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Respiratory tract infections and not paracetamol medication during infancy are associated with asthma development in childhood

To the Editor:

Several observational studies have suggested that treatment with paracetamol might be an important risk factor for the development of asthma.[1] A large cross-sectional study on asthma and allergy in childhood reported an association between retrospectively assessed paracetamol use in infancy and the prevalence of asthma in 6- to 7-year-old children.[2]

However, the potential biases inherent in observational surveys must also be considered when interpreting their findings.[2] Retrospective data collection can cause recall bias and confounding by indication. For example, parents whose children are susceptible to respiratory tract infections are more likely to remember the use of antipyretic medication. Even more importantly, the indication for which paracetamol is used might be responsible for the development of asthma and not paracetamol *per se*, as suspected by Beasely et al.[2]

Prospective cohort studies are necessary to reduce recall bias and to investigate potential reverse causation. A recent prospective follow-up survey analyzed the association of febrile illnesses and antipyretic medication in early childhood with allergic disease morbidity in adolescents.[3] They found more febrile days in infancy among those with asthma. Thus they concluded that previous observational studies assessing paracetamol use in early life and the risk of later development of allergic diseases are probably confounded by increased respiratory tract infection morbidity in asthma-susceptible children. However, they did not investigate whether medical indications for paracetamol use other than respiratory tract illnesses had an effect on the development of asthma.

We hypothesized that paracetamol use for indications other than respiratory tract illnesses would not be associated with an increased onset of asthma. Using data from the prospective population-based birth cohort study Influences of Lifestyle-related Factors on the Immune System and the Development of Allergies in Childhood (LISA), we analyzed the association between febrile illnesses and antipyretic medication use during infancy and the development of allergic disease. In brief, 3097 healthy full-term neonates born between November 1997 and January 1999 were enrolled at selected maternity hospitals in 4 German cities (Munich, Leipzig, Wesel, and Bad Honnef).[4] During the first year of life, parents were asked to record febrile episodes (temperature >38°C); respiratory, gastrointestinal, or urinary tract infections; and medication use, including antipyretics, in monthly diaries. At the ages of 6, 12, 18, and 24 months and annually from 2 to 6 years of age, parents were asked whether their child had been given diagnosis of an allergic disease by a physician since the last follow-up.

Additionally, specific IgE levels against common inhalant allergens (house dust mites, cockroach, cat and dog, mixed grasses, tress, and mold) were measured at the ages of 2 and 6 years by using standardized methods with CAP-RAST FEIA (Pharmacia Diagnostics, Freiburg, Germany). Sensitization was defined as an IgE antibody level of 0.35 kU/L or greater. Information on at least 1 physician-diagnosed allergic disease or positive sensitization was available for 2296 children. Children with and without physician-diagnosed allergic disease or positive sensitization to inhalant allergens by the age of 6 years were compared in terms of the number of febrile days and paracetamol treatment courses during the first year of life. The Poisson regression was used to model the number of febrile days and paracetamol treatment courses as discrete count outcome. From the LISA study, we know that less than 5% of all children were treated with analgesic or antipyretic active ingredients other than paracetamol. Because this small number does not allow a separate analysis, we included these children in the paracetamol treatment group. Mean febrile days and paracetamol treatment courses are presented in Table I to allow for comparison with the results of Tapiainen et al.[3]

We show that children with asthma had, on average, 1.51 more febrile days ($P < .01$) and 1.27 more febrile days during respiratory tract infections ($P < .01$) compared with nonasthmatic children (Table I). A similar trend was observed when analyzing the number of months during the first year of life during which children had at least 1 paracetamol course. Asthmatic children had, on average, 0.23 more months ($P = .01$) with at least 1 treatment with paracetamol and 0.16 more months ($P = .01$) during which paracetamol was prescribed for respiratory tract infections. However, the total number of febrile days (1.57 vs 1.73 days) or paracetamol treatment courses (0.06 vs 0.05 courses) because of gastroenteritis or urinary tract infections did not differ between asthmatic and nonasthmatic children. A further sensitivity analysis, in which we validated the asthma diagnosis based on the use of antiasthma drugs, did not change the results. For atopic eczema, there was only a minor difference regarding febrile days (4.46 vs 4.21 days, $P < .01$) but no difference concerning paracetamol treatment courses (0.75 vs 0.83 courses) between atopic and nonatopic children.

Children with allergic rhinitis had more febrile days caused by gastroenteritis or urinary tract infections (2.48 vs 1.70 days, $P = .01$), but there was no association between allergic rhinitis and paracetamol treatment courses. Beyond this time, children with an allergic sensitization against common inhalant allergens were treated less frequently with paracetamol because of gastroenteritis or urinary tract infections (0.04 vs 0.07 months, $P = .03$). Thus there is also no increased risk for allergic sensitization until the age of 6 years, when children were treated with paracetamol during the first 2 years of life.

This analysis indicates that increased respiratory tract infection morbidity and not paracetamol use during infancy is associated with the later development of asthma. This is in line with several studies pointing out that viral respiratory tract infections, such as those caused by respiratory syncytial virus and rhinovirus, are significant risk factors for the development of asthma in later childhood.[5,6] Because paracetamol is the most common antipyretic drug prescribed for respiratory tract infections during early

TABLE I. Mean febrile days and paracetamol treatment courses during the first year in 2296 children with physician-diagnosed allergic morbidity by the age of 6 years

	Children with allergic disease	Children without allergic disease	
	Asthmatic children (n = 271)	Nonasthmatic children (n = 1772)	*P* value*
Febrile days (with and without medication)	5.66	4.15	<.01
During respiratory tract infection	4.06	2.79	<.01
During gastroenteritis or urinary tract infection	1.57	1.73	.71
Paracetamol treatment courses†	1.02	0.79	<.01
During respiratory tract infection	0.65	0.49	<.01
During gastroenteritis or urinary tract infection	0.06	0.05	.89
	Children with atopic eczema (n = 656)	**Nonatopic children (n = 1488)**	
Febrile days (with and without medication)	4.46	4.21	<.01
During respiratory tract infection	3.09	2.87	<.01
During gastroenteritis or urinary tract infection	1.80	1.61	.23
Paracetamol treatment courses†	0.75	0.83	.09
During respiratory tract infection	0.47	0.51	.23
During gastroenteritis or urinary tract infection	0.06	0.05	.47
	Children with allergic rhinitis (n = 121)	**Nonatopic children (n = 1887)**	
Febrile days (with and without medication)	4.60	4.26	.22
During respiratory tract infection	3.05	2.90	.74
During gastroenteritis or urinary tract infection	2.48	1.70	.01
Paracetamol treatment courses†	0.74	0.82	.13
During respiratory tract infection	0.45	0.51	.19
During gastroenteritis or urinary tract infection	0.07	0.05	.43
	Children with allergic sensitization (n = 330)	**Nonatopic children (n = 771)**	
Febrile days (with and without medication)	4.46	4.61	.15
During respiratory tract infection	3.19	3.06	.47
During gastroenteritis or urinary tract infection	1.75	1.82	.71
Paracetamol treatment courses†	0.83	0.94	.07
During respiratory tract infection	0.53	0.59	.28
During gastroenteritis or urinary tract infection	0.04	0.07	.03

**P* values were calculated with Poisson regression and adjusted for sex, study region, and parental education.
†Mean number of months during the first year of life during which children had at least 1 paracetamol course per month or at least 1 paracetamol course per month only for respiratory tract infection or only for gastroenteritis and urinary tract infection, including a very small group of children with other analgesic or antipyretic medications (<5% of all children).

childhood, it might be spuriously considered a risk factor in the development of asthma. Thus the increased respiratory morbidity in children susceptible to asthma leads to frequent use of paracetamol and not the other way around. Nevertheless, one has to keep in mind that some studies reported that prenatal exposure to paracetamol is associated with an increased risk for later asthma.[1] However, this evidence is also based on observational studies with possible limitations because of recall bias and reverse causation. By contrast, one recent prospective study suggested that paracetamol use during pregnancy does not increase the risk of asthma in children.[7] There is only 1 randomized controlled trial investigating the effect of paracetamol use on asthma morbidity in asthmatic children.[8] Asthmatic children who had a febrile illness were randomized to paracetamol or ibuprofen. Compared with asthmatic children treated with paracetamol during febrile illnesses, children who received ibuprofen had a reduced risk of outpatient visits for asthma in the following 4 weeks. However, this trial investigated short-term effects, whereas our study and several other studies referred to potential long-term effects of paracetamol use on asthma symptoms. Moreover, this risk was more related to respiratory tract infections than to other causes of fever, and it could not be determined whether this difference in morbidity was due to an increased risk after paracetamol or to a decreased risk after ibuprofen. Nevertheless, it has to be kept in mind that paracetamol might have an influence on the duration and severity of respiratory tract infections associated with asthma.[9] Thus the results of a placebo-controlled trial indicated that the use of paracetamol in rhinovirus-infected volunteers might adversely affect immune function and increase nasal symptoms. This observation would suggest that paracetamol might possibly confound the association between the duration of respiratory tract infections in infancy and the later development of asthma. However, these findings, as well as the results of Lesko et al,[8] refer to short-term effects. Thus it is questionable whether these findings are transferable to long-term effects, which are of interest in our study.

Overall, this analysis provides new evidence that the increased number of respiratory tract infections in children vulnerable to asthma and not the paracetamol medication *per se* is associated with the development of asthma. Therefore we conclude that the previously reported effects of paracetamol on asthma are confounded by increased respiratory tract infection morbidity in asthma-susceptible children.

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Identification of an infant with severe combined immunodeficiency by newborn screening

To the Editor:

Severe combined immunodeficiency (SCID) is a life-threatening congenital disorder characterized by lack of autologous T-cell production and caused by a variety of genetic conditions affecting lymphocyte development. Allogeneic hematopoietic cell transplantation has been used successfully to treat SCID, and outcomes are substantially better when transplant occurs early, avoiding acquisition of infection, particularly community-acquired respiratory infection.[1]

The Commonwealth of Massachusetts embarked on a pilot program universally offering newborn screening (NBS) for SCID effective February 1, 2009.[2] SCID is well suited to newborn screening because it is not easily recognizable by clinical evaluation at birth, is amenable to therapy that is best instituted early, and should be identifiable (all genotypes) with a DNA-based screening assay that quantifies T-cell receptor excision circles (TRECs) in NBS dried blood spot specimens.[3] Screen-positive infants had follow-up flow cytometry to enumerate peripheral blood T-cell number. Naive cell markers were included to detect possible engraftment by maternal T cells. Infants with an abnormally low number of naive T cells were referred for clinical evaluation and T-cell functional testing.

TABLE I. Peripheral blood lymphocyte populations and T-cell function *in vitro*

Lymphocyte marker/mitogen	Patient's results	Normal range
Percent $CD3^+$	1%	49-84*
$CD3^+$, absolute	10 cells/mcL	2,500-5,600
Percent $CD3^+/CD4^+$	0%	35-64
$CD3^+/CD4^+$, absolute	4 cells/mcL	1,600-4,000
Percent $CD3^+/CD8^+$	1%	12-28
$CD3^+/CD8^+$, absolute	8 cells/mcL	500-1,700
Percent $CD3^-/CD16^+$ or $CD56^+$	5%	4-18
$CD3^-/CD16^+$ or $CD56^+$, absolute	55 cells/mcL	160-1,100
Percent $CD19^+$	89%	6-32
$CD19^+$, absolute	1,010 cells/mcL	300-2,000
Concanavalin A	1,591 cpm	41,000†
Phytohemagglutinin	2,313 cpm	82,000
Mitogen background	1,520 cpm	

cpm, Counts per minute; *mcL,* microliters.
*Normal values for percent and absolute counts of lymphocyte populations are adapted from Shearer et al.[5]
†Fifth percentile values of cpm of tritiated thymidine incorporation for healthy adult blood donors in the Clinical Flow Cytometry and Cellular Immunology Laboratory of the Division of Laboratory Medicine, Children's Hospital, Boston.

We report confirmation of the first case of SCID identified in the course of our pilot program and after 100,597 infants had been screened by an internally controlled multiplex TREC assay.[4] This infant had undetectable TRECs and was among the 78 (0.08%) meeting criteria for flow cytometry and 29 (0.03%) meeting criteria for clinical evaluation. Lymphocyte subsets and proliferation studies confirmed profound absence of T cells, low natural killer cells, and absent proliferation to mitogens (Table I), consistent with the Janus kinase 3 form of SCID. Genotype analysis showed 1 missense (c.578G>A) and 1 intronic mutation (c.1786+3G>T) in the Janus kinase 3 gene. The infant was detected while still asymptomatic, stayed at home in protective isolation, and received prophylactic immunoglobulin and antibiotics while awaiting hematopoietic cell transplantation. The infant was recently treated with hematopoietic cell transplantation.

We note the following:

1. A quality-controlled high throughput DNA-based assay meets the testing requirements for SCID NBS.
2. The occurrence of undetectable TRECs is highly suspicious for SCID.
3. Flow cytometry laboratories using normal ranges developed by Shearer et al[5] with specialized markers of naive T cells meet the first-tier diagnostic testing requirements for SCID NBS.
4. Ongoing collaboration between the NBS program and a statewide team of clinicians knowledgeable about SCID NBS is essential for optimization of screening algorithms.