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Exposure to paracetamol and asthma symptoms

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Background: Paracetamol is one of the factors that have been associated with the observed increase in asthma prevalence in the last few years. The influence of environmental or genetic factors in this disease may be different in some countries than in others. The purpose of this study was to analyse the relationship between the paracetamol consumption and asthma prevalence in our community. **Methods**: A cross-sectional study was conducted on more than 20 000 children and adolescents in Galicia, Spain. The International Study of Asthma and Allergies in Childhood methodology was used to collect the information on asthma symptoms in children, paracetamol consumption, body mass index (BMI), pets in the home, education level of the mother and parental asthma and smoking habits. The influence of paracetamol consumption on the prevalence of asthma symptoms was calculated using logistic regression, adjusted for the other parameters included in the study. **Results**: After adjusting for gender, BMI, having a cat or dog, maternal education, parental asthma and smoking, in 6- to7-year-old children, the consumption of paracetamol during the first year of life is associated with asthma [odds ratio (OR) 2.04 (1.79–2.31) for wheezing at some time]. Paracetamol consumption in the previous year leads to a significant increase in the probability of wheezing at some time [OR 3.32 (2.51–4.41)] in young children and adolescents [OR 2.12 (1.68–2.67)]. **Conclusions**: Paracetamol consumption is associated with a significant increase in asthma symptoms. The effect is greater the more often the drug is taken.

Introduction

An increase in the prevalence of childhood asthma has been observed over the last few years.[1] At the same time, paracetamol has become the most used treatment for fever in the child. Given that the use of antipyretics is common, even when there is minimal or no fever, ~75% of children in Western countries are treated with paracetamol.[2,3]

Various studies appear to support some effect of paracetamol on the increase in asthma prevalence.[4–6]

However, other studies show discrepant results, with no relationship being observed between paracetamol consumption and asthma.[7,8]

The purpose of this study was to evaluate the relationship between paracetamol consumption and asthma symptoms in our population.

Methods

We performed a multicentre study using the methodology of the International Study of Asthma and Allergies in Childhood (ISAAC; http://isaac.auckland.ac.nz). Written questionnaires, previously translated and validated in Spanish, were used in this study.[9,10]

The target population of the study was all those school children aged 6–7 years and 13–14 years from six of the main health catchment areas of Galicia, which includes a total of 1.9 million inhabitants (69% of the population in this autonomous region).

At these ages, schooling is mandatory by law, thus it can be assumed that the schooling rate is quite close to 100%.

Following the ISAAC protocol, a minimum sample size of 1000 valid questionnaires was established, for each age group and each area studied, to obtain the levels of prevalence and also to detect the possible differences between the areas analysed.[11]

The schools required from each health area were randomly selected, and all children in the targeted age ranges were included. The schools that refused to take part in the study were replaced with others.

The field work was done between October 2006 and February 2007.

Permission was sought from parents or guardians, who also answered the questionnaires in the 6–7 years age group, whereas in the older age group, the responses to the questionnaires were made by the children themselves.

The questionnaire data were introduced manually into a data base, using double entry with subsequent validation, in accordance with the ISAAC protocols.

The environmental questionnaire included questions about consumption of certain foods in the past 12 months, asthma symptoms, self-reported height and weight, parental asthma, exposure to pets, smoking habits of parents and mother's education level.

Paracetamol consumption in the past year was evaluated based on the response to the question: 'How often have you taken paracetamol in the last 12 months?' for 13- to 14-year olds and 'How often have you given your child paracetamol in the last 12 months?' for 6- to 7-year-old children, with three response options: (i) never; (ii) at least once a year; and (iii) at least once a month. In younger children, it also asked about the consumption of paracetamol in the first year of life, with the question: 'In the first 12 months of

life of your child, did you regularly give him/her paracetamol?' with two response options, yes or no.[11] The five brands of paracetamol most frequently consumed in our country are specifically mentioned in the questionnaire.

Obesity and overweight were defined in accordance with the body mass index (BMI) cut-off points mentioned by Cole *et al.*[12] for each age group and sex.

The educational level of the mother was classified into three categories: (i) no education or only primary school education; (ii) secondary school education; and (iii) university education.

For each child, we established four mutually exclusive categories of passive smoking: neither parent smoked, the father only, the mother only and both.

Two categories were established in accordance with parental asthma: if the father or the mother had asthma, or if neither parent had asthma.

The presence of a dog or cat in the home was classified based on the questionnaire questions corresponding to having a cat or dog in the home during the first year of life or during the past year.

For the purpose of this study, wheezing ever was defined as a positive answer to the question: 'Has your child ever had wheezing or whistling in the chest at any time in the past?'

Current asthma was defined as a positive answer to the question: 'Has your child had wheezing or whistling in the chest during the last 12 months?'

Severe asthma was defined as a combination of the three questions assessing the severity of asthma: 'How many attacks of wheezing has your child had during the last 12 months? (none, 1–3, 4–12, >12)', 'In the last 12 months, how often, on average, has your child's sleep been disturbed as a result of wheezing? (never, <1 night/week, ≥1 nights/week)' and 'In the last 12 months, has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths?'. Children were considered to have severe asthma when there were ≥4 asthma attacks or when sleep was disturbed ≥1 nights/week or when there had been an episode of speech limitation.[13]

Exercise induced asthma was defined as a positive answer to the question: 'In the last 12 months, has your child's chest sounded wheezy during or after exercise?'[9,14]

Data analysis

We used multiple logistic regression to obtain adjusted prevalence odds ratios (ORs) and 95% confidence intervals (95% CIs) between asthma symptoms of the school children and paracetamol consumption. Therefore, we considered those children as 'control group' who mentioned not taking paracetamol. These calculations were preferred to other methods (e.g. linear regression) which do not provide information on risk increase and require statistical assumptions (like linearity) that are unverifiable in empirical conditions.

In the multivariate analysis, the results presented are adjusted for parental smoking habits, parental asthma, maternal education level, cat and dog exposure, adherence to Mediterranean diet and obesity of the children. The children with incomplete data were excluded from the study. The statistical analysis was performed using SPSS 17.0 software. The study was approved by the Clinical Research Ethics Committee of Galicia.

Results

A total of 10 371 children were included in the 6- to 7-year-old group (response rate 72.4%). The participation rate was 84.4% in the 13- to 14-year-old group, which included 10 372 children (table 1).

The general characteristics of the children, parental asthma, parental smoking, maternal education level, cat and dog exposure and paracetamol use are shown in table 2.

Table 1 Prevalence of asthma symptoms

	6–7 years *N* (%)	13–14 years *N* (%)
Wheezing ever		
No	6519 (61.0)	8262 (77.0)
Yes	4171 (39.0)	2468 (23.0)
Current asthma		
No	9249 (86.5)	9319 (86.8)
Yes	1441 (13.5)	1411 (13.2)
Exercise induced asthma		
No	10 010 (93.6)	8585 (80.0)
Yes	680 (6.4)	2145 (20.0)
Severe asthma		
No	10 170 (95.1)	10 106 (94.2)
Yes	520 (4.9)	624 (5.8)

All values as number of cases (*N*) and %.

Table 2 Main characteristics of the children and prevalence of risk factors

	6–7 years *N* (%)	13–14 years *N* (%)
Gender		
Male	5321 (50.2)	5269 (49.7)
Female	5270 (49.8)	5323 (50.3)
Obesity		
Normal weight	5261 (67.0)	7421 (82.3)
Overweight	1834 (17.2)	1396 (15.5)
Obesity	752 (9.6)	197 (2.2)
Having cat in the past 12 months		
No	9699 (92.6)	8903 (83.8)
Yes	773 (7.4)	1722 (16.2)
Having cat in the first year of life		
No	10 026 (94.5)	6730 (88.4)
Yes	584 (5.5)	879 (11.6)
Having dog in the past 12 months		
No	9111 (87.4)	7563 (71.3)
Yes	1313 (12.6)	3050 (28.7)
Having dog in the first year of life		
No	9457 (89.4)	6060 (79.5)
Yes	1123 (10.6)	1559 (14.5)
Maternal education		
No education/elementary	2981 (28.4)	2261 (22.1)
High school	4012 (37.5)	4418 (43.2)
University	3519 (32.9)	3553 (34.7)
Parental asthma		
Neither parent asthma	5507 (87.2)	5078 (90.0)
Some parent asthma	806 (12.8)	566 (10.0)
Parental smoking		
Neither parent smoke	5020 (48.7)	5057 (48.4)
Father only	1941 (18.8)	1893 (18.1)
Mother only	1354 (13.1)	1487 (14.2)
Both parents	1999 (19.4)	2016 (19.3)
Paracetamol use in the first year of life		
No	5058 (48.6)	NA (NA)
Yes	5344 (51.4)	NA (NA)
Paracetamol use in the last year		
Never	1323 (12.8)	2422 (23.4)
At least once a year	8117 (78.6)	5440 (52.6)
At least once per month	893 (8.6)	2485 (24.0)

All values as number of cases (*N*) and %. NA, not applicable (there is not data).

The prevalence of asthma in the lower age group was 39.0%, whereas that of current asthma was 13.5%, severe asthma 4.9% and exercise induced asthma 6.4%. In 13- to 14-year olds, these prevalences were 23.0, 13.2, 5.8 and 20.0%, respectively (table 1). More than 50% of the children had a parent who smoked (table 2).

Only 23% of the adolescents (13- to 14-year olds) and 13% of the children stated that they had not taken paracetamol in the previous

Table 3 Odds ratio for prevalence of asthma symptoms according to paracetamol use in children aged 6–7

	Wheezing ever	Current asthma	Exercise induced asthma	Severe asthma
Paracetamol use In the first year of life	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
No	1	1	1	1
Yes	2.04 (1.79–2.31)	1.66 (1.38–1.99)	1.52 (1.16–1.99)	1.82 (1.32–2.53)
In the last year				
Never	1	1	1	1
At least once a year	1.45 (1.20–1.76)	1.71 (1.24–2.37)	1.68 (1.03–2.73)	1.64 (0.91–2.94)
At least once per month	3.32 (2.51–4.41)	5.42 (3.68–7.99)	5.26 (3.03–9.15)	5.36 (2.79–10.27)

Adjusted by gender, body mass index, having cat and dog, maternal education, parental asthma and parental smoking.

Table 4 Odds ratio for prevalence of asthma symptoms according to paracetamol use in children aged 13–14

	Wheezing ever	Current asthma	Exercise induced asthma	Severe asthma
Paracetamol use In the last year	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Never	1	1	1	1
At least once a year	1.41 (1.15–1.73)	1.40 (1.07–1.85)	1.43 (1.15–1.78)	1.34 (0.87–2.06)
At least once per month	2.12 (1.68–2.67)	2.51 (1.87–3.39)	2.40 (1.88–3.06)	3.31 (2.13–5.14)

OR, odds ratio; CI, confidence interval.
Adjusted by gender, body mass index, having cat and dog, maternal education, parental asthma and smoking.

year. In regard to the first year of life, 48.6% of the children had not been given it (table 2).

All the asthma symptoms analysed increased significantly with paracetamol consumption. The effects appear stronger in 6- to 7-year-old children, where the taking of paracetamol at least once a month in the last year is associated with a five times more probability of having asthma symptoms, compared with those children who had never taken paracetamol. For current asthma, an OR is 5.42 with 95% CI of 3.68–7.99 and for severe asthma, an OR is 5.36 with 95% CI 2.79–10.27 (table 3). In the same age group, on analysing the paracetamol consumption in the first year of life, the highest risk increase with consumption of the drug is observed for 'wheezing ever', with an OR of 2.04 with 95% CI of 1.79–2.31 (table 3).

In the adolescents, paracetamol consumption at least once in the past year is associated with an increase of 43% in the prevalence of exercise induced asthma, OR: 1.43 (95% CI: 1.15–1.78) (table 4). When paracetamol is taken once a month, the effect is greater, with an OR between 2.12 (95% CI: 1.68–2.67) for wheezing ever, and 3.31 (95% CI: 2.13–5.14) for severe asthma (table 4).

Discussion

The results obtained in this study seem to support a relationship between paracetamol consumption and an increase in asthma prevalence. The effect could also be dose dependent, as taking paracetamol more often is associated with a higher increase in the probability of presenting with asthma symptoms.

These results are in agreement with those presented in the majority of publications have analysed this relationship.

Thus, in a recent meta-analysis, Etminan *et al.*[4] observed a significant increase in the risk of asthma with exposure to paracetamol (OR: 1.60; 95% CI: 1.48–1.74).[4]

Furthermore, various prospective studies, where the exposure precedes the result, seem to associate the use of paracetamol with asthma in both children and adults. A study conducted in Ethiopia with more than 1000 children evaluated at 3 years old, the use of paracetamol was associated with a higher presence of wheezing, which was also dose dependent, adjusted for respiratory infections and other factors, since with the ingestion of 1–3 tablets of paracetamol per month, the increase in wheezing is not significant (OR: 1.77, 95% CI: 0.96–3.26), but with the consumption of four or more tablets per month, the OR: 6.78 with a 95% CI: 1.89–24.39.[15] In another British study, more than 11 000 children were studied prospectively. The taking of paracetamol in the first 6 months of life of the child was associated with a higher asthma prevalence (OR: 1.11, 95% CI: 1.00–1.23) and wheezing (OR: 1.12, 95% CI: 1.00–1.25), adjusted for infections and other confounding factors.[16]

In the Nurses Health Study in the USA, it was observed that the use of paracetamol more than 14 days a month was associated with a higher asthma incidence (OR: 1.63, 95% CI: 1.1–2.39).[17]

In another Danish study, a more frequent use of paracetamol was associated with a higher prevalence of adult-onset asthma (OR: 2.99, 95% CI: 1.44–6.20).[18]

Other cross-sectional studies give similar conclusions. In a study including more than 200 000 children from 73 centres in 31 countries, higher paracetamol consumption was associated with a higher prevalence of allergic diseases, such as asthma (OR: 3.23, 95% CI: 2.91–3.60) or rhinitis.[19]

In adolescents, the exposure to paracetamol in the previous year was associated with a higher asthma prevalence, adjusted for other co-factors. The risk of current asthma symptoms increases depending on the dose (OR: 1.43, 95% CI: 1.33–1.53 for medium use vs. no use and OR: 2.51, 95% CI: 2.33–2.70 for high use vs. no use). The study included more than 300 000 adolescents, from 50 countries, using the methodology of the ISAAC study. The relationship was dose dependent.[6]

In a multicentre Canadian study, using the ISAAC methodology, significant differences between different centres were observed in asthma prevalences, as well as in the use of paracetamol, in 13- to 14-year-old adolescents. In the multivariate analysis, paracetamol intake at least once a month showed an increase in current wheezing (OR: 1.92, CI 95%: 1.71–2.17) compared with acetaminophen used less than once a month.[20]

An increase in asthma associated with taking paracetamol more often was also observed in young adults (20–44 years) from 12 European populations (OR: 2.87, 95% CI: 1.49–5.37).[5]

In other studies where the effect of paracetamol is analysed in comparison with other drugs, they appear to reinforce the effect of paracetamol for the increase in asthma.

A randomized study on children in Boston, USA, obtained a lower asthma risk when ibuprofen rather than paracetamol was taken. Compared with children who were assigned to receive acetaminophen, the relative risk estimate of outpatient visits for asthma for those assigned to ibuprofen was 0.56 (95% CI: 0.34–0.95) after

adjusting for age, gender and race. A placebo group was not used in this study, which meant it could not be determined whether the results depended on ibuprofen being a protector, or paracetamol a risk factor.[21]

In a Danish study, pregnant women treated more often with paracetamol had children with a higher risk of hospitalization for asthma (OR: 1.24, 95% CI: 1.11–1.38). The fact that the main indication for taking the drug was pain and not fever, as well as similar effects not being seen with other analgesics, seems to support a real effect of paracetamol, and not a confounding effect, as could be the case if the indication was for respiratory infections.[22]

However, other authors did not observe any relationship between paracetamol use and asthma.[7,8] Some methodological weaknesses were observed in these studies.

In a study with Norwegian children, no relationship was found between the use of paracetamol by the mother during pregnancy, nor by boys in the first 6 months of life who had asthma at 10 years old, although they did find a relationship between the higher use of paracetamol and a history of asthma in the girls. The study by Bakkeheim included few children who were given paracetamol in the first 6 months of life (83 children, which was 8% of the sample included), with no data on subsequent paracetamol consumption and the asthma assessed at 10 years.[8] In other studies with Western populations, the prevalence of taking paracetamol in the first year of life generally exceed 50%.[7,23,24]

The study by Lowe *et al.*, was a prospective study that analysed the relationship between treatment with paracetamol in the first 2 years of life and the presence of asthma at 7 years. This relationship disappeared if it was considered that the paracetamol was taken for non-respiratory diseases, while it remained if it was considered that the patients were given paracetamol for a respiratory disease. This seemed to suggest a confounding effect of the respiratory infection, more than an effect of the paracetamol itself.[7] A weakness of this study was that it only evaluated the administration of paracetamol between 0 and 2 years, but not that currently or recently. Another weakness was that the number of children treated with paracetamol for diseases other than respiratory was limited, although it did not specify the total figure, 495 children completed the follow up, and of these 88.7% were treated for an upper airway infection, which would leave about 63 children treated with paracetamol for a non-respiratory disease.[7]

Furthermore, various pathophysiological mechanisms are known that could explain this relationship.

On one hand, paracetamol has been shown to dose dependently reduce lung and serum glutathione concentrations in lungs and blood.[25,26] Antioxidant activity is reduced on reducing the glutathione levels. This may lead to tissue damage, smooth muscle contraction, bronchial hyperresponsiveness, increase in vascular patency, release of inflammatory mediators and interfere with the activity of beta receptors.[27]

The depletion of glutathione also reduces the levels of Th1 cytokinases favouring the predominance of Th2.[27]

Another possible mechanism is, that on reducing the fever, the levels of cytokinases released during febrile episodes, which are mainly Th1, are reduced as such that they also lead to a predominance of Th2.[27]

High doses of paracetamol are cytotoxic for pneumocytes and can cause acute lung damage.[28]Paracetamol also has a modulating effect on the activity of myeloperoxidase, an enzyme that takes part in various oxidation mechanisms.[29]

It has been demonstrated in animal models that the activation of transient receptor potential ankyrin-1 receptor by paracetamol metabolites induces inflammatory activity in the lung, with an increase in the number of neutrophils, myeloperoxidase activity and cytokinase levels.[30]

A possible antigenic effect of paracetamol has also been described, with an increase in histamine and IgE.[31]

Our study has some limitations. On one hand, on being a cross-sectional study, a causal relationship cannot be established.

On the other hand, the possibility of 'inverse causality' must be considered, as children with asthma had a higher tendency for respiratory infections and thus, a higher use of paracetamol.[32] But this should not influence the prevalence of eczema, which was also increased in children who took more paracetamol.[6,19]

There could have been a memory bias, since the taking of paracetamol would be remembered better by those children who had more, or more severe, episodes of infections, and this higher frequency or severity of respiratory infections could be favoured as a result of being asthmatics.[33,34]

Given the range of the randomly selected population sample included, and the application of extensively validated methodology, the findings of our study seem to support some relationship between paracetamol consumption and asthma symptoms in our population.

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Conflicts of interest: None declared.

Key points

- Paracetamol consumption is associated with a significant increase in asthma symptoms.
- The effect is greater the more often the drug is taken.
- The effects appear stronger in children than in adolescents.

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Work–family conflict and health in Swedish working women and men: a 2-year prospective analysis (the SLOSH study)

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Background: Research has suggested that gender is related to perceptions of work–family conflict (WFC) and an underlying assumption is that interference of paid work with family life will burden women more than men. There is, however, mixed evidence as to whether men and women report different levels of WFC. Even less studies investigate gender differences in health outcomes of WFC. Also the number of longitudinal studies in this field is low. **Methods:** Based on the Swedish Longitudinal Occupational Survey of Health, we prospectively examined the effects of WFC on three different health measures representing a wide spectrum off ill health (i.e. self-rated health, emotional exhaustion and problem drinking). Logistic regression analyses were used to analyse multivariate associations between WFC in 2008 and health 2 years later. **Results:** The results show that WFC was associated with an increased risk of emotional exhaustion among both men and women. Gender differences are suggested as WFC was related to an increased risk for poor self-rated health among women and problem drinking among men. Interaction analyses revealed that the risk of poor self-rated health was substantially more influenced by WFC among women than among men. **Conclusions:** We conclude that, despite the fact that women experience conflict between work and family life slightly more often than men, both men's and women's health is negatively affected by this phenomenon.