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Paracetamol Use in Early Life and Link to Childhood Asthma: A Systematic Review

Miranda Prejean

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Paracetamol Use in Early Life and Link to Childhood Asthma: A Systematic Review

Abstract

Background: Exposure to paracetamol in the first two years of life may increase the risk of developing asthma in childhood. Recent epidemiologic studies have identified an increased risk of asthma with paracetamol use. Quantifying the relationship between paracetamol use and risk of asthma in children was investigated. In previous systematic reviews and metaanalysis, results have been conflicting; studies have had inconsistent confounders, size, and no use of control groups.

Method: An exhaustive search of all the available medical literature was conducted using 4 databases, Medline-OVID, CINAHL, EBMR Multifile and Web of Science to identify pertinent articles. All clinical trials and observational studies were considered. For observational studies, those that clearly defined paracetamol exposure in the first two years of life and asthma diagnosis as a child (5-7) years were selected. Study quality was assessed with GRADE criteria.

Results: Three birth cohort studies, and one multicenter cross-sectional ranging from 469 to 205 487 participants, from birth up to two years of life were included in the review that were later followed up between 5-7.5 years of age. In the large multicenter study after adjustments for sex, region of world, language and income, multivariate analysis with complete data only and risk of asthma in childhood and total days of paracetamol use in early life for fever was (OR 1.46 [95%CI 1.36-1.56]). In the largest birth cohort when adjusted for maternal factors in pregnancy and postnatal factors there was no significant effects of paracetamol use and childhood asthma (OR 1.11 [95%CI 1.00-1.23]). In this same study when children who had preexisting wheeze versus no wheeze, and effects of paracetamol and childhood asthma, there was a significant association for child with wheeze (OR 1.44[95%CI 1.13-1.83]). When adjustments were made for frequency of respiratory tract infections and total days of paracetamol use any indication in the other smaller birth cohort, there was no significance in a child with family history of atopy (OR 1.08 [95% CI 0.91-1.29]). In the smallest of studies included, after adjustments for chest infections, antibiotic use, and family history of atopy, there was no significance of childhood asthma and exposure to paracetamol (OR 1.78[95%CI .75-4.21]).

Conclusion: The results from the review are inconsistent. It is suggested that exposure to paracetamol in the first years of life might be a risk factor for the development of asthma in childhood and direct causation is still questionable. Results do suggest that children with family history of atopy, or current asthma, and the use of paracetamol may precipitate asthma. Future RCT studies are needed.

Keywords: Paracetamol, acetaminophen, asthma, child, infant.

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Paracetamol Use in Early Life and Link to Childhood Asthma: A Systematic Review

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A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 11th, 2012

Faculty Advisor: James Ferguson, PA-C, MPH
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Biography

[Information redacted for privacy]
Abstract

**Background:** Exposure to paracetamol in the first two years of life may increase the risk of developing asthma in childhood. Recent epidemiologic studies have identified an increased risk of asthma with paracetamol use. Quantifying the relationship between paracetamol use and risk of asthma in children was investigated. In previous systematic reviews and metaanalysis, results have been conflicting; studies have had inconsistent confounders, size, and no use of control groups.

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**Conclusion:** The results from the review are inconsistent. It is suggested that exposure to paracetamol in the first years of life might be a risk factor for the development of asthma in childhood and direct causation is still questionable. Results do suggest that children with family history of atopy, or current asthma, and the use of paracetamol may precipitate asthma. Future RCT studies are needed.

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Table I: Grading of Recommendations Assessment, Development and Evaluation (GRADE), Characteristics of Reviewed Studies

Table II: Summary of Findings

List of Abbreviations

AAP……………………………………………………..American Academy of Pediatrics
ALSPAC………………………………Avon Longitudinal Study of Parents and Children
BMI………………………………………………………………………Body mass index
CI…………………………………………………………………..…..Confidence Interval
GRADE… …….Grading of Recommendations Assessment, Development and Evaluation
ISAAC……… …………...……International Study of Asthma and Allergies in Childhood
OR…………………………………………………………………………..…..Odds Ratio
RCT……………………………………………………………. Randomized Control Trial

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Appendix A……………………………………………………. ISAAC Sample Questionnaire
Paracetamol Use in Early Life and Link to Childhood Asthma: A Systematic Review

BACKGROUND

Asthma has become one of the most common disorders among children. Reasons for the increase in asthma over recent decades and international patterns of asthma prevalence are poorly understood and cannot be adequately explained by current knowledge of the causation of asthma. Epidemiologic studies have demonstrated a higher prevalence of asthma in more developed countries than developing countries. This has led to the investigation of the role of risk factors that may increase susceptibility to the development of asthma. Attracting recent interest, but lacking study support, is the hypothesis that paracetamol (commonly named acetaminophen in the United States) use might increase the risk of asthma.

Other risk factors and possible causes of asthma in the first years of life that have been investigated include: respiratory infections, family history or early childhood atopy symptoms, antibiotic use, pollution, and toxins. Respiratory infections are among the more known substantial risk factors for asthma and are important contributors to clinical indices for the predictions of asthma risk in childhood. As well as a common reason for ingesting paracetamol. Moreover, dietary changes are a suspect, with a decrease in antioxidant rich diets, reducing levels of pulmonary antioxidants and making the lungs more susceptible to oxidative stress. Interesting enough, there has been a link to pharmaceutical sales of paracetamol and the asthma epidemic. Despite major research efforts and the importance of these many risk factors in development of asthma, the exact cause of asthma still remains uncertain.
Evidence to date implicating paracetamol in the etiology of asthma has been consistent with adverse effects reported in paracetamol exposure in utero, during infancy, in childhood, and during adult life. These studies previously mentioned have relied on retrospective data collection and failed to account for and adjust for common confounders leading to inconsistencies.

Paracetamol is the preferred drug to relieve pain and fever in children under 6 months of age. Some evidence may suggest that ingestion of paracetamol early in life may cause asthma. Possibly the shift from aspirin to paracetamol use may have contributed to the rise in childhood asthma. Paracetamol use became prevalent when it replaced aspirin particularly in children at risk for Reyes syndrome, which can damage the brain and liver, with the use of aspirin to treat chickenpox and flu in infants. Paracetamol emerged as the safer alternative for children at this time. Since that time, the increase of incidence of asthma in the US went from 3.6% to 5.8% and similar increases were seen throughout the world. Time may be revealing paracetamol’s danger, its use has paralleled the rise in asthma prevalence in children. Along with other factors such as a decrease in physical activity, increase in obesity and the amount of time spent indoors, and increase in the use of group daycare. The trend is noteworthy that asthma prevalence leveled off in the 1990’s when paracetamol was already the most common used analgesic for children. In addition to risk factors coexisting with paracetamol intake, it may be contained under multiple names or combinations. Paracetamol was found under 64 names in the Kang et al study. These factors have resulted in much confusion in determining if paracetamol causes asthma.
Paracetamol use has three common proposed mechanisms for causing asthma.\textsuperscript{25,28} It has been thought to be a risk for asthma because this agent induces depletion of antioxidant rich glutathione in lung tissue. Oxidative damage to the lungs may occur more readily and low glutathione levels may lead to defective antigen processing, thereby promoting the Th2 allergic pathway during a critical time in immune system development.\textsuperscript{29} This process might be critical to consider when giving paracetamol to a young child with under developed lungs during a respiratory infection. Secondly, there may be higher production of prostaglandin E2 and suppression of the COX-2 receptor, both of which favor the Th2 allergic pathway over a Th 1 immune response. Furthermore, this impaired Th1 response, can result in an inability to clear infections.\textsuperscript{30} Thirdly, the paracetamol molecule has similar molecular weight to chemicals known to cause asthma from occupational exposures.\textsuperscript{28}

A systematic review was conducted in 2008 which looked at 8 studies in children and their exposure to paracetamol and incidence of wheeze or asthma.\textsuperscript{31} It concluded that the results were consistent with an increase in the risk of asthma in children and adults with early and concurrent paracetamol use and it was recommended that future studies are needed.

Dr. John T. McBride, in a recent report for PEDIATRICS, the Official Journal of the American Academy of Pediatrics (AAP), sends a warning about paracetamol and its relationship with asthma. He stated in the December 2011 issue\textsuperscript{32} that “I need further studies not to prove that acetaminophen is dangerous but rather to prove that it is safe," McBride concludes in his report. "Until such evidence is forthcoming, I will recommend avoidance of acetaminophen by all children with asthma or those at risk of asthma.”\textsuperscript{32}
This is a powerful statement and warrants attention to determine if paracetamol use in early life causes asthma.

Therefore, the aim of this systematic review was to determine if recent research since the last systematic review,\textsuperscript{31} has been conducted and to establish what the relationship is between the use of paracetamol early in life and the incidence of childhood asthma. This review will help guide our prescribing of paracetamol, and make patients, parents and primary care providers aware of the possibility that paracetamol exposure may have dangerous side effects.

**METHOD**

An exhaustive search of the medical literature was conducted using 4 databases, Medline-OVID, CINAHL, EBMR Multifile and Web of Science. The following terms were used to narrow the search: “paracetamol/paracetamol and asthma”, and “infant or child”. Duplicates were removed. The search was then narrowed using the following eligibility criteria: inclusion of articles in the English language, on human subjects, and published after the year 2008. Studies were also excluded if they were not relevant or did not evaluate paracetamol ingestion in the first 2 years of life and incidence of asthma in childhood. For this review childhood was defined as 5-7 years old, which asthma symptoms at this age have been shown to predict adult asthma.\textsuperscript{33} The works cited of the articles were further searched for relevant sources. The articles in this review were assessed for quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) developed by the GRADE Working Group.\textsuperscript{34}

**RESULTS**

Initial result of the search yielded 206 articles for review. One hundred thirty three
articles were excluded as duplicates, leaving 73 articles. After exclusions were applied only 4 studies were included in qualitative synthesis. These articles included 3 birth cohort, and one multicenter, cross sectional study used for its strength in numbers.

**Lowe et al**

In this prospective birth cohort study,\(^{35}\) paracetamol use in early life and asthma was assessed in 620 infants. They were recruited before birth and enrolled in the Melbourne Atopy Cohort Study. Infants were eligible to be enrolled if one or more of their first degree family members had eczema, asthma, allergic rhinitis, or severe food allergy. A telephone survey was performed every four weeks until the age of 64 weeks, then 78 weeks, and age of 2. An annual telephone interview was performed from 3 to 7 years of age. Illnesses since previous interview, oral exposures to food or medicine, including paracetamol, were all documented. The classification of indications for the exposure to paracetamol was tracked, to include number of episodes, days of use, and reason for administration. These were recorded for each exposure. For each child the classified reason for use of paracetamol for each episode of illness was put into one of four categories. Parental report of contact with medical professionals for infection was also documented. The number of days of exposure to paracetamol for each child regardless of dose or frequency within the first two years of life was recorded, including any preparation that contained paracetamol. Current childhood asthma for this study was defined as one or more episodes of asthma diagnosed by a family physician in the previous 12 months, this was the primary outcome. Infantile wheeze was a parental report of a doctor diagnosis of an asthma-like condition before 2. Standard confounders adjusted for were infants sex, parental history of asthma or eczema, and presence of older siblings
at the time of birth. The final model made adjustments for frequency of medical contact for infections (otitis media, upper respiratory tract infection, bronchitis, and gastroenteritis).  

Twenty five were lost to follow up, 14 refused, 6 missed but rejoined later. A total of 495 completed follow up at 6 or 7 years or both. A questionnaire at 6 or 7 years was filled out to ascertain childhood asthma or other atopic conditions, allergic rhinitis, eczema, and indications for paracetamol use was also tracked, lower or upper respiratory tract symptoms, non respiratory illness or any indication. Associations between total days of paracetamol use for any indication during early life and risk of allergic disease, as well as associations between paracetamol intake for non respiratory causes during early life and risk of allergic disease later in childhood were adjusted for.  

During the first two years of life 97% of infants received paracetamol, on average the median total number of days of exposure was 17, and most, 537, were exposed to paracetamol for non respiratory illness. The next most common reason for use was upper respiratory tract symptoms, 510. At age 6-7 29.9% had current childhood asthma diagnosed as described earlier by a doctor. Children who had current childhood asthma or allergic rhinitis total number of days of paracetamol use in the first two years was slightly higher. The unadjusted regression analysis showed a greater number of days of paracetamol exposure (all cause), had increased risk of childhood asthma OR 1.18 (1.00-1.39). Adjustment for standard confounders in this study did not alter observed associations. Adjustment for frequency of respiratory tract infections strengthened the association with childhood asthma 1.08 (.91-1.29), leaving no evidence of an independent association of asthma and infantile paracetamol use.
There was no evidence of any association between paracetamol use for non-respiratory illness and risk of any allergic disease outcome. Paracetamol use for lower respiratory tract illness (defined as infantile wheeze, bronchitis, drugs for lower respiratory tract illness) when compared to upper respiratory tract illness was strongly associated with increased risk of childhood asthma OR 1.49 (1.25-1.78), 244 children had lower respiratory tract symptoms, 43% received paracetamol for the symptoms. When analysis was restricted to the subgroup who had lower respiratory tract symptoms, minimal evidence that any use category 1.16 (.68-1.98) or frequent use 1.12 (.91-1.38) for lower respiratory tract symptoms was associated with increased risk of childhood asthma.35

Paracetamol use for upper respiratory tract symptoms was associated with increased risk of childhood asthma OR 1.20 (1.05-1.38). Only 2.4% of children did not have upper respiratory tract symptoms within the first two years of life. The number of events of upper respiratory tract symptoms strongly related to increased risk of childhood asthma, when adjusted, days of paracetamol use for upper respiratory tract symptoms, for number of events, the evidence of association was strengthened 1.10 (.95-1.28).35

The authors concluded consistent results with previous studies in this area, finding evidence of a weak or “crude” association between paracetamol use in early life and increased asthma. Lowes et al study classified indications for exposure to paracetamol, it showed no evidence of association after adjustments were made for history of early infections, or when association was limited to paracetamol use for non respiratory tract illness. Although use of paracetamol for lower respiratory tract infections and wheeze was associated with increased risk of allergic disease, increasing days of use did not
increase risk of allergic disease. It was concluded by the authors that paracetamol use in early life is not an independent risk factor for childhood asthma.35

Beasley et al

This study36 was a multicenter, cross sectional study of school children, and the association between paracetamol use in infancy and childhood and the risk of asthma. International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three studied 6-7 year old children, a multicountry cross sectional study, who were chosen from a random sample of schools in defined geographical areas. Standardized questionnaires (see Appendix) were completed by the parents or guardian, the first being about asthma symptoms and the second an environmental questionnaire about possible protective and risk factors for development of allergic disease. Demographic information was gathered and paracetamol use in the first year of life and in the past 12 months was obtained. Questionnaires when necessary were translated into the local language. A positive response was referred to as reported use of paracetamol for fever in the first year of life. Symptom of wheeze were identified by a positive answer to the question “Has your child had wheezing or whistling in the chest in the past 12 months?” Severe asthma symptoms were identified by one or more answers to “How many attacks of wheezing has your child had in past 12 months?” The study sponsors had no role in study design, data collection, analysis, data interpretation, writing of the report, or in the decision to submit the paper for publication. The authors were responsible to write and submit the manuscript for publication with the ISAAC Phase Three Steering Group.36

To date this is the largest study to consider this question, 205 487 children, 73 centers, and 31 countries, 194 555 children aged 6-7 from 69 centers in 29 countries were
included in the analysis of paracetamol use for fever during first year of life. Multivariate analysis included 105,041 children, 47 centers, 20 countries. To be included in the analysis, centers had to assess at least 1000 children and have a response rate of more than 60%. Analysis of all study participants were adjusted for sex, region of world, language, and gross international income. Analyses were done separate for paracetamol use in first year of life and at 6-7 years. In the multivariate analysis, children who had a missing value for any of the covariates (maternal education, antibiotic use in first year of life, ever breast fed, parental smoking, current diet, and siblings) were removed.  

Reported results were that use of paracetamol was associated with a significantly increased risk of asthma symptoms, the risk was similar in all children, and in those with complete covariate data, 1.76 (1.68-1.85) and 1.77 (1.66-1.89) respectively. In the multivariate analysis, the reported use of paracetamol for fever in the first year of life was also associated with a significantly increased risk of current asthma symptoms, 1.46 (1.36-1.56). The risk of asthma symptoms was increased in different countries worldwide, p value for homogeneity between regions was <0.005. For the 47 centers combined, the population attributable risk for asthma symptoms due to paracetamol use for fever in the first year of life was 21%. The reported use of paracetamol for fever in the first year of life was also associated with a significantly increased risk of severe asthma symptoms, adjusted 1.82 (1.70-1.95), complete covariate data 1.82 (1.65-2.00), and multivariate 1.43 (1.30-1.58). The increase in the risk for severe asthma symptoms was similar to that for current wheeze. In the 47 centers combined, the population attributable risk for severe asthma symptoms due to paracetamol use for fever in the first year of life was
year of life was 22%. This study also reported paracetamol use in the past 12 months, and current use. This data will not be reviewed in this study.\textsuperscript{36}

The authors concluded from this study that the use of paracetamol for fever in the first year of life is associated with symptoms of asthma in childhood worldwide. Associations between use of paracetamol in the first year of life and the risk of severe asthma symptoms with population attributable risks were also identified. Causality cannot be established from a study with this design, the authors “suggest that exposure to paracetamol might be an important putative risk factor for the development of asthma.” They also state evidence is insufficient to advise parents and health care workers of the risk benefit of taking paracetamol in childhood, or its comparative efficacy and safety with other approaches. Further research was also advised.\textsuperscript{36}

\textbf{Wickens et al}

This study\textsuperscript{37} was a birth observational study that reported paracetamol exposure between birth and 15 months, data was collected during this time and between 5-6 years of age. This was part of the New Zealand Asthma and Allergy Cohort Study, mothers were recruited during pregnancy through a random sample of midwives in Wellington and Christchurch New Zealand. Study nurses administered questionnaires at recruitment, 3 and 15 months, and yearly until 6 years. Family history of the person completing the questionnaire, usually the mother was collected, and questions about the biological father were asked only if he was part of the household. Adjustments were made for family history, 11 households were excluded where the father was absent, and participants with missing data were not entered. Participants were assessed in their home at 3 and 15 months, and at the research facilities in each center at 6 years. At each contact,
prevalence of wheeze, hayfever, rhinitis symptoms, and eczema were assessed using the standard questions from the ISAAC questionnaire (See Appendix A). The recall period was restated as, since the last questionnaire to ensure continuity of data. Prevalence rates of diagnosed asthma were reported as history of diagnosed asthma ever, plus a reported history in last 12 months of either wheeze or inhaler use, or both. The indicators of severe asthma symptoms were speech limiting wheeze and sleep disturbance due to wheeze. Children with non severe wheeze were classified together with children without wheeze, as non–cases. Wheeze was characterized as transient (only in first 3 years), late onset (wheeze occurring between 3 and 6 only), persistent (in the first 3 years of life and between 3 and 6 years), and never. Atopy conditions were assessed with skin prick testing and serum samples obtained analyzing IgE, these test results will not be investigated further in this review.37

At 3 and 15 months, only the Christchurch center had collected data on whether or not paracetamol had been used. The Wellington center had commenced the study before the paracetamol hypotheses. At 6 years, the number of doses of paracetamol taken during the last 5 years was collected. The Christchurch center recruited 553 subjects, 535 at 3 months, 505 at 15 months, and 473 at 6 years. Data at both 15 months and 6 years was 469 (84.8%) of recruited participants. Among the Christchurch center children, 89.9% had received at least one dose of paracetamol by 15 months of age. Models were constructed for paracetamol exposure from birth to 15 months, and adjusted for number of chest infections and systemic antibiotics, gender, family history, parity, birth weight, maternal age, maternal smoking during pregnancy and any household exposure to smoking or second hand smoke.37
The odds ratios (OR) were elevated for effects of early paracetamol use on current asthma and wheeze at 6 years, adjusted OR 1.78 (.75-4.21), and strengthened in the subgroup with atopic current asthma, adjusted OR 4.13 (.93-18.48), with both almost reaching significance. The number of participants meeting severe asthma symptoms and criteria were too small to analyze. Both environmental tobacco smoke and paracetamol may influence the development or severity of asthma through depleting glutathione levels.38 Results of whether or not environmental smoke (as a independent risk factor) at 15 months modified the relationship between paracetamol and wheeze were analyzed, but found no significant interactive effect (P=.53).37

The authors of this study concluded that children in the Christchurch center who had used paracetamol before 15 months (89.9%) were more than three times likely to be atopic at 6 years than children not using paracetamol in infancy. The effects of paracetamol on current asthma or wheeze at 5-6 years old although elevated, were not statistically significant before and after adjustments. Direct causation has not been established and the maintenance of asthma symptoms with paracetamol.37

Shaheen et al

This is a population based birth cohort39 that recruited 14 541 pregnant women residing in Avon, United Kingdom, which is also referred to as the Avon Longitudinal Study of Parents and Children, (ALSPAC) cohort. Of these births, 13 988 of these children were alive at age 1 year and followed up. The cohort has been followed since birth with annual questionnaires and until age 7 years with objective measures in annual research clinics. At six months after birth, mothers were asked how often they had given their infant paracetamol since birth (never, once, more than once). Additional information
was gathered during intrauterine including genotyping, this data and studied results will not be discussed in this review. Only specific data collection and studied results that met the search criteria from this study will be included.\textsuperscript{39}

When children were 7.5 years old mothers were asked, “Has your child had any of the following in the past 12 months: wheezing, asthma, eczema, hay fever?” Children were defined as having current doctor diagnosed asthma at 7.5 years if mothers responded positively to the question, “Has a doctor ever actually said that your study child has asthma?” and mom had responded positively to 1 or both of the questions on wheezing and asthma in the past 12 months. Paracetamol exposure in infancy propensity scores were defined by a list of confounders as predictive factors, the propensity score for this study was a measure of paracetamol proneness of infants based on a list of confounding variables: maternal factors during pregnancy, smoking infections, anxiety score, antibiotic use, alcohol intake educational level, housing tenure, financial difficulties, BMI, ethnicity, age, parity, history of asthma, eczema, rhinoconjunctivitis, migraine, sex of child, season of birth, multiple pregnancy, gestational age, birth weight, head circumference, birth length, and postnatal factors breast feeding, day care, pets, damp/mold, environmental tobacco smoke exposure, number of younger siblings, and BMI at age 7. In the analyses of infant paracetamol exposure, maternal paracetamol use in pregnancy and use of antibiotics in the first 6 months after birth were controlled for and the confounders used to generate aforementioned paracetamol propensity scores.\textsuperscript{39}

Of 11 438 infants with data on infant paracetamol use, 14% had not received the drug in the first 6 months after birth, 20% were given it once, 66% were given it on 2 or more occasions. The unadjusted effects of infant paracetamol use on childhood asthma was
1.19 (1.08-1.32), and adjusted was 1.11 (1.00-1.23). When controlled just for prenatal paracetamol exposure the association between infant use and asthma was attenuated a little, OR reduced from 1.19-1.16. After controlling for all confounders, infant use was associated with an increased risk of childhood asthma. When stratified, the risks of asthma were greater in children who wheezed in infancy.\(^{39}\) 1.44 (1.13-1.83).

The authors concluded that a longitudinal association with childhood asthma was independent of prenatal paracetamol exposure. It was limited to children who had wheezed in infancy, most likely explained by the fact that infants who already have a wheezing tendency are more likely to be given paracetamol for viral respiratory infections with fever. The authors also recommend confirmation of data with experimental studies in animals, which could provide supportive evidence, with human studies as definitive evidence. They recommended randomized controlled trials (RCT) which have their own challenges.\(^ {40}\)

**DISCUSSION**

Implications for practice are still unclear. Findings were not significant for childhood asthma when adjusted in the infant exposure group for infections and other confounders. There was significance in the exposure group when not adjusted for indication of use, frequency and dosing, and specificity of febrile illness. It is unknown if the benefits outweigh the risks. Of the four articles included in this systematic review, the overall combined quality of evidence as evaluated by GRADE is very low. At this time a weak recommendation is warranted. Paracetamol should be used with caution and sparingly to the infant with preexisting wheeze or risk of asthma under six months of age as described by the Shaheen et al study.\(^ {40}\) In children up to 2 with family history of atopy.
that are currently asymptomatic, there is no significant difference in childhood asthma
with use of acetaminophen as shown by Lowe et al.\textsuperscript{41} It should be clear that results from
the present studies reveal that paracetamol has no beneficial effect on disease outcomes
when used as an antipyretic. Is it worth taking unknown risks without knowing
alternative benefits of treatment?

Current clinical practice should question the indications of use for paracetamol
and what the risks are. In considering the risks and benefits of paracetamol use with the
need for clearly stated implications in practice from studies, moving forward with its use
should be done with caution. With some studies suggesting indications of precipitating
asthma prevalence in adolescence, and the weak correlation of causing asthma symptoms,
the suggestions from McBride last month in PEDIATRICS are warranted.\textsuperscript{32} Treating
current asthmatic infants and children and those who are at risk for developing asthma
should be done with caution and not at all when possible when choosing paracetamol as
the analgesic or antipyretic of choice. Guidelines for its indication of use are unclear. Its
use in febrile illness needs further investigation. Confounders of prenatal use, concurrent
antibiotic use, infection rate, particularly respiratory infections as a risk factor for asthma
need to be researched. A family history of atopy or current symptoms of allergic disease,
along with other risk factors need to be considered also.

Lowe et al\textsuperscript{41} demonstrated that after making adjustments for frequency of
infections, there was no significance when compared to the unadjusted group for
paracetamol exposure. To be included in this study the child must have had a first degree
relative with history of atopy or allergic disease, this could have limitations in eligibility
criteria for the study. All participants were exposed to at least one dose of paracetamol
with no control due to the nature of the observational study. Frequency of exposure to paracetamol and indication of use were important outcomes considered in this study and demonstrated a strength of design. There was less recall bias with the prospective design of this study and frequent follow up. Confounders were controlled for all participants and considered in the indication of use analysis so the results were able to be adjusted for frequency of infections and standard adjustments. The evidence reported by Lowe et al for any indication and non respiratory causes were examined, when confounders were adjusted there was no significant difference in paracetamol exposure. This is the only study in the review that offered valuable data of indication of use and adjustment for respiratory infections that is a known risk factor for asthma. The evidence from this study does not support the conclusion that paracetamol exposure is a causal factor for asthma.

However, this study is not without limitations. Since this study only included children with family history of atopy, the results need to be applied to the general population with care. Another limit to this study is that parental report of asthma symptoms is relied upon as opposed to a doctor diagnosis of asthma. This could be a weakness or strength, minimizing bias and differences in healthcare practices in some cases, or some cases of asthma may have been missed. As with other birth cohort observational studies in the review, no use of placebo was possible, it is anticipated that there would be widespread non compliance, and it may be unethical to ask participants to not use paracetamol with their infant. As an observational study, this study started off with a low GRADE quality of data. This study received a downgrade for failure to include control population, selection of biased exposed group with atopy, and confidence intervals when adjustments were made include no effect or appreciable benefit or harm.
This study receives an upgrade for its use of relevant confounders adjusted for in analyzing risk of asthma. The quality of evidence in this study was then given an overall GRADE of very low, with an overall significance rating of “critical”.

Beasley et al\textsuperscript{36} demonstrated that use of paracetamol for fever in the first year of life was associated with an increased risk of asthma symptoms with a multivariate analyses. The evidence reported supports the hypothesis that paracetamol presents as a risk factor for asthma. The strengths of this study were its power, size, and its multinational nature. This study received an upgrade for having such a large sample size. It was included in this review for these purposes and it met inclusion criteria but it should be noted that it is the oldest of the studies considered with the fewest confounders. This study did not look at indications of use for paracetamol, respiratory infections in early life, specifically a known risk factor for asthma. Due to the nature of the study, recall bias could exist, and it should be considered that parents of children with asthma are more likely to report paracetamol use. Frequency or dose response in the first year of life was not examined, only current frequency of use was looked at. Current use of paracetamol was associated with a dose dependent increased risk of asthma symptoms. Although a surrogate outcome of interest, this deserves an upgrade of one. Because of the nature of this large multinational study, it should be considered that paracetamol comes in different names and combinations. Off label use and dosing differences internationally were not considered. English translation of questionnaires could have affected the validity of the study when interpreted. Parental report of asthma symptoms could have excluded or included participants. Due to the observational nature of this study it started off with a low GRADE quality of data. This study received a single downgrade for
having no control group, lack of relevant confounders, no information on indication for use, and questionable validity with translation of questionnaires. It should be noted that no adjustments or considerations were made for the use of different names for paracetamol or combinations of it internationally, or its off label use.36

There was little or no bias by limiting the multivariate analysis to children with complete covariate data, greater than 70%. Sensitivity analyses were performed adjusting the association between paracetamol use for fever in the first year of life and symptoms of asthma later in childhood for paracetamol use in the past 12 months and vice versa.36 Although indications for use in infancy were not analyzed it should be noted that paracetamol use for febrile illness was indicated, there are many causes of febrile illness in infancy, including respiratory tract illness, and unrelated illnesses to respiratory tract, paracetamol use for such episodes could cause confounding in this study.

Questionnaires were translated to native language and then back to English, completed by parents, and retrospectively gathered, which contribute to the recall bias. Poor recall could reduce the ability to measure any effect of paracetamol, and there were no differences in parents of children with asthma than those without when adjustments were made. No emphasis was given to a paracetamol question in the ISAAC study questionnaire (see Appendix A), eliminating source of bias. Parent reported symptoms of asthma were used. This was explained in this large study in developed and undeveloped countries to avoid major diagnosis differences related to access to medical care, language barrier, and medical practice population changes. Since all important plausible confounding were not considered, the demonstrated association between paracetamol use and asthma was overestimated. This will decrease the quality of evidence by one.
The data from this study has contributed to establishing whether what risk factors exist for developing asthma worldwide, their prevalence and frequency, while considering the nature of childhood febrile disorders, different medical practices, health behaviors, environment, and lifestyle. The overall GRADE of this study still is very low, with an overall significance rating of “critical.”

In the Wickens et al42 study paracetamol questions were only asked at the Christchurch center in this study, so data was limited, study sample size was reduced to half. The Wellington center had already commenced the study and questionnaire portion prior to considering the paracetamol hypothesis. To ensure continuity of data from questionnaires in the event that participants had answered the questionnaire earlier or later than the target date, the recall period was changed to “since last telephone conversation”. No data was collected for indication of use of paracetamol in the first 15 months, but data was independent of both lower respiratory tract infection and antibiotic use. When confounded for it still was not significantly significant. Imprecision was controlled for with exact definitions and categories for wheeze defined, and asthma diagnosed by a doctor. There was no collection of information on paracetamol exposure during pregnancy so this could have been confounding with recent studies suggesting increased risk of asthma with intra uterine use of paracetamol.12 Failure of this study to have a control population due to the nature of the study, probability of recall bias, not adequately confounding for indication of use of paracetamol in infancy, and lack of precision seen in the wide CI’s, this study received a downgrade from low at baseline because of its status as an observational study.
The possibility that later use of paracetamol in childhood may maintain asthma symptoms was demonstrated with this study, possibly explained by the glutathione mechanism earlier described. Although not the primary outcome, it cannot be ignored. Reverse causation could contribute to positive associations if paracetamol were used to treat wheeze related illness. Or respiratory infection may have confounded, since they are independently associated with asthma and paracetamol use. Findings from this study raise concern about maintenance of asthma symptoms with current paracetamol use, direct causation in infancy has not been established due to the nature of the study. The quality of evidence in this study was given GRADE of very low, with an overall significance of “critical”.

Shaheen et al\(^4\) significantly significant results were limited to those who had wheezed in infancy only. Asthma was defined when a doctor diagnosed the study child with asthma or wheezing in the past 12 months. An advantage to this study design was the use of propensity scores which reduced the number of model parameters which controlled for confounders to prevent potential nonconvergence of the regression models for infant exposure. The studies data were not complete on exposures, outcomes, or confounders for the whole cohort. Exclusion of children without complete information might have biased findings. Confounding by indication is of concern, it couldn’t be adjusted for because there was no data on indication for paracetamol use during infancy in this study because no one asked why the paracetamol was taken. The possibility that infant paracetamol exposure might contribute to maintenance of asthma symptoms should be considered, but the exposure and results would argue against a causal interpretation. This study confirmed a longitudinal association with childhood asthma, independent of
prenatal paracetamol exposure, it was limited or significant to children in the first 6 months of life that had wheeze. Children who already had a wheeze tendency were more likely to be given paracetamol for viral respiratory infections with fever. The quality of evidence of this study was given a GRADE of very low, with an overall significance rating of “critical”.

In review, due to the nature of the studies being observational without a control group, they were all downgraded to very low quality without the possibility of being upgraded even when considering all plausible confounders or dose response gradient magnitude of effect. Regardless of the GRADE criteria, recall bias and reverse causation need to be considered in the studies results. The large cross sectional study design is limiting in causal interpretation of paracetamol and asthma as well as observational studies have no direct causation due to the nature of the study. Children with wheeze associated with febrile illness and respiratory infection will be given paracetamol as an antipyretic, this should be considered as an important confounder by indication.

CONCLUSION

Further research is warranted. It is likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate. RCT are urgently required to determine whether associations are sufficiently causal to form basis for future recommendations for clinical practice in use of paracetamol in treatment of children.

The results from the studies in this review are inconsistent. It is suggested that exposure to paracetamol in the first years of life might be a risk factor for the development of asthma in childhood and direct causation is still questionable. Consistent studies are needed that use a control group and the same confounders to account for
inconsistencies in the results of current studies. There is some suggestion from the results in this review that children with preexisting wheeze or asthma, and family history of atopy may be at greater risk for childhood asthma when using paracetamol early in life. At this point without further RCT studies, it is unknown if it is causative. Well conducted RCT studies are recommended to further explore the causes of childhood asthma and the risk factor of paracetamol exposure.
References


Table I. Characteristics of Reviewed Studies

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>No of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total days of paracetamol use (any indication) during early life and risk of asthma. Lowe et al. (follow-up 5-7 patient-years; assessed with: Adjusted for frequency of infections)</strong></td>
<td>1 observational studies</td>
<td>serious</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious²</td>
<td>none</td>
<td>☀️⊕ΟΟΟ VERY LOW CRITICAL</td>
</tr>
<tr>
<td><strong>Total days of paracetamol use for fever during first year of life and risk of asthma. Beasley et al. (follow-up 6-7 patient-years; assessed with: Multivariate analysis complete covariate data only)</strong></td>
<td>1 observational studies</td>
<td>serious³</td>
<td>serious⁴</td>
<td>no serious indirectness</td>
<td>serious⁵</td>
<td>none</td>
<td>☀️⊕ΟΟΟ VERY LOW CRITICAL</td>
</tr>
<tr>
<td><strong>Paracetamol use before 15 months and outcome current asthma. Wickens et al. (follow-up 5-6 patient-years; assessed with: Adjusted for chest infections and antibiotic use.)</strong></td>
<td>1 observational studies</td>
<td>serious⁶</td>
<td>no serious inconsistency</td>
<td>serious⁷</td>
<td>serious⁸</td>
<td>none</td>
<td>☀️⊕ΟΟΟ VERY LOW CRITICAL</td>
</tr>
<tr>
<td><strong>Effects of infant acetaminophen use on childhood asthma. Shaheen et al. (follow-up 7.5 patient-years; assessed with: Adjusted for wheeze/no wheeze in first 6 months.)</strong></td>
<td>1 observational studies</td>
<td>serious⁹</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>☀️⊕ΟΟΟ VERY LOW CRITICAL</td>
</tr>
</tbody>
</table>

1 Infant were eligible to be enrolled if one or more of their first degree family members had eczema, asthma, allergic rhinitis, severe food allergy.

2 After adjustment for frequency of infections, not significant 1.08 (0.91-1.29).

3 Failure to adequately control for confounding, no indication of use reported, and recall bias due to multicenter cross sectional study design.

4 Paracetamol is marketed in combinations, and differently internationally, with off label use and dosing differences.

5 No indication of use information gathered, or paracetamol exposure during pregnancy as a confounder.

6 Variability in results with no explanation to the wide confidence intervals in study.

7 Lack of precision with wide confidence intervals, sample size was reduced to half prior to questioning about paracetamol and the start of study.

8 Recall bias, studies data not complete on exposures, outcomes, or confounders for the whole cohort. No indication of acetaminophen use during infancy.
Table II. Summary of Findings

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Age Paracetamol Exposure</th>
<th>Age of Follow Up</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total days of paracetamol use (any indication) during early life and risk of asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowe et al</td>
<td>Birth cohort</td>
<td>620</td>
<td>Up to 2 years with family hx of atopy</td>
<td>5-7 years</td>
<td>Unadjusted</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.18 (1.00 to 1.39)</td>
</tr>
<tr>
<td>Total days of paracetamol use (non respiratory causes) during early life and risk of asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.95 (.81-1.12)</td>
</tr>
<tr>
<td>Total days of paracetamol use for fever during first year of life and risk of asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjusted³</td>
</tr>
<tr>
<td>Beasley et al</td>
<td>Multicenter Cross-Sectional</td>
<td>205 487</td>
<td>First year of life</td>
<td>6-7 years</td>
<td>1.76 (1.68-1.85)</td>
</tr>
<tr>
<td>Total days of paracetamol use for fever during first year of life and risk of severe asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.82 (1.70-1.95)</td>
</tr>
<tr>
<td>Paracetamol use before 15 months and outcome current asthma at 6 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Wickens et al</td>
<td>Birth Cohort</td>
<td>469</td>
<td>Birth to 15 months</td>
<td>5-6 years</td>
<td>1.85 (.81-4.25)</td>
</tr>
<tr>
<td>Paracetamol use before 15 months and outcome of atopy and current asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.35 (.77-14.25)</td>
</tr>
<tr>
<td>Paracetamol use before 15 months and outcome current asthma no atopy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.51 (.43-5.22)</td>
</tr>
<tr>
<td>Effects of infant paracetamol use on childhood asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Shaheen et al</td>
<td>Birth Cohort</td>
<td>7735</td>
<td>Birth to 6 months</td>
<td>7.5 years</td>
<td>1.19 (1.08-1.32)</td>
</tr>
<tr>
<td>Adjusted for wheeze/no wheeze in first 6 months and effects acetaminophen and childhood asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No Wheeze</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.03 (.92-1.16)</td>
</tr>
</tbody>
</table>

1 Infant's sex, parental history of asthma, and presence of older siblings at time of birth
2 Upper and lower respiratory tract infections, otitis media, and gastrointestinal infections during first 2 years of life
3 Adjusted for sex, region of the world, language, and gross national income
4 Adjusted, children with complete covariate data only, adjusted for sex, region of the world, language, and gross national income
5 Multivariate analysis children with complete covariate data only, at least 70% data available for all covariates, children with missing data for any covariates removed
6 Adjusted for number of chest infections before 15 months, antibiotic use before 15 months, gender, family history, parity, birth wt, maternal age, maternal smoker during pregnancy, any household smoking between birth and 15 months
7 Adjusted for maternal factors in pregnancy, sex of child, season of birth, multiple pregnancy, gestational age, birth weight, head circumference, birth length, and postnatal factors
Appendix A

ISAAC QUESTIONNAIRE SAMPLE

Original Article:


MATERIAL:
Table 4, 5 and 6

<table>
<thead>
<tr>
<th>Table 4. – Core questionnaire wheezing module for 6–7 year olds</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Has your child ever had wheezing or whistling in the chest at any time in the past?</td>
</tr>
<tr>
<td>Yes [ ] No [ ]</td>
</tr>
<tr>
<td>IF YOU ANSWERED &quot;NO&quot; PLEASE SKIP TO QUESTION 6</td>
</tr>
<tr>
<td>2. Has your child had wheezing or whistling in the chest in the last 12 months?</td>
</tr>
<tr>
<td>Yes [ ] No [ ]</td>
</tr>
<tr>
<td>IF YOU ANSWERED &quot;NO&quot; PLEASE SKIP TO QUESTION 6</td>
</tr>
<tr>
<td>3. How many attacks of wheezing has your child had in the last 12 months?</td>
</tr>
<tr>
<td>None [ ] 1 to 3 [ ] 4 to 12 [ ] More than 12 [ ]</td>
</tr>
<tr>
<td>4. In the last 12 months, how often, on average, has your child's sleep been disturbed due to wheezing? Never woken with wheezing [ ] Less than one night per week [ ] One or more nights per week [ ]</td>
</tr>
<tr>
<td>5. 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? Yes [ ] No [ ]</td>
</tr>
<tr>
<td>6. Has your child ever had asthma? Yes [ ] No [ ]</td>
</tr>
<tr>
<td>7. In the last 12 months, has your child's chest sounded wheezy during or after exercise?</td>
</tr>
<tr>
<td>Yes [ ] No [ ]</td>
</tr>
<tr>
<td>8. In the last 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or a chest infection? Yes [ ] No [ ]</td>
</tr>
</tbody>
</table>

Table 5. — Core questionnaire rhinitis module for 6–7 year olds

1. Has your child ever had a problem with sneezing, or a runny, or a blocked nose when he/she DID NOT have a cold or the flu? Yes [ ] No [ ]
   
   IF YOU ANSWERED “NO” PLEASE SKIP TO QUESTION 6

2. In the past 12 months, has your child had a problem with sneezing, or a runny, or a blocked nose when he/she DID NOT have a cold or the flu? Yes [ ] No [ ]
   
   IF YOU ANSWERED “NO” PLEASE SKIP TO QUESTION 6

3. In the past 12 months, has this nose problem been accompanied by itchy-watery eyes? Yes [ ] No [ ]

4. In which of the past 12 months did this nose problem occur? (please tick any which apply) January [ ] February [ ] March [ ] April [ ] May [ ] June [ ] July [ ] August [ ] September [ ] October [ ] November [ ] December [ ]

5. In the past 12 months, how much did this nose problem interfere with your child’s daily activities? Not at all [ ] A little [ ] A moderate amount [ ] A lot [ ]

6. Has your child ever had hay fever? Yes [ ] No [ ]

Table 6. — Core questionnaire eczema module for 6–7 year olds

1. Has your child ever had an itchy rash which was coming and going for at least 6 months? Yes [ ] No [ ]
   
   IF YOU ANSWERED “NO” PLEASE SKIP TO QUESTION 7

2. Has your child had this itchy rash at any time in the last 12 months? Yes [ ] No [ ]
   
   IF YOU ANSWERED “NO” PLEASE SKIP TO QUESTION 7

3. Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes? Yes [ ] No [ ]

4. At what age did this itchy rash first occur? Under 2 years [ ] Age 2–4 [ ] Age 5 or more [ ]

5. Has this rash cleared completely at any time during the last 12 months? Yes [ ] No [ ]

6. In the last 12 months, how often, on average, has your child been kept awake at night by this itchy rash? Never in the last 12 months [ ] Less than one night per week [ ] One or more nights per week [ ]

7. Has your child ever had eczema? Yes [ ] No [ ]
