

Letters to the Editor

Adolescents with asthma or atopic eczema have more febrile days in early childhood: A possible explanation for the connection between paracetamol and asthma?

To the Editor:

It has been proposed in several observational studies that paracetamol might be a risk factor for asthma (see the recent review by Farquhar et al¹ in the *Journal of Allergy and Clinical Immunology*). Confounding factors are difficult to control in observational studies because the allocation to treatment groups does not take place at random. A large sample size will increase the statistical precision, however, and allow adjustment for multiple confounders, but it does not eliminate the problems entailed in observational surveys.²

Current evidence on the use of paracetamol in infancy and the later development of asthma is based on observational studies with retrospective data collection on febrile medication.^{2,3} Because no results of randomized clinical trials are available, the second best option would be a prospective cohort study collecting data on both febrile medication and febrile episodes during respiratory tract infections. This would reduce the recall bias and could shed light on possible reverse causation (ie, increased respiratory tract morbidity leading to increased use of antipyretics). Because we had earlier collected detailed daily data on medications and infectious disease symptoms in a cohort of children attending day care in early childhood on a prospective basis in the 1990's and had later evaluated the same subjects for allergic diseases in adolescence,^{4,5} we now used this database to evaluate the association of febrile illnesses and antipyretic medication in early childhood with the later development of asthma.

In brief, data were collected prospectively in child day care centers in the 1990's by asking parents to record daily symptoms that included a temperature of greater than 38.0 °C measured at any body site and medications that included antipyretics in pre-designed symptom diaries to be completed daily and returned to the day care centers monthly.⁴ The original randomized trial covered 1,354 children, and the later follow-up survey of allergic disease

morbidity covered 928 adolescents.⁵ In the present analysis we compared the adolescents who had an allergic disease diagnosed by a physician by the time of the follow-up survey and those who had remained healthy in terms of the number of febrile days during the childhood survey and their use of antipyretic medication, testing the difference per person-year at risk (PYR) by means of a 2-sample *t* test. We assumed unequal variances after testing the homogeneity of variances using the Levene's test.

The adolescents with asthma in the follow-up survey had 2.72 more reported febrile days per PYR in early childhood (95% CI, 0.23-5.20; *P* = .03) than those who were healthy (Table I). The number of febrile days per PYR during gastroenteritis episodes did not differ between the groups (Table I). Likewise, the subjects with asthma at follow-up had 0.85 more days of paracetamol medication per PYR and 1.37 more days of any antipyretic medication per PYR than the healthy adolescents (differences not statistically significant, Table I). The adolescents with atopic eczema at follow-up had had 1.46 more febrile days per PYR in early childhood (95% CI, 0.10-2.83; *P* = .04) than the healthy adolescents (Table I).

The greater number of febrile days in early childhood observed in the adolescents with asthma in our prospective study appears to be explained by increased morbidity from respiratory tract infections because no difference was observed in febrile episodes caused by gastroenteritis. Thus observational studies assessing the association of paracetamol medication in early life with the later development of allergic diseases are likely to be confounded by increased respiratory tract infection morbidity in asthma-susceptible children.

The fact that even adolescents with atopic eczema appeared to have more febrile days in early childhood than the healthy adolescents is probably explained by susceptibility to wheezing episodes during infancy, leading to increased respiratory tract infection morbidity in these children as well.⁶

The increased morbidity of asthma-susceptible children, together with the concern shown by their parents, could easily have led to frequent temperature measurements and increased medication with symptom-relieving drugs, such as paracetamol. Nevertheless, the possibility of an increased number of febrile days has not been investigated in any previous study of the

TABLE I. Numbers of febrile days and days of paracetamol medication in early childhood per PYR in 928 children with allergic morbidity diagnosed by a physician by the time of the follow-up survey in adolescence

	Children with allergic disease	Children without allergic disease	Difference	95% CI of the difference	P value
	Asthma (n = 93)	Healthy (n = 826)			
Febrile days/PYR	8.21	5.49	2.72	0.23 to 5.20	.03
During gastroenteritis	0.66	0.77	-0.11	-0.71 to 0.49	.72
During respiratory tract infection	5.95	3.80	2.15	-0.06 to 4.35	.06
Days of paracetamol use per PYR	2.36	1.51	0.85	-0.64 to 2.33	.26
Days of antipyretic* use per PYR	3.29	1.92	1.37	-0.60 to 3.34	.17
	Atopic eczema (n = 233)	Healthy children (n = 663)			
Febrile days per PYR	6.79	5.33	1.46	0.10 to 2.83	.04
During gastroenteritis	0.90	0.73	0.17	-0.25 to 0.59	.42
During respiratory tract infection	4.95	3.65	1.30	0.09 to 2.50	.04
Days of paracetamol use per PYR	1.67	1.63	0.04	-0.77 to 0.85	.92
Days of antipyretic use per PYR	2.00	2.05	-0.05	-1.01 to 0.92	.93

The population includes all the children with data available on febrile days, symptoms, and later allergic disease.

PYR, Person-year at risk.

*Includes all antipyretics (paracetamol, aspirin, naproxen, ibuprofen, and diclofenac).

relation between paracetamol and the later development of asthma in children.^{2,3}

The problems of paracetamol and asthma could ideally be resolved by means of a randomized controlled trial, as proposed by Farquhar et al.¹ A long-term follow-up would be needed, however, and protocol violations would be probable because paracetamol is a common over-the-counter drug. In one previous randomized trial, short-term paracetamol medication during febrile illness in children aged 6 months to 12 years with asthma was found to be associated with more outpatient visits for asthma in the next 4 weeks than among children treated with ibuprofen.⁷ It could not be determined, however, whether this was due to an increased risk of asthma exacerbations after paracetamol or to a protective effect of ibuprofen because there was no placebo group. Thus a randomized controlled trial assessing the safety of paracetamol would require a placebo group, which would be difficult for parents to accept.

We conclude that previous observational studies on the long-term effects of paracetamol medication on allergic disease morbidity in children appear to be confounded by an increase in the number of days with fever during respiratory tract infections in asthma-susceptible children. This might explain the previously reported effects of paracetamol on asthma.

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