

## ORIGINAL ARTICLE

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# Acetaminophen Intake and Risk of Asthma, Hay Fever and Eczema in Early Adolescence

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## ABSTRACT

A positive association between acetaminophen intake and allergic diseases has recently been reported in developed countries with impaired oxidant/antioxidant balance and promotion of atopy as proposed underlying mechanisms. The aim of the study was to explore the relationship between acetaminophen intake and asthma, hay fever, and eczema in The Republic of Macedonia as a country with acetaminophen intake not physician-controlled, high passive smoke exposure and dietary antioxidant intake, and moderately low prevalence of allergic diseases.

Self-reported data obtained through the standardized International Study of Asthma and Allergies in Childhood Phase Three written questionnaires of 3026 adolescents aged 13/14 years from randomly selected schools in Skopje, the capital of Macedonia, were used. The frequency of current acetaminophen intake -both unadjusted and adjusted for confounding factors- was correlated to current and ever-diagnosed asthma, hay fever and eczema by odds ratios (OR, 95% CI) in binary logistic regression.

Use of acetaminophen at least once monthly increased the risk of current wheeze (adjusted OR 2.04, 1.31-3.20  $p = 0.002$ ), asthma 'ever' (adjusted OR 2.77, 1.06-7.26  $p=0.039$ ), current allergic rhinoconjunctivitis (adjusted OR 2.95, 1.79-4.88  $p=0.000$ ) and hay fever 'ever' (adjusted OR 2.25, 1.36-3.70  $p=0.002$ ). A significant association between frequent acetaminophen intake and atopic eczema and also between infrequent acetaminophen intake and investigated allergic diseases was not established.

The findings suggest an increased risk of asthma and hay fever, but not atopic eczema associated with frequent acetaminophen use in a developing country.

**Key words:** Acetaminophen; Adolescent; Asthma; Atopic eczema; Hay fever

## INTRODUCTION

Compared to the great number of countries that have participated in the International Study of Asthma and Allergies in Childhood (ISAAC), The Republic of

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Macedonia appears to have moderately low prevalence rates of asthma and hay fever and a low prevalence of eczema.<sup>1-5</sup>

An ecological study using data from the European Community Respiratory Health Survey (ECRHS) and ISAAC has shown a positive association between acetaminophen (paracetamol) sales and prevalence rates of asthma, allergic rhinitis and atopic eczema in adults and children.<sup>6</sup> Moreover, an increased risk of wheeze in early childhood<sup>7</sup> and an increased risk of asthma and elevated blood total IgE in school age children<sup>8</sup> related to a prenatal paracetamol exposure have been found with a proportion of asthma attributable to paracetamol use, assuming a causal relationship, of 1% and 7%, respectively.

Acetaminophen may deplete stores of glutathione, whose reduced form is one of the major antioxidants present in the airways and plays a role in drug detoxification, thus leading to oxidant damage in the lung, inflammation and bronchial hyperresponsiveness.

<sup>6,9,10</sup> Furthermore, acetaminophen is hypothesized to promote atopy through defective antigen processing by decreased glutathione level<sup>10</sup> or through a lack of suppression of cyclooxygenase pathway and an increased prostaglandin E2 production,<sup>11,12</sup> thereby promoting T-helper cell 2-type cytokine responses.<sup>10,13</sup> The least developed is the theory of an IgE-mediated mechanism with acetaminophen as the antigenic agent.<sup>10,13</sup> There is evidence that respiratory antioxidant defense may also be impaired if dietary antioxidant intake (vitamin C, vitamin E, carotene, flavonoids, trace elements) is inadequate or if the oxidant burden is increased by inhaled pollutants or by drug metabolites such as acetaminophen reactive metabolite *N*-acetyl-*p*-benzoquinonemine.<sup>7,14,15</sup>

Dietary antioxidant intake in early adolescence in The Republic of Macedonia is documented to be high,<sup>5</sup> which may be explained by the geographical area where it is situated and its climate. However, the oxidant burden through the passive smoke exposure is demonstrated to be high as well.<sup>5</sup>

The study was aimed to explore the relationship between acetaminophen use and asthma, hay fever, and eczema in 13/14 year old adolescents in Skopje, The Republic of Macedonia, as a developing country where acetaminophen use is not physician-controlled and passive smoke exposure is high, fruit and vegetables and cereals intake is frequent, and the prevalence of allergic diseases is moderately low.

## MATERIALS AND METHODS

The study was cross-sectional and carried out in accordance with the ISAAC Phase Three protocol,<sup>16,17</sup> in Skopje, the capital of The Republic of Macedonia, as a part of the Macedonian arm of the third phase of ISAAC.

After the consent from their parents, 3026 young adolescents 13/14 year old out of the approached 3330 from 17 randomly selected schools self-completed in their schools the ISAAC written core questionnaires on asthma, allergic rhinitis, eczema and the environmental questionnaire. A response-rate of 90.9% was achieved. The data collection was conducted outside of the main pollen season,<sup>16</sup> during the period from December, 2001 to March, 2002.

Outcome measures used in this study were the 12-month prevalence rates of symptoms of asthma (current wheeze), symptoms of hay fever (current allergic rhinoconjunctivitis) and symptoms of atopic eczema (current itchy rash). These outcome measures were obtained from core questions about the presence of wheezing or whistling in the chest in the last 12 months, sneezing/runny/blocked nose accompanied with itchy-watery eyes apart from a cold or the flu in the last 12 months and about the presence of an itchy rash which was coming and going for at least 6 months at any time in the last 12 months, respectively. Information related to lifetime diagnosis of asthma, hay fever and atopic eczema was obtained from answers to questions about ever having had any physician-diagnosed asthma, hay fever or atopic eczema (asthma 'ever', hay fever 'ever' or eczema 'ever').<sup>2,3,16,18</sup>

Acetaminophen intake in the last 12 months (current acetaminophen intake) regarding its frequency was subcategorised as never intake, infrequent intake for at least once yearly and frequent intake for at least once monthly.<sup>16</sup> Intake per week in the last 12 months of fruits and vegetables as rich sources of flavonoid and antioxidant vitamins, fish and cereals as selenium and vitamin E-rich foods (current fruits, vegetables, fish and cereals intake), indoor air-pollution (gas usually used for cooking, one or more smokers in the house) and outdoor air-pollution (trucks passage through the residential street during weekdays), as dietary sources of antioxidants and inhaled oxidants, were all used as confounding factors for acetaminophen intake adjustment.

## Acetaminophen Intake and Risk of Atopy

Of all respondents, 1568 (51.8%) were boys and 1458 (48.2%) were girls. Their mean age was 13.45 years (SD 0.50); 13.46 years (SD 0.50) in boys and 13.44 years (SD 0.50) in girls.

### Ethical Approval

The Ethics Committee at the Medical Faculty and The Ministry of Education and Science, Skopje, The Republic of Macedonia, approved the conduct of the ISAAC Phase Three in The Republic of Macedonia.

### Statistical Analyses

In accordance with the ISAAC recommendations,<sup>19</sup> missing or "any other" responses were part of the denominator for calculation of prevalence figures.

The relationship between acetaminophen intake both unadjusted and adjusted for confounding factors and current and ever-diagnosed asthma, hay fever and eczema, as dependent variables, by odds ratios with 95% confidence interval (OR, 95% CI) in binary logistic regression in SPSS 11.0 for Windows were analysed. For the questions related to asthma, hay fever and eczema missing responses were treated as negative responses whereas for the questions on environmental exposures, missing values were treated as 'missing' in the analysis. No intake of acetaminophen in the last 12 months was used as a referent category in statistical analysis. A resulting P-value of <0.05 was considered significant.

## RESULTS

The prevalence of self-reported asthma 'ever' (1.7%) was much lower than the prevalence of current wheeze (8.8%) and more similar to the prevalence of current sleep-disturbing wheeze and speech-limiting wheeze as parameters of asthma severity (2.9% and 1.2%, respectively). Regarding the prevalence rates of hay fever 'ever' and current allergic rhinoconjunctivitis (6.7% and 5.8%, respectively) as well eczema 'ever' and current itchy rash (3.7% and 4.3%, respectively), such difference was not found.

The majority of young adolescents reported passive smoke exposure (73.1%), frequent fruits (80.9%) and cereals (86.9%) intakes. One third of the respondents were exposed to great outdoor air pollution. A frequent acetaminophen use for at least once monthly in 6.5% of the respondents only was found (Table 1).

The relationship between current acetaminophen intake and asthma, hay fever and atopic eczema is shown in Table 2.

**Table 1. Prevalence of acetaminophen use and confounding factors (written questionnaire) in 3026 adolescents aged 13-14 yrs in Skopje, Republic of Macedonia, 2002**

| Acetaminophen use/confounding factor                 | n (%)       |
|------------------------------------------------------|-------------|
| <b>Current acetaminophen use</b>                     |             |
| never                                                | 1430 (47.3) |
| at least once yearly                                 | 1289 (42.6) |
| at least once monthly                                | 197 (6.5)   |
| <b>Gas cooking at home</b>                           |             |
| no                                                   | 2664 (88.0) |
| yes                                                  | 362 (12.0)  |
| <b>Passive smoking at home</b>                       |             |
| no                                                   | 813 (26.9)  |
| yes                                                  | 2211 (73.1) |
| <b>Trucks passage through the residential street</b> |             |
| never                                                | 294 (9.7)   |
| seldom                                               | 1660 (54.9) |
| frequently through the day                           | 770 (25.4)  |
| almost the whole day                                 | 301 (9.9)   |
| <b>Current fruit intake</b>                          |             |
| never/occasionally                                   | 79 (2.6)    |
| 1-2 times weekly                                     | 475 (15.7)  |
| ≥3 times weekly                                      | 2447 (80.9) |
| <b>Current vegetables intake</b>                     |             |
| never/occasionally                                   | 331 (10.9)  |
| 1-2 times weekly                                     | 994 (32.8)  |
| ≥3 times weekly                                      | 1659 (54.8) |
| <b>Current fish intake</b>                           |             |
| never/occasionally                                   | 1622 (53.6) |
| 1-2 times weekly                                     | 1256 (41.5) |
| ≥3 times weekly                                      | 100 (3.3)   |
| <b>Current cereals intake</b>                        |             |
| never/occasionally                                   | 99 (3.3)    |
| 1-2 times weekly                                     | 270 (8.9)   |
| ≥3 times weekly                                      | 2631 (86.9) |

Current = in the last 12 months.

\*Prevalence calculated by dividing positive responses to the given question by the total number of completed questionnaires (including missing or "any other" responses).

**Table 2. Relationship between acetaminophen use (unadjusted and adjusted for confounding factors) and asthma, hay fever, and eczema in 3026 adolescents aged 13-14 yrs in Skopje.**

| Symptom/disease                      | Current acetaminophen use at least once yearly† |           |         | Current acetaminophen use at least once monthly† |           |         |
|--------------------------------------|-------------------------------------------------|-----------|---------|--------------------------------------------------|-----------|---------|
|                                      | OR                                              | 95% CI    | P-value | OR                                               | 95% CI    | P-value |
| Current wheeze                       |                                                 |           |         |                                                  |           |         |
| Unadjusted                           | 1.19                                            | 0.90-1.56 | 0.219   | 2.53                                             | 1.66-3.84 | 0.000   |
| Adjusted*                            | 1.11                                            | 0.84-1.47 | 0.478   | 2.04                                             | 1.31-3.20 | 0.002   |
| Asthma 'ever'                        |                                                 |           |         |                                                  |           |         |
| Unadjusted                           | 1.78                                            | 0.97-3.28 | 0.065   | 3.06                                             | 1.25-7.48 | 0.014   |
| Adjusted                             | 1.63                                            | 0.86-3.07 | 0.132   | 2.77                                             | 1.06-7.26 | 0.039   |
| Current allergic rhinoconjunctivitis |                                                 |           |         |                                                  |           |         |
| Unadjusted                           | 1.24                                            | 0.88-1.75 | 0.216   | 3.14                                             | 1.94-5.08 | 0.000   |
| Adjusted                             | 1.23                                            | 0.86-1.75 | 0.264   | 2.95                                             | 1.79-4.88 | 0.000   |
| Hay fever 'ever'                     |                                                 |           |         |                                                  |           |         |
| Unadjusted                           | 1.35                                            | 0.99-1.83 | 0.060   | 2.26                                             | 1.38-3.69 | 0.001   |
| Adjusted                             | 1.31                                            | 0.96-1.80 | 0.093   | 2.25                                             | 1.36-3.70 | 0.002   |
| Current itchy rash                   |                                                 |           |         |                                                  |           |         |
| Unadjusted                           | 1.63                                            | 1.12-2.37 | 0.011   | 1.22                                             | 0.57-2.62 | 0.612   |
| Adjusted                             | 1.59                                            | 1.08-2.34 | 0.020   | 0.93                                             | 0.41-2.10 | 0.853   |
| Eczema 'ever'                        |                                                 |           |         |                                                  |           |         |
| Unadjusted                           | 1.32                                            | 0.88-1.96 | 0.180   | 1.44                                             | 0.69-2.99 | 0.328   |
| Adjusted                             | 1.22                                            | 0.81-1.85 | 0.341   | 1.16                                             | 0.54-2.53 | 0.701   |

OR = Odds ratio; CI = confidence interval; Current = in the last 12 months.

\*Adjusted for sex, gas cooking exposure at home, passive smoking exposure at home, outdoor air pollutants exposure, current fruit, vegetables, fish and cereals intake.

†Current acetaminophen use at least once yearly or at least once monthly vs. never acetaminophen use.

Current wheeze, asthma 'ever', current rhinoconjunctivitis and hay fever 'ever' were all positively associated with frequent acetaminophen intake at least once monthly and the significance remained after controlling for potential confounding factors (adjusted OR 2.04, 95% CI 1.31-3.20  $p = 0.002$ , adjusted OR 2.77, 95% CI 1.06-7.26  $p = 0.039$ , adjusted OR 2.95, 95% CI 1.79-4.88  $p = 0.000$  and adjusted OR 2.25, 95% CI 1.36-3.70  $p = 0.002$ , respectively).

Current acetaminophen intake for at least once yearly, compared to never acetaminophen intake, increased the risk of current itchy rash (adjusted OR 1.59, 95% CI 1.08-2.34  $p = 0.020$ ), but significant association regarding the more frequent acetaminophen intake and current itchy rash or infrequent and frequent acetaminophen intake and eczema 'ever' was not found ( $p = 0.853$  or  $p = 0.341$  and  $p = 0.701$ , respectively).

## DISCUSSION

In this cross-sectional study we found evidence that frequent acetaminophen use may increase the risk of current and ever-diagnosed asthma and hay fever, but not atopic eczema in young adolescents. The acetaminophen intake was only weakly associated positively with ever-diagnosed asthma compared to current wheeze, current allergic rhinoconjunctivitis and ever-diagnosed hay fever. This finding may be due to a very low prevalence of self-reported physician-diagnosed asthma 'ever', which regarding to the established prevalence rates of current wheeze, current sleep-disturbing wheeze and current speech-limiting wheeze points out that intermittent asthma in young adolescents seems to be under-diagnosed in The Republic of Macedonia.<sup>4</sup> Our findings are consistent with the previous research demonstrating a positive

association between acetaminophen use and asthma and hay fever.

An ISAAC study from New Zealand has demonstrated the same results as ours in children aged 6-7 years.<sup>20</sup> Furthermore, while Shaheen *et al.*<sup>9</sup> in a population-based cross-sectional study have shown a clear relation between paracetamol use and asthma and rhinitis in daily and weekly adult users, we found such a relation in monthly users also, which makes the association stronger. Significantly lower risk of asthma-related outpatient visits in asthmatic children treated with ibuprofen compared with those treated with acetaminophen because of fever has been established.<sup>21</sup> Davey *et al.*<sup>22</sup> in a large sample of Ethiopian adults and children found a dose-related positive association between acetaminophen use and self-reported wheeze, nocturnal shortness of breath, rhinitis and eczema. Finally, in adults an increased rate of newly diagnosed asthma<sup>23</sup> and an increased risk of asthma, COPD and decreased lung function,<sup>24</sup> all associated with a frequent acetaminophen use has been documented.

In contrast to studies that have documented an association between acetaminophen intake and eczema<sup>6,22</sup> other studies, including the present one, have not found such an association. In the population-based Avon Longitudinal Study of Parents and Children (ALSPAC), Shaheen *et al.*<sup>7,8</sup> have found that frequent paracetamol use in late pregnancy was associated with an increased risk of wheeze, but not eczema in the offspring at 18-30 months and with an increased risk of wheeze, asthma and total IgE, but not hay fever, skin test positivity or eczema in the offspring aged 7 years. No association between the recent use of paracetamol and eczema and only a weak association regarding the paracetamol use during the first year of life in children aged 6-7 years have been reported.<sup>20</sup>

Regarding the proposed underlying mechanisms of the positive association between acetaminophen and allergic diseases<sup>6, 9-11</sup> and the lack of its association with atopic eczema in the present study, our findings would suggest that the established increased risk of asthma and hay fever by frequent acetaminophen intake is mediated through impaired oxidant/antioxidant balance and not through an effect on atopy. An alternative explanation that acetaminophen might be taken to relieve symptoms associated with asthma and the use of asthma medications or that the positive association between

acetaminophen and allergic diseases is a result from aspirin avoidance has already been explored and found to be unlikely by studies previously published.<sup>7-9, 22-24</sup> Considering two types of relations between paracetamol and asthma - paracetamol intolerance leading to bronchospasm in analgesic-induced asthmatics and the relation of asthma with the amount or frequency of paracetamol consumption,<sup>25</sup> the first one seems an unlikely explanation as the analgesic-induced asthma in childhood occurs rarely.<sup>26</sup> Recent in vitro observations have demonstrated that clinically relevant concentrations of acetaminophen decreased intracellular glutathione levels in human alveolar macrophages and type II pneumocytes.<sup>27</sup> Furthermore, a decrease in serum total antioxidant capacity after regular paracetamol ingestion in therapeutic doses in healthy volunteers<sup>28</sup> and reduced antioxidant status and erythrocyte glutathione concentrations after repeated supratherapeutic doses of paracetamol in febrile children have recently been reported.<sup>29</sup> Finally, it is anticipated that reduced endogenous antioxidant capacity, as assessed by glutathione S-transferase genotype, or exposure to higher levels of exogenous inhaled oxidants after paracetamol exposure would provide susceptibility for developing asthma.<sup>15</sup>

There are a limited number of studies concerning the recently developed paracetamol hypothesis. While most of them have been conducted in developed countries, to the best of our knowledge, the present study is the second one performed in a developing country where awareness of the adverse effects of aspirin in asthmatic patients and the use of asthma medications are both relatively low, which makes the reverse causation of the established association between acetaminophen and asthma and hay fever less likely.<sup>13</sup> Another advantage of the study is the large sample investigated and a high response-rate achieved. The current study has some limitations as well. Like in other questionnaire-based studies there is a possibility of information bias. However, the ISAAC questionnaires are standardised and validated questionnaires, accompanied by validated study protocol.<sup>30</sup> Furthermore, in the ISAAC environmental questionnaire there is a lack of more detailed information on frequency of acetaminophen intake or its dosage or intake of compound preparations containing acetaminophen, which may influence the results of our study. However, as the positive association between acetaminophen use for at least

once monthly and asthma and hay fever has been established in our study, it is likely that a stronger association would have to be demonstrated if more frequent acetaminophen intake or intake of acetaminophen in compound preparations would be considered.

In conclusion, the findings of this questionnaire-based study in young adolescents in The Republic of Macedonia, as a country with a moderately low prevalence of allergic diseases and acetaminophen intake, high tobacco smoke exposure and dietary antioxidant intake, are further support to the paracetamol (acetaminophen) hypothesis regarding asthma and hay fever that is coming from a developing country. The impaired oxidant/antioxidant balance in airways by acetaminophen and not promotion of atopy is a proposed underlying mechanism of the established relationship. The results derived from the present study are sufficient for caution to the frequent acetaminophen use. Until further epidemiological and biological research results come, acetaminophen remains a preferred analgesic and antipyretic in childhood, but only if physician-recommended within therapeutic doses and used not frequently.

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