

Letter to the Editor

Infant acetaminophen use associates with early asthmatic symptoms independently of respiratory tract infections: The Copenhagen Prospective Study on Asthma in Childhood 2000 (COPSAC₂₀₀₀) cohort

To the Editor:

Acetaminophen exposure in early childhood has been associated with the development of asthma.^{1,2} Acetaminophen exposure during pregnancy has also been associated with asthma in the child, but a meta-analysis showed significant heterogeneity between studies,³ possibly because of differences in end point definitions and lack of covariate adjustment. Asthma is also related to recurrent lower respiratory tract infections (LRTIs),⁴ which are a frequent indication for acetaminophen use in both pregnant women and young children and hence a potential confounder. It was therefore the aim of this study to investigate the relationship between acetaminophen exposure in the third trimester and first year of life on the risk of asthma adjusted for concurrent LRTIs.

The study is part of the prospective birth cohort Copenhagen Prospective Study on Asthma in Childhood 2000 (COPSAC₂₀₀₀), which includes 411 children born to asthmatic mothers. The children attended our research clinic every 6 months for scheduled investigations. Acute visits were arranged immediately on onset of any respiratory symptoms. Diaries were used to monitor airway symptoms between visits and reviewed by the research doctor at every visit.^{4,5}

Asthmatic symptoms were evaluated, treated, and classified strictly based on predefined standard operating procedures and treatment algorithms solely by the COPSAC doctors, as previously detailed.⁵ LRTIs (pneumonia, bronchitis, and bronchiolitis) were recorded and in most cases verified by the doctor in the clinical research unit. At every visit, all medication use, including type, duration, dose, and frequency, were registered.⁴

Acetaminophen use was analyzed as the number of days exposed within the child's first year of life and the number of days of maternal intake during the third trimester.

Any troublesome lower lung symptoms (TROLLS) within the first 3 years of life and current asthma in the seventh year of life were chosen as end points. TROLLS were used as an intermediate asthma phenotype diagnosed as 5 episodes within 6 months, as previously described.⁵ Each episode was defined from the diary as at least 3 consecutive days with significantly troublesome lower respiratory tract symptoms of any kind (wheeze, cough, breathlessness, or "other"). The presence of TROLLS resulted in a 3-month course of inhaled corticosteroid treatment.⁶ Asthma was diagnosed when children with recurrent TROLLS responded to the corticosteroid treatment as described above and experienced a relapse when treatment was stopped.⁵

Logistic regression was used for the binary asthma outcomes. Poisson regression was used when analyzing the relationship between LRTIs and acetaminophen use, adjusting for overdispersion by quasi-poisson. Acetaminophen use was log₂ transformed, with an offset of 1. One unit of the transformed variable hence corresponds to a doubling of the original untransformed variable, and the reported risks then correspond to the effect of a doubling in days of acetaminophen use. Statistical analyses

were performed with SAS software version 9.3 (SAS Institute, Cary, NC) using a significance level of *P* less than .05.

Four hundred eleven children were included in the study. Twenty-seven children attended neither 12-month nor 18-month scheduled visits, leaving 384 children with complete data on medical use and infections in the first year of life. Complete data were available for 345 children until age 3 years, and 19% (65/345) were given a diagnosis of TROLLS in that period (median age, 1.35 years). Three hundred thirty-six (82%) children were evaluated for asthma at age 7 years, of whom 14% (47/336) had current asthma.

We found a significant relationship between acetaminophen use in the first year of life and diagnoses of TROLLS at 0 to 3 years (odds ratio [OR], 1.34; 95% CI, 1.10-1.64; *P* = .005; Table I), as well as between acetaminophen use in the first year of life and the number of LRTIs (rate ratio, 1.21; 95% CI, 1.07-1.38; *P* = .002). The association between acetaminophen use in the first year of life and TROLLS persisted when adjusting for the concurrent number of LRTIs (OR, 1.28; 95% CI, 1.03-1.58; *P* = .023; Table I). In a sensitivity analysis we restricted TROLLS to 1 to 3 years of age, which showed similar results (unadjusted OR, 1.29; 95% CI, 1.03-1.63; *P* = .027). Further sensitivity analysis of acetaminophen use in the second year of life revealed no association. Sensitivity analysis of the exposure variable revealed similar effect sizes as number of days exposed in crude analysis to TROLLS for both number of doses and accumulated dose.

We found no relationship between acetaminophen in the first year of life and asthma at age 7 years. Maternal acetaminophen use during the third trimester was not associated with any asthma outcomes.

Doubling the infancy acetaminophen exposure days gave a clinically relevant and modest 28% increase in odds for early life asthmatic symptoms, but the lack of association at age 7 suggests a temporary effect. Acetaminophen exposure was also associated with LRTIs. When adjusting acetaminophen use and asthma symptoms for LRTIs, the association remained significant, suggesting partial confounding.

The major strength of this study is its design as a single-center prospective clinical study with objective monitoring of the cohort and a particular focus on respiratory problems. The COPSAC₂₀₀₀ study population is a high-risk cohort of children born to asthmatic mothers, and the results must be verified in other population-based studies.

The major weakness is that acetaminophen is an over-the-counter medicine that can be obtained without prescription. Because of this, we could not use our standard registry on prescriptions filled at pharmacies, making the data prone to recall bias on the quantity of the exposure, and therefore we had no data on indication for use. However, parents kept symptoms diaries, and recall bias was minimized with the frequent clinical visits.

The International Study of Asthma and Allergies in Childhood found an association between early-life acetaminophen exposure and asthma at school age by using retrospective questionnaire data, with major limitations in the classification of both exposure and outcome and, importantly, the risk of recall bias.² One particular limitation was that there was no adjustment for respiratory tract infections. Previous prospective birth cohort studies

TABLE I. Unadjusted and adjusted odds ratios for childhood TROLLS and asthma by infancy acetaminophen exposure

	Unadjusted				Adjusted			
	No.	OR*	95% CI	P value	OR*	95% CI	P value	
TROLLS, 0-3 y								
Acetaminophen, third trimester	345	0.98	0.73	1.31	.878	—	—	—
Acetaminophen, 0-1 y	342	1.34	1.10	1.64	.005	1.28	1.03	1.58
Current asthma, 7 y								
Acetaminophen, third trimester	336	0.95	0.66	1.37	.781	—	—	—
Acetaminophen, 0-1 y	327	1.04	0.80	1.36	.753	0.98	0.75	1.29

*Doubling of exposure days. Adjusted analyses were adjusted for concurrent LRTIs (number during first year of life).

investigating the possible confounding effect of infections showed that there is a connection between acetaminophen exposure in early life and the development of asthma in childhood but that this association disappears when adjusting for respiratory tract infections.^{7,8} We see an effect from acetaminophen after adjustment for LRTIs for early asthma symptoms. This could be due to an independent effect from acetaminophen or residual confounding. The temporary effect could be due to difference in temporal endotypes over time,⁵ lack of statistical power, or other unknown mechanisms.

One randomized clinical trial has been performed randomizing febrile children (0.5-12 years) to acetaminophen or ibuprofen on asthma hospitalization and outpatient clinic visits. Acetaminophen increased the risk of an outpatient visit for asthma in the month after the treatment, suggesting an adverse effect of the drug, but this could also be due to a protective effect of ibuprofen.⁹

Our study suggests that acetaminophen in infancy is associated with early childhood asthma. Further prospective clinical studies are needed to confirm this independent association.

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