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Intrauterine Exposure To Acetaminophen (paracetamol) And Childhood Asthma: Systematic Review And Meta-Analysis

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_____May 1, 2012_____
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Abstract

Background: Past studies have reported conflicting results regarding the association between acetaminophen use during pregnancy and the risk of developing childhood asthma.

Objectives: To perform an updated review on past studies investigating the association between prenatal acetaminophen use and the risk of developing asthma within the first ten years of life.

Methods: A systematic review and meta-analysis was conducted using PubMed search (1950-December 1, 2011) to identify studies that investigated the association between intrauterine exposure to acetaminophen and childhood asthma. Inclusion criteria consisted of a study design restricted to prospective cohort studies, primary exposure of acetaminophen intake during pregnancy, and primary outcome of physician-diagnosed asthma or a combination of two of the following indicators of asthma (use of asthma medication, hospitalization due to asthmatic symptoms, wheezing, and ER visits due to wheezing). Study quality was assessed and data was extracted by one reviewer. An inverse variance fixed-effects model was used, and adjusted odds ratio was calculated to compare effect sizes of studies.

Results: The review comprised of six studies: two studies assessed physician-diagnosed asthma among children under the age of 2 years and four studies ascertained asthma outcome between the ages 2 and 10 years. The overall pooled estimate calculated from all six studies was 1.12 (95%CI: 1.03, 1.22). Children whose asthma status was recorded before the age of 2 had an overall pooled aOR of 1.18 [95%CI:1.13,1.23] while children between the ages of 2 and 10 years had a pooled aOR of 1.13[95%CI:1.01, 1.26]. For studies that did a follow-up among children under the age of 2 years, subgroup analyses of acetaminophen exposure during different stages of pregnancy displayed consistent statistically significant associations between prenatal acetaminophen use and childhood asthma. The subgroup analysis of different stages of pregnancy for studies that reported asthma outcome among children older than 2 years of age showed that risk of childhood asthma was only associated with intrauterine exposure to acetaminophen during the later stages of pregnancy (aOR[95%CI]: 1.23[1.08, 1.42]). There was not enough information to verify a dose-response relationship.

Conclusions: The findings support a modest association of exposure to prenatal acetaminophen use with childhood asthma development. By reviewing only prospective studies, we established temporality, thus further strengthening our hypothesis that acetaminophen use during pregnancy causes an increased risk of childhood asthma. Further studies need to be conducted to confirm this association, and specify the dose, frequency and trimester use of acetaminophen.

(Word count 398)

Background

Asthma is a chronic inflammatory airway disorder that affects approximately 9 million children in the United States (1). It is caused by both genetic and environmental risk factors, and is characterized by bronchoconstriction, which is the tightening of muscles surrounding the bronchioles, inflammation and thickening as well as excessive mucous production of the airway walls, and hyperresponsiveness to triggers such as allergens and air pollution (2, 4). Common symptoms among asthmatic children include chest tightness, shortness of breath, wheezing and coughing (2). These symptoms can lead to hospitalizations, ER visits, and school absences if the disease is not managed. The severity of one's asthma condition ranges widely depending on the individual, environmental exposure, and the level of asthma management (2). Although it cannot be cured, it can be controlled by careful management of the disease including the use of short acting beta2-agonists and long-term control medicines (2).

Decreasing the prevalence of asthma or even the severity of asthma among children has important public health implications since childhood asthma is the most common chronic condition among children under the age of 18 (3). Moreover, asthma is not just a problem within the U.S. The World Health Organization recognizes it as a worldwide public health problem (4). Because this chronic disease is often under-diagnosed, WHO's estimation of 235 million people with asthma is most likely an underestimation (4).

Mild analgesic over-the-counter (OTC) medication use is common during pregnancy (6, 7). It is known to reduce pain, fever, and inflammation. According to Werler et al, rates of mild analgesic use during pregnancy are higher than during the 3 months prior to pregnancy, suggesting that OTC drugs are used more during pregnancy (6). The top 10 medications that were taken in pregnancy, in rank order, were acetaminophen (aka paracetamol), ibuprofen, pseudoephedrine, aspirin, naproxen, diphenhydramine, guaifenesin, albuterol, amoxicillin, and dextromethorphan (6). Other studies have also shown that acetaminophen is the most preferred and commonly used

analgesic and pyretic drug among pregnant mothers (5-9) since it is not associated with teratogenic effects (8-11). One study approximates about two-thirds of pregnant mothers taking it at one point during their pregnancy (6).

Within the past five decades, the increasing prevalence of acetaminophen use has paralleled the increasing prevalence of asthma among children and adults (5- 7, 12-16), causing several epidemiologists to question whether acetaminophen use poses a risk of asthma development. The suspected association between acetaminophen and asthma development began in 1998, when Varner et al. published one of the first studies, suggesting an epidemiological trend between increased analgesics consumption and increased prevalence in asthma. The authors noted that the rising asthma trend also coincided with the transition from aspirin to acetaminophen use, which was precipitated by the discovery of aspirin's association with Reye's syndrome (5). Two years later, Newson et al. supported this finding with an ecological analysis on multiple countries that showed a positive correlation between the amount of acetaminophen consumption and prevalence of asthma and other atopic conditions among both adults and children (13). Shaheen et al. also published a population based case-control study, which demonstrated an association between acetaminophen intake and asthma development in adults (17). In 2004, Barr et al. reported similar results among women enrolled in a prospective study (18), and Koniman et al. discovered similar results in a matched patient-sibling study in 2007 (12). In 2008, Beasley et al. reported a statistically significant association between acetaminophen use during first year of life and the development of asthma symptoms at the age of 6-7 years (19).

Furthermore, there is epidemiologic evidence that suggests a positive association between intrauterine exposure to acetaminophen and the development of childhood asthma (20-25), including a recent systematic review that concluded that acetaminophen use during pregnancy increases the risk of childhood asthma (26). However, a recent rigorous prospective cohort study suggests otherwise (27). Because both acetaminophen use during pregnancy and childhood asthma

are common, with asthma being a multi-factorial complex disease and acetaminophen being used for several purposes, it has been challenging to confirm an association between prenatal acetaminophen use and the risk of childhood asthma. Evidence of true association between intrauterine exposure to acetaminophen and childhood development of asthma would have important public health implications for pregnant women since acetaminophen is the recommended pain-reliever and fever-reducer during pregnancy, and currently about two-thirds of pregnant women take acetaminophen at some point during their pregnancy.

Our study conducted a more rigorous systematic review and meta-analysis in an attempt to further clarify if prenatal acetaminophen is associated with physician-diagnosed childhood asthma. Specifically, it addressed the question, "Among pregnant women, does acetaminophen use compared with non-use increase the risk for physician-diagnosed asthma before the age of 10?" An overall analysis was conducted prior to performing a pre-specified subgroup analysis, which included age of child at diagnosis and stages of pregnancy.

Methods

Search Methods For Identification of Studies and Study Selection Criteria

PubMed search between the date of index start 1950 and December 1, 2011 was performed to identify prospective cohort studies that examined the association between intrauterine exposure to acetaminophen and asthma development during childhood. The search was restricted to English language and human studies only. The following query string was used: (acetaminophen[Title/Abstract] OR paracetamol[Title/Abstract] OR tylenol[Title/Abstract]) AND (asthma[Title/Abstract] OR wheez*[Title/Abstract]) AND (pregn*[Title/Abstract] OR child*[Title/Abstract] OR prenatal[Title/Abstract]).

The primary exposure of interest was acetaminophen (paracetamol) intake during pregnancy (all trimesters included), and the primary outcome of interest was either physician-diagnosed asthma or at least two symptoms (e.g. wheezing, emergency room visits, medication use for asthma, etc) that suggest asthmatic condition among children younger than or at 10 years of age. Studies were included based on the following criteria: 1) The study design was a prospective cohort, 2) the primary exposure of interest was recorded 3) the primary outcome of interest was recorded. Conversely, studies were excluded based on the following criteria: 1) The study design was retrospective, cross-sectional, case-control, case series, or a case report, 2) the publication was a review, guideline, or editorial, 3) the study was only available in abstract form 4) the study did not have a clearly defined exposure or outcome, 5) "wheezing" was the only asthma-related outcome, 6) the study did not assess asthma prior to 10 years of age, 7) there was a lack of a reported statistical measure of the association.

Searches were performed by one reviewer. Titles and then abstracts were evaluated and rejected on initial screen based on the inclusion and exclusion criteria. Reference lists were also reviewed for relevant studies. Each study included was scored, using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist, and studies were excluded

if they had <50% of STROBE checklist criteria. The Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines for conducting and reporting meta-analysis of observational studies were also utilized. Study investigators were contacted if additional information or data was required.

Data extraction and management

Data was extracted by one reviewer. The following values were extracted: authors' names, study design, year of publication, sample size, average age of children, confounders that were controlled for, estimated effect measure (preferably adjusted OR or adjusted RR), trimester, dose and frequency of acetaminophen intake, number of children with asthma, number of women who took acetaminophen during pregnancy.

Statistical significance at α level of 0.05 (or at 95%CI) for pooled estimates was calculated using Review Manager (Revman) 5.1 (Cochrane Collaboration, Oxford, United Kingdom [http://ims.cochrane.org/revman]). The inverse-variance fixed-effects model was used for meta-analysis calculation. Depending on the study, odds ratios or relative risks were recorded with adjusted estimates taken preference over unadjusted estimates. These estimates were entered into RevMan under the "Generic inverse variance" methodology for meta-analysis. Revman automatically calculates the natural logarithm estimates and their standard errors. With these calculations, RevMan produced a weighted average weight, utilizing the equation, $\Sigma Y_i(1/SE_i^2)/\Sigma(1/SE_i^2)$, where Y_i is the intervention effect estimated in the ith study, SE_i is the standard error of that estimate, and the summation is across all studies (Cochrane Handbook, 9.4.3).

Heterogeneity was assessed using the I-squared statistic with low heterogeneity considered as <50%, moderate heterogeneity between 50- 75%, and high heterogeneity >75%. Meta-analysis was not conducted if heterogeneity was high. Since the I-squared statistic showed low to moderate heterogeneity (<75%), sensitivity analysis was not performed to address heterogeneity problems.

Publication bias was assessed using funnel plots. Other potential biases included information bias (e.g. recall bias) and selection bias due to attrition bias. Although it is difficult to detect information bias, attrition bias was assessed by observing the response rate. Subgroup analyses stratified by trimesters of exposure and age of diagnosis were also conducted. Sensitivity analysis was performed to test any assumptions or decisions we encountered when creating the subgroups.

Results

Study Selection

The outcome of the literature review is shown in Figure 1. Eighty-five citations were initially identified in the electronic search. Seventy-five studies were excluded after screening titles and abstracts, and out of the ten potentially eligible prospective studies, only six of them met the inclusion criteria after thorough review of the articles. Two studies were excluded because the outcome studied did not qualify for inclusion criteria; both assessed wheezing as the only outcome (30, 31). The other two studies were excluded since both studies extracted data from a previously published study that was already included in this review (32, 33). The six studies that were included in the review were all prospective studies, conducted during 2005~ 2010 across various countries including the US, UK, Denmark, Norway and Sweden (Table 1; see Appendix I for more details).

Bakkeheim et al. used a group of participants from a 10-year follow-up prospective birth cohort, *Environment and Childhood Asthma*, in Oslo, Norway (34). 1,016 mothers were enrolled and assessed for acetaminophen exposure with the use of a questionnaire throughout all three trimesters and during the first 6 months since birth. A structured interview followed by a clinical examination including pulmonary function tests, exercise test, skin prick test and blood test were performed for each child at the age of 10 years. The primary outcomes were history of asthma and symptoms and/or medication within the last year and/or positive exercise test. History of asthma was defined as having at least 2 of the following criteria: physician-diagnosed asthma; dyspnea, chest tightness and/or wheezing; and use of asthma medications.

Goksor et al. reported data from a prospective study consisting of 4, 496 participants in Sweden (35). Prenatal acetaminophen exposure was obtained from a questionnaire that was given when the child was 6 months of age. Because of the timing of the questionnaire, there is a possibility of recall bias as it is possible for children to be diagnosed with asthma by the age of 6-

months. Supplemental data such as gender, gestational age, etc were also obtained from Swedish Medical Birth Records. 'Inhaled corticosteroids (ICS)-treated wheeze' was used as a proxy for physician-diagnosed asthma at the age of 4.5 years. Recurrent wheeze and episodic viral wheeze were also recorded as separate outcomes.

Kang et al. recruited 1,505 pregnant mothers in southern New England, U.S. and followed their children until the age of 6 years for physician-diagnosed asthma (27). Intrauterine acetaminophen exposure (trimester, frequency and dose) was assessed through structured interviews during first trimester of pregnancy, and postpartum (to assess for exposure during last trimester of pregnancy). Secondary outcomes included wheezing, bronchitis, and allergy, with the primary outcome being physician-diagnosed asthma ever with history of wheezing at age 6 years.

Persky et al. prospectively studied 345 pregnant women and their children who were enrolled in a randomized controlled trial that assessed the effects of home visits by community health educators and asthma-triggering environmental exposures in households (36). Pregnant women participating in this study were enrolled and given a structured interview during their first trimester. At age 1, children were assessed for the following outcomes: asthma diagnosis, occurrence of any wheeze, wheeze that disturbed sleep, cough that disturbed sleep, emergency department visits for respiratory problems, and hospitalization secondary to respiratory problems. This study was conducted in Chicago, United States.

Rebordosa et al. followed 66,445 pregnant women and their children from the Danish National Birth Cohort (37). One baseline questionnaire was given at enrollment, along with two phone interviews during pregnancy, one parental phone interview when the child was 18 months of age, and a final parental phone interview and questionnaire at the age of 7. In total, 66,445 children at age 18 months were interviewed and 12,733 children at age 7 years were interviewed. The trimester, frequency and dose (only 2nd and 3rd trimester) of acetaminophen exposure were recorded through a computerized telephone interview, which was given during gestational weeks

12 and 30, and respiratory outcomes were physician-diagnosed asthma, wheezing and hospitalization due to asthma. Some of the data was also extracted from the participants' unique civil registration number, which is linked to the Danish National Hospital Registry.

Shaheen et al. utilized the population-based Avon Longitudinal Study of Parents and Children in the county of Avon, England to study 8,511 pregnant women and their children (38). Bristol district-residing women were eligible if their expected date of delivery fell within the time frame of April 1, 1991 and December 31, 1992. Acetaminophen intake during pregnancy (both trimester and frequency) was obtained from a questionnaire that was given during 18-20 weeks of pregnancy and again at 32 weeks of pregnancy. Outcomes that were assessed when the child was 81 months old were the following: physician-diagnosed asthma, frequency of wheezing, hay fever, eczema and atopy.

Table 2 displays the prevalence of intrauterine exposure to acetaminophen by studies. The prevalence ranges widely from 3% to 70% with Bakkeheim et al. and Goksor et al. having the lowest prevalence of 3% and 7.7%, respectively and the others having prevalences greater than 45%.

All six studies controlled for various confounders (Table 3). They calculated adjusted odds ratio measurements with the exception of Bakkenheim et al. who presented their estimates as unadjusted ORs, and Reberdosa et al. who presented their adjusted estimate measurements as adjusted relative risks. While Goksor et al., Reberdosa et al. and Shaheen et al. found a statistically significant association between prenatal acetaminophen intake and risk of childhood asthma, Persky et al., Bakkenheim et al. and Kang et al. reported null results. Moreover, Kang et al. suggested a protective effect when acetaminophen is ingested during both first and second trimester of pregnancy [aOR(95%CI): 0.59(0.36, 0.98)].

Lastly, the review identified any study that included multiple children from the same mother as independent enrollments and/or twins. Kang et al. excluded women from the analysis if

they had multiple births during the study enrollment period (April 1997- June 2000). Neither Goksor et al. nor Persky et al. specified their method of adjusting for multiple births and twins. Reberdosa et al. required that women give births to singletons, but did not address the issue of multiple births. And both Shaheen et al. and Reberdosa et al. had a one year enrollment period, which eliminated the possibility of multiple births from a single mother. However, they did not address the concern of twins.

Estimated Effect Measurements

The pooled fixed-effects OR for all six studies was 1.12 (1.03, 1.22), (Fig. 2). Three studies presented ORs within the stratified groups, but did not present the overall effect (33, 34, 37). Both Shaheen et al. and Bakkeheim et al. calculated ORs for the different pregnancy stages of acetaminophen exposure (0-20 weeks of pregnancy and 20-32 weeks of pregnancy; 1st and 2nd/3rd trimesters, respectively). For both studies, the two pregnancy stages could not be collapsed into one group since women who took acetaminophen throughout their entire pregnancy would be accounted for twice. Consequently, we could not calculate the overall effect that acetaminophen exposure during any period of pregnancy had on childhood asthma. Sensitivity analyses demonstrated that while either of the two pregnancy groups in Bakkeheim et al.'s groups produced the same overall pooled fixed-effects OR calculation for the six studies, Shaheen et al.'s ORs from the two pregnancy stages produced slightly different pooled estimates. When we included Shaheen et al.'s OR from the "0-20 weeks of pregnancy" group, we calculated the previously stated pooled fixed-effects OR of 1.12 (1.03, 1.22). When we used the OR from the "20-32 weeks of pregnancy" instead, we concluded with a pooled fixed-effects OR of 1.17 (1.07, 1.27). Finally, Reberdosa et al. published two aORs that revealed the association between acetaminophen exposure during any time of pregnancy and the risk of childhood development of asthma at ages 18 months and 7 years. Instead of doing a sensitivity analysis, we used the OR from the group that was diagnosed with asthma at 7 years of age since it is difficult to diagnose asthma among children under 6 (39).

The meta-analysis was stratified into studies that examined children under the age of 2 years and studies that diagnosed asthma in children over the age of 2. The age cut-off of 2 years was selected as there was a clear division between two studies that assessed asthma in children at ages 1 year and 18 months, and the rest of the studies that focused on children between the ages 4.5 years and 7 years. Reberdosa et al. conducted a longitudinal follow-up on children at ages 18 months and 7 years, and these two outcomes were analyzed separately.

Acetaminophen use during any stage of the entire pregnancy significantly increased the risk of asthma in children under the age of 2 years, with a pooled fixed-effects OR of 1.18 (95%CI: 1.13, 1.23) (Fig. 3a). The subgroup analysis of acetaminophen intake during different trimesters showed that acetaminophen intake during any one trimester was significantly associated with an increased risk of asthma development in children (Fig. 3b). However, Persky et al.'s study reported a statistically insignificant association between acetaminophen intake during 2nd and 3rd trimester and childhood asthma. Intrauterine acetaminophen exposure during the first trimester of pregnancy produced a statistically significant pooled OR of 1.15 (95%CI: 1.10, 1.20). Similarly exposure during the second trimester of pregnancy resulted in a pooled OR of 1.13 (95%CI: 1.09, 1.17), and exposure during the third trimester of pregnancy resulted in a pooled OR of 1.17 (95%CI: 1.13, 1.21).

Acetaminophen use during any stage of the entire pregnancy significantly increased the risk of asthma in children between ages 2- 10 years, with a pooled fixed-effects OR of 1.13 (95%CI: 1.01, 1.26) (Fig. 4a). The stratified analysis of acetaminophen intake during different stages of pregnancy produced mixed results (Fig. 4b). There were no significant associations between acetaminophen intake during the first two trimesters of pregnancy and asthma in offsprings. However, acetaminophen intake during medium to late stages of pregnancy (a combination of 2nd and 3rd trimester or 20-32 weeks of pregnancy) significantly increased the risk of asthma in children by 23% (pooled OR and 95%CI of 1.23[1.08, 1.42]). Lastly, intrauterine acetaminophen exposure

during the third trimester of pregnancy produced a statistically significant pooled OR of 1.16 (95%CI: 1.03, 1.30).

There was no evidence of high heterogeneity among the studies. The majority of I^2 calculations resulted in 0% with the exception of I^2= 31% in the overall pooled estimate of the six studies, and 71% in the overall pooled estimate for asthma outcome in children over 2 years of age.

A variety of biases were noted (see Appendix I for more details). Because most of these studies relied on self-report, incomplete ascertainment of exposure and outcome may have caused information bias. However, recall bias was minimized by interviewing pregnant women during pregnancy when the asthma outcome was yet to be determined, and the acetaminophen intake can be more accurately reported. Detection bias was minimized by using physician-diagnosed asthma as the primary outcome of interest. Selection bias due to attrition bias may have been a concern for some of these studies as non-participants were noted to be different from the participants (Goksor et al. 2011). Specifically, those who did not participate tended to smoke before pregnancy, have preterm birth and have lower education. Even after stratifying the meta-analysis by study qualities by excluding Goksor et al's study, we concluded with a significant association of acetaminophen ingestion during pregnancy and the risk of developing asthma during childhood years (OR[95%CI]: 1.10[1.01, 1.20]).

Lastly, in terms of publication bias, the funnel plot (Fig. 5) demonstrated a normal trend, with findings from studies with smaller sample sizes found dispersed at the bottom of the funnel and results from studies with larger sample sizes located toward the top of the funnel in the high precision area. The plot indicated a slight trend to the right of the reference line, suggesting that studies with insignificant or protective association were missing.

Discussion

Acetaminophen has been considered the preferred choice of over-the-counter pain-reliever and fever-reducer medication during pregnancy (5-11, 44-47). It is labeled as FDA Category B across all trimesters, indicating that animal studies have not demonstrated any fetal risk or if it has, there have been no randomized controlled studies among pregnant women to prove this finding (47). Guidelines for medication use during pregnancy have recommended using acetaminophen minimally and only when necessary (44-46). Pregnant women should follow the dosage instructions on the back of the medication package, and ingestion of acetaminophen should not exceed the recommended dose of 4 grams a day (44- 46). Currently, we do not know how much acetaminophen crosses the placenta.

Overall, prenatal acetaminophen exposure increases the risk of childhood asthma development with a pooled fixed-effects OR (95 CI%) of 1.12 (1.03, 1.22). The studies were subgrouped by age of asthma diagnosis (≤ 2 years vs. >2 years) as clinical diagnosis of asthma have been reported to be more accurate as the child nears 6 years of age (39). The pooled fixed-effects ORs for both subgroups were consistent with the overall estimate, with the subgroup estimates being 1.13 (1.01, 1.26) and 1.18 (1.13, 1.23) for children being diagnosed with asthma at ages 2 years and above and less than 2 years, respectively.

These results are consistent with past reviews conducted by Etiman et al. and Eyers et al. (26, 29). Etiman et al. (2009) had conducted a larger systematic review, which consisted of studies that investigated acetaminophen exposure during pregnancy, childhood years, and adult years. Although Etiman et al. demonstrated an association between acetaminophen use during pregnancy and increased risk of childhood asthma with an OR (95%CI) of 1.28 (1.13-1.39), Eyers et al. (2011) argued that there were several methodological problems. For instance, the outcome was not standardized across all studies and the details necessary to assess the validity of this systematic review were missing (29). Additionally, Etiman et al.'s systematic review was not focused solely on

prenatal acetaminophen use and risk of childhood asthma (29). Lastly, one of the ORs reported in Etiman et al.'s paper is nowhere to be found in the original paper, and Etiman et al. used hazards ratio for "hospitalization for asthma" instead of relative risk for "physician-diagnosed asthma" for one of the selected studies (Reberdosa et al. 2008) (Table 4).

For the reasons stated above, Eyers et al. (2011) conducted a systematic review and meta-analysis, and concluded that acetaminophen use during pregnancy remained a risk factor for childhood asthma development. However, there were several methodological limitations. First, only studies that provided raw data were included in the review as the pooled summary estimate was calculated utilizing unadjusted odds ratios from the raw data. Consequently, the authors neglected to take into account confounders such as parental history of asthma, maternal age, antibiotic use, smoking and alcohol status and child's gender. Additionally, by restricting studies to those that provide raw data, the authors may have overlooked studies that may have otherwise qualified for inclusion. Second, the authors defined 'wheeze in the past 12 months' as the primary outcome of interest. The condition 'wheezing' is subjective to individual interpretation and may not accurately capture those with asthma. Furthermore, this outcome may have included non-asthmatic children, thereby overestimating the number of cases. Lastly, the inclusion criteria included a range of observational studies, resulting in the inclusion of both prospective and cross-sectional studies. This combination may have weakened the conclusion that would have been more viable if cross sectional studies were removed from the review. Unlike prospective cohort studies, cross-sectional studies do not establish temporality. Consequently, cross-sectional studies cannot establish evidence of causality between acetaminophen use and risk of asthma development.

Table 4 compares and contrasts the studies that were selected for analysis in Eyers et al., Etiman et al. and this systematic review. Three out of the total six studies from Eyers et al.'s review were included in the current review. However, this review utilized the adjusted OR while Eyers et al. calculated the unadjusted OR from the raw data. Although three out of the total five studies from

Etiman et al.'s review were used, two of the estimates did not coincide with this review's ORs. While Etiman et al. recorded the hazard ratio for "hospitalization for asthma" from Reberdosa et al.'s study, this review retrieved the relative risk for "physician-diagnosed asthma". Also, Etiman et al.'s OR from Shaheen et al.'s study was nowhere to be located in the original publication.

This meta-analysis showed a significant positive association between acetaminophen intake during the later stages of pregnancy and risk of asthma diagnosis at ages 2 years and older. Meanwhile, studies that recorded asthma outcome in children younger than 2 years of age displayed an increased risk of childhood asthma when acetaminophen was ingested during any trimester of one's pregnancy. More studies need to be conducted to compare the different trimesters to assess which trimester(s) produces the highest risk of childhood asthma.

There was surprisingly a wide range of prenatal acetaminophen-use prevalence rates among the six studies. Although Bakkeheim et al. had a high response rate of 99.7%, the low prevalence rate of acetaminophen use of 3% may have been due to information bias since mothers were asked to recall their acetaminophen use during pregnancy when their child turned 6 months old. Consequently, it is possible that mothers underreported their exposure to prenatal acetaminophen use. Goksor et al. also had a low prevalence rate of 7.7%, however, this can be explained by the low response rate of 55%, which caused selection bias. Goksor et al. reported that non-responders tended to smoke during pregnancy, have preterm birth and have lower education level. To determine if these two studies invalidated the pooled fixed-effects OR of 1.12 (1.03, 1.22), sensitivity analysis was conducted. Excluding these two studies from the pooled fixed-effects OR did not change the result as the newly calculated estimate was 1.10 (1.01, 1.20) when the OR from Shaheen et al.'s "1-20 weeks of pregnancy" group was used, and 1.16 (1.06, 1.26) when the OR from Shaheen et al.'s "20-32 weeks of pregnancy" group was used. The other five studies have prevalence rates that were reasonably proximal to 66%, which was the recorded rate by a previous study (6).

This meta-analysis has several strengths. First, we used a more stringent exposure and outcome inclusion criteria for study selection compared to previous systematic reviews. We narrowed our search to prospective studies, and we only included studies that reported physician-diagnosed asthma or two of the three asthma conditions as outcomes. Second, unlike previous meta-analyses, we took preference of adjusted estimates over unadjusted estimates when calculating the pooled inverse variance fixed-effects OR. Third, all six studies had rigorous study designs such that biases were minimized. Additionally, by looking into prenatal exposure to acetaminophen, we were able to negate the possibility of reverse causality, which is a common problem for studies that investigated the association between postnatal acetaminophen intake and risk of asthma development. In reverse causality, it is difficult to prove the causality between acetaminophen intake and asthma since those with asthma may be more likely to ingest acetaminophen due to increased co-morbidities such as respiratory infections and headaches (40-43). Fourth, our meta-analysis had low heterogeneity, allowing us to use fixed-effects to calculate pooled estimates. Lastly, since Eyers et al.'s publication, one new study has been published and included in this review.

Our study also has limitations. First, this systematic review did not look into randomized controlled studies. However, randomized controlled studies that investigate the association of prenatal acetaminophen use of risk of childhood asthma do not exist due to ethical reasons. Consequently, we chose to review prospective cohort studies, which are the next preferred study design. Second, we were unable to stratify the reported estimates by confounders as each study adjusted for varying combination of confounders. Third, as with any study, there is a possibility of residual confounding. For example, the reasons for ingesting acetaminophen during pregnancy may be a confounder as mothers who have asthma may potentially be taking acetaminophen for their asthma. Despite these limitations, we used a sound and rigorous methodology under the

condition given to us (e.g. RCTs not being available, studies adjusting for different confounders, etc.).

In conclusion, this systematic review and meta-analysis supports previous studies and meta-analyses (26, 29) that have reported an association between prenatal acetaminophen exposure and increased risk of childhood asthma. Although Eyers et al. reported an increased risk of childhood asthma due to prenatal acetaminophen use, an editorial on Eyers et al.'s findings concluded "for the time being, there is no need to recommend any changes to the clinical practice" (48). This review revisits this topic and underscores the importance of further investigation as this review suggests that intrauterine acetaminophen exposure increases the risk of childhood asthma by approximately 12%- 17%. This result has significant clinical implications as more than half of pregnant women ingest acetaminophen, and asthma is the most prevalent chronic illness among children. Future studies that look into the timing of acetaminophen intake during pregnancy will further help mothers time their acetaminophen intake during pregnancy. Moreover, it would be beneficial if studies investigate how frequency and dose of acetaminophen use during pregnancy affects the risk of childhood asthma.

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Figure 1: Flow Chart for Identifying Studies

Table 1: Basic Characteristics of Included Studies

Study	Publication Year	Country	Population	Acetaminophen Dose/Frequency
Bakkeheim et al.	2010	Norway	Children 10 yrs	No
Goksor et al.	2011	Sweden	Children 4.5 yrs	No
Kang et al.	2009	US	Children 6 yrs	Dose [a] and Frequency [b]
Persky et al.	2008	US	Children 1 yr	No
Reberdosa et al.	2008	Denmark	Children 18 mo and 7 yrs	Dose [c] and Frequency [d]
Shaheen et al.	2005	UK	Children 6-7 yrs	Frequency [e]

a) # of tablets or doses of acetaminophen per day in a month
b) "none", "1-7 days per month", "8-14 days per month", "more than 14 days (but not every day) per month", and "everyday"
c) Only for 2nd and 3rd trimester
d) Total # of weeks of acetaminophen exposure per trimester
e) "not at all", "sometimes", "most days", "everyday"

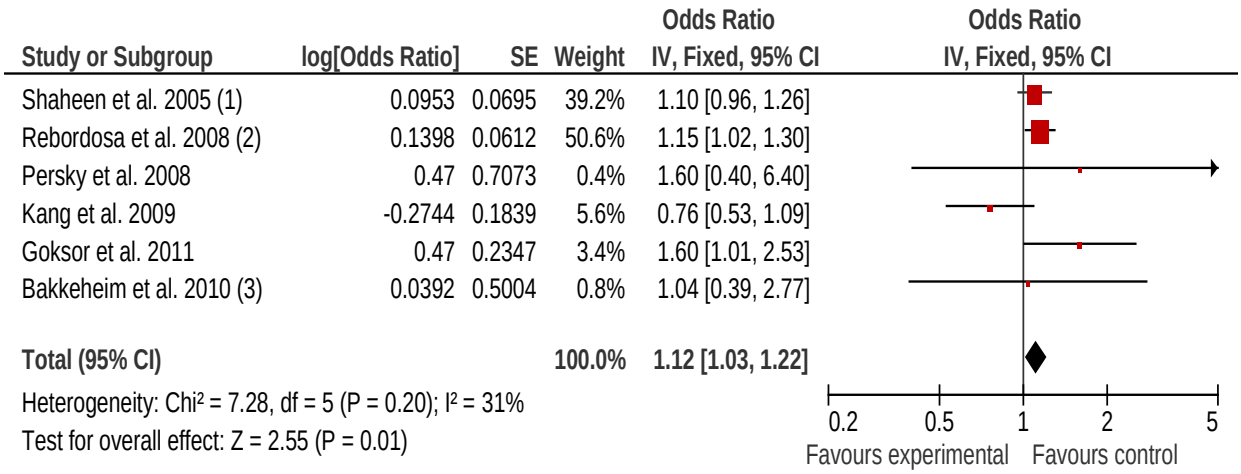
Table 2: Prevalence of intrauterine exposure to acetaminophen by studies

Study	Percent of mothers taking acetaminophen during pregnancy
Bakkeheim et al.	3.0
Goksor et al.	7.7
Kang et al.	69.0
Persky et al.	70.0
Reberdosa et al.	53.9
Shaheen et al.	46.3

Table 3: Estimates of Included Studies

Study	Population (N=)	Period of Exposure	Asthma Risk Estimate (95% CI)	Risk Adjustment
Bakkeheim et al.	Children 10 yrs (1016)	1st trimester 2nd/3rd trimester	OR: 1.04 (0.39, 2.75) OR: 1.00 (0.38, 2.62)	Parental asthma and allergy, smoking during pregnancy, education level (father and mother), family income at child's birth, maternal health in pregnancy, upper and lower respiratory infections from 0-6 mo of age of children.
Goksor et al.	Children 4.5 yrs (4496)	All trimesters	aOR: 1.6 (1.01, 2.60)	Parental asthma, eczema and rhinoconjunctivitis, child's gender, antibiotic use and smoking during pregnancy, gestational age (<37 weeks), caesarean section, asphyxia, antibiotics during first week of life, breast feeding≥ 4 months, early fish introduction, own eczema of doctor-diagnosed food allergy during first year of life, parental education.
Kang et al.	Children 6 yrs (1505)	1st trimester 3rd trimester Ever 1st/3rd trimester Both 1st/3rd trimester	aOR: 0.68 (0.39, 1.2) aOR: 0.91 (0.48, 1.69) aOR: 0.76 (0.53, 1.10) aOR: 0.59 (0.36, 0.98)	Mother's ethnicity, mother's asthma status and symptoms during pregnancy, mother's allergy, father's wheezing, child's ethnicity, child's visit to emergency department for respiratory illnesses, child's antibiotic use during first years of life, child's exposure to tobacco smoke 2h or greater, child's use of allergy medication, child's allergy, child's sneezy or runny nose, child's bronchitis, respiratory syncytial virus, and tonsillitis
Persky et al.	Children 1 yr (345)	1st trimester 2nd/3rd trimester All trimesters	aOR: 1.3 (0.50, 3.80) aOR: 2.0 (0.60, 7.20) aOR: 1.6 (0.40, 6.40)	Maternal age, child's gender, maternal ethnicity, active and passive smoking during pregnancy, low birth weight, age formula started, antibiotic use in late pregnancy, family history of asthma breastfeeding, home environment, intervention group

Reberdosa et al.	Children 18 mo (66,445) Children 7 yrs (12,733)	1st trimester 2nd trimester 3rd trimester Ever during any trimester 1st trimester 2nd trimester 3rd trimester Ever during any trimester	aRR: 1.15 (1.10-1.19) aRR: 1.13 (1.09-1.18) aRR: 1.17 (1.13- 1.23) aRR: 1.18 (1.13- 1.23) aRR: 1.15 (1.01- 1.29) aRR: 1.06 (0.92- 1.22) aRR: 1.17 (1.04- 1.32) aRR: 1.15 (1.02- 1.29)	Parental asthma, child's gender, social class, gestational age, breast feeding, tobacco exposure during pregnancy, antibiotic use in pregnancy
Shaheen et al.	Children 6-7 yrs	0-20 wks	Never aOR: 1.00 Sometimes aOR: 1.09 (0.95, 1.26) Most days aOR: 1.29 (0.74, 2.27) p trend= 0.16	Child's gender, mother's age, smoking education, housing tenure, parity, anxiety score in pregnancy, ethnicity and number of pregnancies, child's birthweight, gestational age and head circumference, mother ever having asthma, eczema, rhinitis and/or migraine, flu, UTI or other infections during late
	(8511)	20-32 wks	Never aOR: 1.00 Sometimes aOR: 1.22 (1.06, 1.41) Most days aOR: 1.62 (0.86, 3.04) p trend= 0.0037	pregnancy, antibiotic use during pregnancy, number of siblings at age 7 years, pet ownership, breast feeding, day care use in first 8 months, damp and/or mold in home, tobacco exposure, child's BMI at 7 years.



(1) 0-20 weeks of pregnancy; Pooled estimate was 1.17(1.07, 1.27) when 20-32 weeks of pregnancy was used instead.

(2) Children 7 years of age

(3) First trimester of pregnancy; The pooled estimate was the same even when the group, 2nd/3rd trimesters of pregnancy, was u

Figure 2: Meta-analysis of all six studies

Figure 3: Meta-analysis of studies that diagnosed asthma in children < 2 years of age:

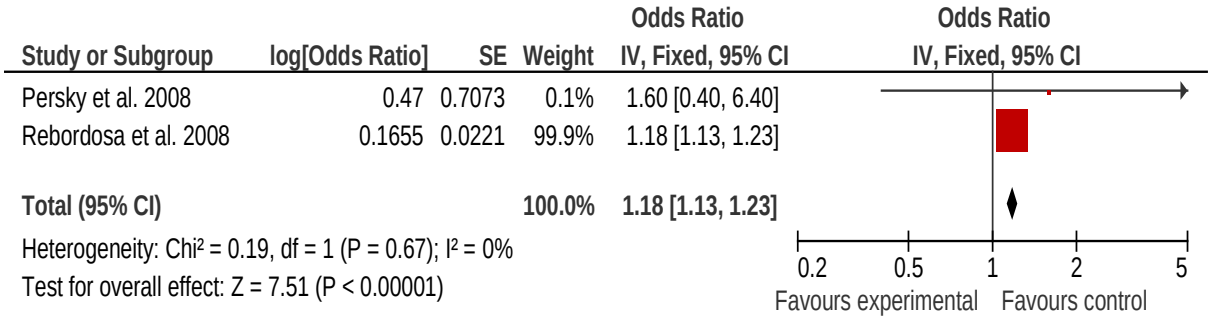


Figure 3a: Exposure during entire pregnancy

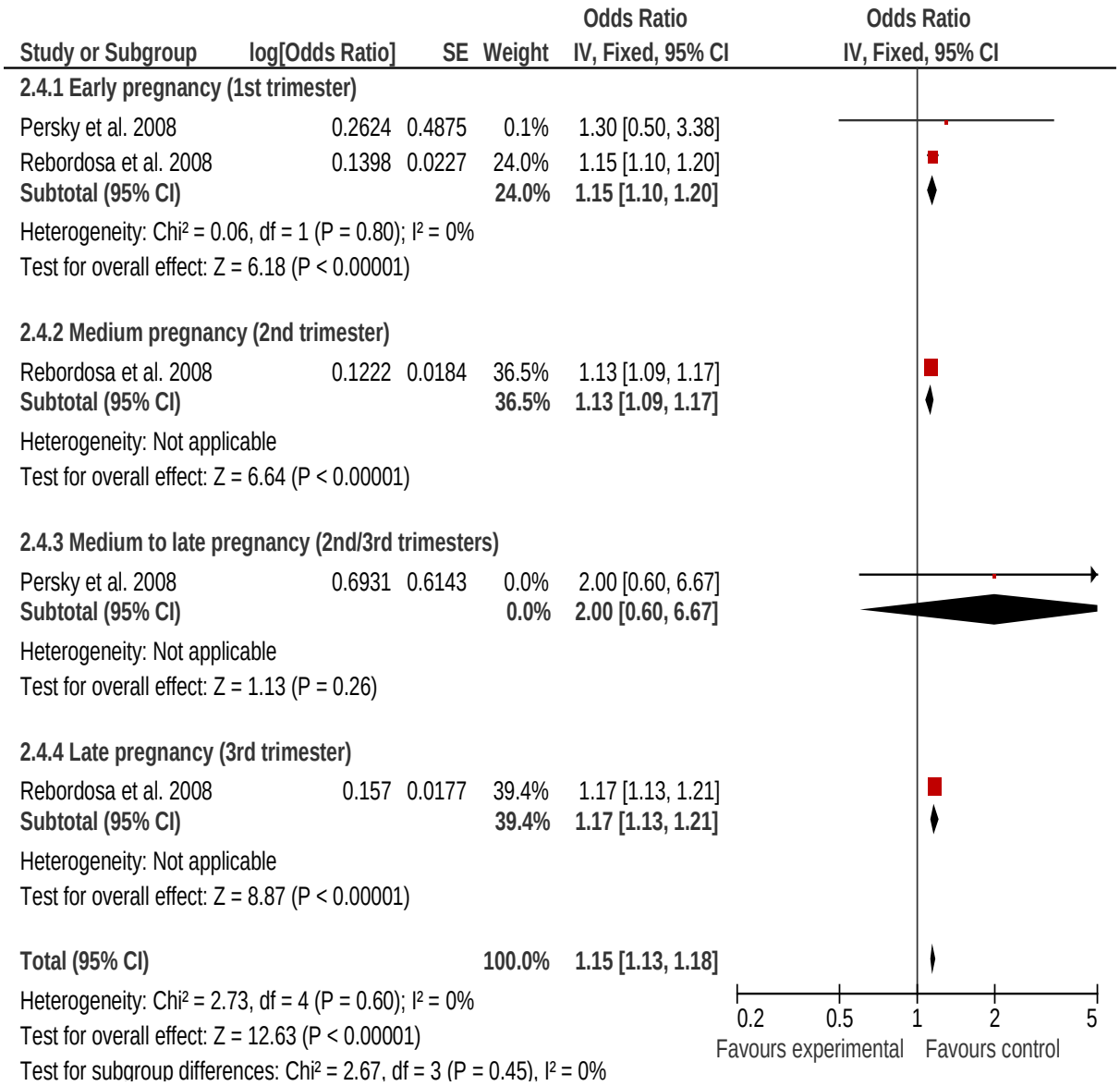


Figure 3b: Exposure during different periods of pregnancy

Figure 4: Meta-analysis of studies that diagnosed asthma in children > 2 years of age:

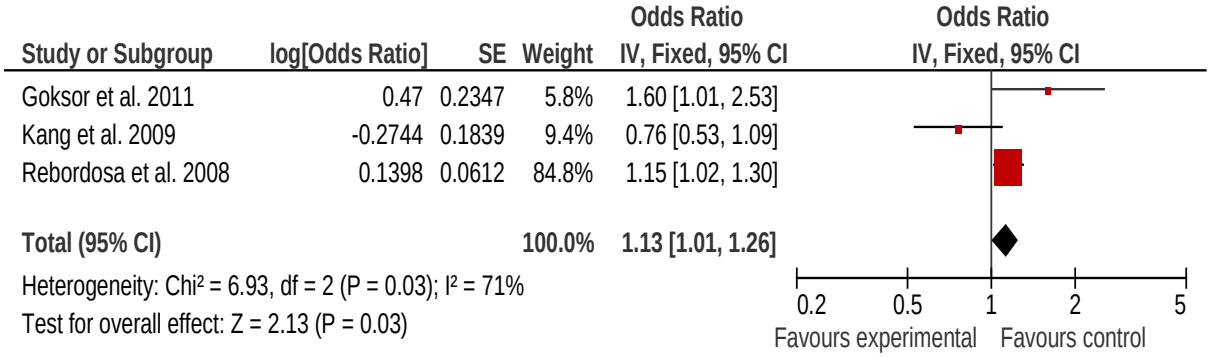


Figure 4a: Exposure during entire pregnancy

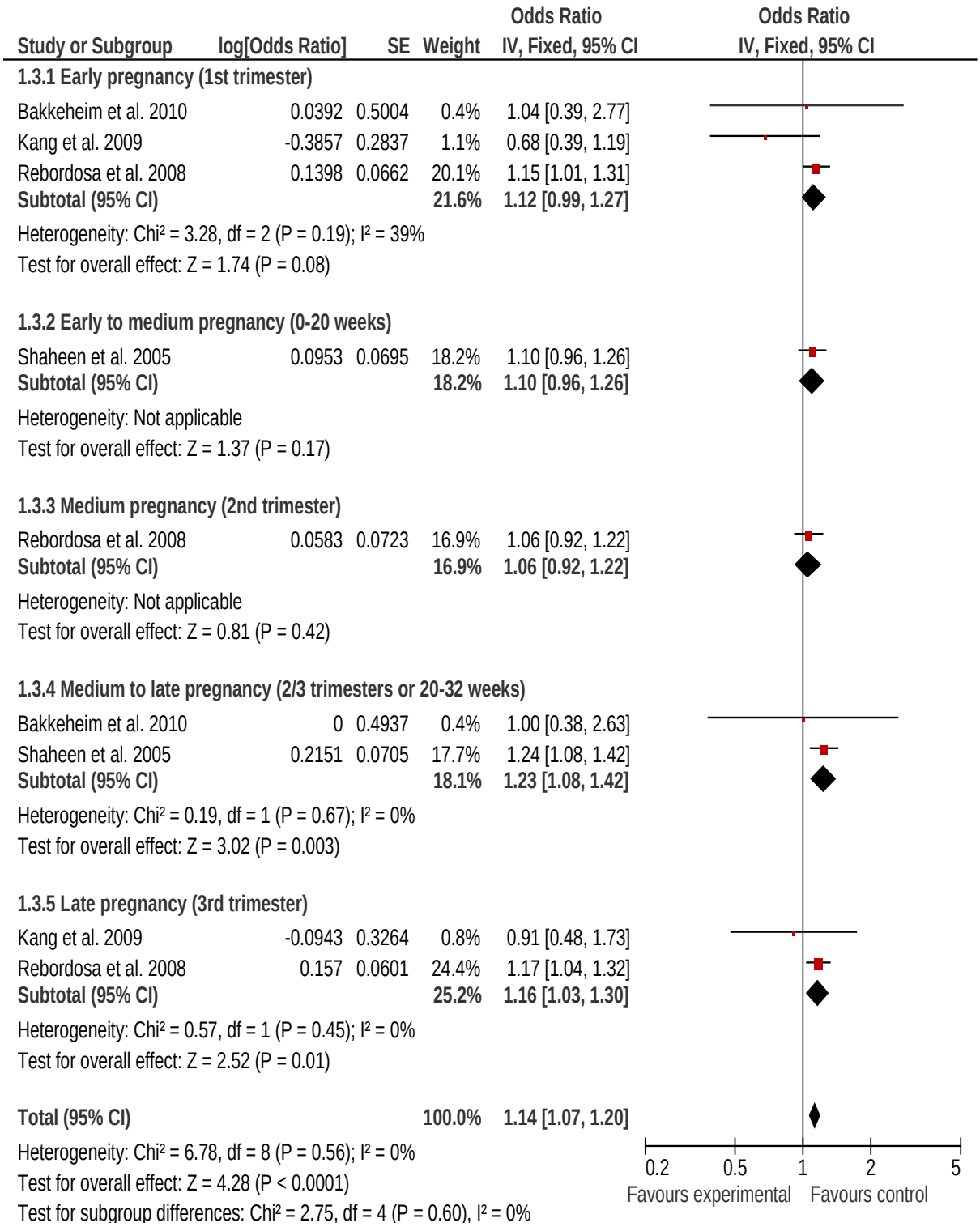


Figure 4b: Exposure during different periods of pregnancy

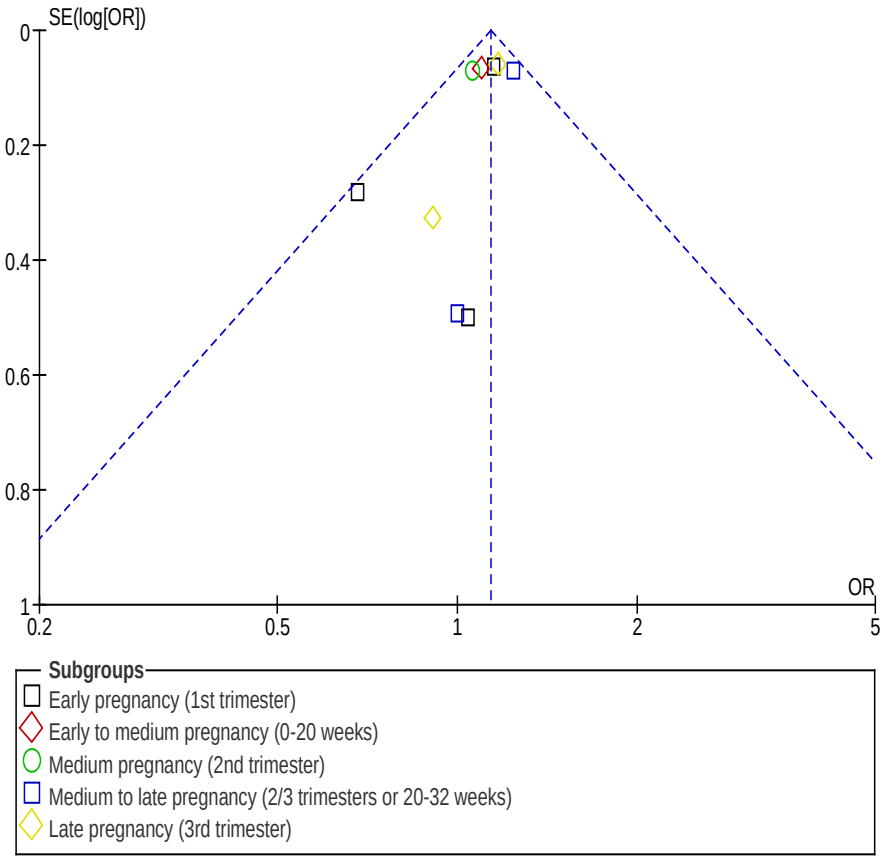


Figure 5: Funnel plot of comparison: Prenatal acetaminophen use during entire pregnancy (Children diagnosed with asthma >2 years of age).

Table 4: Current vs. Past Systematic Reviews

Studies included in current vs. past systematic reviews						
Authors	**Fujii-Rios et al. ***		**Eyers et al. (2011)**		**Etiman et al. (2009)**	
	Included Studies	**Study Design**	**Included Studies**	**Study Design**	**Included Studies**	**Study Design**
	Reberdosa (2008)	Prospective	Reberdosa (2008)[c]	Prospective	Reberdosa (2008)[d]	Prospective
	Kang (2009)	Prospective	Kang (2009)[c]	Prospective	Persky (2008)	Prospective
	Goksor (2011)	Prospective	Goksor (2011)[c]	Prospective	Shaheen (2005)[e]	Prospective
	Persky (2008)	Prospective	Shaheen (2002)[a]	Prospective	Perzanowski (2010)[b]	Prospective
	Shaheen (2005)	Prospective	Perzanowski (2010)[b]	Prospective	Garcia-Marcos (2009)	Cross-sectional
	Bakkeheim (2010)	Prospective	Garcia-Marcos (2009)	Cross-sectional		

* Note: Shaded background indicates overlapping studies between the current and past reviews.

a and b: These two studies were not included in our study as the primary outcome was "wheezing".

c: ORs were calculated using raw data, where as this review used aORs

d: Etiman et al. used hazards ratio of "hospitalization for asthma" instead of using RR of "physician-diagnosed asthma"

e: Etiman et al. extracted aOR that is nowhere to be found in the original publication

Appendix

Table I: Characteristics of Included Studies

Author	Year	Study Design	Participants	Exposure	Outcomes	Confounder adjusted for
Bakkeheim et al.	2010	Prospective cohort, Norway	Children 10 yrs, N=1,016	Maternal use of acetaminophen or aspirin for any pain or fever, respectively, in the first trimester of pregnancy or in the second and third trimester (frequency and dose not reported)	**Primary Outcome:** - Current asthma consisting of history of asthma defined by fulfilling two of three criteria (1. Dyspnoea, chest tightness and/or wheezing; 2. Doctor's diagnosis of asthma; 3. Use of asthma medication) plus symptoms and/or medication within the last year and/or a positive exercise test. - Allergic sensitization - Current allergic rhinitis **Secondary Outcome:** - Current wheeze in the past 12 months - FeNO greater than or equal to 16.77ppb - Mild to moderate bronchial hyper-responsiveness defined as PD20 ≤ 8µmol metacholine - Severe bronchial hyper-responsiveness defined as PD20 ≤ 1µmol metacholine	Parental asthma and allergy, maternal smoking in pregnancy, education level (father and mother), family income at child's birth, maternal health in pregnancy, upper and lower respiratory tract infections from 0 to 6 months of age of children
Goksor et al.	2011	Prospective Cohort, Sweden	Mothers and children of 4.5 yrs of age, N= 4496	Maternal use of paracetamol and exclusive paracetamol use during pregnancy (frequency and dose not reported)	Recurrent wheeze (defined as 3 or more episodes of wheezing during the last 12 months) and inhaled corticosteroid-treated wheeze (defined as ICS treated wheeze during the last 12 months) at 4.5 years of age. Note: ICS-treated wheeze is regarded as a proxy for doctor-diagnosed asthma.	Having a mother or father with asthma, eczema or rhinoconjunctivitis, gender, antibiotic use during pregnancy, smoking during pregnancy, gestational age, caesarean section , asphyxia, antibiotics during first week of life, breast feeding, early fish introduction, own eczema of doctor-diagnosed food allergy during first year of life, parental education.
Kang et al.	2009	Prospective cohort, US	Women during pregnancy and children of 6 yrs from 56 obstetric practices and 15 clinics at six hospitals. N=1,505	Maternal use of acetaminophen during first and/or third trimester of pregnancy. The monthly dose was categorized into 6 levels: 0, ≤ 1,300mg, 1,301-2,600mg, 2,601-5,200mg, 5,201-10,400mg, and >10,400mg per month. The frequency of intake was divided into the following categories: none, 1-7 days per month, 8-14 days per month, more than 14 days per month (but not every day), and every day.	Physician-diagnosed asthma ever with history of wheezing at age 6 years.	Mother's ethnicity, mother's asthma status and symptoms during pregnancy, mother's allergy, father's wheezing, child's ethnicity, child's visit to emergency department for respiratory illnesses, child's antibiotic use during first years of life, child's exposure to tobacco smoke 2h or greater, child's use of allergy medication, child's allergy, child's sneezy or runny nose, child's bronchitis, respiratory syncytial virus, and tonsillitis

Persky et al.	2008	Prospective Cohort, US	Pregnant women and children of 1 yr of age, N=345	Maternal use of acetaminophen during pregnancy (frequency and dose not reported)	Physician-diagnosed asthma, any wheeze, wheeze or cough that disturbed sleep, ER visit for respiratory problem, hospitalizationi for respiratory problem	Confounders adjusted for: Maternal age, child's gender, maternal ethnicity, active and passive smoking during pregnancy, low birth weight, age formula started, antibiotic use in late pregnancy, family history of asthma, breastfeeding, home environment, intervention group
Reberdosa et al.	2008	Prospective Cohort, Denmark	Danish National Birth Cohort with children of 18 months (N=66,445) and 7 yrs (N=12,733)	Maternal use of acetaminophen, aspirin and ibuprofen during pregnancy. Specific gestational weeks of use, on a week-by-week basis was recorded. Number of pills per week was only collected in second and third interview (thus complete dose is not reported).	Primary outcome at 18 months of age: Physician-diagnosed asthma or bronchitis; ever wheezing or whistling; and hospitalization for asthma. Primary outcome at 7 years of age: Physician-diagnosed asthma; wheezing during the past 12 months; transient or persistent wheezing; and late onset of wheezing	Parental asthma, child's gender, social class, gestational age, breast feeding, tobacco exposure during pregnancy, antibiotic use in pregnancy
Shaheen et al.	2005	Prospective Cohort, UK	UK parents and children of age 6-7 yrs, N= 8,511	Maternal use of acetaminophen and aspirin in early (<18-20 weeks) and late (20-32 weeks) pregnancy (never, sometimes, most days/daily, unknown). (Dosage was not reported)	Physician-diagnosed asthma, frequency of wheezing, hay fever, eczema and atopy.	Child's gender, mother's age, smoking education, housing tenure, parity, anxiety score in pregnancy, ethnicity and number of pregnancies, child's birthweight, gestational age and head circumference, mother ever having asthma, eczema, rhinitis and/or migraine, flu, UTI or other infections during late pregnancy, antibiotic use during pregnancy, number of siblings at age 7 years, pet ownership, breast feeding, day care use in first 8 months, damp and/or mold in home, tobacco exposure, child's BMI at 7 years.

Table II: Risk of Biases

Study	Bias	Level of Risk	Notes
Bakkeheim et al.	Detection Bias	Low	Detection bias unlikely since outcome was diagnosed by physician.
	Attrition Bias	Low	Follow-up rate was reasonable (99.7%).
	Reporting Bias	Unclear	Possible underreporting of acetaminophen intake due to recall bias since mothers are asked to recall their exposure to paracetamol during pregnancy when the child is 6 months of age.
	Other Bias	Unclear	Dose and frequency of acetaminophen use were not recorded.
Goksor et al.	Detection Bias	Unclear	Unclear if the interviewers were blinded to the participant's exposure.
	Attrition Bias	High	Low participation rate of 55% may cause selection bias, especially since non-responders tended to smoke during pregnancy, have preterm birth and have lower education.
	Reporting Bias	Low	Possible underreporting of acetaminophen intake due to recall bias since mothers are asked to recall their exposure to paracetamol during pregnancy when the child is 6 months of age.
	Other Bias	Unclear	Dose and frequency of acetaminophen use were not recorded.
Kang et al.	Detection Bias	Low	Interviewers were blind to exposure.
	Attrition Bias	Low	Follow-up rate (83.3%).
	Reporting Bias	Low	Possible recall bias since mothers are asked to recall their exposure to paracetamol before 24 weeks of gestation. Acetaminophen exposure was based on self-report. Child's asthma is reported by the mother, and not confirmed through medical records.
	Other Bias	None	None

Persky et al.	Detection Bias	Unclear	Unclear if interviewers were blinded.
	Attrition Bias	Low	Follow-up rate (90.1%).
	Reporting Bias	Unclear	Possible recall bias since both acetaminophen use and diagnosis of asthma were assessed through self-report (survey).
	Other Bias	Unclear	Frequency or dosage of APAP use was not recorded.
Reberdosa et al.	Detection Bias	Unclear	Unclear if interviewers were blinded.
	Attrition Bias	Unclear	Follow-up rate (73.4%).
	Reporting Bias	Low	Underreporting due to self report may be problematic. All hospitalizations due to asthma were ascertained by linking participants to their registration numbers. Thus validity is maintained to a certain degree.
	Other Bias	None	None
Shaheen et al.	Detection Bias	Unclear	Unclear if interviewers were blinded
	Attrition Bias	Unclear	Unclear what the follow-up rate was.
	Reporting Bias	Low	Possible recall bias.
	Other Bias	Low	Dosage of APAP was not ascertained.