



Effect of paracetamol use on the modification of the development of asthma by reactive oxygen species genes

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ABSTRACT

Background: Recent studies have identified an increase in the prevalence of asthma associated with paracetamol use.

Objective: To identify the relationship among asthma, biomarkers, genes, and paracetamol use in preschool children.

Methods: We undertook a population-based, cross-sectional survey of 933 preschool children. Asthma status was classified according to medical history and asthmatic symptoms. History of paracetamol use in infancy was recorded. Impulse oscillometry, blood tests for eosinophils and total IgE, and genotyping of *NAT2*, *Nrf2*, and *GSTP1* polymorphisms by TaqMan assay were conducted.

Result: Paracetamol use in infancy was associated with an increased risk of treatment for asthma within the previous 12 months. Paracetamol use together with a family history of asthma increased the risk of asthma diagnosis ever, current asthma, and treatment for asthma within the previous 12 months. Gene polymorphisms in *NAT2* (rs4271002), *Nrf2* (rd6726395), and *GSTP1* (rd1695) increased the risk of treatment for asthma within the last 12 months. Eosinophils were significantly elevated in the group with paracetamol use and a family history of asthma; however, the serum total IgE level and IOS did not show any significant difference.

Conclusion: Paracetamol use in infancy was significantly associated with increased risk of asthma. The association is more significant in genetically susceptible children, related to antioxidant genes, and the effect may be mediated by eosinophilic inflammation.

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Introduction

The recent increase in the prevalence of allergic disease^{1–4} has been attributed to a variety of factors, such as greater exposures to environmental tobacco smoke, air pollution, and allergens; an increased prevalence of obesity; and a decreased incidence of bacterial infection.⁵ Although the exact reasons for this increase remain unclear, recent investigations have focused on identifying

novel risk factors for asthma, including the use of paracetamol (acetaminophen).

A relationship between asthma and analgesics consumption was first suggested more than 10 years ago,⁶ and this was subsequently confirmed in several studies during the last decade.^{7–12} Among the underlying mechanisms explored thus far, the importance of a decrease in glutathione levels, which leads to a redox imbalance and may thus cause airway inflammation, and of impaired cyclooxygenase inhibition, resulting in the development of T_H2 immune responses is recognized.^{6,8,13–15} In addition, genetic factors, such as polymorphisms in genes associated with the antioxidant response, may also contribute to the relationship between analgesic use and asthma. In this study, we focused on 3 specific polymorphisms in the *NAT2*, *Nrf2*, and *GSTP1* genes (rs4271002, rs6726395, and rs1695, respectively). These polymorphisms have been associated with asthma-related phenotypes: rs4271002 with aspirin-intolerant asthma,¹⁶ rs6726395 with forced expiratory volume in 1 second,¹⁷ and rs1695 with airway reactivity¹⁸ and lung function.¹⁹ Although we did not analyze all polymorphisms in each gene, we assumed that the 3 polymorphisms were at least partly representative of other polymorphisms. The overall purpose of our study was to determine the associations among asthma, specific biomarkers, and genetic factors with paracetamol use, especially in children of preschool age.

Methods

Between July and August, 2010, we recruited 986 preschool children aged 3 to 7 years from 16 kindergartens randomly selected from Seoul, Ilsan, and Gwacheon in the Gyeonggi-do province in Korea. A modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire²⁰ was used to determine the prevalence of symptoms and the diagnosis of allergic diseases. Children whose sex was not reported were excluded, so responses from 933 preschool children and their parents were included in the analyses. Of these, 919 preschool children and their parents completed the study questionnaires, corresponding to an overall response rate of 98.5%.

The mean (SD) age of the preschool children included in this survey was 4.87 (1.05) years. The prevalence of a parental history of allergic disease (including atopic dermatitis, asthma, and allergic rhinitis) previously diagnosed by a physician was 49%, and the prevalence of a parental history of asthma was 5% (Table 1).

This study was approved by the institutional review board of Asan Medical Center. Written consent was obtained from all parents and guardians after they had received a detailed explanation of the study.

ISAAC Questionnaire

The modified Korean version of the ISAAC was previously validated as a tool to assess allergic symptoms and the diagnosis of allergy in Korean children.³ The questionnaire consists of 3 main sections: (1) general characteristics, including name, sex, date of birth, height, and weight; (2) a history of symptoms related to asthma, allergic rhinitis, atopic dermatitis, allergic conjunctivitis, and food allergy; and (3) exposure to environmental factors associated with allergic disease. The dosage of paracetamol was measured using the questionnaire by asking the frequency of paracetamol use within the first 12 months of life. Paracetamol use was defined as taking the medication for 3 or more days. The Korean version of the ISAAC questionnaire was completed by the parents or guardians of the preschool children.

Prevalence of Asthma and Wheezing

The prevalence of asthma and wheezing was determined by questions addressing the following: (1) wheezing episodes once or

Table 1

Characteristics of the study participants

Characteristics	No./total No. (%) ^a (N = 933)
Responded to questionnaire	919/933 (98.5)
Age, mean (SD), y	4.87 (1.05)
Sex, male/female	480/453
BMI, mean (SD)	15.9 (1.65)
Parental history of allergic disease	449/916 (49.0)
Parental history of asthma	46/914 (5.0)
Parental history of AR	403/915 (44.0)
Parental history of AD	105/915 (11.5)
Environmental tobacco smoking	412/911 (45.2)
Educational level of mother	
High school graduate or lower	240/905 (26.5)
University graduate or higher	665/905 (73.5)
Economic status (monthly income)	
Low (<\$300)	328/890 (36.9)
Middle (\$300–\$500)	341/890 (38.3)
High (≥\$500)	221/890 (24.8)
Paracetamol use	
During infancy	550/908 (60.6)
During the previous year	625/910 (68.7)
Biomarker	
Eosinophil, mean ± SD, %	4.17 (3.20)
Total IgE, mean (SD), IU/mL	194.35 (376.47)
Atopy ^b	147/659 (22.3)

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; BMI, body mass index.

^aData are presented as number/total number (percentage) of patients unless otherwise indicated.

^bDefined as at least one positive skin prick test result (an allergen wheal diameter greater than a histamine wheal diameter and a histamine wheal diameter >3 mm).

more in their lifetime (wheeze ever), (2) wheezing episodes once or more within the previous 12 months (wheeze within the last 12 months), (3) a diagnosis of asthma in their lifetime (asthma diagnosis ever), or (4) asthma treatment within the previous 12 months (treatment for asthma within the last 12 months). Current asthma was defined as a diagnosis of asthma any time during the child's lifetime and wheezing in the previous 12 months.⁴

White Blood Cells, Eosinophils, and Total IgE

White blood cell counts and the percentage of blood eosinophils were measured. Serum total IgE concentration was measured with a fluorescent enzyme immunoassay using the ImmunoCAP system (Phadia AB, Uppsala, Sweden).

Bronchodilator Response Measured Using Impulse Oscillometry

Impulse oscillometry (IOS) using the Master Screen Spirometry—IOS Digital System (Jaeger Company, Würzburg, Germany) was performed according to American Thoracic Society/European Respiratory Society recommendations.²¹ Respiratory resistance and respiratory reactance at 5, 10, 15, 20, 25, and 35 Hz, total respiratory impedance, and resonance frequency were recorded. The bronchodilator response was assessed by repeating the measurements 15 minutes after the child had inhaled 200 µg of salbutamol and then calculating the relative changes (percentage change from the baseline) in the IOS variables. We considered a 20% decrease in respiratory resistance at 5 Hz after bronchodilator administration as a positive bronchodilator response.²²

Genotyping

Genomic DNA was extracted from peripheral blood of the study participants. *NAT2*, *Nrf2*, and *GSTP1* polymorphisms were genotyped with the TaqMan assay, using assay IDs C_31028511_10, C_155538_10 and C_3237198_20 (ABI, Foster City, California), respectively. The TaqMan assay was performed according to the manufacturer's instructions. End point readings were performed with an ABI PRISM 7900 HT Sequence Detection System (ABI).

Statistical Analysis

Statistical analyses were performed using SPSS statistical software, version 18.0 (SPSS Inc, Cary, North Carolina). Prevalence rates are presented with their 95% confidence intervals (CIs). Logistic regression analyses were conducted to identify independent risk factors for asthma. Tests for trends were performed using a logistic regression model as a continuous variable. In the multivariate analysis, age, sex, body mass index, and a history of bronchiolitis were adjusted as personal factors; parental asthma was adjusted as a familial factor; and family income and environmental tobacco smoke were adjusted as socioeconomic factors. We chose the recessive model for gene-environmental interaction because the recessive model (AA+Aa vs aa) increased the risk of asthma than either the additive or the dominant models without environmental factors (data not shown). For all analyses, $P < .05$ was defined as statistically significant.

Results

Association Between Paracetamol Use and Asthma

Paracetamol use, defined as consumption for more than 3 days within the first 12 months of life, was observed in 550 of 908 study participants (60.7%). In these children, the adjusted odds ratio (aOR) for treatment of asthma within the previous 12 months increased to 3.471 (95% CI, 1.291–9.331) (Table 2). Specifically, in children who had used paracetamol on 1 or 2 occasions or on 3 or more occasions, the aOR for treatment for asthma within the last 12 months increased to 4.042 (95% CI, 1.431–11.415) and 2.838 (95% CI, 0.946–8.520), respectively (Table 3).

Combined Effect of Paracetamol Use and Parental History of Asthma

For children with both a history of paracetamol use during infancy and a parental history of asthma, the aORs for asthma diagnosis ever, treatment for asthma within the previous 12 months, and current asthma were 4.097 (95% CI, 1.362–12.32), 19.083 (95% CI, 4.891–74.453), and 5.083 (95% CI, 1.267–20.396), respectively. For a history of paracetamol use only without a family history of asthma, the aOR for treatment for asthma within the previous 12 months was 3.290 (95% CI, 1.106–9.791). For family history of asthma only, the aOR for asthma diagnosis ever was 4.703 (95% CI, 1.147–19.284) (Table 4).

Combined Effect of Paracetamol Use and Polymorphisms in Oxidative Stress–Related Genes

There was an additive effect between paracetamol use during infancy and polymorphisms of *NAT2*, *Nrf2*, and *GSTP1*. For children

with a history of paracetamol use and AA+Aa for polymorphisms in *NAT2*, *Nrf2*, and *GSTP1*, the aORs for treatment for asthma within the previous 12 months were 5.110 (95% CI, 1.468–17.788), 3.741 (95% CI, 1.036–13.513), and 4.244 (95% CI, 1.194–15.085), respectively. Paracetamol use during infancy and polymorphisms in *NAT2*, *Nrf2*, and *GSTP1* progressively increased the risk of asthma treatment during infancy. For no paracetamol use and aa, paracetamol use and AA+Aa, and paracetamol use and aa compared with no paracetamol use and AA+Aa, the P values for trend were .03, .02, and .02, respectively (Table 5). Serum IgE levels, eosinophil counts, and measurements of IOS were not significantly associated with polymorphisms in any of these genes (data not shown).

Association Between Paracetamol Use and Biomarkers of Asthma

Mean eosinophil counts were significantly higher in children with both a history of paracetamol use and a family history of asthma than in children without these corresponding histories (mean eosinophil counts, 5.33% vs 4.00%; $P = .02$) (eFig 1). However, the total serum IgE levels did not show any significant difference (data not shown).

Association Between Paracetamol Use and IOS Measurements

Measurements of bronchodilator response, calculated as a relative change in respiratory resistance, did not significantly differ among the groups defined on the basis of either a family history of asthma or paracetamol use (data not shown).

Discussion

This study found evidence of an association between paracetamol use in the first year of life and an increased risk of asthma in preschool children 3 to 7 years of age. Paracetamol use significantly increased the risk in children with a family history of asthma. Our data also suggest that the gene polymorphisms related to oxidative stress, such as the *NAT2*, *Nrf2*, and *GSTP1* genes, may play a role in these associations. Further investigations, such as cohort studies, will be needed in the future to focus on cause and effect.

There are several situations that could act as confounding factors, such as paracetamol use during lower respiratory viral infections, which are associated with an increased risk of asthma in childhood.^{23,24} Furthermore, severe asthma requires either a high dose or the prolonged use of paracetamol for respiratory infections that are either related to asthma or that precede its diagnosis, leading to the appearance of a causal relationship.^{10,25} Indeed, one prospective birth cohort study concluded that paracetamol use in early life was not an independent risk factor after adjusting for early infections.²⁶ However, it is highly probable that paracetamol is also

Table 2
Association between paracetamol use and asthma^a

Variable	Paracetamol (infancy)	No. (%) of patients	Unadjusted		Adjusted	
			OR (95% CI)	P value	OR ^b (95% CI)	P value
Wheeze ever	No	70/321 (21.8)	1 (Reference)		1 (Reference)	
	Yes	130/493 (26.4)	1.239 (0.909–1.69)	.18	0.912 (0.634–1.312)	.62
Wheeze within the previous 12 months	No	23/321 (7.2)	1 (Reference)		1 (Reference)	
	Yes	50/493 (10.1)	1.426 (0.884–2.301)	.15	1.202 (0.703–2.055)	.50
Asthma diagnosis ever	No	18/319 (5.6)	1 (Reference)		1 (Reference)	
	Yes	49/492 (10.0)	1.497 (0.907–2.469)	.11	1.447 (0.799–2.621)	.22
Treatment for asthma within the previous 12 months	No	5/316 (1.6)	1 (Reference)		1 (Reference)	
	Yes	29/486 (6.0)	2.957 (1.288–6.793)	.01	3.471 (1.291–9.331)	.01
Current asthma ^c	No	8/321 (2.5)	1 (Reference)		1 (Reference)	
	Yes	24/493 (4.9)	1.733 (0.825–3.64)	.1461	1.646 (0.706–3.839)	.25

Abbreviations: CI, confidence interval; OR, odds ratio.

^aData were analyzed by logistic regression multivariate analysis.

^bThe ORs were adjusted for age, sex, body mass index, parental history of asthma, family income, environmental tobacco smoke, and bronchiolitis.

^cCurrent asthma is lifetime asthma diagnosis by questionnaire together with asthma symptoms in past 12 months.

Table 3Association between paracetamol dose and asthma^a

Variable	Paracetamol (infancy)	No. (%) of patients	Unadjusted		Adjusted	
			OR (95% CI)	P value	OR ^b (95% CI)	P value
Wheeze ever	0	70/321 (21.8)	1 (Reference)		1 (Reference)	
	1–2	64/258 (24.8)	1.164 (0.810–1.674)	.41	0.899 (0.591–1.366)	.62
	≥3	66/235 (28.1)	1.322 (0.919–1.901)	.13	0.927 (0.603–1.427)	.73
Wheeze within the previous 12 months	0	23/321 (7.2)	1 (Reference)		1 (Reference)	
	1–2	27/258 (10.5)	1.454 (0.843–2.507)	.18	1.316 (0.724–2.392)	.37
	≥3	23/235 (9.8)	1.396 (0.799–2.442)	.24	1.079 (0.572–2.034)	.81
Asthma diagnosis ever	0	18/319 (5.6)	1 (Reference)		1 (Reference)	
	1–2	24/258 (9.3)	1.388 (0.778–2.475)	.27	1.460 (0.750–2.841)	.27
	≥3	25/234 (10.7)	1.615 (0.913–2.856)	.10	1.433 (0.726–2.829)	.30
Treatment for asthma within the previous 12 months	0	5/316 (1.6)	1 (Reference)		1 (Reference)	
	1–2	17/255 (6.7)	3.324 (1.368–8.074)	.008	4.042 (1.431–11.415)	.008
	≥3	12/231 (5.2)	2.566 (1.009–6.526)	.05	2.838 (0.946–8.520)	.06
Current asthma ^c	0	8/321 (2.5)	1 (Reference)		1 (Reference)	
	1–2	12/258 (4.7)	1.669 (0.721–3.865)	.23	1.694 (0.665–4.319)	.27
	≥3	12/235 (5.1)	1.802 (0.778–4.176)	.17	1.594 (0.611–4.162)	.34

Abbreviations: CI, confidence interval; OR, odds ratio.

^aData were analyzed by logistic regression multivariate analysis.^bThe ORs were adjusted for age, sex, body mass index, parental history of asthma, family income, environmental tobacco smoke, and bronchiolitis.^cCurrent asthma is lifetime asthma diagnosis by questionnaire together with asthma symptoms in past 12 months.

used to treat fevers caused by a variety of diseases not related to the respiratory tract, thereby minimizing the potential confounding effect.^{7,25,27} We also tried to minimize such confounding by adjusting for a history of bronchiolitis. Positive associations were maintained after this adjustment, decreasing the likelihood of reverse causation.

In ISAAC, in more than 100,000 children aged 6 to 7 years, paracetamol use was associated with an increased risk of wheeze within the previous 12 months,^{7,27} which is consistent with meta-analysis of other studies.²⁵ Similarly, we found that paracetamol use was associated with an increased risk of asthma treatment within the previous 12 months. In a prospective study with a 10-year follow-up, current asthma status was not associated with paracetamol use,²⁸ although history of asthma at 10 years of age was associated with paracetamol use. Both ISAAC^{7,27} and a study from New Zealand²⁹ found a dose-dependent effect of paracetamol

on childhood asthma development, whereas a dosage effect was not significant in our study, perhaps because of the relatively small size of the study population.

Only a few reports have examined the effects of paracetamol use on the incidence of asthma in children with a parental history of asthma. A previous study did not show a significant association²⁶; however, in our study, a family history significantly increased the risk of asthma associated with paracetamol use. This finding supports the concept that paracetamol affects the risk of asthma, especially in susceptible children, which might be genetic.

No genotypes have been definitively associated with the development of asthma in children who are administered paracetamol in early life. Prenatal exposure, however, to maternal *Nrf2* and *GST* genes (*GSTT1* and *GSTM1*) was associated with the development of asthma in offspring.¹² In addition, the risk of asthma was modified by a functional polymorphism of *GSTP1* in children with

Table 4Association between paracetamol use and parental history of asthma^a

Variable	Paracetamol (infancy)	Family history of asthma	No. (%) of patients	Unadjusted		Adjusted	
				OR (95% CI)	P value	OR ^b (95% CI)	P value
Wheeze ever	No	No	66/305 (21.6)	1 (Reference)		1 (Reference)	
	No	Yes	4/16 (25.0)	1.128 (0.354–3.597)	.84	0.930 (0.263–3.288)	.91
	Yes	No	117/465 (25.2)	1.190 (0.864–1.638)	.29	0.864 (0.594–1.256)	.44
	Yes	Yes	13/28 (46.4)	2.934 (1.339–6.429)	.007	1.959 (0.811–4.734)	.14
Wheeze within the previous 12 months	No	No	22/305 (7.2)	1 (Reference)		1 (Reference)	
	No	Yes	1/16 (6.3)	0.810 (0.103–6.379)	.84	0.773 (0.095–6.271)	.81
	Yes	No	45/465 (9.7)	1.333 (0.814–2.183)	.25	1.142 (0.658–1.983)	.64
	Yes	Yes	5/28 (17.9)	2.642 (0.928–7.525)	.07	2.001 (0.657–6.099)	.22
Asthma diagnosis ever	No	No	15/303 (5.0)	1 (Reference)		1 (Reference)	
	No	Yes	3/16 (18.8)	3.462 (0.915–13.099)	.07	4.703 (1.147–19.284)	.03
	Yes	No	42/464 (9.1)	1.503 (0.881–2.564)	.14	1.550 (0.821–2.928)	.18
	Yes	Yes	7/28 (25.0)	5.000 (1.909–13.094)	.001	4.097 (1.362–12.32)	.01
Treatment for asthma within the previous 12 months	No	No	4/300 (1.3)	1 (Reference)		1 (Reference)	
	No	Yes	1/16 (6.3)	3.611 (0.408–31.919)	.25	4.433 (0.456–43.069)	.20
	Yes	No	22/458 (4.8)	2.680 (1.084–6.628)	.03	3.290 (1.106–9.791)	.03
	Yes	Yes	7/28 (25)	18.053 (5.568–58.534)	<.001	19.083 (4.891–74.453)	<.001
Current asthma ^c	No	No	7/305 (2.3)	1 (Reference)		1 (Reference)	
	No	Yes	1/16 (6.3)	2.467 (0.293–20.752)	.41	2.953 (0.328–26.595)	.33
	Yes	No	20/465 (4.3)	1.644 (0.748–3.616)	.22	1.636 (0.666–4.019)	.28
	Yes	Yes	4/28 (14.3)	6.168 (1.770–21.495)	.004	5.083 (1.267–20.396)	.02

Abbreviations: CI, confidence interval; OR, odds ratio.

^aData were analyzed by logistic regression multivariate analysis.^bThe ORs were adjusted for age, sex, body mass index, family income, environmental tobacco smoke, and bronchiolitis.^cCurrent asthma is lifetime asthma diagnosis by questionnaire together with asthma symptoms in past 12 months.

Table 5

Association between paracetamol use and polymorphisms in oxidative stress–related genes and asthma treatment during the previous 12 months

Gene	Paracetamol (infancy)	Genotype	Patients with/without asthma treated within the previous 12 months	Adjusted OR ^a (95% CI)	Trend <i>P</i> value
NAT2	No	GG+GC	4/242	1 (Reference)	.03
	No	CC	0/8	NA	
	Yes	GG+GC	20/345	5.110 (1.468–17.788) ^b	
	Yes	CC	0/14	NA	
Nrf2	No	GG+GA	4/215	1 (Reference)	.02
	No	AA	0/38	NA	
	Yes	GG+GA	16/304	3.741 (1.036–13.513) ^c	
	Yes	AA	4/56	4.364 (0.903–21.089)	
GSTP1	No	AA+AG	4/240	1 (Reference)	.02
	No	GG	0/13	NA	
	Yes	AA+AG	19/347	4.244 (1.194–15.085) ^d	
	Yes	GG	1/13	5.603 (0.495–63.371)	

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

^aThe OR was adjusted for age, sex, body mass index, family income, parental history of asthma, environmental tobacco smoke, and bronchiolitis.^b*P* = .01.^c*P* = .04.^d*P* = .02.

prenatal exposure.³⁰ However, the genotype of children exposed during infancy did not show any significant association with asthma.¹² By contrast, we found a positive association between reactive oxygen species–related gene polymorphisms and the development of childhood asthma. To the best of our knowledge, this association has not been previously reported.

Glutathione is present in tissues in its reduced form and acts as an antioxidant and an indirect anti-inflammatory mediator.^{13,14} Thus, a decrease in glutathione levels, as a result of paracetamol use,¹³ may cause airway inflammation.¹⁵ In addition, the increased use of paracetamol and the corresponding decreased use of aspirin reduce cyclooxygenase inhibition, such that the production of prostaglandin E2 is no longer inhibited. This, in turn, promotes T_H2 immune response.^{6,8} In addition to glutathione and cyclooxygenase, the IgE-mediated antigenic effect of paracetamol itself is another possibly related hypothesis.^{31,32} The elevated levels of IgE and histamine after paracetamol ingestion³¹ are indicative of an inflammatory process. The Avon Longitudinal Study of Parents and Children showed a positive association between prenatal paracetamol exposure and increased IgE levels at 7 years of age.³³ By contrast, in our study eosinophil levels, but not IgE levels, were significantly higher in children with a history of paracetamol use and a family history of asthma, consistent with previous studies in New Zealand²⁹ and the United Kingdom.³⁴ Considering that prenatal exposure caused IgE elevation,³³ such a discrepancy might be explained by the different timing of paracetamol exposure (ie, in utero, during infancy, or during adulthood).²⁹ To our knowledge, no report has shown a relationship between eosinophil levels and asthma in children with a history of paracetamol use.

An inverse association of forced expiratory volume in 1 second with paracetamol use was previously reported in adults¹⁰; however, there are no reports of pulmonary function in association with paracetamol use in preschool-aged children. Although we measured IOS in our study participants, there was no evidence of a positive relationship between IOS and paracetamol use.

Our study has several limitations. First, as a cross-sectional study, a causal relationship could not be determined. Second, as discussed extensively herein, viral infection may have been a confounding factor because it is independently associated with the exacerbation of asthma.³⁵ However, we sought to minimize this effect by adjusting for bronchiolitis. Third, there may be some recall bias because our study was based on parental reporting. Finally, the number of children included in the study was relatively small because it was limited to those aged 3 to 7 years, although we achieved a relatively high response rate (98.5%).

The strengths of our study are as follows. First, it is the first study of preschool children aged 3 to 7 years. Second, eosinophils, IgE, and IOS have not been previously evaluated as biomarkers in relation to paracetamol use and asthma. Third, our study is the first to identify genetic polymorphisms that, in combination with paracetamol use, are associated with childhood asthma. The clinical implications of these findings are important because paracetamol is widely used in children.

In conclusion, paracetamol use during an early period of infancy was significantly associated with an increased risk of asthma, especially in genetically susceptible children. Gene polymorphisms in NAT2, Nrf2, and GSTP1 were found to be associated with the relationship between paracetamol use and asthma. The underlying mechanism for the association may be mediated by eosinophilic inflammation. Further prospective, long-term follow-up studies are needed to confirm and extend these findings.

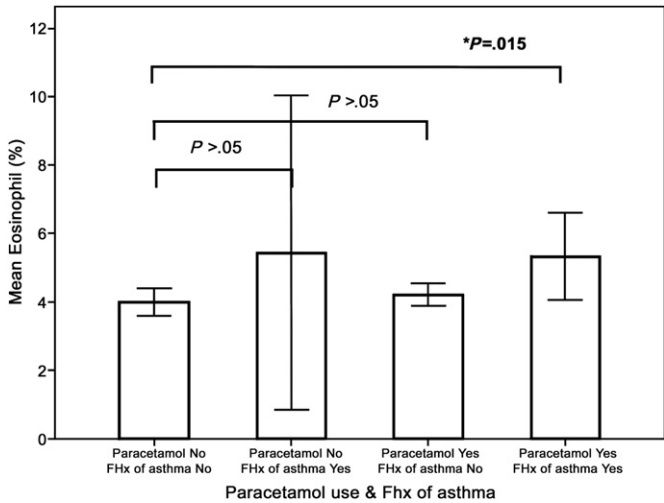
Supplementary Data

Supplementary data related to this article can be found online at <http://dx.doi.org/10.1016/j.anai.2013.03.008>.

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eFigure 1. Mean percentage of eosinophils in the peripheral blood of children grouped according to family history of asthma and paracetamol use during the first 12 month of life. Bars represent 95% confidence intervals. Fhx indicates family history.