

Case study: does paracetamol cause asthma?

1. Asthma epidemic in the Western world

Children

Year/place	Data	Reference
End '80s South Africa	Rural vs. urban asthma prevalence in Xhosa children	Van Nierkerk et al. 1979
End '80s New Zealand	Rural vs. urban asthma prevalence in Tokeluan children	Waite et al. 1980
End '90s New Zealand Australia	Asthma prevalence has doubled among children in New Zealand and Australia.	Mitchell, 1983; Robertson, 1991
End '90s UK	Serial prevalence studies show childhood asthma is becoming more common: overall prevalence of episodic wheeze and diagnosed asthma has doubled over last two decades.	Ninan et al. 1992; Burr et al. 1989

Adults

Year/place	Data	Reference
End '80s Papua New Guinea	Increase of asthma in South Fore people upon migration from subsistence societies to developed countries	Woolcock et al. 1983.
End '90s Finland, Sweden	Analysis of data from conscripts to Finnish defence forces reveals a 6fold increase in asthma prevalence at call-up examination between 1966 and 1989 47% increase in Sweden between 1971 and 1981	Haahtela et al. 1990; Aberg, 1989.
End '90s Australia	In Busselton, Australia, Prevalence of diagnosed asthma in adults (18-55) increased from 9% to 16,3% between 1981 and 1990.	Peat et al. 1992
End '90s Canada	In Manitoba, Canada, physician-diagnosed asthma increased in all age groups between 1980 and 1990	Manfreda et al. 1993

2. Statistical evidence for causal association between paracetamol and asthma:

Strength of the association

Authors/Method/Purpose	Population	Results
Barr RG, Wentowski CC, Curhan GC, et al. (2004). Prospective cohort Examine the relationship between paracetamol use and new onset of asthma in adults (women).	121,700 women – 73,321 included in the analysis, (11 centres in US).	Increased risk of diagnosis of new-onset asthma with frequency of use Adjusted RR 1.63, 95% CI 1.11-2.39 p value for trend = 0.006
Shaheen, Newson, Sheriff et al. (2002) Prospective cohort (Birth cohort) Examine the relationship between prenatal paracetamol use and wheezing in offspring at 6 mo.	9400 children of women identified as paracetamol intakers during pregnancy. UK	Increased risk of wheezing before 6 mo for offspring of frequent paracetamol users over 20-32 wk prenatally: OR 2.34 (95% CI 1.24-4.40; p 0.0008).
Lesko SM, Louik C, Vezina RM, Mitchell AA. (2002). RCT double blinded without placebo Compare the incidence of adverse reactions among children administered	84,000 febrile children Age ≤ 12 yr Randomly assigned acetaminophen, low-dose ibuprofen, or high-dose ibuprofen Boston area	Among 1879 children with asthma, outpatient visits for asthma were lower in the ibuprofen arm than the paracetamol arm (RR 0.56 95% CI 0.34-0.95); Hospitalizations were nonsignificantly lower (RR 0.63 95% CI 0.25-1.60).

paracetamol or ibuprofen		
Shaheen, Sterne, Songhurst et al. (2000)*. Case control study Determine if frequent paracetamol use is a risk factor for asthma.	Adults aged 16-49 years registered with 40 general practices in Greenwich, South London. Frequency of use of paracetamol and aspirin was compared in 664 individuals with asthma and in 910 without asthma.	After controlling for potential confounding factors the odds ratio for asthma, compared with never users, was 1.06 (95% CI 0.77 to 1.45) in infrequent users (<monthly), 1.22 (0.87 to 1.72) in monthly users, 1.79 (1.21 to 2.65) in weekly users, and 2.38 (1.22 to 4.64) in daily users (p (trend) = 0.0002).

*(Association was present in users and non-users of aspirin).

Amongst cases increasing paracetamol use was associated with more severe disease. Frequency of aspirin use was not associated with asthma when cases as a whole were compared with controls, nor with severity of asthma amongst cases).

Robustness of association across geography, culture and age

Authors, method, objective	Population	Results
Wickens, Beasley, Town et al. (2011). Prospective cohort (Birth cohort). <i>Logistic regression models were adjusted for potential confounders.</i> Investigate the associations between infant and childhood paracetamol use and atopy and allergic disease at 5-6 years.	New Zealand Paracetamol exposure between birth and 15 months in Christchurch (n=505) and between 5 and 6 years for all participants (Christchurch and Wellington) (n=914). Outcome data collected at 6 years for all participants.	Paracetamol exposure before the age of 15 months was associated with atopy at 6 years [adjusted odds ratio (OR)=3.61, 95% confidence interval (CI) 1.33-9.77]. Paracetamol exposure between 5 and 6 years showed dose-dependent associations with reported wheeze and current asthma but there was no association with atopy. Compared with use 0-2 times, the adjusted OR (95% CI) were wheeze 1.83 (1.04-3.23) for use 3-10 times, and 2.30 (1.28-4.16) for use >10 times: current asthma 1.63 (0.92-2.89) for use 3-10 times and 2.16 (1.19-3.92) for use >10 times: atopy 0.96 (0.59-1.56) for use 3-10 times, and 1.05 (0.62-1.77) for use >10 times.
Amberbir et al. Longitudinal birth-cohort study Investigate the independent effects of paracetamol and geohelminth infection on the incidence of wheeze and eczema in a birth cohort.	Population-based cohort of 1,065 pregnant women from Butajira, Ethiopia,	Paracetamol use was significantly associated with a dose-dependent increased risk of incident wheeze (adjusted odds ratio = 1.88 and 95% confidence interval 1.03-3.44 for one to three tablets and 7.25 and 2.02-25.95 for ≥ 4 tablets in the past month at age 1 vs. never), but not eczema.
Beasley, Clayton, Crane et al. (2011). Cross-cultural study Examine the risk of asthma rhinoconjunctivitis and eczema in adolescents using paracetamol	122 centers in 54 countries 320,000 children 13-14 yr old	Dose dependent increase in prevalence and severity of asthma > once per year: OR 1.43 (95% CI 1.33-1.53) ≥ once per month: OR 2.51 (95% CI 2.33-2.70) <i>Association identified at almost all sites regardless of geography, culture, stage of development</i>
Etminan, Sadtsafavi, Jafari (2009). Systematic review and meta-analysis of epidemiologic studies Quantify the association between acetaminophen use and the risk of asthma in children and adults.	Thirteen cross-sectional studies, four cohort studies, and two case-control studies comprising 425,140 subjects	Pooled odds ratio (OR) for asthma among subjects using acetaminophen was 1.63 (95% CI, 1.46 to 1.77). The risk of asthma in children among users of acetaminophen in the year prior to asthma diagnosis and within the first year of life was elevated (OR: 1.60 [95% CI, 1.48 to 1.74] and 1.47 [95% CI, 1.36 to 1.56], respectively). Only one study reported the association between high acetaminophen dose and asthma in children (OR, 3.23; 95% CI, 2.9 to 3.6). There was an increase in the risk of asthma and wheezing with prenatal use of acetaminophen (OR: 1.28 [95% CI, 1.16 to 41] and 1.50 [95% CI, 1.10 to 2.05], respectively).
Beasley et al. Cross-cultural study Examine the risk of asthma, rhinoconjunctivitis and eczema in children using paracetamol	122 centres in 54 countries 200,000 children 6-7 yr	Dose dependent increase in prevalence and severity of asthma > once per year: OR 1.61 (95% CI 1.46-1.77) ≥ once per month: OR 3.23 (95% CI 2.91-3.60) <i>Association identified at almost all sites regardless of geography, culture, stage of development</i>
Shaheen SO, Potts J, Gnatiuc L, et al. (2008). Random effects meta of –analysis Case-control studies Investigate paracetamol-asthma relationship in Europe	1028 people 20-45 yrs from 12 centres across Europe (Amsterdam, Berlin, Barcelona, Coimbra, Ghent, London, Łódź, Palermo, Odense, Rome, Stockholm, Vienna).	Comparison of asthma risk for weekly use of paracetamol vs <weekly use: adjusted OR 2.87 (1.49–5.37), p. value: 0.002 Comparison of asthma risk for weekly use of other painkillers vs <weekly use: adjusted OR 1.85 (0.79–4.31), p. value: 0.15.
McKeever, Lewis, Smit et al. (2005). Cross-sectional analysis using the Third National Health and Nutrition Examination Survey. To investigate the associations between use of pain medication, particularly acetaminophen, and asthma, COPD, and FEV1 in adults.	U.S. citizens across ages and ethnicities.	Evidence that use of acetaminophen is associated with an increased risk of asthma and COPD, and with decreased lung function. Dose-response association of acetaminophen use and asthma (adjusted odds ratio, 1.20; 95% CI, 1.12-1.28; p value for trend < 0.001).

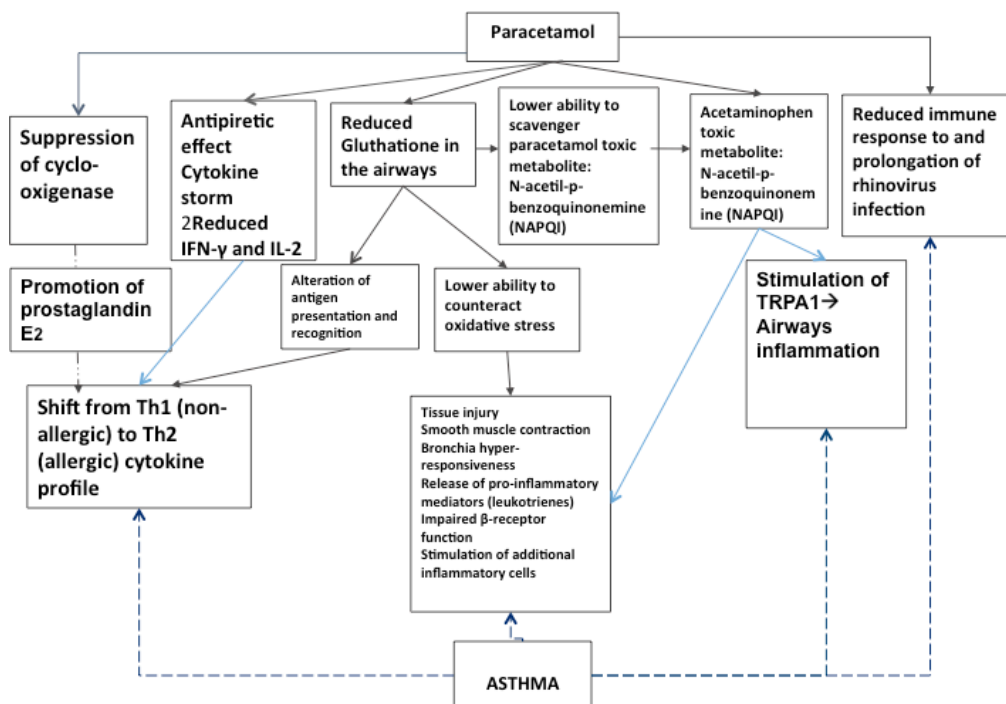
Dose response relationship

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Lesko SM, Louik C, Vezina RM, Mitchell AA. (2002). RCT double blinded without placebo Compare the incidence of adverse reactions among children administered paracetamol or ibuprofen	84,000 febrile children Age ≤ 12 yr Randomly assigned acetaminophen, low-dose ibuprofen, or high-dose ibuprofen Boston area	Among 1879 children with asthma, outpatient visits for asthma were lower in the ibuprofen arm than the paracetamol arm (RR 0.56 95% CI 0.34-0.95); Hospitalizations were non-significantly lower (RR 0.63 95% CI 0.25-1.60).
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Relationship between asthma epidemic and per-capita sales of acetaminophen across countries

Authors/Method/Purpose	Population	Results
Newson et al. (2000) Ecologic Study Examine the rate of Asthma and aggregate consumption of acetaminophen in 1994-95.	English speaking countries in the ECHRIS study.	Prevalence of wheeze increased by 0.52% for 13-14 yr olds; By 0.26% for young adults, For each gram increase in per capita paracetamol sales.

Possible molecular mechanisms



Coincidence in time trends

Authors/Method/Purpose	Population	Results
Varner et al. (1998) Systematic review of U.S. studies Investigate the relationship between substitution of Aspirin with paracetamol and increased asthma prevalence in developed countries	U.S. citizens < 20 years	Hypothesis generation based on epidemiologic trends and changed prescription practices regarding aspirin use in paediatrics.

