ACTA PÆDIATRICA
NURTURING THE CHILD

Acta Pædiatrica ISSN 0803–5253

REGULAR ARTICLE

Paracetamol in early infancy: the risk of childhood allergy and asthma

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Keywords
Allergic sensitization, Allergy, Asthma, Gender, Paracetamol

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Received
22 February 2010; revised 1 June 2010; accepted 1 July 2010.

DOI:10.1111/j.1651-2227.2010.01942.x

ABSTRACT

Aim: We investigated whether paracetamol exposure in pregnancy and until 6 months of age was associated with allergic disease in school children.

Methods: In a prospective birth cohort study in Oslo, 1016 children included at birth were re-investigated at 10 years. Paracetamol exposure in pregnancy and until 6 months of age was registered. Outcomes at 10 years included current asthma, a history of asthma, allergic sensitization and allergic rhinitis.

Results: Maternal paracetamol use in the first trimester increased the risk for allergic rhinitis at 10 years OR (odds ratio) (95%CI) 2.30 (1.06, 4.97) in boys and girls. Paracetamol use until 6 months in girls increased the risk for allergic sensitization OR 2.20 (1.15, 4.22) and a history of asthma OR 2.20 (1.13, 4.30). The ORs for allergic sensitization and history of asthma in girls remained unchanged adjusting for upper or lower airway infections during the first 6 months of life.

Conclusion: Paracetamol exposure in pregnancy was associated with allergic rhinitis, but not with asthma or allergic sensitization at 10 years of age. Paracetamol used until 6 months of age was associated with allergic sensitization and having a history of asthma in girls at 10 years of age, even considering concomitant airway infections.

INTRODUCTION

Use of therapeutic doses of paracetamol during pregnancy or early months of life may play a role in the development of asthma in children (1,2). A moderately increased risk of asthma, rhinoconjunctivitis and eczema in children at age 6–7 with reported paracetamol use was recently described in the multinational cross-sectional ISAAC study (3), whereas frequent paracetamol use, but not the use of aspirin, was associated with asthma morbidity and allergic rhinitis in British adults (4). A randomized trial in the USA of paracetamol and ibuprofen use for paediatric febrile illness found increased risk of asthma morbidity in the paracetamol group compared to the ibuprofen group (5).

Reduced antioxidant protection during foetal and early childhood life may increase the likelihood for initial critical encounters between Th cells and allergens and subsequent influence on Th-cell polarization in the Th2 direction (6,7). In contrast to acetylsalicylic acid (aspirin), paracetamol does not inhibit cyclooxygenase-2 (COX-2), which is involved in prostaglandin E2 (PGE2) production during the resolution of common respiratory viral infections (8). As PGE2 promotes Th2 and inhibits Th1-type cytokine generation, decreased use of aspirin in favour of paracetamol may be a factor in facilitating allergic sensitization and asthma by augmenting the relative Th1/Th2 cytokine imbalance in genetically predisposed children (8).

Untangling possible causative versus confounding risk factors in asthma development remains a significant challenge. Airway infections in early childhood are among the more substantial risk factors for asthma (9) and are important contributors to clinical indexes for the prediction of asthma risk in childhood (10,11), in addition to being a common reason for ingesting paracetamol.

Within a prospective birth cohort study with information from pregnancy through childhood, we aimed to investigate whether paracetamol intake during pregnancy or in early infancy was associated with asthma or allergy at 10 years of age. Secondarily, we assessed possible modifying effects of early infancy upper or lower airway infections (UAI and LAI, respectively) and gender on the risk of asthma or allergy 10 years later.

Abbreviations
aOR, adjusted odds ratio; BHR, bronchial hyper-responsiveness; COX-2, cyclooxygenase-2; ECA, environment and childhood asthma; FeNO, fractional exhaled Nitric Oxide; GA^{2}LEN, Global Allergy and Asthma European Network; IgE, immunoglobulin E; ISAAC, International Study group of Asthma and Allergies in Childhood; FEF_{50}, forced expiratory flow at 50% of the vital capacity; OR, odds ratio; PGE2, prostaglandin E2; SPT, skin prick test.

METHODS

Study design

This study is a 10-year follow-up of children in the prospective birth cohort 'environment and childhood asthma' (ECA) study in Oslo, described elsewhere (12). In brief, all healthy term children with a birth weight of at least 2000 g living in the township of Oslo during 15 months from January 1, 1992 were invited provided sufficient language skills were present among the parents with 3754 children included.

The initial ECA study concerned the first 2 years of life with half-yearly questionnaires from birth, lung function measurements at birth in 802 children and a nested case–control study at 2 years including children with physician confirmed bronchial obstruction (n = 306) and age-matched controls (n = 306) whom underwent detailed examinations (12). The case–control study at 2 years included specific questions of paracetamol use.

The 10-year follow-up study (2001–2004) with detailed relevant investigations included 1019/1215 (84%) of the children with lung function measurements at birth and/or a clinical 2-year investigation (13).

Written informed consent was obtained from parents of all subjects; the study was approved by the regional medical ethics committee and the Norwegian Data Inspectorate and reported to the Norwegian Biobank registry.

Study subjects

The 1019 children were similar to the non-included birth cohort regarding gender, maternal smoking and paracetamol use in pregnancy and between 0- and 6 -month age of the child, parental atopic disease and family income. Because of lack of data, three subjects could not be classified in relation to asthma; thus, results for 1016 (99.7%) are given (Table S1 in Supporting Information).

Methods pregnancy and 0–6 months

The questionnaire at the maternity ward included detailed questions related to family health, pregnancy complications, medication use (what and when) as well as environmental and socio-economic aspects throughout the three trimesters of pregnancy. At 6 months, parents recorded specifically all health events (what, how often and age), medication use and contact with health care. Infectious diseases were listed including common UAI and LAI, as well as other common febrile conditions. Medication use was listed in relation to possible asthma-related treatment, antibiotic use and given with open questions for any other medication. Ascertained for negative answers was done answering no to any medications in the first 6 months of life.

Methods at 10 -year follow-up

A detailed parental structured interview included central ISAAC questions related to airways symptoms of the child was performed (13), with detailed questions regarding environmental exposure, lifestyle, atopic eczema and allergic rhinitis.

Lung function (presently reported only in relation to BHR measurement) was measured by forced expiratory flow volumes according to the ERS/ATS guidelines (13,14), using a SensorMedics VMax 20c (SensorMedics Diagnostics, Yorba Linda, CA, USA).

Bronchial hyper-responsiveness (BHR) was performed by methacholine provocation with the Spira nebulizer (Spira Respiratory Care Centre Ltd, Hämeenlinna, Finland), consistent with international guidelines (15). We reported the dose causing 20% reduction in FEV_1 (PD_{20}), with a maximum cumulated dose metacholine of 22.4 μmol.

FeNO was measured in (n = 602) of the children by the Ecomedis CLD 88, and the mean of the three best manoeuvres was assessed according to the ERS/ATS guidelines (16).

A standardized exercise test (17) was performed on a second test day (within 1 week) by a 6- to 8 -min treadmill run, of which the last 4 min at 95% of maximal pulse rate with a 5% incline. An exercise test was regarded as positive with a fall in $FEV_1 \geq 10\%$ of baseline FEV_1 within 3–20 min after termination of running.

Skin prick tests (SPT) were performed with Soluprick® allergens (ALK Albello Horsholm, Denmark) (18) with histamine as positive and saline as negative controls. Sensitization was considered positive with a wheal diameter ≥3 mm larger than the negative control. Allergens used were dust mite (*Dermatophagoides pteronnysinus* and *Dermatophagoides farinae*), German cockroach, dog, cat, rabbit dander, birch, timothy (grass), mugwort, moulds (*Cladosporium herbarium* and *Alternaria alternata*), egg white, milk, peanut and codfish.

Serum was analysed for total and specific immunoglobulin E (IgE) and (s-IgE), respectively, using the UniCAP fluoroenzyme immunoassay according to the manufacturer's instructions (Pharmacia Upjohn, Uppsala, Sweden). For s-IgE, common inhalant and food allergens were used as listed earlier.

Outcomes at 10 years

On the basis of the structured interview and clinical examination, the following definitions were applied:

History of asthma: at least two of three criteria being fulfilled at any time in the life of the child:

1. Dyspnoea, chest tightness and/or wheezing.
2. Doctor's diagnosis of asthma.
3. Use of asthma medication (ß-2 agonist, sodium chromoglycate, inhaled or systemic corticosteroids, leukotriene antagonists and/or aminophylline).

Primary outcomes

Current asthma: history of asthma as by aforementioned definition, plus symptoms and/or medication within the last year and/or a positive exercise test (13).

Allergic sensitization: defined as a positive SPT to at least one allergen and/or any s- IgE ≥ 0.35 kU/L.

Current allergic rhinitis: defined as doctor's diagnosis of allergic rhinitis, nasal allergic symptoms within the last 12 months prior to study investigation and allergic sensitization.

Secondary outcomes

History of asthma: as defined earlier.

Current wheeze: Wheezing, tightness or whistling in the chest in the past 12 months.

FeNO ≥ 16.7 (ppb): the cut-off value for FeNO corresponding to the upper reference limit for healthy children (19).

Mild to moderate bronchial hyper-responsiveness: defined as $PD_{20} \leq 8$ μmol metacholine.

Severe bronchial hyper-responsiveness: defined as $PD_{20} \leq 1$ μmol metacholine.

Explanatory variables

All the following were entered into analyses as dichotomous (no/yes) information:

Maternal use of paracetamol or aspirin for any pain or fever, respectively, in the first trimester of pregnancy or in the second and third trimester.

Use of paracetamol or aspirin for fever by the child from 0 to 6 months of age.

Report of any (no/yes) upper airway infection (tonsillitis, otitis media or laryngitis) in the child from 0 to 6 months of age (UAI 0–6).

Report of any (no/yes) lower airway infection (pneumonia, bronchitis or bronchiolitis) in the child from 0 to 6 months of age (LAI 0–6).

Statistical analysis

Demographic results are given as n (%) as stated. Pearson's chi-square tests were used for categorical variables. We used Hosmer backward elimination technique for the multivariate logistic regression models to estimate associations between binominal outcomes and explanatory variables, including the following variables: Gender (*when appropriate stratified by boy/girl*), paracetamol exposure (1. trimester, 2.+3. trimester and between 0 and 6 months of age), current asthma at 10 years, current allergic rhinitis at 10 years, allergic sensitization at 10 years, history of asthma at 10 years, current wheeze at 10 years, maternal smoking in pregnancy, mother's education level at birth of child, father's education level at birth of child, family income at the time of birth of child, parental asthma, parental allergy and maternal health in pregnancy. Further we controlled for gender, (UAI 0–6) and (LAI 0–6) in forward logistic regression to explore the confounding effect of these variables on the associations between binominal outcomes and paracetamol exposure. The model assumptions were tested out using Hosmer's and Lemeschow's goodness of fit test. Analyses were performed using Statistical Package for Social Sciences 15.0 (SPSS inc. Chicago, IL, USA). All p-values (two-sided) equal to or below 0.05 were considered significant.

RESULTS

Maternal use of paracetamol was reported by 31 and 32 women in the first and second-third trimester, respectively, and never in 972 women, whereas 83 infants (42 boys and 41 girls) received at least one dose of paracetamol by 6 months of age (Table S1). Characteristics of the subjects stratified for gender are demonstrated in Table S1.

Main outcomes (current asthma, allergic sensitization and current allergic rhinitis)

Crude risks for current asthma, allergic sensitization and current allergic rhinitis by paracetamol exposure and relevant confounders are presented in (Table S2 in Supporting Information). The risk of current asthma and allergic sensitization at 10 years was not associated with paracetamol use in pregnancy or use between 0 and 6 months of age adjusting for the significant confounders in logistic regression analyses (Table S2).

The risk of current allergic rhinitis was, however, increased by maternal intake of paracetamol in the first trimester, and this association remained significant after adjustment for the significant confounders (Table S2).

Gender differences

Gender was a clinically relevant robust confounder, demonstrating that in girls, but not boys, paracetamol used in the first 6 months of age increased the risk of allergic sensitization [odds ratio (OR) 2.20 (1.15, 4.22) (Fig. 1A,B)]. Although current wheeze and parental allergy were significant confounders, the adjusted OR for paracetamol remained unchanged 2.23 (1.15, 4.33) for the risk of allergic sensitization in girls.

Secondary outcomes (history of asthma, current wheeze, FeNO and BHR)

Paracetamol use during pregnancy was not associated with a history of asthma at 10 years, but use between 0 and 6 months of age tended ($p = 0.070$) to increase the risk of a history of asthma (Table 1). The multivariate regression analyses demonstrated that paracetamol exposure between 0 and 6 months of age significantly increased the risk of a history of asthma after adjusting for gender and the other significant confounders (Table S3 in Supporting Information).

Maternal use of paracetamol in the second and/or third trimester of pregnancy significantly increased the risk of high FeNO levels in the offspring at 10 years (Table 1). This association remained significant in the multivariate analyses (Table S3 in Supporting Information).

Although an association was found between paracetamol intake by the mother in the first trimester and severe BHR at 10 years (Table 1), this association was no longer

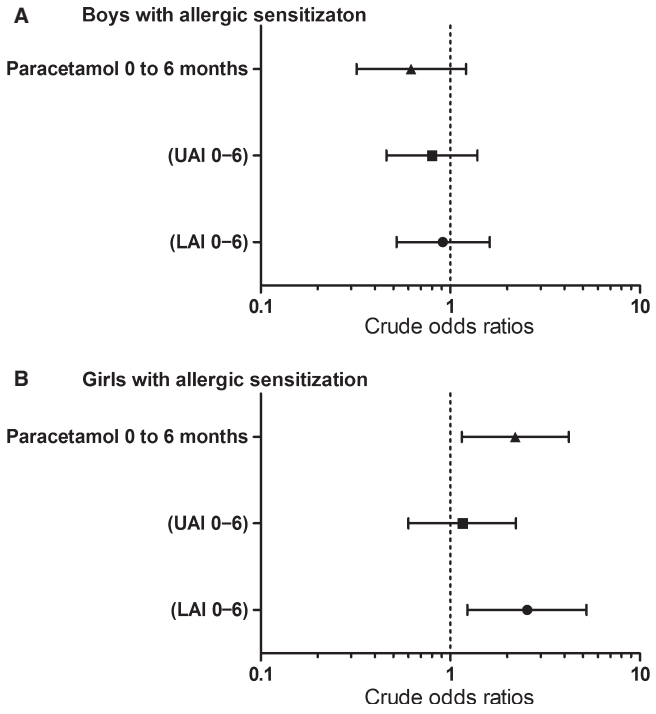

Figure 1 Crude odds ratios for having allergic sensitization at 10 years after paracetamol use between 0 and 6 months of age in (A) boys and (B) girls. UAI 0–6, presence of upper airway infections (no/yes) 0–6 months of age. LAI 0–6, presence of lower airway infections (no/yes) 0–6 months of age.

significant after adjustment for the relevant confounders (data not shown).

We found no significant associations between paracetamol exposure and current wheeze or moderate BHR (Table 1).

Gender differences

Paracetamol intake between 0 and 6 months was significantly associated with a history of asthma at 10 years in girls, but not in boys OR 2.20 (1.13, 4.30) and 1.16 (0.61, 2.23), respectively. Although parental asthma was a significant confounder, the adjusted OR for paracetamol use between 0 and 6 months remained almost unchanged 2.24 (1.13, 4.14) for the risk of a history of asthma in girls.

Daughters of mothers who used paracetamol in the first trimester or in the second and/or third trimester of pregnancy had increased risk of severe BHR with unadjusted OR 6.10 (1.83, 20.4) and 4.04 (1.08, 15.13), respectively. In multivariate analyses, the OR for paracetamol use in the first trimester only remained significant after adjustment for the significant confounders (Table S3 in Supporting Information). The other secondary outcomes were not significantly influenced by gender (data not shown).

Paracetamol exposure between 0 and 6 months of age in relation to concomitant UAI and LAI

Primary outcomes

Although LAI increased the risk of current asthma ($p = 0.001$) and current allergic rhinitis ($p = 0.050$) (Fig. 2A–C), the ORs and significance levels for the association between paracetamol intake and the primary outcomes remained largely unchanged after adjusting for gender and airway infections (Table 2). The risk of allergic sensitization in girls was increased by LAI (Fig. 2A,B), but the OR for paracetamol use between 0- and 6 -month risk for the risk of allergic sensitization in girls was not significantly altered after adjusting for UAI and LAI (adjusted OR 2.18 (1.13, 4.24)).

Secondary outcomes

The crude risks of a history of asthma, current wheeze, high FeNO or BHR by UAI and LAI are given in Table 1. A history of asthma was not significantly associated with paracetamol use after adjusting for gender and UAI a OR 1.44 (0.89, 2.32), but when adjusting for gender and LAI only, use of paracetamol was significantly associated with a history of asthma 1.67 (1.04, 2.68). This association was abridged after adjusting for UAI as well 1.55 (0.95, 2.51). However, the ORs for a history of asthma separated for boys and girls were not significantly altered after adjustment for airway infections (Fig. 3A,B).

Table 1 Crude odds ratio (OR) for a history of asthma, current wheeze, FeNO ≥ 16.7 ppb and PD 20 ≤ 1 and ≤8 μmol metacholine at 10 years by paracetamol exposure and the presence of upper or lower airway infections until 6 months of age

	History of asthma (n = 303) OR (95%CI)	Current wheeze (n = 138) OR (95%CI)	FeNO ≥16.7 ppb (n = 62) OR (95%CI)	PD 20 ≤ 1 μmol metacholine. (n = 87) OR (95%CI)	PD 20 ≤ 8 μmol metacholine. (n = 324) OR (95%CI)
Paracetamol (no/yes) 1 trimester of pregnancy	1.51 (0.72, 3.14)	1.53 (0.61, 3.80)	2.69 (0.84, 8.55)	**2.63** (1.05, 6.58)	0.98 (0.46, 2.12)
Paracetamol (no/yes) 2 + 3 trimester of pregnancy	1.43 (0.69, 2.96)	0.64 (0.19, 2.14)	**3.87** (1.31, 11.37)	2,07 (0.78, 5.54)	0.99 (0.46, 2.16)
Paracetamol (no/yes) 0–6 months of age	1.53 (0.94, 2.43)	1.32 (0.72, 2.41)	1.13 (0.46, 2.79)	0.96 (0.42, 2.15)	0.89 (0.54, 1.44)
Upper airway infections (no/yes) 0–6 months of age	**2.36** (1.57, 3.56)	1.36 (0.79, 2.33)	0.89 (0.37, 2.16)	0.97 (0.48, 2.01)	1.26 (0.83, 1.91)
Lower airway infections (no/yes) 0–6 months of age	**4.23** (2.68, 6.67)	1.48 (0.83, 2.63)	1.51 (0.65, 3.53)	**2.46** (1.34, 4.51)	**1.73** (1.10, 2.70)

FeNO, fractional exhaled nitric oxide.
Significant ORs in bold.

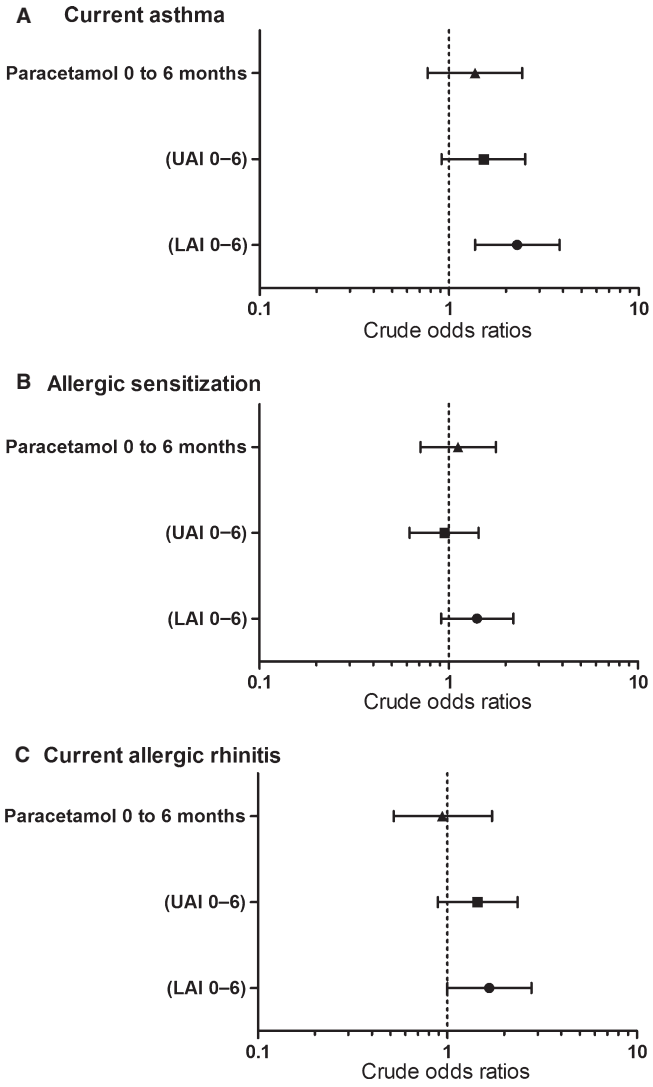

Figure 2 Crude odds ratios (95% CI) for having current asthma (A), allergic sensitization (B) or current allergic rhinitis (C) by lower airway infections until 6 months of age (LAI 0–6), upper airway infections until 6 months of age (UAI 0–6) and by paracetamol use in the child between birth and 6 months of age.

Aspirin

Only five women used aspirin during pregnancy, and there were no reports of aspirin use in infancy in children; thus, no analyses were performed on aspirin use.

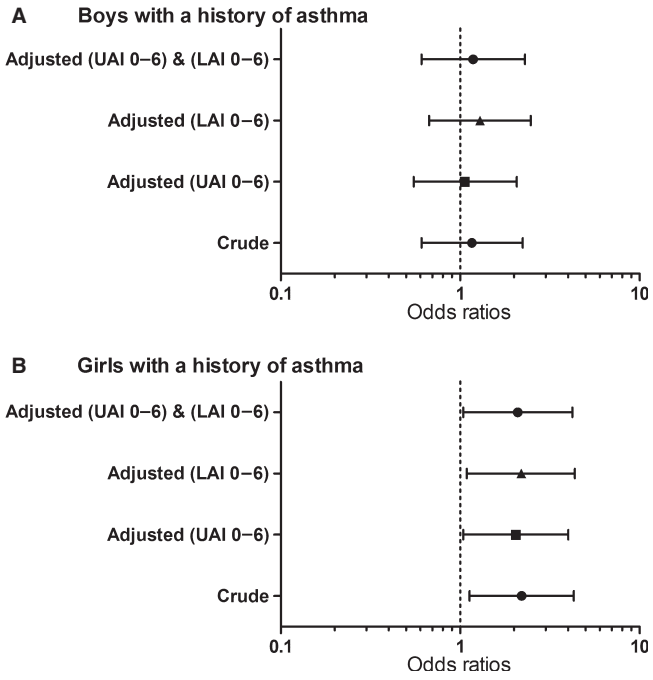

Figure 3 Crude and adjusted odds ratios for having a history of asthma at 10 years after paracetamol use between 0- and 6 -month age intake in A) boys and B) girls. UAI 0–6, presence of upper airway infections (no/yes) 0–6 months of age. LAI 0–6, presence of lower airway infections (no/yes) 0–6 months of age.

DISCUSSION

Current asthma and allergic sensitization at 10 years were not associated with early paracetamol exposure, but maternal intake of paracetamol used in the first trimester of pregnancy increased the risk of current allergic rhinitis. An elevated FeNO was associated with paracetamol use in the second or third trimester, and daughters of women using paracetamol during pregnancy were at increased risk of severe BHR at 10 years of age. However, girls had increased risk of allergic sensitization and a history of asthma at 10 years of age subsequent to intake of paracetamol before 6 months of age, and the risk was not significantly influenced by UAI and LAI in the same time period.

Supporting this study, a few recent reports observed increased risk of wheeze, asthma and allergic disease after paracetamol intake in pregnancy (1,20,21), and in line with our 10-year-old children, increased BHR was observed in

Table 2 Adjusted odds ratios (aOR) of having current asthma, allergic sensitization current allergic rhinitis at 10 years by intake of paracetamol until 6 months of age

	Adjusted for	Current asthma (n = 157) aOR (95%CI)	Allergic sensitization (n = 379) aOR (95%CI)	Current allergic rhinitis (n = 179) aOR (95%CI)
Paracetamol (no/yes) 0–6 months of age	Gender	1.43 (0.80, 2.56)	1.15 (0.72, 1.83)	0.96 (0.52, 1.75)
Paracetamol (no/yes) 0–6 months of age,	Gender & (UAI 0–6)	1.36 (0.76, 2.46)	1.16 (0.72, 1.84)	0.92 (0.51, 1.67)
Paracetamol (no/yes) 0–6 months of age,	Gender & (LAI 0–6)	1.48 (0.82, 2.58)	1.16 (0.73, 1.84)	0.98 (0.54, 1.78)
Paracetamol (no/yes) 0–6 months of age,	Gender, (UAI 0–6) & (LAI 0-6)	1.43 (0.79, 2.58)	1.18 (0.74, 1.88)	0.94 (0.51, 1.72)

UAI 0–6, upper airway infections (no/yes) 0–6 months of age. LAI, lower airway infections (no/yes) 0–6 months of age.

Danish neonates after maternal intake of paracetamol during the third trimester (22). We are not aware of previous reports of associations between FeNO, indicating an inflammatory process, and paracetamol intake during early childhood. Previous prospective studies demonstrated that frequent use of paracetamol in pregnancy may increase the risk of wheezing in the offspring (23,24).

The increased risk of current rhinitis, elevated FeNO and BHR after paracetamol exposure in pregnancy indicates that intrauterine inflammatory processes may be altered owing to biological effects of paracetamol.

Paracetamol use before 6 months of age was significantly associated with a history of asthma at 10 years after adjusting for relevant confounders. This is in line with studies from Singapore (1), New Zeeland (25) and the ISAAC phase III study (3) for childhood asthma and current wheeze after paracetamol intake in the first year of life. The increased risk of a history of asthma in this study supports the assumption of a relationship between paracetamol exposure in early life and later childhood asthma, but in this population the more strict definition of current asthma is more likely to reflect the clinical disease state of the children (13). The significant association between paracetamol exposure in infancy and a history of asthma, but not current asthma, may question a causal relationship, as the former outcome may reflect early wheezing and reverse causation. Paracetamol use was in this study not associated with current wheeze at 10 years, and although relatively few children in this study were exposed to paracetamol between 0 and 6 months, we know from previous studies that the incidence of wheezing declines with age and that the associations between risk factors for allergic disease and clinical outcomes are likely to be strongest early in life (26).

Increased risk of allergic sensitization at 10 years in girls after paracetamol intake in infancy in this study is consistent with reports from Ethiopia (27), the association between reported paracetamol use and eczema and hay fever in New Zealand children (25) and increased risk of allergic rhinitis in Mexican children, respectively (28). Paracetamol for fever in the first year of life increased the risk of allergic rhinitis and eczema in the children in the ISAAC phase three study, and a possible biological explanation is a modification in Th1/Th2 balance towards atopic disposition after early exposure for paracetamol (3).

Strengths and limitations

This is one of the first *prospective* birth cohort studies addressing risk of asthma and allergic disease with contemporary recording (past trimesters and past 6 months) of maternal paracetamol use in pregnancy and intake in early infancy, respectively. We used a strict definition of asthma, which has been found to correlate with objective measures and genetic markers of allergic disease (29). A major strength of this study was the use of recorded data at the maternity ward of any medication during pregnancy and the detailed recording of medication, respiratory and other infections of the child at 6 months for the analyses of outcomes 10 years later. The analyses could separate the effects of the infections itself and the use of paracetamol, and as paracetamol in childhood mainly is used for febrile infections, the consistency of the ORs after adjustment for UAI and LAI strengthens the significance of the present results.

A shortcoming of this study was that we could not, for the entire cohort report the number of doses paracetamol taken by the pregnant mothers or given to the children, and were subsequently not able to analyse on dose–response associations. The use of open questions for paracetamol use in epidemiological studies may be associated with underreporting of the exposure in contrast to the use of specific questions, although we calculated the exposure difference to be limited to 20% or less.

CONCLUSION

In contrast to current asthma and allergic sensitization, a history of asthma and allergic rhinitis were significantly associated with early paracetamol exposure in boys and girls. However, a gender effect was observed revealing that allergic sensitization and a history of asthma were associated with paracetamol use in early infancy in female offspring, even in relation to concomitant airway infections. Causality could not be determined in this study.

FUNDING

The study was supported by Oslo University Hospital, Ullevål, and was performed within the ORAACLE (the Oslo Research group for Asthma and Allergy in Childhood; the Lung and Environment), which is member of the GA^{2}LEN, European Network of Centres of Excellence in asthma and allergy.

CONFLICTS OF INTEREST

All authors disclose no personal affiliation, financial agreement or other involvement with any company whose product figures in the submitted manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Table S1 Clinical data and paracetamol use of the 1016 children in the prospective birth cohort study, also stratified by boys and girls.

Table S2 Crude and adjusted odds ratios for the main outcomes of current asthma at 10 years, allergic sensitization at 10 years and current rhinitis at 10 years by paracetamol intake, gender and the included confounders.

Table S3 Adjusted odds ratios (aOR).

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