

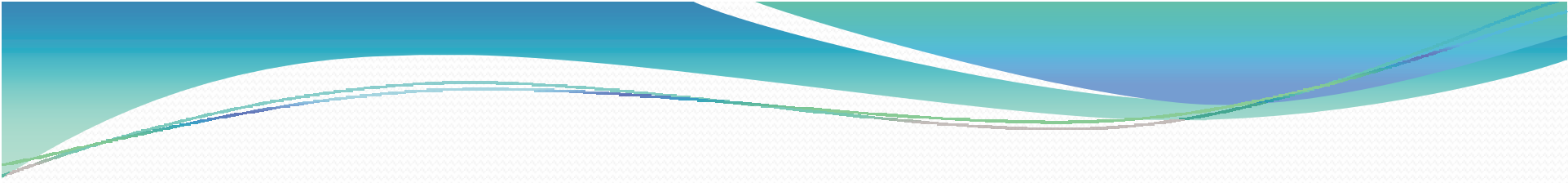
# Paracetamol use in early life and asthma: prospective birth cohort study


*BMJ* 2010; 341: c4616




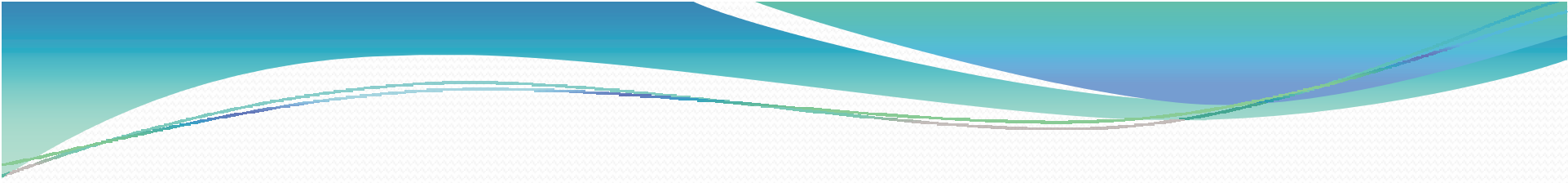
# INTRODUCTION

- Paracetamol (acetaminophen) is the most commonly used analgesic in young children.
- Some evidence suggests that ingestion of paracetamol in early life may cause asthma, eczema, and allergic rhinitis in some children.
- Exposure to paracetamol may increase respiratory oxidative stress by depleting glutathione in the lungs, thereby enhancing airway inflammation and bronchoconstriction
- Decreased glutathione concentrations may also induce a shift from a T helper cell type 1 response to a T helper cell type 2 response with cytokine production favouring the development of allergic disease.

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- The largest study was the International Study of Asthma and Allergy in Childhood (ISAAC) phase III, which included data from 72 countries. It showed that exposure to paracetamol in the first year of life was associated with an increased risk of asthma at age 6-7 years, allergic rhinitis, and eczema.

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- THE LANCET Volume 372, Issue 9643, 20-26 September 2008, Pages 1039-1048 **“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”**
  - 205,487 children aged 6–7 years from 73 centres in 31 countries were included in the analysis. In the multivariate analyses, use of paracetamol for fever in the first year of life was associated with an increased risk of asthma symptoms when aged 6–7 years.
  - Use of paracetamol was similarly associated with the risk of severe asthma symptoms, with population-attributable risks between 22% and 38%.

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- [Am J Respir Crit Care Med.](#) 2011 Jan 15;183(2):171-8. Epub 2010 Aug 13. **“Acetaminophen use and risk of asthma, rhinoconjunctivitis, and eczema in adolescents: International Study of Asthma and Allergies in Childhood Phase Three.”**
  - A total of 322,959 adolescent children from 113 centers in 50 countries participated. In the multivariate analyses the recent use of acetaminophen was associated with an exposure-dependent increased risk of current asthma symptoms

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- However, the results from ISAAC may have been confounded by respiratory infections in early life. particularly lower respiratory tract infections, is a known risk factor for asthma.
  - Given the current global burden of asthma, if paracetamol is a cause of asthma its use needs to be urgently re-evaluated, particularly in the first two years of life during pulmonary development.
  - Murdoch Childrens Research Institute, Royal Children's Hospital, Parkville, Australia "*Paracetamol use in early life and asthma: prospective birthcohort study*" *BMJ* 2010;341:c4616



# METHODS

- **Study population**
- 620 infants before birth, between 1990 and 1994 in Melbourne, Australia. Infants whose family members had eczema, asthma, allergic rhinitis, or severe food allergy.
- **Data collection**
- After the birth of the infant, an allergy trained nurse (CA) did a telephone survey every four weeks until the age of 64 weeks and then at 78 weeks and at 2 years (a total of 18 times). Each survey documented any illnesses since the previous interview and oral exposures to food or medicine, including paracetamol. The number of episodes, the days of use, and the reason for the administration of paracetamol were recorded for each exposure. An annual telephone interview took place from 3 to 7 years of age.
- One of three allergy trained research nurses did skin prick tests at 6, 12, and 24 months, using a standard technique. Allergen extracts used were cows' milk, egg white, peanut, house dust mite, rye grass, and cat dander, and tests were read at 15-20 minutes.

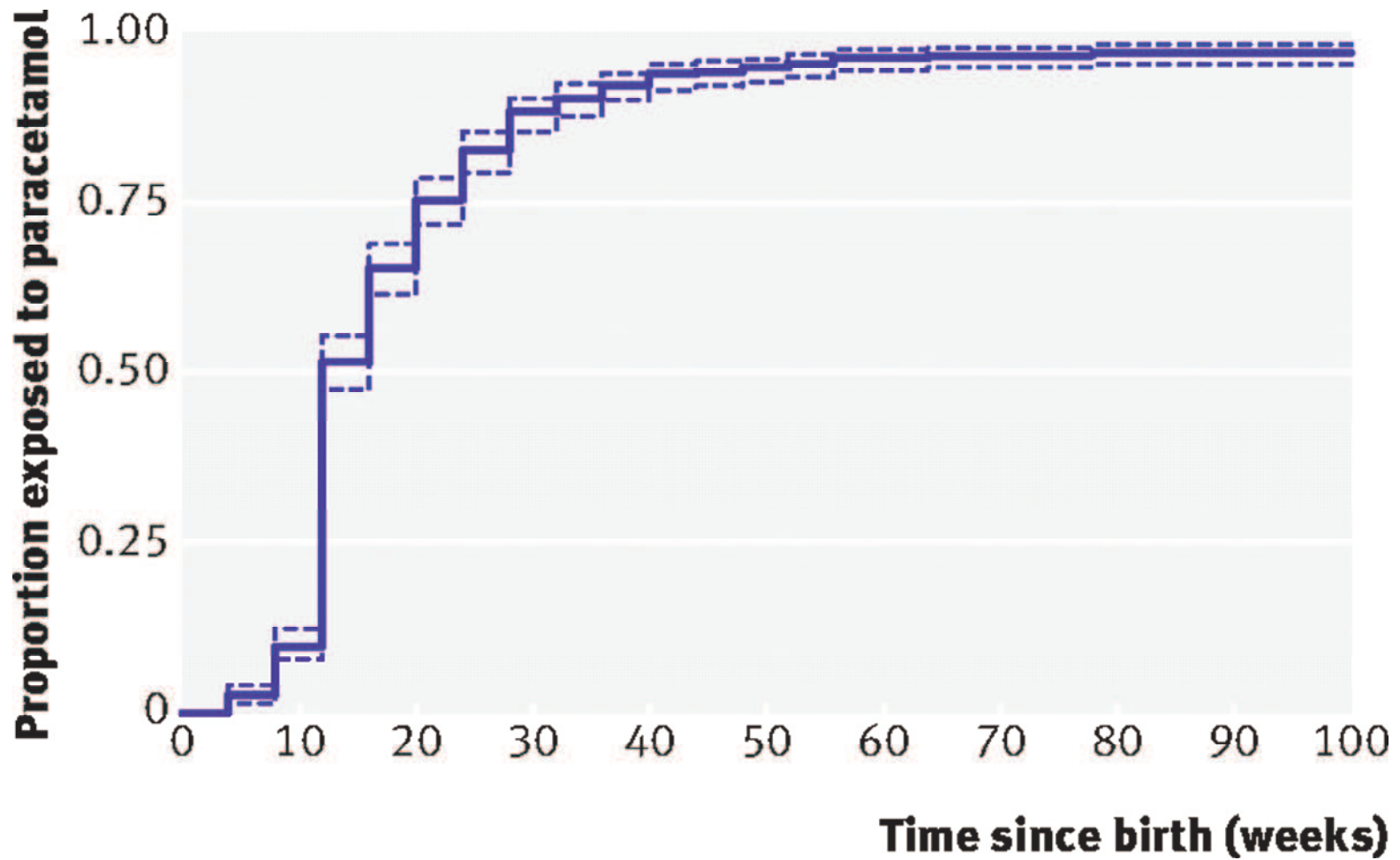


# RESULTS

- **Study population and paracetamol exposure**
- Of the 620 infants in Study, 575 (92.7%) were followed to age 2 years (25 were lost to follow-up, 14 refused participation, and six were missed at 2 years but rejoined the study after this time).
- A total of 495 (79.8%) completed a follow-up at either 6 or 7 years or both (88 lost, 37 refused participation).
- Children who were lost to follow-up were not systematically different in terms of exposure to paracetamol
- Almost all (97%, 556/575) infants received paracetamol during the first two years of life The median age at first exposure was 12 weeks the median total number of days of exposure was 17



Fig 1 Age at first introduction of paracetamol (with 95% confidence interval).



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**Table 2**

Paracetamol intake up to 2 years of age according to stated reason for use (n=575)

Reason for use	No (%) children exposed	Episodes of exposure*		Cumulative days of exposure*	
		Median (IQR)	Range	Median (IQR)	Range
Any indication	556 (96.7)	7 (4-9)	1-16	17 (10-27)	1-84
Lower respiratory tract symptoms	104 (18.1)	1 (1-1)	1-5	4 (2-5)	1-27
Allergy	13 (2.3)	1 (1-1)	1-2	2 (2-3)	1-8
Upper respiratory tract symptoms	510 (88.7)	3 (2-5)	1-12	9 (5-16)	1-69
Non-respiratory illness	537 (93.4)	3 (2-5)	1-11	7 (4-11)	1-50

IQR=interquartile range.

\*Calculated in children exposed to paracetamol for each reason.



## Frequency of outcomes

- The cumulative incidence of eczema up to 2 years of age was 45.9% (264/575). At age 6-7, 29.9% (148/495) of children had current childhood asthma, 23.6% (117/495) had current allergic rhinitis, and 31.8% (157/493) had current childhood eczema.
- Skin prick tests were done on 445 children at 2 years of age, and 30.3% (135/445) reacted to one or more allergens.



## Total days of paracetamol use

- The total number of days of paracetamol use in the first two years of life was slightly higher in children who had current childhood asthma or allergic rhinitis
- The unadjusted regression analysis showed that a greater number of days of paracetamol exposure (all causes) was associated with increasing risk of childhood asthma
- We also found an association for the outcomes of allergic rhinitis and infantile wheeze but no clear evidence of associations with eczema or skin prick test positivity at 2 years of age

### Table 3

Paracetamol use in early life among children with and without childhood asthma and allergic rhinitis. Values are medians (interquartile range) unless stated otherwise

Reason for use	Asthma at age 6-7 years			Allergic rhinitis at age 6-7 years		
	No (n=347)	Yes (n=148)	P value*	No (n=378)	Yes (n=117)	P value*
Any indication	16 (9-25)	18 (10.5-29)	0.05	16 (9-26)	19 (12-31)	0.01
Lower respiratory tract symptoms	0 (0-0)	0 (0-2)	<0.01	0 (0-0)	0 (0-3)	<0.01
Upper respiratory tract symptoms	7 (3-14)	9 (4-17)	0.04	8 (3-14)	10 (5-17)	0.01
Non-respiratory illness	6 (3-10)	6 (3-10)	0.53	6 (3-10)	6 (3-9)	0.48

\*Mann-Whitney U tests.

**Table 4**

Associations between total days of paracetamol use (any indication) during early life and risk of allergic disease

	Unadjusted		Model 2—adjusted for standard confounders*		Model 3—adjusted for frequency of infections†	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
<b>Early life (up to 2 years) outcomes</b>						
Infantile wheeze	1.45 (1.23 to 1.71)	<0.01	1.44 (1.21 to 1.71)	<0.01	1.44 (1.17 to 1.77)	<0.01
Infantile eczema	1.13 (0.99 to 1.30)	0.08	1.16 (1.01 to 1.33)	0.04	1.13 (0.97 to 1.31)	0.11
Positive skin prick test‡	0.97 (0.82 to 1.14)	0.68	0.96 (0.81 to 1.13)	0.62	0.98 (0.82 to 1.18)	0.86
<b>Childhood (5-7 years) outcomes</b>						
Asthma	1.18 (1.00 to 1.39)	0.05	1.16 (0.98 to 1.38)	0.09	1.08 (0.91 to 1.29)	0.39
Incident asthma§	0.94 (0.75 to 1.18)	0.60	0.96 (0.76 to 1.22)	0.73	0.97 (0.76 to 1.25)	0.83
Allergic rhinitis	1.21 (1.01 to 1.46)	0.04	1.19 (0.99 to 1.44)	0.07	1.17 (0.96 to 1.43)	0.12
Eczema	1.05 (0.90 to 1.22)	0.52	1.09 (0.93 to 1.27)	0.29	1.10 (0.93 to 1.29)	0.26

Associations expressed as effect per doubling of number of days of intake (regression on  $\log_2(\text{days paracetamol}+1)$ ).

\*Infant's sex, parental history of asthma, and presence of older siblings at time of birth.

†As per model 2, plus frequency of infections (upper and lower respiratory tract infections, otitis media, and gastrointestinal infections) during first 2 years of life (frequency of each form of infection classified as 0, 1-2, or  $\geq 3$ ).

‡ $\geq 3$  mm to at least one of six allergens at 2 year test.

§Excludes children who had lower respiratory symptoms within first 2 years of life.



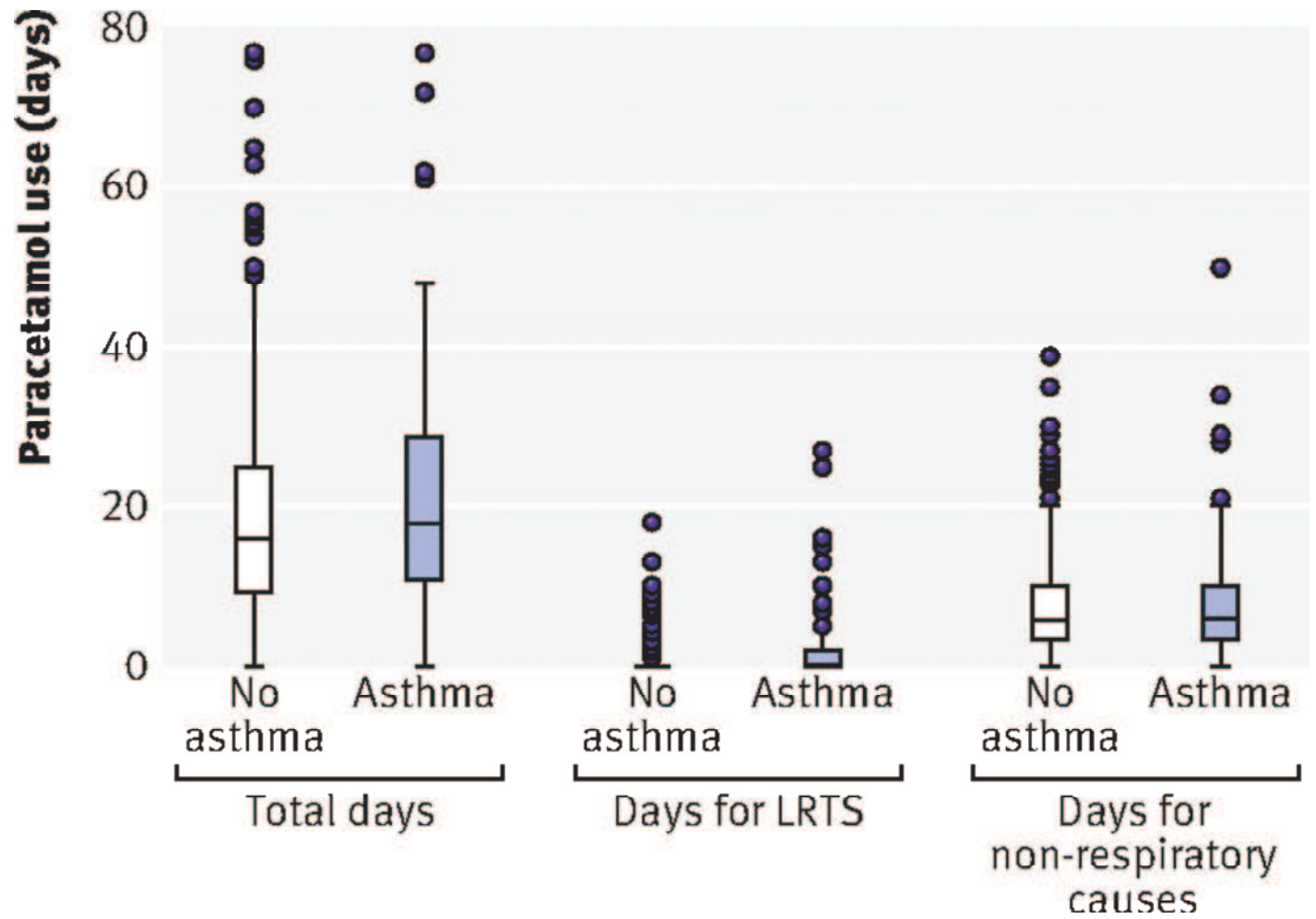


## Paracetamol use for non-respiratory illness

- We found no evidence of any association between paracetamol use for non-respiratory illness and risk of any allergic disease outcome



Fig 2 Days of paracetamol use (by indication) between children with and without asthma in childhood.



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## Paracetamol use for lower respiratory tract illness

- Use of paracetamol for lower respiratory tract symptoms was strongly associated with increased risk of childhood asthma
- 244 children had lower respiratory tract symptoms (infantile wheeze, bronchitis, or drugs for lower respiratory tract symptoms). In this subgroup, 43% (104/244) had received at least one day of paracetamol for lower respiratory tract symptoms.



## Paracetamol use for upper respiratory tract illness

- Paracetamol use for upper respiratory tract symptoms was associated with increased risk of childhood asthma
- Only 2.4% of children (14/575) did not have upper respiratory tract symptoms within the first two years of life.
- upper respiratory tract symptoms was strongly related to increased risk of childhood asthma (35%, 14% to 61%, per event).
- When we adjusted the days of paracetamol use for upper respiratory tract symptoms for the number of events, the evidence of an association was substantially attenuated (1.10, 0.95 to 1.28).



# Conclusions

- Consistent with previous studies in this area, this prospective cohort study found evidence of a crude association between paracetamol use in early life and increased risk of asthma.
- However, we found no evidence of such an association after adjustment for history of early infections, nor when the association was limited to paracetamol use for non-respiratory tract illness.
- Moreover, although use of paracetamol for lower respiratory tract infections and wheeze was associated with increased risk of allergic disease,
- We conclude that paracetamol use in early life is not an independent risk factor for childhood asthma.