4–0.9]; >3-year sibling exposure, OR: 0.4 [95% CI: 0.3–0.8]). This effect was dose dependent, with a P value of .001 for trend. This was stronger than the effect of sibling exposure before 6 months or before 4 years. The trend for the effect of sibling exposure before the age of 2 was apparent (P = .001), although weaker, in late-onset allergic rhinitis. Early- but not later-onset allergic rhinitis decreased with viral infections during childhood (OR: 0.7 [95% CI: 0.5–0.9]). Tonsillectomy before the age of 7 increased the rate of early- but not later-onset allergic rhinitis (OR: 1.7 [95% CI: 1.2–2.5]).

CONCLUSIONS. Exposures related to the hygiene hypothesis are more strongly related to early- than late-onset allergic rhinitis. The immunologic mechanisms for these risk factors are poorly understood. Additional research should focus on early-onset allergic rhinitis when ex-
### Allergic Disease and Atopic Sensitization in Children in Relation to Measles Vaccination and Measles Infection

Christopher Randolph  
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