Paracetamol exposure and Asthma: What does the Evidence say? An Overview of Systematic reviews

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Abstract

Objective: To conduct an umbrella review collating the existing evidence to determine whether there is an association between exposure of Paracetamol in-utero or in infancy and the development of childhood Asthma.

Methods: In this review, systematic reviews with or without meta-analysis that reported the association between paracetamol and asthma in children were included. To identify relevant reviews, a search was performed in the electronic databases PubMed, the Cochrane Library, and Ovid MEDLINE. The protocol was registered in PROSPERO CRD42020156023. A separate search was conducted for primary studies from the last 5 years not yet included in systematic reviews reporting the association from January 2016 to March 2021.

Results: The electronic searches identified 1966 review titles. After the removal of 493 duplicates,1475 titles and abstracts were screened against the eligibility criteria. Full-text screening yielded six systematic reviews to be included in this review. The search for primary studies in the last five years yielded 1214 hits, out of which 5 studies were found suitable for inclusion. Three of them, that were not included in the systematic reviews, and have been summarised in this paper. The Odds Ratios(ORs) for the outcome of asthma in offspring of mothers with prenatal paracetamol consumption in any trimester were 1.28(1.13-1.39) and 1.21(1.02-1.44). For first trimester exposures, they were 1.12 (0.99- 1.27), 1.39(1.01-1.91) and 1.21(1.14-1.28), for the second or third trimester, they were 1.49(1.37-1.63) and 1.13(1.04-1.23). For the third trimester only, the figure was 1.17(1.04-1.31). Of the six reviews included, 1 had a low risk of bias, 2 had an unclear risk while 3 had a high risk of bias assessed using the ROBIS tool. There was no significant increased risk of asthma with early infancy exposure.The inter-study heterogeneity varied from I^2=41% to I^2=76% across reviews. In the primary studies, the OR for prenatal exposure ranged from 1.12 (0.25 to 4.98) to 4.66 (1.92-11.3) and for infancy exposure was 1.56 (1.06 to 2.30). All three included primary studies were adjudged to be of high quality using the Newcastle Ottawa scale.

Conclusions: There is a modest association between paracetamol exposure in-utero and the future development of asthma. Exposure in infancy has a less consistant association. All the studies done thus far are observational in nature, with their inherent biases. Further research, preferably randomized controlled trials are recommended to answer this pertinent question.

Introduction:

Asthma is a chronic respiratory disorder, which causes episodic wheezing ranging from mild symptoms to life-threatening episodes. [1]. Common symptoms of asthma in children include coughing and whistling or wheezing sounds when breathing [2].“As indicated by the United States Centers for Disease Control and Prevention (CDC), 1 of every 13 individuals has asthma “[3].

Asthma is the most common cause of chronic morbidity in children.[4] At present, 1 out of 12 children have asthma. It is the significant reason behind missed school days. The risk factors of asthma are divided into genetic factors and environmental factors. Genetic factors include a positive family history for atopy and environmental factors include exposure to allergens, dust, toxic chemicals, and drugs [5]. NSAIDs, Beta-blockers, Radiological contrast media, and opiates have been known to aggravate bronchospasm in asthmatics. The list of pharmacological agents implicated in the causation and aggravation is exhaustive, and an extensive medication review is warranted in newly diagnosed and poorly controlled patients.

Paracetamol (acetaminophen) is a frequently used over-the-counter analgesic for the self-management of some of the common disorders in children. Several epidemiologic observational studies suggested that its use can be a risk factor for asthma development [7]. It is believed that the metabolite of paracetamol diminishes glutathione levels in the respiratory tract and thus leads to susceptibility to oxidative stress. This process causes airway inflammation, which leads to bronchoconstriction, and subsequently, symptoms of asthma [8].

Why it is important to do this overview

Paracetamol has been used commonly during all stages of pregnancy for pain relief and fever.Paracetamol is easily available over the counter and therefore readily accessible for self-medication [9]. There are no specific guidelines/policy recommendations regarding paracetamol use in the context of asthma prevention. It is necessary to shed some light on the effects of early-life exposure to paracetamol on respiratory health during childhood. Prenatal exposure as well as exposure during the first year of life constitutes early life exposure. There has been a plethora of systematic reviews exploring the association between paracetamol exposure in utero and early infancy and the subsequent development of asthma in children. There is a need to critically appraise this secondary research as well as shed some light on the latest primary studies addressing this dilemma. We therefore conducted an overview of systematic reviews on the topic as well as a systematic review of the studies published in the last 5 years to provide the complete evidence summary to policy makers as well as clinicians.

Methods

We have reported this review in accordance with the PRISMA guidelines. All the Systematic reviews with or without meta-analysis that reported the association between the exposure of Paracetamol in early life and Asthma were included. The protocol of this review was registered in PROSPERO CRD42020156023[10]. The population of interest was pregnant women and children less than 1 year of age. Paracetamol, given by any route, any dose, and any duration, was the exposure. The comparator was any other analgesic or placebo. The outcome was childhood asthma defined till the age of 18 years. We included systematic reviews of cohort and cross-sectional studies. No time and language restrictions were applied. We also ran a search for primary studies conducted in the last 5 years, from January 2016 to March 2021 using similar search parameters, to ensure the complete body of evidence was taken into the picture.

Search methods

To identify the relevant reviews, an extensive search was performed in three electronic databases: PubMed, the Cochrane Central Register of Controlled Trials Library, and Ovid MEDLINE till November 4, 2020. Search terms included MeSH terms and synonyms of ‘‘asthma,’’ ‘‘acetaminophen,’’ ‘‘paracetamol,’’ “children,” ‘‘infants,” “pregnancy,” “prenatal,” and “systematic review”. We did not apply any date or language restrictions in the electronic searches. Two authors (VS, MS) independently screened the abstracts and titles of every record to identify studies potentially relevant to the predefined eligibility criteria. Full texts of all included studies during primary screening were retrieved and screened by two authors (VS, MS) independently, to determine the eligibility of the study. Where differences in opinion existed, they were resolved through discussion with a third author (MeS). The search strategy is available in the supplementary material (Document S1).

Primary studies from the last 5 years (January 2016 to March 2021) were also searched for in databases PubMed, EMBASE and Ovid (Medline), to cover the evidence not yet included in systematic reviews.The Cochrane library was also searched, without using the publication year filter. The search strategy is appended as Supplementary Document S2. Two authors MS and AC searched the titles and abstracts for relevant publications.

Data Extraction

For reviews that met the inclusion criteria, four authors (VS, MS, NJ, AC) extracted data using data extraction templates. Discrepancies were resolved through discussion with the fifth author (MeS). All the relevant data were extracted from each included review.

The primary studies from the last 5 years were also subjected to the data extraction process by two authors (AC and MS), on a pre designed data extraction sheet. Disagreements were resolved by consulting an arbitrator(JLM), who also critically reviewed the draft.

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Risk of bias assessment

Four reviewers (VS,MS,NJ, and AC) used the ROBIS tool to assess the risk of bias of each included systematic review. This tool assesses the level of bias present in four domains, namely, eligibility criteria of the study, identification and selection of studies, data collection and study appraisal, and synthesis and findings[11].Any discrepancy in quality assessment was discussed and resolved through mutual discussion between authors. The quality of the primary studies was assessed using the Newcaslte-Ottawa scale for cross sectional and cohort studies. [12] This tool assigns a score to each study based on the selection of the sample, comparability of the groups and outcomes. The study quality is graded based on the score, as poor (0-3),fair (4-6), and good (7-9).

Data synthesis

Due to the existence of heterogeneity and overlap of studies between included systematic reviews, a narrative evidence synthesis was done instead of pooling the results of the systematic reviews. The data from the primary studies published in the last 5 years has also been provided in a table.

Results

The systematic search identified 1966 potentially eligible studies; among these 493 duplicates were removed. Two additional systematic reviews, that were thesis dissertations published online were identified as part of grey literature search. Screening of titles of 1475 studies, eliminated 1433 studies. The full text of the remaining 40 studies was screened, which yielded 6 systematic reviews to be included in this review. The reasons excluding 34 studies are presented in the PRISMA chart [Fig 1].

The 6 included systematic reviews were published between 2009 and 2016. The characteristics of the included reviews are given in Table 1. The various tools for assessing and reporting the data in the reviews were STROBE(13), PRISMA(14), QUORUM(15), and MOOSE(16) checklists. One systematic review had a low risk of bias, 4 had an unclear risk of bias and one had a high risk of bias.[Table 2]

Mahyar et al identified five studies from 8 databases, up to 2008. Out of five included studies in the prenatal subgroup, three were cohort studies and two were cross-sectional surveys. Paracetamol use in the pregnancy, and development of asthma symptoms was explored in 425140 infants. There was no

information on the dose, duration, or indication of paracetamol use. The authors included studies if they clearly defined asthma or wheezing as the primary outcome. The age of diagnosis of asthma was not specified. This review used the Newcastle-Ottawa scale to assess the risk of bias. The review reported higher odds for the development of persistent wheeze [OR: 1.50 (1.10-2.05)] and asthma [OR:1.28 (1.13-1.39)] in children [17]. We assessed an unclear risk of bias in this systematic review. Eyers et al identified six studies in four databases upto 2010. They included five prospective cohorts and one cross-sectional survey consisting of 28038 subjects. This review had a high risk of bias, as it did not report any details about the risk of bias assessment of included studies. The review reported that paracetamol use in pregnancy was associated with a higher odds of development of wheezing in offspring [OR: 1.21(1.02–1.44)][18].

Cheelo et al identified eleven studies in two databases till August 2013. This review included retrospective and prospective cohort studies, reporting both prenatal and infantile paracetamol exposure data of 907751 subjects. This review used the Newcastle-Ottawa scale to assess the bias in the included studies. There higher odds of asthma in children when the exposure was prenatal, during 1st trimester [OR: 1.39(1.01-1.91)], during 2nd and 3rd trimester [OR: 1.49(1.37-1.63)], during 3rd trimester [OR: 1.17(1.04-1.31)] and during Infancy [OR: 1.41(0.96-2.08)]. [19]. Overall, this review had a low risk of bias. This review also used the most robust definition of asthma by pre-specifying the age of diagnosis above 5 years.

Fan et al identified thirteen studies in two databases up to 2016. They reported data from 1043109 subjects. Risk of bias in the included studies was assessed by using the Newcastle Ottawa scale. This review also reported higher odds of developing asthma[OR 1.19 (1.12-1.27)]. Subgroup analysis showed an OR of 1.21[1.14-1.28] for the 1st trimester and 1.13[1.04-1.23] for the 2nd and 3rd trimester[20].The results of the risk of bias assessment were not reported in the manuscript, making the overall risk of bias unclear.

Fujii-Rios authored a systematic review in a thesis. Six prospective studies with 28606 participants were identified in PubMed alone. The pooled OR was1.12(1.03-1.22), however it was statistically insignificant

during the first and second trimesters.[21] In this systematic review, only 1 database was searched,the entire systematic review was conducted by a single author, and the risk of bias assessments for individual studies was not done. For these reasons, the overall risk of bias for this review was reported as high.

Prejean et al studied only post-natal exposure. They searched 4 databases and included 3 birth cohorts and 1 multicenter cross-sectional study studying the exposure in the first 2 years of life. The outcome was assessed at 5-7 years of age. Only qualitative synthesis was done. All included studies were judged to have a serious risk of bias. Outcomes from three out of four included studies showed no association between paracetamol exposure in the first 2 years of life and asthma. The GRADE level of certainty was adjudged to be very low.[22] The risk of bias in the review using the ROBIS tool was unclear. The six reviews together included 36 different studies[23-58](Supplementary Table S1).

In summary, the Odds Ratios(ORs) for the outcome of asthma in offspring of mothers with prenatal paracetamol consumption in any trimester were 1.28(1.13-1.39) and 1.21(1.02-1.44). For first trimester exposures, they were 1.12 (0.99- 1.27), 1.39(1.01-1.91) and 1.21(1.14-1.28), for the second or third trimester, they were 1.49(1.37-1.63) and 1.13(1.04-1.23). For the third trimester only, the figure was 1.17(1.04-1.31). Most of the confidence intervals from prenatal exposures did not cross the line of no effect, proving the association to be consistently statistically significant. Only the outcome CIs of ORs for the first 2 trimesters from one review (Fujii-Rios 2012) and one of asthma in infancy exposure of paracetamol was crossing the line of no effect. Publication bias was assessed in only one systematic review.[21] The funnel plot suggests a publication bias.

The search for primary studies from 2015 to 2021 yielded 1214 results. After the removal of 259 duplicates, 955 titles and abstracts were screened. Of these, 19 full texts were retrieved and 5 studies were included. Two of these were already included in aforementioned systematic reviews (Sordillo[56], Magnus[58]). The data from the remaining 3 studies is presented in Table 3. For prenatal exposure, the ORs from the study by Malaeb et al was 4.66 (1.92-11.30).[59] Piler et al found no association with prenatal and combined exposures while a mild association was seen with infant exposure on the outcome

of pediatrician diagnosed asthma at 11 years of age.The adjusted OR(CI) for development of asthma was 1.83 (0.91 to 3.71) with combined prenatal and postnatal exposure to paracetamol, 1.56 (1.06 to 2.30) with postnatal exposure and 1.12 (0.25 to 4.98) with prenatal exposure.[60] Shaheen et al reported an OR of 1.50 (1.35–1.66) from analysis of 152797 asthmatic subjects from the cohort at 5 years of age.[61] All studies scored > 7 on the Newcastle Ottawa scale.

Discussion

Overall, our analysis of six systematic reviews, and 3 additional studies suggest that there is a significant association between paracetamol exposure in utero and the development of childhood asthma. There was heterogeneity among the studies included in the reviews as well as methodological differences between the systematic reviews. For instance, Eyers et al utilized raw data, and the outcome variables were standardized, whereas Mahyar et al utilized adjusted ORs and did not standardize the outcomes. Association does not imply causation and non-causal explanations for such associations cannot be ruled out. There are several limitations when the Bradford Hill causal criteria were applied, and these are summarized in Supplementary Table S2[62] . Here we must mention the main limitations.

The strength of the association is modest, with at maximum, a 1.5 fold increase in odds of asthma in paracetamol exposed children. One of the challenges in identifying an association between paracetamol exposure, and the occurrence of asthma in later life, is the frequent prevalence of the risk factor, as well as outcome. In such a situation, it is difficult to confidently attribute whether a statistically significant association, could also be due to mere chance. Further, paracetamol usage could itself be a surrogate for some other proximal risk factor such as fever, respiratory tract infections and other conditions with inflammation during pregnancy and in early life. [19] Also, the issue of temporality is difficult to gauge in such a situation. Since episodes of infantile wheezing are associated with viral infections(with fever), paracetamol exposure could be after, rather than before, the outcome being measured. Thus, two of the Bradford-Hill criteria viz. specificity and temporality, are challenged. This makes a strong case for confounding by indication, and the reverse causality bias.[63,64]

Unmeasured confounders linked to both the exposure and the outcome, can give rise to an apparent association between the drug and outcome. None of the included reviews, barring Cheelo et al, conducted a sensitivity analysis for this. Systematic reviews of RCTs comparing the asthma incidence in children with postnatal exposure to paracetamol or ibuprofen have not found any difference between the two, again supporting confounding by indication. [65,66] One RCT comparing prenatal paracetamol and ibuprofen exposure, enrolling children above 2 months of age, with a six year follow up is currently underway .[67]

The association is biologically plausible by considering increased oxidative stress to the respiratory system due to a paracetamol metabolite, and the dominant Th2 response by exposure to paracetamol in the developing fetus. Other pathophysiological mechanisms that may explain the link are glutathione depletion at paracetamol dose greater than 4g/day, Cyclo-oxygenase enzyme inhibition and the antigenic effect of paracetamol leading to the upregulation of histamines and IgE. Experimental evidence from animal and human studies is conflicting, and RCTs are lacking. [68, 69]

Strength and limitations of the study

The strengths of this umbrella review are a rigorous literature search and a meticulous appraisal of the included studies. We followed the methods recommended by the Cochrane. The protocol was registered in PROSPERO. As recommended, we used a validated tool, ROBIS, to assess the risk of bias in systematic reviews. However, we were unable to pool the results because of significant heterogeneity and variable confounders. Also, none of the reviews provided the certainty of evidence by the GRADE approach. The inclusion of 2 reviews that were not peer reviewed and sourced from grey literature was also done.[21,22]This was done to provide a more balanced perspective of the evidence and to decrease the publication bias, bringing to light the “null” or negative results.[70] In conclusion, we suggest a modest association between paracetamol exposure in pre-natal life and early infancy, with the occurrence of wheezing and/or asthma in infancy and/or childhood. However, there are several limitations to this conclusion and there is a need to generate higher quality evidence. Trials in pregnant women, while desirable, will be difficult to conduct.

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References

1. Medical definition of asthma. [online]. [cited on 18-11-2019]. Available from: https://www.medicinenet.com/script/main/art.asp?articlekey=2373
2. Quirt J, Hildebrand KJ, Mazza J,Noya F, Kim H et al. Asthma. Allergy Asthma Clin Immunol. 2018; 14(Suppl 2): 50.
3. Asthma facts and figures; Asthma and allergy foundation of America. [online]. [cited on: 22-11-2019] Available form:https://www.aafa.org/asthma-facts/
4. Asthma Risk Factors: [online]. [cited on: 22-11-2019] Available from: https://www.lung.org/lung-health-and-diseases/lung-disease-lookup/asthma/asthma-symptoms-causes-risk-factors/asthma-risk-factors.html
5. [5] CDC.gov. (2018). Asthma | Healthy Schools | CDC. [online] Available at: https://www.cdc.gov/healthyschools/asthma [Accessed 16 Feb. 2018].
6. Asthma. [online]. [cited on: 23-11-2019]. Available from: https://www.mayoclinic.org/diseases-conditions/asthma/diagnosis-treatment/drc-20369660
7. Graham GG, Davies MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity, and recent pharmacological findings. Inflammopharmacology. 2013;21(3):201–32. Epub 2013 May 30.
8. Dimova S, Hoet PH, 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(8):1727–37. Epub 2005 Apr 26

9. https://www.nhs.uk/common-health-questions/pregnancy/can-i-take-paracetamol-when-i-am-pregnant/
10. Varukolu S, Singh M, Pradhan P, Singh M. Paracetamol and Asthma: Is the evidence robust enough to change the guidelines: an Overview. PROSPERO 2020 CRD42020156023 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020156023
11. Whiting P, Savović J, Higgins JPT, Caldwell DM, Reeves BC, Shea B, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016 Jan 1;69:225–34..
12. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. http://www ohri ca/programs/clinical_epidemiology/oxford htm 2009 [cited 2009 Oct 19];Available from: URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007 Oct 16;147(8):573–7.
14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. PLoS Med. 2021 Mar;18(3):e1003583.
15. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet Lond Engl. 1999 Nov 27;354(9193):1896–900.
16. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000 Apr 19;283(15):2008–12.

17. Mahyar E, Mohsen S, Siavash J, Mimi D W, Kevin A, Mark J F. Acetaminophen Use and the Risk of Asthma in Children and Adults A Systematic Review and Metaanalysis. CHEST Nov 2019;136 (5):1316-23.

18. Eyers 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 J. Br. Soc. Allergy Clin. Immunol. 2011;41:482–489.

19. Cheelo M, Lodge C J, Dharmage S C, Simpson J A, Matheson M, Heinrich J et al.Paracetamol Exposure in Pregnancy and Early Childhood and Development of Childhood Asthma: A Systematic Review and Meta-Analysis. Arch Dis Child. 100 (1); Jan 2015:81-9

20. Fan G, Wang B, Liu C, Li D et al. Prenatal Paracetamol Use and Asthma in Childhood: A Systematic Review and Meta-Analysis. AllergolImmunopathol (Madr). Nov-Dec 2017;45 (6): 528-33.

21. Fujii-Rios, Hanae, "Intrauterine Exposure To Acetaminophen (paracetamol) And Childhood Asthma: Systematic Review And Meta-Analysis" (2012). Public Health Theses. 1094. Available at http://elischolar.library.yale.edu/ysphtdl/1094

22. Prejean M. Paracetamol Use in Early Life and Link to Childhood Asthma: A Systematic Review" (2012). School of Physician Assistant Studies. Paper 287.

23. McKeever TM, Lewis SA, Smit 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(9):966-71.

24. Shaheen S, Potts J, Gnatiuc L, Makowska J, Kowalski ML, Joos G, et al. The relation between paracetamol use and asthma: a GA2LEN European case-control study. Eur Respir J. 2008;32(5):1231-6

25. Thomsen SF, Kyvik KO, Skadhauge L, Steffensen I, Backer V. Intake of paracetamol and risk of asthma in adults. J Asthma. 2008;45(8):675-6.
26. Davey G, Berhane Y, Duncan P, Aref-Adib G, Britton J, Venn A. Use of acetaminophen and the risk of self-reported allergic symptoms and skin sensitization in Butajira, Ethiopia. J Allergy Clin Immunol. 2005;116(4):863-8.
27. Shaheen SO, Sterne JA, Songhurst CE, Burney PG. Frequent paracetamol use and asthma in adults. Thorax. 2000;55(4):266-70.
28. Barr RG, Wentowski CC, Curhan GC, Somers SC, Stampfer MJ, Schwartz J, et al. Prospective study of acetaminophen use and newly diagnosed asthma among women. Am J Respir Crit Care Med. 2004;169(7):836-41.
29. Wong GW, Leung TF, Ma Y, Liu EK, Yung E, Lai CK. Symptoms of asthma and atopic disorders in preschool children: prevalence and risk factors. Clin Exp Allergy. 2007;37(2):174-9.
30. Beasley R, Clayton T, Crane J, von Mutius E, Lai CK, Montefort S, et al. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years: analysis from Phase Three of the ISAAC programme. Lancet. 2008;372(9643):1039-48.
31. Cohet C, Cheng S, MacDonald C, Baker M, Foliaki S, Huntington N, et al. Infections, medication use, and the prevalence of symptoms of asthma, rhinitis, and eczema in childhood. J Epidemiol Community Health. 2004;58(10):852-7.
32. Rodriguez Martinez C, Sossa M, Goss CH. Factors associated with severe disease in a population of asthmatic children of Bogota, Colombia. J Asthma. 2008;45(2):141-7.
33. Castro-Rodriguez JA, Garcia-Marcos L, Alfonseda Rojas JD, Valverde-Molina J, Sanchez-Solis M. Mediterranean diet as a protective factor for wheezing in preschool children. J Pediatr. 2008;152(6):823-8, 8 e1-2.

34. Barragan-Meijueiro MM, Morfin-Maciel B, Nava-Ocampo AA. A Mexican population-based study on exposure to paracetamol and the risk of wheezing, rhinitis, and eeczema in childhood. J Investig Allergol Clin Immunol. 2006;16(4):247-52.
35. Sharma SK, Banga A. Prevalence and risk factors for wheezing in children from rural areas of north India. Allergy Asthma Proc. 2007;28(6):647-53.
36. Karimi M, Mirzaei M, Ahmadieh MH. Acetaminophen use and the symptoms of asthma, allergic rhinitis and eczema in children. Iran J Allergy Asthma Immunol. 2006;5(2):63-7.
37. Shaheen SO, Newson RB, Henderson AJ, Headley JE, Stratton FD, Jones RW, et al. Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. Clin Exp Allergy. 2005;35(1):18-25.
38. Persky V, Piorkowski J, Hernandez E, Chavez N, Wagner-Cassanova C, Vergara C, et al. Prenatal exposure to acetaminophen and respiratory symptoms in the first year of life. Ann Allergy Asthma Immunol. 2008;101(3):271-8.
39. 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(3):583-90.
40. Perzanwoski MS MR, Ali DB, et al. Prenatal acetaminophen use is a risk for wheeze at age 5 years in a low income urban population with a high risk for asthma. J Allergy Clin Immunol. 2008(121):S 231.
41. 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(1):33-7.
42. Kallen B, Finnstrom O, Nygren KG, Otterblad Olausson P. Maternal drug use during pregnancy and asthma risk among children. Pediatr Allergy Immunol. 2013;24(1):28-32.

43. Andersen AB, Farkas DK, Mehnert F, Ehrenstein V, Erichsen R. Use of prescription paracetamol during pregnancy and risk of asthma in children: a population-based Danish cohort study. Clin Epidemiol. 2012;4:33-40.

44. Kreiner-Moller E, Sevelsted A, Vissing NH, Schoos AM, Bisgaard H. Infant acetaminophen use associates with early asthmatic symptoms independently of respiratory tract infections: the Copenhagen Prospective Study on Asthma in Childhood 2000 (COPSAC(2000)) cohort. J Allergy Clin Immunol. 2012;130(6):1434-6.

45. Bakkeheim E, Mowinckel P, Carlsen KH, Haland G, Carlsen KC. Paracetamol in early infancy: the risk of childhood allergy and asthma. Acta Paediatr. 2011;100(1):90-6.

46. Lowe AJ, Carlin JB, Bennett CM, Hosking CS, Allen KJ, Robertson CF, et al. Paracetamol use in early life and asthma: prospective birth cohort study. BMJ. 2010;341:c4616.

47. Schnabel E, Heinrich J, Group LS. Respiratory tract infections and not paracetamol medication during infancy are associated with asthma development in childhood. J Allergy Clin Immunol. 2010;126(5):1071-3.

48. Wickens K, Beasley R, Town I, Epton M, Pattemore P, Ingham T, et al. The effects of early and late paracetamol exposure on asthma and atopy: a birth cohort. Clin Exp Allergy. 2011;41(3):399-406.

49. Shaheen SO, Newson RB, Ring SM, Rose-Zerilli MJ, Holloway JW, Henderson AJ. Prenatal and infant acetaminophen exposure, antioxidant gene polymorphisms, and childhood asthma. J Allergy Clin Immunol. 2010;126(6):1141-8 e7.

50. Kang EM, Lundsberg LS, Illuzzi JL, Bracken MB. Prenatal exposure to acetaminophen and asthma in children. Obstet Gynecol. 2009;114(6):1295-306.

51. Perzanowski MS, Miller RL, Tang D, Ali D, Garfinkel RS, Chew GL, et al. Prenatal acetaminophen exposure and risk of wheeze at age 5 years in an urban low-income cohort. Thorax. 2010;65(2):118-23.

52. Shaheen SO, Newson RB, Sherriff A, Henderson AJ, Heron JE, Burney PG, et al. Paracetamol use in pregnancy and wheezing in early childhood. Thorax. 2002;57(11):958-63.
53. Thengilsdottir H, Goksor E, Alm B, Erdes L, Mollborg P, Pettersson R, et al. Paracetamol in pregnancy seems to increase the risk of multiple-trigger wheeze but not of overall wheezing disorder in preschool age2010. 15- p.
54. Goksor E, Thengilsdottir H, Alm B, Norvenius G, Wennergren G. Prenatal paracetamol exposure and risk of wheeze at preschool age. Acta Paediatr. 2011;100(12):1567-71.
55. Migliore E, Zugna D, Galassi C, Merletti F, Gagliardi L, Rasero L, et al. Prenatal Paracetamol Exposure and Wheezing in Childhood: Causation or Confounding? PLoS One. 2015;10(8):e0135775.
56. Sordillo JE, Scirica CV, Rifas-Shiman SL, Gillman MW, Bunyavanich S, Camargo CA, Jr., et al. Prenatal and infant exposure to acetaminophen and ibuprofen and the risk for wheeze and asthma in children. J Allergy Clin Immunol. 2015;135(2):441-8.
57. Liu X, Liew Z, Olsen J, Pedersen LH, Bech BH, Agerbo E, et al. Association of prenatal exposure to acetaminophen and coffee with childhood asthma. Pharmacoepidemiol Drug Saf. 2016;25(2):188-95.
58. Magnus MC, Karlstad O, Haberg SE, Nafstad P, Davey Smith G, Nystad W. Prenatal and infant paracetamol exposure and development of asthma: the Norwegian Mother and Child Cohort Study. Int J Epidemiol. 2016;45(2):512-22.
59. Malaeb D, Hallit S, Sacre H, Rahme C, Malaeb B, Hallit R, et al. Preconception exposure to over-the-counter medications and antibiotics and the risk of childhood asthma in Lebanon: A cross-sectional study. Allergol Immunopathol (Madr). 2021;49(2):104–12.
60. Piler P, Švancara J, Kukla L, Pikhart H. Role of combined prenatal and postnatal paracetamol exposure on asthma development: the Czech ELSPAC study. J Epidemiol Community Health. 2018 Apr;72(4):349–55.

61. Shaheen SO, Lundholm C, Brew BK, Almqvist C. Prescribed analgesics in pregnancy and risk of childhood asthma. Eur Respir J. 2019 May;53(5).

62. Lucas RM, McMichael AJ. Association or causation: evaluating links between “environment and disease.” Bull World Health Organ. 2005;4.

63. Heintze K, Petersen K-U. The case of drug causation of childhood asthma: antibiotics and paracetamol. Eur J Clin Pharmacol. 2013;69(6):1197–209.

64. Schisterman E, Whitcomb B, Bowers K. Invited Commentary: Causation or “noitasuaC”? Am J Epidemiol. 2011 May 1;173(9):984–7.

65. Sherbash M, Furuya-Kanamori L, Nader JD, Thalib L. Risk of wheezing and asthma exacerbation in children treated with paracetamol versus ibuprofen: a systematic review and meta-analysis of randomised controlled trials. BMC Pulm Med. 2020 Mar 23;20(1):72.

66. Tan E, Braithwaite I, McKinlay CJD, Dalziel SR. Comparison of Acetaminophen (Paracetamol) With Ibuprofen for Treatment of Fever or Pain in Children Younger Than 2 Years: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020 Oct 1;3(10):e2022398.

67. Tan E, Braithwaite I, McKinlay C, Riley J, Hoare K, Okesene-Gafa K, et al. Randomised controlled trial of paracetamol or ibuprofen, as required for fever and pain in the first year of life, for prevention of asthma at age 6 years: paracetamol or ibuprofen in the primary prevention of asthma in Tamariki (PIPPA Tamariki) protocol. BMJ Open. 2020 Dec 10;10(12):e038296.

68. Thiele K, Solano ME, Huber S, Flavell RA, Kessler T, Barikbin R, et al. Prenatal acetaminophen affects maternal immune and endocrine adaptation to pregnancy, induces placental damage, and impairs fetal development in mice. Am J Pathol. 2015 Oct;185(10):2805–18.

69. Bremer L, Goletzke J, Wiessner C, PagenkemperM,Gehbauer C, Becher H et al. Paracetamol Medication During Pregnancy: Insights on Intake Frequencies, Dosages and Effects on

Hematopoietic Stem Cell Populations in Cord Blood From a Longitudinal Prospective Pregnancy Cohort. EBioMedicine. 2017 Dec; 26: 146–151.

70. Paez A. Grey literature: An important resource in systematic reviews. J Evid-Based Med. 2017 Dec 21

Tables:

Table 1: Reviews included in this umbrella review

Table 2: Risk of bias assessment in the included reviews using the ROBIS tool

Table 3: Characteristics of primary studies included in this review

Supplementary material

Supplementary Document S1: Search strategy for Systematic Reviews

Supplementary Document S2a: Search strategy for Primary Studies (PubMed)

Supplementary Document S2b: Search strategy for Primary Studies (EMBASE)

Supplementary Document S2c: Search strategy for Primary Studies (Ovid MEDLINE)

Supplementary Document S2d: Search strategy for Primary Studies (Cochrane)

Supplementary Table S1: Details of included reviews in this overview

Supplementary Table S2: Hills causal criteria applied to the association between prenatal and early infancy paracetamol exposure and asthma

Figure Legends:

Figure 1: PRISMA flow diagram for systematic review selection for this umbrella review

Figure 2: PRISMA flow diagram for primary studies selection from the last 5 years