



The association between paracetamol and asthma is still under debate

Tamara Lourido-Cebreiro MD, Francisco-Javier Salgado PhD, Luis Valdes PhD & Francisco-Javier Gonzalez-Barcala MD, PhD

To cite this article: Tamara Lourido-Cebreiro MD, Francisco-Javier Salgado PhD, Luis Valdes PhD & Francisco-Javier Gonzalez-Barcala MD, PhD (2017) The association between paracetamol and asthma is still under debate, Journal of Asthma, 54:1, 32-38, DOI: 10.1080/02770903.2016.1194431

To link to this article: <http://dx.doi.org/10.1080/02770903.2016.1194431>



Accepted author version posted online: 30 Aug 2016.
Published online: 30 Aug 2016.



Submit your article to this journal [↗](#)



Article views: 133



View related articles [↗](#)



View Crossmark data [↗](#)



RISK FACTORS

The association between paracetamol and asthma is still under debate

Tamara Lourido-Cebreiro, MD^a, Francisco-Javier Salgado, PhD^{b,c}, Luis Valdes, PhD^{a,d,e}, and Francisco-Javier Gonzalez-Barcala, MD, PhD^{a,b,d,e}

^aDepartment of Respiratory Medicine-University Hospital of Santiago de Compostela, Spain; ^bSpanish Biomedical Research Networking Centre-CIBERES, Madrid, Spain; ^cDepartment of Biochemistry and Molecular Biology, Faculty of Biology/CIBUS University of Santiago de Compostela, Spain; ^dDepartment of Medicine-University of Santiago de Compostela, Spain; ^eHealth Research Institute of Santiago de Compostela (IDIS), Spain

ABSTRACT

Objective: To analyse the relationship between paracetamol and asthma. **Data sources:** An English literature search using electronic search engines (PubMed and EMBASE) was conducted. **Study selections:** Articles published in peer-review journals, from 1990 to December 2015 were included. To perform the search for the most suitable and representative articles, keywords were selected ("asthma," "paracetamol" and "acetaminophen"). The evidence level was rated according to the criteria of the Oxford Centre For Evidence-Based Medicine. **Results:** The exposure to paracetamol during pregnancy was analysed in several cohort studies, showing an association between the prenatal exposure to paracetamol with suffering from asthma or presence of wheezing in childhood, especially for persistent wheezing. Nevertheless, a recent study concluded that the relationship between asthma and paracetamol is explained, at least in part, by confounding factors. Several works have also associated the exposure to paracetamol in the first years of life or in adults with the development of childhood asthma. Several pathophysiological mechanisms are known that could explain this relationship, such as the glutathione pathway, the decrease in the release of Th1 cytokines that are normally produced during febrile episodes, which would then lead to a predominance of Th2 cytokines, the cytotoxic effect of paracetamol for pneumocytes, a modulator effect on the activity of myeloperoxidase, as well as the possible antigenic effect of paracetamol, mediated by IgE. **Conclusions:** There are many arguments that suggest a relationship between the use of paracetamol with the appearance of asthmatic symptoms, however the evidence is inconclusive.

ARTICLE HISTORY

Received 2 February 2016
Revised 19 May 2016
Accepted 22 May 2016

KEYWORDS

Pathophysiology;
epidemiology; mechanisms;
morbidity and mortality;
reviews

Introduction

Asthma is a chronic inflammatory disease of the respiratory tract. It is determined by genetic and environmental factors that include bronchial hyperresponsiveness and a variable obstruction of the airflow [1]. According to the WHO, it affects more than 300 million people in the world, which is increasing, particularly in the more industrialised countries, making it a significant public health problem. The cause of this increase is still not clear and is probably due to multiple factors. Relationships have been found with various environmental factors: dietary, economic, smoking tobacco, environmental pollution, respiratory infections, and drugs [2].

Paracetamol, an analgesic and antipyretic used frequently during pregnancy and in childhood has been associated with the increased incidence of asthma. Varner et al. were the first to note that the increase in the prevalence of asthma occurred in the 1980s, coinciding with the

reduction in the use of aspirin in favour of paracetamol [3]. Since then, a considerable number of observational epidemiological studies have been published, associating the exposure to paracetamol with asthma, and covering different populations and age groups. The purpose of this review is to analyse the currently available evidence on the association between exposure to paracetamol and asthma.

Methods

An English literature search using electronic search engines (PubMed and EMBASE) was conducted in peer-review journals, from 1990 to December 2015. To perform the search for the most suitable and representative articles, keywords were selected ("asthma," "paracetamol" and "acetaminophen"). The main characteristics of the articles are in Table 1. The evidence level was rated according to the criteria of the Oxford Centre For Evidence-Based Medicine [4].

Table 1. Main characteristics of the reviewed articles.

Author, year:	Study design	Exposure to paracetamol	Population number included	Results	Risk adjustment	Evidence level
Shaheen, 2002	Cohort	Pregnancy	9,400	Increased risk of wheezing, OR:2.10 (CI 95%:1.30–3.41)	Age, gender, ethnic origin, social class, smoking	2
Shaheen, 2005	Cohort	Pregnancy	8,511	Increased risk of asthma, OR:1.22 (CI 95%:1.06–1.41), and wheezing: OR: 1.20 (CI 95%: 1.02–1.40)	Child's sex, mother's age, smoking, education level, mother's parity, maternal asthma, pets, antibiotic use	2
Perzanowski 2010	Cohort	Pregnancy	301	Increased risk of wheezing RR: 1.71 (CI 95%:1.20–2.42)	Ethnic origin, maternal asthma, smoking, cat exposure, mother's age, social class, ibuprofen or aspirin use	2
Goksoör 2011	Cohort	Pregnancy	8,176	Increased risk of wheezing OR: 2.4 (CI 95%:1.2–4.8)	Parental asthma, gender, antibiotic use, smoking, caesarean section, breast feeding, diet, parental education	2
Rebordosa 2008	Cohort	Pregnancy	66,445	Increased risk of asthma RR: 1.17 (CI 95%: 1.13–1.23)	Gender, smoking, antibiotic use, social class, breast feeding	2
García – Marcos 2009	Cross-sectional	Pregnancy	1,741	Increased risk of wheezing OR: 1.74; CI 95% (1.15–2.61)	Smoking, breast feeding, preterm birth, cat exposure, older siblings	4
Kang 2009	Cohort	Pregnancy	1,505	Not increased risk of asthma OR:0.76 (CI 95%: 0.53–1.10)	Ethnic origin, allergy, respiratory infection, smoking, antibiotic use, maternal asthma, pets, gestational age	2
Migliore* 2015	Cohort	Pregnancy	3,538	Not increased risk of wheezing or asthma RR: 1.10 (CI 95%:0.94–1.30) in the first trimester RR: 1.10 (CI 95%:0.93–1.29) in the third trimester	Smoking, maternal asthma, siblings, gestational duration, paracetamol indication	2
Beasley 2008	Cross-sectional	child's first year of life	205,487	Increased risk of asthma, OR: 1.46 (CI 95%:1.36–1.56).	Maternal education, antibiotic use, diet, smoking	4
Beasley 2011	Cross-sectional	Children	322,959	Increased asthma risk, OR: 1.43; (CI 95%: 1.33–1.5) for medium dose; OR 2.51 (CI 95%: 2.33 – 2.70) for high dose.	Maternal education, maternal smoking, diet, older siblings	4
González-Barcala* 2013	Cross-sectional	Children	20,343	Increased risk of wheezing, OR: 2.04 (CI 95%:1.79–2.31).	Gender, BMI, cat or dog at home, maternal education, parental asthma, parental smoking	4
Lowe 2010	Cohort	Children	620	Increased risk of infantile wheeze (up to 2 years) OR: 1.44 (CI 95%:1.17–1.77). Not increase of childhood (5–7 years) asthma OR:1.08 (CI 95%:0.91–1.29)	Gender, older siblings, parental history of asthma, respiratory tract infections	2
Bakkeheim 2011	Cohort	Pregnancy and until 6 months of age	1,016	Increased risk of asthma in girls, OR:2.20 (CI 95%:1.13–4.30)	Gender, respiratory tract infections	2
Amberbir 2014*	Cohort	Children	1,006	Increased risk of wheezing, OR: 3.64 (CI 95%:1.34 a 9.90)	Gender, area of residence, maternal education, respiratory infections	2
Sordillo 2015*	Cohort	Pregnancy and first year of life	1,490	Increased risk of asthma, OR:1.26 (CI 95%:1.02–1.58) Adjusted by respiratory infections: OR:1.03 (CI 95%:0.88–1.22)	Gender, birth weight, maternal age, race/ethnicity, pre-pregnancy BMI, household income, number of children under 12 years of age in the home, breastfeeding duration, passive smoking exposure, smoking during pregnancy, childcare attendance, parental asthma	2
Shaheen 2000	Case-control	Adults	1,574	Increased asthma risk, OR: 2.38 (CI 95%:1.22–4.64)	Gender, age, social class, smoking	3
Barr 2004	Cohort	Adult women	121,700	Increased asthma incidence, OR:1.63 (CI 95%:1.1–2.39).	Age, aspirin use, other NSAID use, race/ethnicity, husband's education, smoking, BMI, postmenopausal hormone use, and type of menopause.	2
McKeever 2005	Cross-sectional	Adults	17,000	Increased risk of asthma, OR:1.20 (CI 95%:1.12–1.28)	Gender, age, smoke, race/ethnicity	4
Thomsen 2008	Cross sectional	Adults	19,349	Increased asthma risk, OR:2.16 (CI 95%:1.03–4.53)	Gender, age, smoking, BMI, hay fever, eczema, and intake of medications other than paracetamol	4
Shaheen 2008	Case-control	Adults	1,028	Increased asthma risk, OR:2.87 (CI 95%:1.49–5.37)	Gender, age, smoking, BMI, social class	3
Ioannides 2014*	Case-control	Adults	181	No significant effect on BHR and asthma control.		3

Notes. Evidence level was rated according to the Oxford Centre For Evidence-Based Medicine (Reference 4). Studies not included in previous publications (*). OR: Odds Ratio; RR: relative risk; CI: Confidence Interval. BHR: bronchial hyper-responsiveness testing; BMI: body mass index; NSAID: nonsteroidal anti-inflammatory drugs.

Results and discussion

Exposure to paracetamol during pregnancy and childhood asthma

Several cohort studies associate the prenatal exposure to paracetamol with suffering from asthma or presence of wheezing in childhood. The first data were published by the Shaheen group, who performed a longitudinal study (ALSPAC) and they observe that taking this drug at the end of pregnancy was a risk factor for persistent wheezing in 3-year-old children (OR 2.34; 95% CI: 1.24–4.40), but not for transient childhood wheezing (OR 0.88, 95% CI: 0.44–1.73) [5]. This observation is important since persistent wheezing are what frequently progress to asthma in contrast with transient wheezing, which is believed to occur in the context of respiratory infections as a result of the calibre of the airway, and are subsequently resolved [6]. The ALSPAC cohort was studied again when the children were 7 years old, noting that the consumption of paracetamol, but not of aspirin, was associated with asthma and elevation of IgE [7].

Other studies along the same line also observed an association between prenatal exposure to paracetamol and the subsequent appearance of wheezing or asthma [8, 9]. In a Danish study, they observed that the children of pregnant mothers who took paracetamol frequently had more risk of being hospitalised due to asthma (OR: 1.24; 95% CI: 1.11–1.38). It should be mentioned that the main indication for taking paracetamol was for pain, which seems to support a real effect of paracetamol and not a confounding effect, as could be the case if the indication was fever in the context of a respiratory infection [10].

A study published by Garcia-Marcos with a Spanish cohort, had as its aim to analyse the influence of the mother being asthmatic and the exposure to paracetamol during pregnancy and prevalence of wheezing in childhood. A total of 1741 children of pre-school age with wheezing were included, and a significant association was found between the use of paracetamol by the mother and the risk of wheezing at pre-school age (OR 1.74; 95% CI: 1.15–2.61), but only between non-asthmatic mothers; thus, it appears that asthma in the mother could modify this association. There was no association between the prenatal use of paracetamol and asthma in the children of both non-asthmatic or asthmatic mothers [11].

Eyers et al. performed a systematic review and meta-analysis, in which they concluded that there is an association between the appearance of wheezing and exposure to paracetamol during all the pregnancy trimesters, although they recognised that these results might be affected by confounding factors, such as maternal

smoking, having domestic pets, and social class [12]. Thus, in the work by Kang et al., where they took into account possible confounding factors, an increase in asthma was not observed in the children whose mothers took paracetamol; but it should be remembered that 45% of the mothers were already asthmatics, which could have affected the results [13].

A study has recently been published in which it analyses if the association between exposure to paracetamol during pregnancy and wheezing in infants is causal or can be explained by confounding factors. More than 3,300 newborns were included for this study, and they analysed paracetamol consumption in the first and third trimesters of pregnancy. The authors found a positive association between exposure to paracetamol and the presence of asthma and wheezing in the babies.

But, when they were adjusted for confounding factors, mainly due to respiratory infections, the relative risk for appearance of wheezing decreased from 1.25 [1.07–1.47] to 1.10 [0.94–1.30] in the first trimester, and from 1.26 [1.08–1.47] to 1.10 [0.93–1.29] in the third. Furthermore, when they analysed the sub-group of patients who used paracetamol as an analgesic (sciatica, headaches) and not as an anti-pyretic, they found that in this case that it did not lead to an increased risk of wheezing in the children. For this reason, the authors concluded that the relationship between asthma and paracetamol is explained, at least in part, by confounding factors. The results of this study give rise to some doubts, given the small number of cases in which paracetamol was used as an analgesic (5 in the first trimester and 7 in the third) [14].

Exposure to paracetamol in the first years of life and asthma in infancy

Several works have also associated the exposure to paracetamol in the first years of life with the development of childhood asthma. In an analysis of a large sample of children and adolescents enrolled in the ISAAC study, the Beasley group found a positive and dose-dependent association between the consumption of paracetamol and the presence of allergic diseases, such as asthma, rhinitis, or eczema [15,16]. We have also published a cross-sectional study with more than 20,000 Galician (Spain) children and adolescents, in which we analysed paracetamol consumption and asthma prevalence. It was observed that paracetamol consumption was associated with a significant increase in wheezing, and that this effect appears to be dose-dependent [17].

However, a prospective study published by the Lowe group, analysed the relationship between treatment with paracetamol in the first 2 years of life and the presence of asthma at 7 years old. The authors found a positive

association if the paracetamol was used in the context of a respiratory infection, but disappeared if it was used in non-respiratory illnesses. The authors established that that association was due to respiratory infections that can act as a confounding factor. This work had some weaknesses, since it only evaluated the administration of paracetamol between 0 and 2 years old, and that the number of patients treated with paracetamol for illnesses other than respiratory tract was limited [18].

Another study with Norwegian children did not find any relationship between the presence of asthma at 10 years old and the exposure to paracetamol during pregnancy, or in the first 6 months of life, although they did find a relationship between a higher paracetamol consumption and the presence of asthma in girls. It should be mentioned that this study had a limited number of patients that were exposed to paracetamol in the first 6 months of life (83, which is 8% of the sample included) [19].

Amberbir et al. have conducted a prospective longitudinal study with a 5-year follow-up on an Ethiopian cohort, in which they analysed the relationship between exposure to paracetamol, the developing of wheezing, and allergic disease. In 1,006 newborns included, it was observed that 60% took paracetamol in the first 3 years of life and this was associated with a higher incidence of wheezing, eczema, and allergic rhinitis. This association was dose-dependent. When the authors adjusted the results for confounding factors, including respiratory infections, they found that the strength of the association decreased, but was still statistically significant, concluding that the exposure to paracetamol in the first years of life is a risk factor for allergic disease in childhood [20].

A study has recently been published by the Sordillo group, in which they investigated the exposure to paracetamol and ibuprofen in pregnancy and the first year of life with the presence of asthma in two age groups: 3–5 years and 7–10 years. The authors observed a positive relationship between exposure to paracetamol in pregnancy and in the first years of life in both age groups, but this relationship weakened, but remained statistically significant, when it was adjusted for respiratory infections [21].

Exposure to paracetamol in adults

Other studies have analysed the relationship between asthma and paracetamol in adults. One English case-control study, including 664 individuals with asthma, and 910 without asthma, analysed the previous consumption of paracetamol and aspirin. A dose-dependent relationship was found between the use of paracetamol and asthma, with an increased risk of 1.79 (1.21–2.65) in those who consumed it weekly, and 2.38 (1.22–4.64)

those who took it daily. Another finding was, that among the cases, the daily use of paracetamol was associated with a more severe disease, with an OR of 1.35 (95% CI; 0.55 – 3.34), 2.25 (IC 95%; 0.90 – 5.66), and 8.15 (95% CI; 2.84–23.40) for mild, moderate and, severe asthma, respectively. Furthermore, this association was maintained independently of aspirin use [22].

In the Nurses Health Study in the United States, it was observed that a paracetamol use of more than 14 days a month was associated with a higher incidence of recently diagnosed asthma in women (OR: 1.63, 95% CI: 1.1–2.39) [23]. Another, cross-sectional, study conducted in the United States found a positive association between paracetamol use and asthma, with an OR of 1.20; (95% CI; 1.12–1.28; $P < .001$) regardless of the dose. They also found an inverse relationship with the 1-second forced expiratory volume, with a mean reduction of 54.0 ml (95% CI; 17.7–90.3 ml) in those who consumed paracetamol [24]. A Danish prospective study analysed the data collected from a cohort of 19,349 twins using a questionnaire. It was observed that there was a higher prevalence of recent onset of asthma during a period of 8 years in subjects who reported frequent use of paracetamol at the beginning of the study compared to those who did not (12.0% versus 4.3%), OR = 3.03 (1.51 – 6.11), $P = .005$. The results were still significant after adjusting for confounding factors, OR = 2.16 (1.03 – 4.53), $P = .041$. The authors concluded that the frequent use of paracetamol is an independent risk factor for asthma in the adult [25].

An increase in the prevalence of asthma associated with the frequent use of paracetamol (OR: 2.87, 95% CI: 1.49–5.37) was also observed young people in a multicentre, case controlled study that included patients from 12 European populations [26]. A randomised, controlled study evaluated the effects of paracetamol on bronchial hyper-reactivity and asthma control in adults. A total of 94 patients with mild or moderate asthma were randomised to receive placebo or 1g of paracetamol 2 times a day for 12 weeks. No statistically significant differences were found between the two groups; but the sample size was small and the study results were limited due to the low statistical power [27].

The evidence from *in vivo* and *in vitro* studies seems to support some relationship between taking paracetamol and asthma. Thus, several pathophysiological mechanisms are known that could explain this relationship:

On the one hand, there is the glutathione pathway. This is found in the respiratory tract, in more than 95% of cases in the reduced form, as an antioxidant and is involved in lung inflammation. Its reduction has been demonstrated in exhaled condensates of asthmatic children during exacerbations. Depending on the dose, paracetamol decreases glutathione levels as such that it weakens the capacity of the body against the effects of oxidative stress [28]. This

can lead to tissue damage, smooth muscle contraction, bronchial hyperreactivity, increase in vascular patency, release of inflammatory mediators, and interfere with the activity of beta-receptors [29].

It has been shown that paracetamol at therapeutic doses can reduce the serum antioxidant capacity for 14 days [30]. A work published by Barr et al. demonstrated that prenatal exposure to paracetamol was associated with the appearance of wheezing in that population at 5 years old, and that risk was modified by a functional polymorph in glutathione S-transferase P1 (GSTP1), which suggests even more the existence of a glutathione pathway dependent-mechanism [8]. Furthermore, glutathione exhaustion may lead to an exchange of T helper 1 (Th1) for Th2 that favours the appearance of allergic diseases [31]. Another possible mechanism could be the decrease in the release of Th1 cytokines that are normally produced during febrile episodes, which would then lead to a predominance of Th2 cytokines [29]. Baudouin et al. established that high doses of paracetamol are cytotoxic for pneumocytes, and can cause acute lung damage [32].

Paracetamol also has a modulator effect on the activity of myeloperoxidase, an enzyme that takes part in several oxidation mechanisms [33]. In animal models, it has been shown that the activation of transient receptor potential ankyrin-1 (TRPA1) by paracetamol metabolites NAPQI (N-acetyl-p-benzoquinone imine) induces inflammatory activity of the lung, with an increase in the number of neutrophils, increased activation of myeloperoxidase and cytokine levels [34].

Another theory that has been put forward is the possible antigenic effect of paracetamol, mediated by IgE [35]. Karimi et al. have recently developed a mouse model in which it studies the effect of prenatal paracetamol in the new-borns, and it was observed that the animals exposed to paracetamol had more lung inflammation in the histology specimens, as well as higher white cell and eosinophil count in bronchoalveolar lavage (BAL) [36].

All these studies have several limitations that need to be taken into consideration: in the majority of cases they are non-experimental studies, the paracetamol exposure rate is very heterogeneous, and that the diagnosis of asthma / asthma symptoms is usually “self-reported.” On the other hand, it should be mentioned that some studies use wheezing to define asthma, but this is difficult to diagnose before 6 years old, and wheezing in early infancy is not always a good predictor of the subsequent development of asthma.

In short, the majority of works that studied the relationship between asthma and paracetamol are non-experimental, but appear to demonstrate a positive association between asthma and paracetamol. Along this line, a review was published in 2009, in which it established an

increase in asthma and wheezing in adults and children exposed to paracetamol [37]. We have seen that, there is a strong association in different age groups and populations of the world, that the exposure to paracetamol precedes the appearance of asthma, that there is a biological gradient, since the effect depends on the dose of paracetamol administered, and also biological plausibility.

A systematic review and meta-analysis has recently been published, in which it shows that the studies are heterogeneous, the relationship between asthma and paracetamol could be over-estimated as respiratory infections may act as a confounding factor, and that future well designed clinical trials should be conducted that take into account the history of infections and include lung function data [38].

The conducting of a clinical trial that provides greater scientific evidence may have ethical problems if the control group is treated with placebo. One possible solution could be to use and ibuprofen control group, as did the Lesko group, who observed that ibuprofen appeared to decrease the morbidity of asthma in the short-term compared to paracetamol [39,40]; but when analysing the results could not see if the effect is due to the harmful effect of paracetamol or a possible protector effect of ibuprofen. In another case-controlled double blind study, they evaluated the effect of a single paracetamol dose in 42 asthmatic children and 21 healthy controls. They analysed symptoms, spirometry, and exhaled nitric oxide levels after taking the dose, without observing any differences between the two groups [41].

Conclusion

Although there are many arguments that suggest a relationship between the use of paracetamol with the appearance of asthmatic symptoms, the evidence is inconclusive, and more research work that includes long-term randomised clinical trials are required to evaluate the solidity of this relationship before proposing changes to the indications of use for this treatment.

Declaration of interest

The authors report no conflicts of interest.

References

1. Spanish Guide for Asthma Management-GEMA 4.0. 2015 May. Available from: <http://www.semg.es/documentos-semg/guias/1164-gema-4-0-2015.html> [last accessed 17 December 2015].
2. Asher MI. Recent perspectives on global epidemiology of asthma in childhood. *Allergol Immunopathol* 2010;38:83–87.

3. Varner AE, Busse WW, Lemanske RF. Hypothesis: decreased use of pediatric aspirin has contributed to the increasing prevalence of childhood asthma. *Ann Allergy Asthma Immunol* 1998;81:347–351.
4. Centre for Evidence-based Medicine - Levels of evidence (March 2009). Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009. Available from: <http://www.cebm.net/?O=1025> [last accessed 10 April 2016].
5. Shaheen SO, Newson RB, Sherriff A, Henderson AJ, Heron JE, Burney PG, Golding J. Paracetamol use in pregnancy and wheezing in early childhood. *Thorax* 2002;57: 958–963.
6. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six sources of life. *N Engl J Med* 1995;332:133–138.
7. Shaheen SO, Newson RB, Henderson AJ, Headley JE, Stratton FD, Jones RW, Strachan DP. Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. *Clin Exp Allergy* 2005;35: 18–25.
8. Perzanowski M, Miller R, Tang D, Ali D, Garfinkel RS, Chew GL, Goldstein IF, et al. Prenatal acetaminophen exposure and risk of wheeze at age 5 sources in an urban low-income cohort. *Thorax* 2010;65:118–123.
9. Goksoör E, Thengilsdottir H, Alm B, Norvenius G, Wennergren G. Prenatal paracetamol exposure and risk of wheeze at preschool age. *Acta Paediatr* 2011;100:1567–1571.
10. Rebordosa C, Kogevinas M, Sorensen HT, Olsen J. Prenatal exposure to paracetamol and risk of wheezing and asthma in children: a birth cohort study. *Int J Epidemiol* 2008;37:583–590.
11. Garcia-Marcos L, Sanchez-Solis M, Perez-Fernandez V, Pastor-Vivero MD, Mondejar-Lopez P, Valverde-Molina J. Is the effect of prenatal paracetamol exposure on wheezing in preschool children modified by asthma in the mother? *Int Arch Allergy Immunol* 2009;149:33–37.
12. Evers S, Weatherall M, Jefferies S, Beasley R. Paracetamol in pregnancy and the risk of wheezing in offspring: a systematic review and meta-analysis. *Clin Exp Allergy* 2011;41:482–489.
13. Kang EM, Lundsberg LS, Illuzzi JL, Bracken MB. Prenatal exposure to acetaminophen and asthma in children. *Obstet Gynecol* 2009;114:1295–1306.
14. Migliore E, Zugna D, Galassi C, Merletti F, Gagliardi L, Rasero L, Trevisan M, et al. Prenatal paracetamol exposure and wheezing in childhood: Causation or confounding? *Plos One* 2015 Aug 25;10(8):e0135775.doi:1371.
15. Beasley R, Clayton T, Crane J, Von Mutius E, Lai CK, Montefort S, Stewart A. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6–7 sources: analysis from Phase Three of the ISAAC programme. *Lancet* 2008;372:1039–1048.
16. Beasley RW, Clayton TO, Crane J, Lai CKW, Montefort SR, von Mutius E, Stewart AW. Acetaminophen use and risk of asthma, rhinoconjunctivitis and eczema in adolescents: ISAAC Phase Three. *Am J Respir Crit Care Med* 2011;183:171–178.
17. González-Barcala FJ, Pertega S, Pérez Castro T, Sampedro M, Sánchez Lastres J, San José González MA, Bamonde L, et al. Exposure to paracetamol and asthma symptoms. *Eur J Public Health* 2013;23:706–710.
18. Lowe AJ, Carlin JB, Bennett CM, Hosking CS, Allen KJ, Robertson CF, Axelrad C, et al. Paracetamol use in early life and asthma: prospective birth cohort study. *Br Med J* 2010;341:c4616.
19. Bakkeheim E, Mowinckel P, Carlsen KH, Håland G, Carlsen KC. Paracetamol in early infancy: the risk of childhood allergy and asthma. *Acta Paediatr* 2011;100: 90–96.
20. Amberbir A, Medhin G, Hanlon C, Britton J, Davey G and Venn A. Effects of early life paracetamol use on the incidence of allergic disease and sensitization: 5 Source follow-up of an Ethiopian birth cohort. *PLoS One* 2014; 9: e93869.
21. Sordillo JE, Scirica CV, Rifas-Shiman SL, Gillman MW, Bunyavanich S, Camargo CA Jr, Weiss ST, et al. Prenatal and infant exposure to acetaminophen and ibuprofen and the risk for wheeze and asthma in children. *J Allergy Clin Immunol* 2015 Feb;135:441–448.
22. Shaheen SO, Sterne JAC, Songhurst CE, Burney PG. Frequent paracetamol use and asthma in adults. *Thorax* 2000;55:266–270.
23. Barr RG, Wentowski CC, Curhan GC, Somers SC, Stampfer MJ, Schwartz J, Speizer FE, et al. Prospective study of acetaminophen use and newly diagnosed asthma among women. *Am J Respir Crit Care Med* 2004;169: 836–841.
24. McKeever TM, Lewis SA, Smith HA, Burney P, Britton JR, Cassano PA. The association of acetaminophen, aspirin, and ibuprofen with respiratory disease and lung function. *Am J Respir Crit Care Med* 2005; 171: 966–971.
25. Thomsen SF, Kyvik KO, Skadhauge L, Steffensen I, Backer V. Intake of paracetamol and risk of asthma in adults. *J Asthma* 2008;45:675–676.
26. Shaheen S, Potts J, Gnatiuc L, Makowska J, Kowalski ML, Joos G, van Zele T, et al. The relation between paracetamol use and asthma: a GA2LEN European case-control study. *Eur Respir J* 2008; 32:1231–1236.
27. Ioannides SJ, Williams M, Jefferies S, Perrin K, Weatherall M, Siebers R, Crane J, Patel M, Travers J, Shirtcliffe P, Beasley R. Randomised placebo controlled study of the effect of paracetamol on asthma severity in adults. *BMJ Open* 2014; 4:e004324.
28. Eneli I, Sadri K, Camargo C JR, Barr RG. Acetaminophen and the risk of asthma: the epidemiologic and pathophysiologic evidence. *Chest* 2005;127:604–612.
29. Farquhar H, Stewart A, Mitchell E, Crane J, Evers S, Weatherall M, Beasley R. The role of paracetamol in the pathogenesis of asthma. *Clin Exp Allergy* 2010;40: 32–41.
30. Nuttall SL, Khan JN, Thorpe GH, Langford N, Kendall MJ. The impact of therapeutic doses of paracetamol on serum total antioxidant capacity. *J Clin Pharm Ther* 2003;28:289–294.
31. 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;95:3071–3076.

32. Baudouin SV, Howdle P, O'Grady JG, Webster NR. Acute lung injury in fulminant hepatic failure following paracetamol poisoning. *Thorax* 1995;50:399–402.
33. Koelsch M, Mallak R, Graham GG, Kajer T, Milligan MK, Nguyen LQ, Newsham DW, et al. Acetaminophen (paracetamol) inhibits myeloperoxidase-catalyzed oxidant production and biological damage at therapeutically achievable concentrations. *Biochem Pharmacol* 2010;79:1156–1164.
34. Nassini R, Materazzi S, André E, Sartiani L, Aldini G, Trevisani M, Carnini C, 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;24:4904–4916.
35. De Paramo BJ, Gancedo SQ, Cuevas M, Camo IP, Martin JA, Cosmes EL. Paracetamol hypersensitivity. *Ann Allergy Asthma Immunol* 2000;85:508–511.
36. Karimi K, Kebler T, Thiele K, Ramisch K, Erhardt A, Huebener P, Barikbin R, et al. Prenatal acetaminophen induces liver toxicity in dams, reduces fetal liver stem cells, and increases airway inflammation in adult offspring. *J Hepatol* 2015;62:1085–1091.
37. Etminan M, Sadatsafavi M, Jafari S, Doyle-Waters M, Aminzadeh K, Fitzgerald JM. Acetaminophen use and the risk of asthma in children and adults: a systematic review and metaanalysis. *Chest* 2009;136:1316–1323.
38. Cheelo M, Lodge J, Dharmage SC, Simpson JA, Matheson M, Heinrich J, Lowe AL. Paracetamol exposure in pregnancy and early childhood and development of childhood asthma: a systematic review and meta-analysis. *Arch Dis Child* 2015;100:81–89.
39. Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. *JAMA* 1995;273:929–933.
40. Lesko SM, Louik C, Vezina RM, Mitchell AA. Asthma morbidity after the short-term use of ibuprofen in children. *Pediatrics* 2002;109:e20.
41. 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* 48 2013;52:42–48.