

Early exposure to paracetamol or to antibiotics and eczema at school age: Modification by asthma and rhinoconjunctivitis

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The association between early exposure to paracetamol or to antibiotics and eczema is conflicting. This study aims to know whether the early exposure to those drugs is associated with eczema at school age, and whether the strength of the association is modified by the presence of asthma or rhinoconjunctivitis. Children aged 6–7 ($n = 13908$) from the International Study of Asthma and Allergies in Childhood in Spain provided data about current asthma, rhinoconjunctivitis and eczema. Parent-reported information was also obtained on paracetamol and antibiotic consumption during the first year of life. Logistic regression analysis with eczema as outcome and including exposure to paracetamol or to antibiotics, together with possible confounders, was carried out in the whole sample of children and in five different strata: no respiratory symptom and any respiratory symptom further subdivided into: asthma with rhinoconjunctivitis, asthma without rhinoconjunctivitis and rhinoconjunctivitis without asthma. In the whole sample, exposure to paracetamol was associated with eczema (aOR 1.56 [1.36–1.80]) as was antibiotic consumption (aOR 1.66 [1.43–1.92]). These associations did not substantially change after additionally adjusting for the other drug. A similar pattern was found among children without respiratory symptoms. In children with symptoms, adjusting for the other drug modified the association with paracetamol (aOR from 1.32 [1.03–1.71] to 1.09 [0.83–1.43]) but did not change that with antibiotics (aOR from 1.80 [1.38–2.35] to 1.81 [1.37–2.39]). Early exposure to paracetamol or to antibiotics is associated with an increased prevalence of eczema at school age. Asthma and/or rhinoconjunctivitis substantially modifies this association.

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Although the association between paracetamol consumption and asthma has been quite widely studied both in adults and children, suggesting that the positive association found is probably not attributed to confusion by indication (1–4), only few studies have explored the relationship

between paracetamol and eczema in schoolchildren. The study by Barragan et al. (5), using the International Study of SAssthma and Allergies in Childhood (ISAAC) methodology, found an association between frequent paracetamol intake during the previous year and eczema. Using the

same methodology in children aged 13–14 and 6–7 from Iran, Karimi et al. (6) found an association between eczema and frequent paracetamol use during the previous year only in the older group. No association was established by Vlaski et al. (7), using the aforementioned protocol in a different population. More recently, an ISAAC global study (4) found an association of paracetamol use during the first year of life and during the previous year with eczema at 6–7 yr of age, which was consistent for most regions of the world.

With respect to antibiotics as a risk factor of eczema, the results are also conflicting. Several birth cohort studies could not find any association between being exposed to those drugs during the first year of life and suffering from eczema at preschool age, either in general population (8, 9) or in high atopic risk children (10). However, quite recently, another birth cohort has shown that antibiotic exposure before 3 months of age was not associated with eczema between birth and 15 months, but exposure before 15 months was related to eczema developing after 15 months. Furthermore, antibiotic use during pregnancy has been associated with eczema in the offspring (11). Cross-sectional studies, usually performed in older children, have found a positive association between antibiotic use during the first year of life and eczema (12).

To the best of our knowledge, only one study has addressed the issue of the consumption of both paracetamol and antibiotics, and suffering from eczema. In the study by Cohet et al. (13), which compared a group of children 6–7 yr of age who suffered a severe infection between 0 and 4 yr of life and a group of children of similar age from the general population, there was an association of both paracetamol and antibiotic use in the first year of life with current eczema, this association being higher with antibiotics than with paracetamol after adjusting for the two drugs and other potential confounders.

We wanted to know whether those results could be replicated in an unselected population of schoolchildren of a similar age but also to know how and to what extent those associations are modified by the concomitant presence of asthma and/or rhinoconjunctivitis.

Methods

Population, questionnaires and definitions

By means of the ISAAC Phase Three core and environmental questionnaires (<http://isaac.auckland.ac.nz>), parents of children aged 6–7 were surveyed in the school setting in seven different

Spanish centres: Cartagena, Barcelona, Bilbao, Valencia, Madrid, Asturias and La Coruña. Except for Barcelona, Madrid and Asturias, the rest of the centres included all schools or a random sample of them within the city district and which had children of the targeted age range. Madrid included all schools within the health area of the 'Hospital 12 de Octubre', and Barcelona did the same with the 'Hospital del Mar'. Asturias sampled schools randomly from the entire province. Questionnaires were translated into Spanish and translated back into English according to the ISAAC protocol and were validated later (14). The questionnaires were given to the children by their teachers, filled in by the parents at home and returned to the school within 1 wk.

The core questionnaire included questions on asthma, rhinoconjunctivitis and eczema symptoms. According to this questionnaire, eczema was defined as a positive answer to three questions: (i) 'Has your child ever had an itchy rash that was coming and going for at least 6 months?' (ii) 'Has your child had this itchy rash at any time during the past 12 months?' and (iii) 'Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?' Additionally, there was a question that should have been answered positively for a child considered as having current eczema, which was: 'Has your child ever had eczema or atopic dermatitis?' Children with negative responses to all the previous four questions were considered to be free of eczema. Those with positive answers to the first group of three questions and negative to the last one, or *vice versa*, were not included in the analysis.

Rhinoconjunctivitis was defined as a positive answer to two questions: (i) 'In the past 12 months, has your child had a problem with sneezing or a runny or blocked nose when he/she did not have a cold or the flu?' and (ii) 'In the past months, has this nose problem been accompanied by itchy-watery eyes?' Asthma was defined as a positive answer to the question 'Has your child had wheezing or whistling in the chest during the past 12 months?'

The environmental questionnaire included a question about paracetamol consumption as follows: 'In the first 12 months of your child's life, did you usually give paracetamol (e.g., [local trade names]) for fever?' (yes/no). It also included a question about antibiotic consumption: 'In the first 12 months of life, did your child have any antibiotics?'

Other variables included as potential confounders in this study were smoker mother (yes/no); having a cat or a dog at home during the first year of life (yes/no); traffic in front of the child's house (never, seldom, frequently during the day, almost all day and night); number of older and younger siblings and highest study level achieved by the mother (no studies, primary school, secondary school, college-university).

Statistical analysis

To study the association between paracetamol or antibiotic consumption during the first year of the child's life and eczema according to the child's allergic respiratory comorbidity, generalized logit models were used. Crude and adjusted (for gender, age, centre, smoker mother, cat and dog ownership during that first year, frequency of truck traffic, older and younger siblings and mother education) odds ratios were calculated. Adjustment was made firstly including paracetamol or antibiotics separately in two different logistic regression models: one for antibiotics and another for paracetamol. Each of those two models was calculated for the total sample of children and also for the four following groups: asthmatics with rhinoconjunctivitis, asthmatics without rhinoconjunctivitis, non-asthmatics with rhinoconjunctivitis and children without respiratory symptoms. Secondly, four new logistic regressions were calculated for the four aforementioned groups, but this time including both paracetamol and antibiotics, together with the rest of covariates. As a way of knowing whether paracetamol and antibiotics had been given to the same children, agreement between exposure to the two drugs was calculated using the Cohen's κ statistic (kappa values <0.4 are considered low).

All statistical analyses were performed by means of SPSS 13.0 (Spss Inc, Chicago, IL, USA) and Stata v7 (Stata corporation, College Station, TX, USA) software.

Ethical approval

The regional ethics committee of Asturias approved this study for all ISAAC III centres in Spain.

Results

Details of the participation rate of ISAAC Phase Three in Spain are given elsewhere (15). From a starting data set of 20,455 children, which included those recruited in the previously

mentioned centres, 6255 were not included in the analyses because of inconsistencies in the definition of eczema (i.e., had answered positively to the symptoms and negatively to the diagnostic question or *vice versa*). Additionally, 391 had missing values either in the asthma or in the rhinoconjunctivitis questions. Thus, a total of 13,908 were included, of which 965 were positive to the eczema definition and 12,844 were not. The number of children included in each stratum of respiratory symptoms was: 430 for asthma and rhinoconjunctivitis, 881 for asthma without rhinoconjunctivitis, 579 for rhinoconjunctivitis without asthma and 11,919 for neither symptom. The agreement between consumption of antibiotics and paracetamol during the first year of life was quite low ($\kappa = 0.30$).

Among children without eczema, parents reported having given paracetamol to 49.1% of the children. Among those with eczema, 59.2% ($p < 0.001$) reported in the same way. For antibiotics, the figures were 48.6% and 61.0%, respectively ($p < 0.001$). There were also significant differences in dog ownership during the first year of the child's life; truck traffic; number of younger siblings and highest study level achieved by the mother (Table 1).

In the whole sample of children, there was a significant association between paracetamol consumption during the first year of life and current eczema. The same was found for antibiotics (Table 2). The strength of the associations did not change much after adjustment for potential

Table 1. Demographic characteristics and prevalence of risk factors among children with and without eczema

	Without eczema N = 12844	With eczema N = 965	p
Age	6.52 $\pm$ 0.50	6.51 $\pm$ 0.50	0.46
Male gender	49.8	49.4	0.82
Paracetamol (use 1st yr)	49.1	59.2	<0.001
Antibiotics (use 1st yr)	48.6	61.0	<0.001
Mother smokes currently	39.5	41.8	0.16
Dog at home (1st yr)	12.9	10.2	0.015
Cat at home (1st yr)	5.6	5.6	1.0
Truck traffic on house street			
Never	15.9	14.3	0.21
Seldom	48.0	44.7	0.06
Frequently during the day	31.7	34.6	0.04
Almost all day and night	4.4	6.1	0.017
No older siblings	51.1	53.4	0.27
No younger siblings	64.0	59.7	0.016
Highest study level achieved by mother			
None	1.2	0.4	0.03
Basic	30.6	23.1	<0.001
Secondary	38.6	36.4	0.24
University	29.6	40.0	<0.001

All values as percentages except for age (mean $\pm$ s.d.)

Table 2. Association of consuming paracetamol or antibiotics during the first year of life with suffering from eczema at the age of 6–7

	OR	aOR	aOR*
Paracetamol	1.52 (1.33–1.74)	1.56 (1.36–1.80)	1.38 (1.19–1.61)
Antibiotics	1.75 (1.52–2.00)	1.66 (1.43–1.92)	1.52 (1.30–1.77)

aOR: adjusted for age, gender, mother's studies, current smoking mother, dog at home in the first year of child's life, cat at home in the first year of child's life, truck traffic near the household, older siblings and younger siblings.

aOR*: adjusted for the above and also for antibiotics (for paracetamol) or paracetamol exposure (for antibiotics).

confounders but decreased somewhat when the drugs were adjusted for each other.

When stratified by respiratory disease, the use of antibiotics or paracetamol in healthy children had a similar association strength and was not affected by adjustment or by introducing the other drug in the model (Table 3).

Among children suffering from asthma, rhinoconjunctivitis or both, the use of paracetamol during the first year of life had a certain trend of being associated with eczema. In fact, the strength of the associations of each stratum was similar to that of healthy children but was non-significant probably attributed to the comparatively low numbers. Adjustment for potential confounders increased the trend in two of the strata. However, including antibiotics in the model made any trend of association disappear. Conversely, the use of antibiotics had a robust association with eczema across all disease strata (in fact, higher than among healthy children), and the adjustment for other risk factors, including paracetamol or not, did not change the strength of the association (Table 3).

Discussion

The results of this study show that there is a different effect of paracetamol and antibiotic use during the first year of the child's life and

suffering from eczema at the age of 6–7. Among children with neither asthma nor rhinoconjunctivitis, paracetamol and antibiotics behave as independent risk factors of eczema. However, among children with asthma or rhinoconjunctivitis, paracetamol seems to depend on antibiotics for being a risk factor; i.e., when including both drugs in the model, the association between paracetamol and eczema disappears, while that of antibiotics is maintained, being actually stronger than in the healthy children.

The main limitation of this study is the possible recall bias: recalling correctly about medication given during the first year of a child's life can be inaccurate, although this inaccuracy might be in equilibrium in those parents whose children have or do not have eczema. In this case, the trend would be to the null hypothesis, thus reinforcing any association encountered. However, it is also possible that parents with children with respiratory allergic symptoms may recall better what medication their children received during their first year of life, thus leading to a higher reporting from this group (as most of the wheezing episodes in infancy are related to viral infections) and may be susceptible of being treated (incorrectly) with antibiotics and/or paracetamol (for fever).

Nevertheless, for paracetamol, the strengths of the associations are quite comparable across the different strata (asthma, rhinoconjunctivitis, both and none) -before adjusting for antibiotics-, thus reinforcing the idea that the intake of this drug may not be influenced by the presence of respiratory allergic disease in the child (which usually starts very early). If so, both recall and confounding by indication biases are probably not very important here. This is not the case of antibiotics, where the strength of the association is higher among children with respiratory symptoms, thus suggesting the aforementioned biases may play a role in the association among those children.

Table 3. Associations between the use of paracetamol or antibiotics during the first year of life and suffering from current eczema at the age of 6–7, stratified by the concomitant suffering from current respiratory symptoms of asthma and/or rhinoconjunctivitis

	N	Paracetamol			Antibiotics		
		OR	aOR	aOR*	OR	aOR	aOR*
Without asthma/rhinitis symptoms	11919	1.29 (1.08–1.53)	1.37 (1.14–1.64)	1.31 (1.08–1.58)	1.39 (1.17–1.65)	1.36 (1.13–1.63)	1.25 (1.03–1.51)
With asthma/rhinitis symptoms	1890	1.30 (1.03–1.65)	1.32 (1.03–1.71)	1.09 (0.83–1.43)	1.86 (1.45–2.38)	1.80 (1.38–2.35)	1.81 (1.37–2.39)
Asthma+ rhinoconjunctivitis+	430	1.17 (0.77–1.79)	1.33 (0.83–2.13)	1.08 (0.66–1.78)	1.61 (1.05–2.47)	1.51 (0.95–2.42)	1.47 (0.91–2.39)
Asthma+ rhinoconjunctivitis–	881	1.29 (0.85–1.96)	1.41 (0.90–2.21)	1.11 (0.69–1.80)	2.05 (1.31–3.23)	2.09 (1.30–3.38)	2.20 (1.32–3.69)
Asthma– rhinoconjunctivitis+	579	1.25 (0.82–1.91)	1.19 (0.76–1.87)	0.97 (0.60–1.59)	1.98 (1.25–3.13)	1.93 (1.18–3.15)	1.97 (1.18–3.31)

aOR: adjusted for age, gender, mother's studies, current smoking mother, dog at home in the first year of child's life, cat at home in the first year of child's life, truck traffic near the household, older siblings and younger siblings.

aOR*: adjusted for the above and also for antibiotics (paracetamol column) or paracetamol exposure (antibiotics column).

On the other hand, respiratory symptoms are not likely to have influenced any of the positive and significant associations encountered between both drugs and eczema among children without asthma or rhinoconjunctivitis. This might indicate that the exposure to paracetamol or antibiotics (not usually employed just for eczema) during the first year is independent risk factor for eczema at age 6–7.

The fact that paracetamol might be a risk factor for allergic diseases was revealed several years ago in the ecological report by Newson et al. (16). At the individual level, there have been several studies on the relationship between paracetamol and eczema (5–7). Of special interest is the study by Cohet et al. (13) that included two different 6- to 7-year-old populations (one of healthy children and another of children who had had at least one serious infection) and used the ISAAC questionnaire to define conditions. Eczema was associated with frequent paracetamol intake in the first year of life but not in the previous year.

The study by Sasheen et al. (17) in more than 14,000 pregnant mothers showed again an association between paracetamol consumption in infancy and eczema, but very interestingly, and unlike wheeze, there was no such association between the intake of this drug during pregnancy and the skin condition in the child. Children were studied again at school age, and the results were very similar (1).

With respect to antibiotics as a risk factor of eczema, the results are conflicting. For example, Celedon et al. –in a prospective cohort study of children with parental atopy– could not find that antibiotics use in the first year of life was associated with eczema at 5 yr. Similarly, Kusel et al. (10) did not find any association between antibiotics use and this condition in a small birth cohort of high atopic risk followed for 5 yr. The same findings arose from the KOALA birth cohort until age 2 (9). However, the cumulative incidence of eczema during the first 2 yr of life was associated with antibiotic use at least twice yearly in another cohort study (18). Wikens et al. (19) showed recently, in their birth cohort, that antibiotic exposure before 3 months of age was not associated with eczema between birth and 15 months, but exposure before 15 months was related to eczema developing after 15 months, and remaining present at 4 yr. Furthermore, in a small cohort of pregnant mothers, Jedrychowski et al. (11) found that antibiotic use during pregnancy was associated with eczema during the first year of the offspring's life. A large historical birth cohort studied by McKeever

et al. (20) found that the number of antibiotic courses was associated with the incidence of eczema in children from 0 to 11 yr of age, but this association was largely reduced when adjusting for consultation rates during the first year of life. Population-based cross-sectional studies (carried out in older children) such as the one by Floistrup et al. (12) found that antibiotic use during the first year of life is associated with eczema at school age.

Although there are no clear specific mechanisms for the association between paracetamol and eczema, there are two main explanations. The first one is that paracetamol may interfere with antioxidant systems via lowering glutathione levels, thus favouring skin inflammation mediated by reactive oxygen intermediates released by circulating polymorphonuclear leucocytes or local lymphocytes, monocytes and eosinophils (21). The importance of oxidative stress in eczema is shown by the fact that the stratum corneum of non-lesional skin of eczema patients exhibits a significantly less pronounced oxidative state, which may be the consequence of an increase in cutaneous antioxidant defences caused by chronic inflammation (22). Furthermore, urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG), which is a marker of oxidative stress *in vivo*, is elevated in children with eczema without any other allergic disease (23). The second way to connect paracetamol to eczema is again related with the lowering levels of glutathione, which may alter antigen presentation and recognition by antigen presenting cells, favouring a Th2 allergic pathway (24). Glutathione-depleted antigen presenting cells produce less interleukin-12 after contact with allergen, a situation leading to a lower production of interferon gamma by Th cells, thus driving the Th1/Th2 balance to the Th2 (allergic) end (25).

How antibiotics can influence the development of eczema is also far from being clear, although it has been hypothesized, according to the hygiene hypothesis, to be related to gut bacterial flora disruption and the subsequent imbalance of Th1/Th2 to the Th2 part.

The results of this study show that among children with respiratory symptoms, paracetamol associations with eczema disappear when adjusting for antibiotics, which may indicate that it is antibiotic that explains most of the effect, meaning that paracetamol is a risk factor for non-asthmatic non-rhinitic children, while not being so among children with allergic respiratory symptoms. Conversely, the association of antibiotics with eczema is maintained after adjustment for paracetamol, and this association is higher in

children with asthma or rhinoconjunctivitis. It could be hypothesized that children with asthma and/or rhinoconjunctivitis are somewhat protected from paracetamol, while being more susceptible to antibiotics. Moreover, the stronger association of antibiotics with eczema among children with respiratory symptoms may be explained by indication and/or recall biases. A sum of the last two explanations may also be possible, as the shifting to Th2 after gut bacterial flora disruption might be higher among children who are suffering or will suffer from asthma or rhinoconjunctivitis. As for paracetamol, patients with asthma have higher levels of blood (26) and sputum (27, 28) glutathione, and how this situation can modify the normal paracetamol metabolism deserves further investigation.

In summary, this study shows that paracetamol and antibiotics, taken during the first year of life, are independently (of each other) associated with eczema at 6–7 yr in children who neither have asthma nor rhinoconjunctivitis; the strength of the association being similar. Additionally, the present findings show that among children with asthma and/or rhinoconjunctivitis, those associations are modified: that of paracetamol disappears and that of antibiotics is increased, when compared to children without respiratory symptoms. How this could be explained by glutathione metabolism in asthmatics (paracetamol), and by recall or indication biases together with a higher susceptibility of atopic children to gut flora disruption (antibiotics), remains unclear.

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