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THE ASSOCIATION BETWEEN PARACETAMOL USE AND ASTHMA:

CAUSATION OR COINCIDENCE?

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ABSTRACT

A better understanding of the causation of asthma and allergic disorders could potentially lead to intervention strategies that reduce their prevalence and severity. One potential causative factor is the use of paracetamol. Most of the evidence for the link with asthma is from non-experimental studies of paracetamol exposure in utero, infancy, childhood and adult life, however it has been difficult to rule out confounding and bias in the associations observed. The two randomised clinical trials of the effect of paracetamol in patients with asthma have been difficult to interpret, due to methodological issues. There have been no randomised controlled trials of paracetamol use and the development of asthma. Both asthma and paracetamol use are common, and so even if there is a relatively small effect of paracetamol exposure on the development of asthma or its severity, then such an effect would be of major public health significance. It is proposed that randomised controlled trials of the effect of paracetamol on the development of asthma and its severity are a high research priority.

Asthma and allergic diseases are prevalent and represent a major global public health problem [1]. The causal pathway leading to clinical disease is likely a complex interplay between genetic predisposition and environmental exposures. An accurate and valid model for understanding the causes of asthma and allergic disease would be useful for prevention, diagnosis, selection of interventions, and prediction of outcomes. Such a model might explain differences in prevalence and manifestations of disease in individuals, populations, and through time. At an individual and population level reduction in exposures to robustly identified causal environmental causes of asthma and allergic disease may result in decreased prevalence and severity of disease, and the associated public health burden [2].

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An association between paracetamol exposure and asthma exists. However, nearly all the evidence for the link between paracetamol exposure and asthma is from non-experimental studies. In such studies: cross-sectional studies, retrospective and prospective cohort studies, and case-control studies; careful critical appraisal is needed to assess if the association is causal or coincidental. A typical scheme for evaluating the strength of evidence for causation provided by non-experimental studies is to consider: the strength of the association, whether exposure to the putative causal agent precedes the onset of disease, a plausible biological mechanism, consistency across different study settings, a temporal relationship to exposure, reversibility of the causal effect, identification of a dose-response effect, specificity to the suspected causative agent and that there is no convincing alternative explanation for the association [3,4]. A summary of the evidence linking paracetamol use to asthma based on these criteria for causation is provided in Table 1.

There have been a number of reviews and commentaries which comprehensively present and discuss the evidence that suggests paracetamol use may play a role in the pathogenesis of asthma and so contribute to the development of asthma and its severity [5-17]. In this review we consider the published systematic reviews of the non-experimental studies and the limited clinical trials evidence.

Non-experimental studies

Systematic reviews with or without pooled numerical estimates of the strength of association between paracetamol use and asthma have been published in an attempt to address the nature and strength of association. Etminan and colleagues [18] identified 19 studies of the association between paracetamol and asthma from bibliographic databases to October 2008. Thirteen cross-sectional studies, four cohort studies and two case-control studies were included in the review, and a random effects model was used to combine studies with asthma and wheezing amongst both children and adults. The pooled random effects odds ratio for risk of asthma based on use of paracetamol was 1.61 (95% CI 1.47 to 1.77). No statistical evidence of heterogeneity was identified

although the point estimate for I-squared was quite high at 42% and no confidence interval for this was given. An updated systematic review, search date October 2010, included six studies which specifically investigated the association between maternal paracetamol use in pregnancy and subsequent wheeze in the children [19]. There were five cohort studies and one cross-sectional study included in the meta-analysis, which identified a positive association with a pooled random effects odds ratio for the risk of current wheeze in the children of women who were exposed to any paracetamol during any stage of pregnancy of 1.21 (95% CI 1.02 to 1.44) [19]. Statistical evidence of heterogeneity was identified, I-squared 76% (95% CI 46.2 to 89.3), but too few studies with particular study level covariates were identified to attempt meta-regression to explain the heterogeneity. However, features of these studies variably included an association with paracetamol use during all trimesters of pregnancy and an association with persistent asthma, severe asthma and with atopy. In the most recent systematic review, search date November 2012, Heintze and Peterson examined the published literature for the association between antibiotics and/or paracetamol and asthma; but did not attempt a numerical synthesis of the association [20]. The authors note a consistent association between paracetamol use and asthma in most of the 29 individual studies reviewed, that was weakened when covariate adjusted estimates of the association were also calculated.

The issues of confounding and statistical adjustment for possible alternative associations are both important for assessing the two meta-analyses. The analysis of Etminan and colleagues chose to approach this by using the covariate adjusted estimates of the associations in the pooled synthesis [18]. This approach would be more robust if the underlying studies had used the same, or very similar, set of adjusting variables. Unfortunately this was not the case. There was a wide variation in the sets of confounding variables used, reflecting the uncertainty of the causal pathways for asthma and allergic disease. It is unclear therefore whether the pooled estimates were indeed

plausibly from the same hypothetical sample of studies. This is a necessary conceptual underpinning for validity of pooled effects. It seems likely that the estimates of variability for each study were in fact fundamentally dissimilar. In models with a very large number of covariates, inappropriate and spurious precision can be estimated as an artefact of the large number of covariates and those studies with inappropriately high precision then receive inappropriate weightings in the meta-analysis. Also, studies with an inappropriate selection of covariates may lead to reduction in precision. Finally, in the absence of a consensus about which potential causal variables should be in adjusted analyses, many of the studies may still have not adjusted appropriately for confounding. Another limitation of the approach of the analysis of Etminan and colleagues was the variation in the use of surrogate variables for the presence of asthma, such as the risk of hospitalisation for asthma.

The analysis of Eysers and colleagues used the raw data from a subset of association studies, which assessed paracetamol use in pregnancy in relation to the outcome variable of wheeze at 12 months of age in children [19]. The analysis plan in this report was to use study level covariates in a meta-regression to attempt to explain variation between studies but this was unable to be performed as an adequate number of appropriate study level covariates could not be identified. In an attempt to standardise the asthma outcome for children, wheeze at 12 months was used across the studies. However although wheeze at 12 months of age may be sensitive for allergic asthma it may not be specific. In this circumstance, it is possible that paracetamol use may be a confounding factor in the association between other causal factors and wheeze, rather than allergic asthma, which makes an interpretation of the study findings more challenging.

The systematic review of Heintze and Petersen does not attempt a meta-analysis [20]. Although not explicit in the paper, implicit in the approach taken is that the study designs were too disparate to combine. The authors identify that in two prospective birth cohort studies, the association between maternal paracetamol use and subsequent asthma or wheezing in children was weakened by adjustment for respiratory infections or for pre-existing wheezing or allergy. Without explicit meta-analysis however bias can arise if particular studies are highlighted to make a particular point.

Experimental studies

A systematic review identified that there has only been one fully published randomised controlled trial which provides data on the effect of paracetamol use in children with asthma [21] (Table 2). The original study by Lesko and colleagues randomly assigned over 80,000 children aged between six months and 12 years of age to paracetamol (12 mg/kg) or ibuprofen (5mg/kg or 10mg/kg) up to a maximum of five doses per day for treatment of a febrile illness. The study did not have a single primary outcome, as reported in the original trial publication [22], and the main results table reports on hospitalisation for six different outcomes. No sample size description is included in the original trial report nor was the issue of a clinically important difference in any particular outcome discussed in the methods section. In the primary study publication there is no description of planned secondary analyses or sub-group analyses. There is no description of a planned adjustment for multiple statistical testing. Hospitalisation for asthma within four weeks of treatment occurred in 24/28130 (0.085%) of children randomised to receive paracetamol and in 44/55785 (0.079%) randomised to ibuprofen. A relative risk for hospitalisation for asthma is not given in the primary study publication but based on these figures is for paracetamol compared to ibuprofen: 1.08 (95% CI 0.66 to 1.78), P=0.80. Clearly for this outcome variable the risk of hospitalisation for asthma within the scope of the study for either medication was very low and the confidence intervals for the risk very wide. The asthma outcomes paper [21] is a secondary analysis of a sub-group of 1879 children from this original study who were on some form of

asthma treatment. The outcomes considered were hospitalisation for asthma or an outpatient visit for asthma. Only in this secondary sub-group analysis, which was not apparently pre-specified in the primary study, does an association with attendance as an outpatient for asthma appear. The risk of this was 32/632 (5.1%) in those randomised to paracetamol and 37/1247 (2.6%) of those randomised to ibuprofen: relative risk paracetamol compared to ibuprofen 1.71 (1.07 to 2.71), $P=0.027$. It is very difficult to rule out that this association is not a result of multiple statistical testing including the issue of testing differences in sub-groups without a test for interaction. The number of children in the non-asthma drug use group who had an outpatient assessment for asthma is not given in either of the publications discussed.

The systematic review also identified that there has been only one fully published randomised controlled trial that provides data on the effect of paracetamol on asthma severity in adults (Table 2). This is a 12-week randomised double-blind placebo-controlled trial of paracetamol in a dose of 1g twice daily in adults with mild to moderate asthma [23]. The primary outcome variable for the trial was bronchial hyperresponsiveness (BHR), measured as the provocation concentration of methacholine (MCh) causing a 20% reduction in FEV_1 (PC_{20} MCh). Secondary outcome variables included FEV_1 , FeNO, Asthma Control Questionnaire (ACQ) score, blood eosinophil, and serum IgE levels. Recruitment for the study was difficult because of the reluctance of patients with asthma to participate in a study not directly designed to show an improvement of asthma, and the requirement for numerous exclusion criteria to ensure the safety of the participants. In addition, participants with a diagnosis of asthma and on asthma medications commonly did not have enhanced BHR and were thus ineligible. In total 724 potential participants were screened in order to recruit 94 participants. The mean PC_{20} MCh was lower in the treatment group, after controlling for baseline PC_{20} MCh, but the difference was not statistically significant (paracetamol minus placebo): -0.48 doubling doses (95% CI -1.28 to 0.32), $P=0.24$. In addition, there were no statistically significant differences in log FeNO (0.09, 95% CI -0.097 to 0.27), FEV_1 (-0.07

L, 95% CI -0.15 to 0.01), or ACQ score (-0.04, 95% CI -0.27 to 0.18). Thus this study had insufficient statistical power to rule out an important difference in BHR with paracetamol use in relatively stable adults with asthma and the point estimates for the secondary outcome variables were consistent with small negative effects on asthma. It was calculated that a study of similar design would require a sample size of at least 650 participants to attain adequate power to detect a 0.5 doubling dose difference in BHR, an effect which could potentially increase the prevalence of moderate and severe BHR by about one third [24]. Alternatively, a study of crossover design would require a sample size of 140 participants to have sufficient power to detect a similar 0.5 doubling dose difference in BHR. Other issues to consider in the design of future randomised controlled trials are the use of the maximum recommended dose of paracetamol, and repeated shorter durations of treatment to more closely replicate its use in self-limiting illnesses. Paracetamol withdrawal studies or the use of an NSAID as a control treatment are not preferred as these designs would not directly investigate the hypothesis that paracetamol increases the risk of asthma severity.

Future research

What should the continued research approach be? Both asthma and paracetamol use are common so that if there is even a relatively small effect on paracetamol use on asthma then this association could be important. The non-experimental studies are consistent with an association but cannot rule out confounding and bias. The only trial of paracetamol use in children with asthma has important issues of validity [21,22]. The only trial in adults with asthma probably rules out a large adverse effect of short-term low-dose use of paracetamol in participants with relatively stable asthma and provides reassurance that a larger more definitive study should be safe to perform [23]. Further randomised controlled trials in children and adults with asthma are a priority, although will be challenging to perform. Recruitment of participants to placebo-controlled trials of a new treatment that may provide some benefit is difficult enough. Recruitment to trials of a commonly used medication that may cause harm is likely to be more difficult, and

recruitment of sufficient numbers of participants to trials, when the effect may be quite small, adds to the challenge. Ensuring avoidance of over-the-counter medication, both of paracetamol and NSAIDs, would be problematic, and long-term follow-up would be required.

In addition to clinical trials of the effect of paracetamol on asthma severity, investigation of whether paracetamol use has a role in the pathogenesis of asthma is also a priority. The systematic review identified that there have been no clinical trials of the use of paracetamol in infancy and the development of asthma in childhood, or of maternal paracetamol use in pregnancy and risk of subsequent asthma. Such studies have significant ethical and practical issues regarding informed consent, recruitment and the use of placebo for the management of pain or fever in pregnancy and infancy.

However the time has now come to move on from analyses of uncontrolled allocation of paracetamol to human participants and design and perform experimental studies to definitively address the issue of the association of paracetamol use and asthma.

Table 1: Summary of the evidence linking paracetamol use and asthma

<i>Strength of effect:</i>	Increased asthma risk of up to 2.1 (paracetamol exposure in utero), ²⁵⁻³⁴ up to 7.3 (paracetamol use in infancy or childhood), ³⁵⁻³⁸ and up to 2.9 (paracetamol use in adults). ³⁹⁻⁴⁶
<i>Dose-response:</i>	Present for paracetamol exposure in utero, ^{25,26,31} childhood ³⁵⁻³⁸ and adults. ^{39, 41-43,}
<i>Consistency/coherence:</i>	Consistency between different studies in different age groups

in different populations worldwide.²⁵⁻⁴⁶

Modest coherence with some studies reporting lack of effect, bias and/or confounding.⁴⁷⁻⁵⁷

Exposure before response:

Observed in studies of paracetamol exposure in the intrauterine environment,²⁵⁻³⁴ and adult life.^{43,44}

Biological plausibility:

Increased oxidant-induced inflammation, potentially enhanced Th₂ response and TRPA-1 stimulation.⁵⁸⁻⁶²

Removal of exposure prevents disease:

Not yet examined.

Specificity:

No increased risk of asthma associated with aspirin or other non-steroidal anti-inflammatory drugs.^{63,64}

Temporal association:

International trends of increasing paracetamol use and increasing prevalence of asthma.^{65,66}

Analogy:

Oxidant-induced airway inflammation in asthma (e.g. ozone).⁶⁷ Protective effects of anti-oxidant diet in asthma.^{68,69}

Derived with modification from Farquhar et al.¹⁰

Table 2: Search strategy and selection criteria

We searched PubMed for trials of antipyretic therapy and asthma in humans using the terms “antipyretics”, “antipyre*”, “paracetamol”, “acetaminophen”, “asthma”, “wheeze”, “airway responsiveness” using the restriction term “English”. We identified one randomised controlled trial assessing the effects of long term dosing of paracetamol versus placebo in adults with asthma (Ionnades et al [23]), and one randomized controlled trial assessing the effects of paracetamol versus ibuprofen on asthma related outcomes in children with asthma when given for febrile illness (Lesko et al [21,22]). One further randomised controlled trial assessed a single dose of paracetamol versus placebo in children, but this was not included as it was a single dose study (Soferman et al [70]).

REFERENCES

1. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee Report. *Allergy* 2004;**59**:469-78.
2. Beasley, R, Crane J, Lai CKW, Pearce N. Prevalence and etiology of asthma. *J Allergy Clin Immunol* 2000;**105**:5466-72.
3. Woodward M. Epidemiology Study Design and Data Analysis. 2nd Edition. Boca Raton, FL: Chapman and Hall/CRC, 2005; 19-20.
4. Bradford-Hill A. The environment and disease: Association or causation? *Proc Roy Soc Med* 1965;**58**:295-300.
5. Nuttall SL, Williams J, Kendall MJ. Does paracetamol cause asthma? *J Clin Pharmacol Ther* 2003;**28**:251-7.
6. Allmers H. Frequent acetaminophen use and allergic diseases: Is the association clear? *J Allergy Clin Immunol* 2005;**116**:859-62.
7. Eneli I, Sadri K, Camargo C Jr, Barr RG. Acetaminophen and the risk of asthma: the epidemiologic and pathophysiologic evidence. *Chest* 2005;**127**:604-12.

- Accepted Article
8. Barr RG. Does paracetamol cause asthma in children? Time to remove the guesswork. *Lancet* 2008;**372**:1011-2.
 9. Farquhar H, Stewart A, Mitchell E, et al. The role of paracetamol in the pathogenesis of asthma. *Clin Exp Allergy* 2010;**40**:32-41.
 10. Farquhar H, Crane J, Mitchell EA, et al. The acetaminophen and asthma hypothesis 10 years on: A case to answer. *J Allergy Clin Immunol* 2009;**124**:649-51.
 11. Persky VW. Acetaminophen and Asthma. *Thorax* 2010; **65**:99-100.
 12. Dharmage SC, Allen KJ. Does regular paracetamol ingestion increase the risk of developing asthma? *Clin Exp Allergy* 2011; **41**:459-60.
 13. Johnson CC, Ownby DR. Have the efforts to prevent aspirin-related Reye's syndrome fuelled an increase in asthma? *Clin Exp Allergy* 2011;**41**:296-8.
 14. Holgate ST. The acetaminophen enigma in asthma. *Am J Respir Crit Care Med* 2011;**183**:147-8.
 15. McBride JT. The association of acetaminophen and asthma prevalence and severity. *Pediatrics* 2011;**128**:1181-5.
 16. Henderson AJ, Shaheen SO. Acetaminophen and asthma. *Paediatric Resp Rev* 2013;**14**:9-16.
 17. Martinez-Gimeno A, Garcia-Marcos L. The association between acetaminophen and asthma: should its pediatric use be banned? *Expert Rev Resp Med* 2013;**7**:113-22.
 18. Etminan M, Sadatsafavi M, Jafari S, et al. Acetaminophen use and the risk of asthma in children and adults a systematic review and meta-analysis. *Chest* 2009;**136**:1316-23.
 19. Evers S, Weatherall M, Jeffries S, Beasley R. Paracetamol in pregnancy and the risk of wheezing in offspring: a systematic review and meta-analysis. *Clin Exp Allergy* 2011;**41**:482-9.
 20. Heintze K and Petersen KW. The case of drug causation of childhood asthma: antibiotics and paracetamol. *Eur J Clin Pharmacol* 2013;**69**:1197-209.

- Accepted Article
21. Lesko SM, Louik C, Vezina RM, Mitchell AA. Asthma morbidity after the short term use of ibuprofen in children. *Pediatrics* 2002;**109**:E20.
 22. Lesko SM and Mitchell AA. An assessment of the safety of pediatric ibuprofen a practitioner-based randomized clinical trial. *JAMA* 1995;**273**:929-33.
 23. Evers SJ, Williams M, Jefferies S et al. Randomised placebo controlled study of the effect of paracetamol on asthma severity in adults. *BMJ Open* 2014;**4**:e004324.
 24. Weatherall M, Fingleton J, Evers S, Beasley R. A half doubling dose change in bronchial hyperresponsiveness in a population represents an important difference. *Trans Resp Med* 2013;**1**:4.
 25. Shaheen SO, Newson RB, Sherriff A, et al and the ALSPAC Study Team. Paracetamol use in pregnancy and wheezing in early childhood. *Thorax* 2002;**57**:958-63.
 26. Shaheen SO, Newson RB, Henderson AJ, et al and the ALSPAC Study Team. Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. *Clin Exp Allergy* 2005;**35**:18-25.
 27. Rebordosa C, Kogevinas M, Sorensen HT, Olsen J. Pre-natal exposure to paracetamol and risk of wheezing and asthma in children: a birth cohort study. *Int J Epidemiol* 2008;**37**:583-90.
 28. Koniman R, Chan YH, Tan TN, Van Bever HP. A matched patient-sibling study on the usage of paracetamol and the subsequent development of allergy and asthma. *Pediatr Allergy Immunol* 2007;**18**:128-34.
 29. Garcia-Marcos L, Sanchez-Solis M, Perez-Fernandez V, et al. Is the effect of prenatal paracetamol exposure on preschool wheezing modified by asthma in the mother? *Int Arch Allergy Immunol* 2008;**149**:33-7.
 30. Persky V, Piorkowski J, Hernandez E, et al. Prenatal exposure to acetaminophen and respiratory symptoms in the first year of life. *Ann Allergy Asthma Immunol* 2008;**101**:271-8.

- Accepted Article
31. Perzanowski MS, Miller RL, Tang D, et al. Prenatal acetaminophen exposure and risk of wheeze at age 5 years in an urban low-income cohort. *Thorax* 2010;**65**:118-23.
 32. Shaheen S, Newson R, Smith G, Henderson A. Prenatal paracetamol exposure and asthma: further evidence against confounding. *Int J Epidemiol* 2010;**39**:790-4.
 33. Bisgaard H, Loland L, Holst K, Pipper C. Prenatal determinants of neonatal lung function in high-risk newborns. *J Allergy Clin Immunol* 2009;**123**:651-7.
 34. Goksör E, Thengilsdottir H, Alm B, Norvenius G, Wennergren G. Prenatal paracetamol exposure and risk of wheeze at preschool age*. *Acta Paediatric* 2011;**100**:1567-71.
 35. Beasley R, Clayton T, Crane J, et al and the ISAAC Phase Three Study Group. Acetaminophen use in infancy and later childhood and risk of asthma, rhinoconjunctivitis and eczema in 6 to 7 year old children: ISAAC Phase Three. *Lancet* 2008;**372**:1039-48.
 36. Amberbir A, Medhin G, Alem A, Britton J, Davey G, Venn A. The role of acetaminophen and geohelminth infection on the incidence of wheeze and eczema: a longitudinal birth-cohort study. *Am J Respir Crit Care Med* 2011;**183**:165-70.
 37. Beasley R, Clayton T, Crane J, Lai C, Montefort S, von Mutius E, Stewart A, and the ISAAC Phase Three Study Group. Acetaminophen use and risk of asthma, rhinoconjunctivitis, and eczema in adolescents. *Am J Respir Crit Care Med* 2011; **183**:171-8.
 38. Wickens K, Beasley R, Town I, Epton M, Pattemore P, Ingham T, Crane J and the New Zealand Asthma and Allergy Cohort Study. *Clin Exp Allergy* 2011;**41**:399-406.
 39. Shaheen SO, Sterne JAC, Songhurst CE, Burney PGJ. Frequent paracetamol use and asthma in adults. *Thorax* 2000;**55**:266-70.
 40. Shaheen S, Potts J, Gnaniuc L, et al. The relation between paracetamol use and asthma: a GA²LEN European case-control study. *Eur Respir J* 2008;**32**:1231-6.

- Accepted Article
41. Davey G, Berhane Y, Duncan P, et al. Use of acetaminophen and the risk of self-reported allergic symptoms and skin sensitization in Butajira, Ethiopia. *J Allergy Clin Immunol* 2005;**116**:863-8.
 42. McKeever TM, Lewis SA, Smith HA, et al. The association of acetaminophen, aspirin, and ibuprofen with respiratory disease and lung function. *Am J Respir Crit Care Med* 2005;**171**:966-71.
 43. Barr RG, Wentowski CC, Curhan GC, et al. Prospective study of acetaminophen use and newly diagnosed asthma among women. *Am J Respir Crit Care Med* 2004;**169**:836-41.
 44. Thomsen SF, Kyvik KO, Skadhauge L, Steffensen I, Backer V. Intake of paracetamol and risk of asthma in adults. *J Asthma* 2008;**45**:675-6.
 45. Kelkar M, Cleves M, Foster H, Hogan W, James L, Martin B. Prescription-acquired acetaminophen use and the risk of asthma in adults: a case-control study. *Ann Pharmacother* 2012;**46**:1598-608.
 46. Amberbir A, Medhin G, Hanlon C, Britton J, Venn A, Davey G. Frequent use of paracetamol and risk of allergic disease among women in an Ethiopian population. *PLoS ONE* 2011;**6**:e22551.
 47. Singh M. Paracetamol as a risk factor for allergic disorders. *Lancet* 2009;**373**:119.
 48. Lawrence J, Moore E, Port L, Danchin M, Connell T. Paracetamol as a risk factor for allergic disorders. *Lancet* 2009;**373**:119.
 49. Lowe A, Abramson M, Dharmage S, Allen K. Paracetamol as a risk factor for allergic disorders. *Lancet* 2009;**373**:120.
 50. Kreiner-Møller E, Sevelsted A, Vissing NH, et al. Infant acetaminophen use associates with early asthmatic symptoms independently of respiratory tract infections: The Copenhagen Prospective Study on Asthma in Childhood 2000 (COPSAC₂₀₀₀) cohort. *J Allergy Clin Immunol* 2012;**130**:1434-6.
 51. Schnabel E, Heinrich J. Respiratory tract infections and not paracetamol medication during infancy are associated with asthma development in childhood. *J Allergy Clin Immunol* 2010;**126**:1071-3.

- Accepted Article
52. Marquis A, Strippoli M-PF, Spycher BD et al. Paracetamol, nonsteroidal anti-inflammatory drugs, and the risk of asthma in adult survivors of childhood cancer. *J Allergy Clin Immunol* 2011;**127**:270-2.
 53. Lowe AJ, Carlin JB, Bennett CM, et al. Paracetamol use in early life and asthma: prospective birth cohort study. *BMJ* 2010;**341**:c4616.
 54. Tapiainen T, Dunder T, Mottonen M, et al. Adolescents with asthma or atopic eczema have more febrile days in early childhood: a possible explanation for the connection between paracetamol and asthma? *J Allergy Clin Immunol* 2010;**125**:751-2.
 55. Rusconi F, Gagliardi L, Galassi C, Forastiere F, Brunetti L, La Grutta S, Piffer S, Talassi F and the SIDRIA-2 Collaborative Group. Paracetamol and antibiotics in childhood and subsequent development of wheezing/asthma: association or causation? *Int J Epidemiol* 2011;**40**:662-7.
 56. Bakkeheim E, Mowinckel P, Carlsen K, Håland G, Carlsen K. Paracetamol in early infancy: the risk of childhood allergy and asthma. *Acta Paediatric* 2011;**100**:90-6.
 57. Kang E, Lundsberg L, Illuzzi J, Bracken M. Prenatal exposure to acetaminophen and asthma in children. *Obstet Gynecol* 2009;**114**:1295-1306.
 58. Micheli L, Cerretani D, Fiaschi AI, et al. Effect of acetaminophen on glutathione levels in rat testis and lung. *Environ Health Perspect* 1994;**102(Suppl 9)**:63-4.
 59. Dimova S, Hoet PHM, Dinsdale D, Nemery B. Acetaminophen decreases intracellular glutathione levels and modulates cytokine production in human alveolar macrophages and type II pneumocytes in vitro. *Int J Biochem Cell Biol* 2005;**37**:1727-37.
 60. Peterson JD, Herzenberg LA, Vasquez K, Waltenbaugh C. Glutathione levels in antigen-presenting cells modulate Th1 versus Th2 response patterns. *Proc Natl Acad Sci USA* 1998;**95**:3071-6.
 61. Kozar E, Evans S, Barr J, et al. Glutathione, glutathione-dependent enzymes and antioxidant status in erythrocytes from children treated with high-dose paracetamol. *Br J Clin Pharmacol* 2003;**55**:234-40.

- Accepted Article
62. Nassini R, Materazzi S, Andre E, et al. Acetaminophen, via its reactive metabolite N-acetyl-p-benzo-quinoneimine and transient receptor potential ankyrin-1 stimulation, causes neurogenic inflammation in the airways and other tissues in rodents. *FASEB J* 2010;**24**:4904-16.
 63. Kurth T, Barr RG, Gaziano JM, Buring JE. Randomised aspirin assignment and risk of adult-onset asthma in the Women's Health Study. *Thorax* 2008;**63**:514-8.
 64. Barr RG, Kurth T, Stampfer MJ, et al. Aspirin and decreased adult-onset asthma: randomised comparisons from the physicians' health study. *Am J Respir Crit Care Med* 2007;**175**:120-5.
 65. Varner AE, Busse WW, Lemanske RF Jr. Hypothesis: decreased use of pediatric aspirin has contributed to the increasing prevalence of childhood asthma. *Ann Allergy Asthma Immunol* 1998;**81**:347-51.
 66. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006;**355**:2226-35.
 67. McConnell R, Berhane K, Gilliland F, et al. Asthma in exercising children exposed to ozone: a cohort study. *Lancet* 2002;**359**:386-91.
 68. Shaheen SO, Sterne JAC, Thompson RL, et al. Dietary antioxidants and asthma in adults: population-based case-control study. *Am J Respir Crit Care Med* 2001;**164**:1823-8.
 69. Rubin RN, Navon L, Cassano PA. Relationship of serum antioxidants to asthma prevalence in youth. *Am J Respir Crit Care Med* 2004;**169**:393-8.
 70. Soferman R, Tsivion A, Farber M, Sivan Y. The effect of a single dose of acetaminophen on airways response in children with asthma. *Clin Pediatr* 2013;**52**:42-8.