

ORIGINAL ARTICLE

The effects of early and late paracetamol exposure on asthma and atopy: a birth cohort

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Summary

Background Despite reports of positive associations between paracetamol and asthma, the nature of these associations is unclear.

Objective We aimed to investigate the associations between infant and childhood paracetamol use and atopy and allergic disease at 5–6 years.

Methods In a birth cohort study, we collected reported 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 for reported current asthma, reported wheeze and atopy (measured using skin prick tests) were collected at 6 years for all participants. Logistic regression models were adjusted for potential confounders, including the number of chest infections and antibiotic use.

Results 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.

Conclusion and Clinical Relevance Our findings suggest that paracetamol has a role in the development of atopy, and the maintenance of asthma symptoms. Before recommendations for clinical practice can be made, randomized-controlled trials are needed to determine whether these associations are causal.

Keywords allergic sensitization, asthma, birth cohort, children, paracetamol, wheeze
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Introduction

Reasons for the increase in the prevalence of asthma over recent decades, particularly in developed countries, and differences in its distribution across geographical regions have still not been satisfactorily explained. Genetic variability is unlikely to account for these differences in asthma prevalence and the focus needs to be on environmental factors that have both changed over a similar time period and vary across regions.

The marketing of paracetamol since the mid-1950s and its widespread use among children as the antipyretic of

choice [1] have led to studies investigating the relationship between paracetamol and asthma development. These studies have mostly shown that paracetamol use is associated with an increased risk of asthma and wheeze in children. In many of these studies, the cross-sectional [2] or retrospective collection of paracetamol exposure during pregnancy or early life [3–5] means that selective recall bias or reverse causation cannot be excluded as possible explanations for the findings. However, recently published findings from several prospective birth cohort studies support the findings of the cross-sectional studies. Such longitudinal designs have shown that paracetamol

use during pregnancy increases the risk of asthma or wheeze in infancy [6], in pre-school years [7] and later childhood [8–10]. In contrast, one recent study found that pre-natal exposure to paracetamol was associated with a reduced risk of childhood asthma and wheeze [11]. Furthermore, paracetamol use in adults has been associated with prevalent [12, 13] and incident asthma [14, 15]. A recent meta-analysis confirms an increased risk of asthma in children and adults for both early and concurrent paracetamol use [16]. Most studies have found these associations to be frequency or dose dependent [2, 4, 8, 12, 14], consistent with a causal interpretation of the findings. However, despite the consistency in these findings, there is only one birth cohort study that has collected paracetamol exposure in infancy [7]. We are not aware of any previous studies that have controlled for the use of paracetamol in the treatment of respiratory tract infections, which may lead to, or be indistinguishable from, asthma-related wheeze. Thus, confounding by respiratory tract infection cannot be excluded as an explanation of these findings.

Surprisingly, few studies have been able to examine the effect of paracetamol use on atopic sensitization. Among the few that have, results have been contradictory [2, 5, 8, 10]. None of these studies has prospectively investigated the association between infant paracetamol intake and the subsequent development of atopy.

The primary aim of the current study was to examine the associations of paracetamol use in infancy and between 5 and 6 years, with atopy and allergic disease at 6 years. The longitudinal nature of our data collection and availability of data on a large number of potential confounders will contribute to an improved understanding of the role of paracetamol in allergic disease development.

Methods

A full description of the assembly of the New Zealand Asthma and Allergy Cohort Study has been published previously [17]. Briefly, mothers were recruited during pregnancy through a random sample of midwives in Wellington and Christchurch in New Zealand between 1997 and 2001. Ethics committee approval was obtained from the Wellington and Canterbury Regional Ethics Committees and informed consent was obtained from each mother.

Study nurses administered questionnaires at recruitment, 3 and 15 months and yearly until 6 years. Participants were assessed at home at 3 and 15 months and at the research facilities in each centre at 6 years. At other time-points, nurses administered questionnaires by phone. At each contact, the prevalence rates of wheeze, hayfever, rhinitis symptoms and eczema were assessed using standard questions from the International Study of Asthma and Allergies in Childhood (ISAAC) [18] slightly modified

to restrict the recall period to 'since the last (telephone) questionnaire'. This was to ensure continuity of data in the event that participants had answered the questionnaire earlier or later than the target date at either this or the previous contact point. The prevalence rates of diagnosed asthma ('Since our last telephone questionnaire, has a doctor said that he or she has asthma?') and rash ('Since the last telephone questionnaire, has he/she had an itchy scaly rash that comes and goes for at least 6 months?') were assessed using modified ISAAC questions. To estimate the prevalence of severe asthma symptoms, we identified children with a positive response to the ISAAC question: 'Since our last telephone questionnaire, has his or her wheezing been severe enough to limit his or her speech to only one or two words at a time between breaths?' [18] and by a response indicating any sleep disturbance to a modified ISAAC question: 'Which best describes how often on average, his or her sleep has been disturbed due to wheezing, when he or she hasn't had cold or the flu?' The current analyses are based on outcomes collected at 6 years, an age at which asthma symptoms have been shown to predict adult asthma [19]. Additional derived outcome variables covered the period from birth to 6 years. A variable for current asthma was defined as a reported history of diagnosed asthma ever plus a reported history in the last 12 months of either wheeze or inhaler use, or both. We defined all these outcome variables dichotomously (1 = condition present and 0 = condition absent). For indicators of severe asthma symptoms (speech-limiting wheeze and sleep disturbance due to wheeze), children with non-severe wheeze were classified, together with children without wheeze, as non-cases. A variable to characterize wheeze into transient (wheezing only in the first 3 years of life), late onset (wheezing occurring between 3 and 6 years only), persistent (wheezing both in the first 3 years of life and between 3 and 6 years) and never wheeze (wheezing at neither of these periods) was defined as in the Tucson cohort study [20]. We constructed a further variable describing the four possible combinations of atopic status (present or absent) with current asthmatic status (present or absent). Atopic status and wheeze status were similarly combined into one variable.

When children were 6 years old, we assessed their skin prick test (SPT) sensitivity to the following allergens: *Dermatophagoides pteronyssinus*, cat, dog, rye grass, cow's milk, egg white, peanut, *Aspergillus fumigatus*, *Alternaria tenuis*, cockroach, olive, horse hair, as well as a positive histamine control (10 mg/mL) and a negative control (Dome/Hollister-Stier, Spokane, WA, USA). Bayer lancets were used to puncture the skin. The positive control was measured at 10 min, and all other weals were measured at 15 min. A reaction was considered positive if the mean weal diameter was ≥ 3 mm larger than the negative control mean weal diameter. We defined atopy as a positive reaction to any allergen.

Serum samples were collected at 6 years and analysed for total IgE on an Immulite 2000 (Siemens Healthcare Diagnostics, Inc., Deerfield, IL, USA) using a liquid third-generation, solid-phase, two-step, chemiluminescent immunoassay. Total IgE results that returned a result above the upper level of detection limit were diluted with Siemens assay-specific diluents and rerun using appropriate dilution factors until a quantifiable result was obtained. Results are expressed as log values measured in kU/L.

As part of a general medication question at 3 and 15 months, the Christchurch centre collected data on whether or not paracetamol had been used. The Wellington centre had commenced the study before the development of the paracetamol hypothesis and missed the opportunity to collect specific data on paracetamol use between birth and 15 months. Thus, data on paracetamol use between birth and 15 months are limited to Christchurch only. At 6 years, the number of doses of paracetamol taken since 5 years was collected using a standard question in both centres in the following categories: none, 1–2, 3–6, 7–10, 11–15 and >15 (which were further combined for analysis).

Statistical analysis

SAS version 9.1 (SAS Institute, Cary, NC, USA) was used for the statistical analysis. Odds ratios (OR) were estimated using logistic regression models. Initially, we examined the univariate associations of paracetamol use before 15 months (yes vs. no) with outcomes at 5–6 years in Christchurch. Univariate analyses were also used to examine the association of paracetamol use at 5–6 years (0–2 times, 3–10 times and >10 times) and outcomes at 5–6 years in both centres combined. Models were run for each exposure period to assess the associations of para-

cetamol use and health outcomes after adjustment for gender, family history (mother or father with asthma, eczema or hayfever), parity [defined as 'number of births after 22 weeks (gestation), including this one' and analysed as a continuous variable] and New Zealand (NZ) Deprivation Index (an area-based measure) [21]. When the paracetamol exposure period was birth to 15 months, these models also included the number of chest infections before 15 months (1, 2+ vs. none), any systemic antibiotic use before 15 months, birth weight, maternal age, maternal smoking during pregnancy and any household smoking between birth and 15 months. When the exposure variable was paracetamol use between 5 and 6 years, variables in the model also included the number of chest infections between 5 and 6 years (1, 2+ vs. none), any household smoking between 5 and 6 years, systemic antibiotic use between 5 and 6 years, paracetamol use before 15 months and study location. The family history of the person completing the questionnaire, usually the mother, was collected, and only asked about the biological father if he was part of the household. For the analysis that used the family history variable, we excluded the 11 households where the biological father was absent. Missing data were not imputed.

Results

Response rates for the study are given in Fig. 1. Table 1 shows the prevalence of exposure variables and health outcomes. Among Christchurch children, 89.9% had received at least one dose of paracetamol by 15 months and in the total dataset, 95.1% had received at least one dose of paracetamol between 5 and 6 years.

Table 2 shows the concurrent associations of exposure to chest infections and antibiotics with paracetamol use

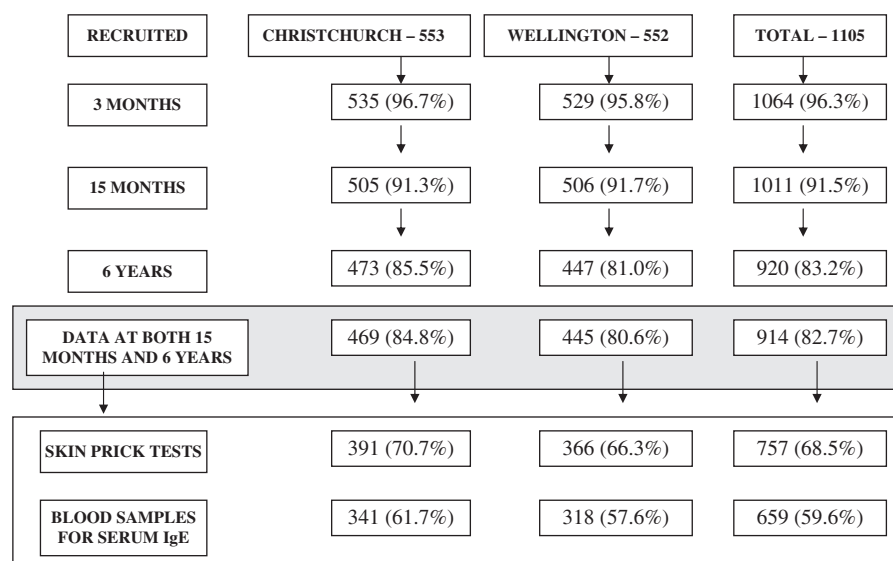


Fig. 1. Response rates.

Table 1. Study population characteristics [*n/N* (%)]

Exposure and potential confounders	Christchurch sub-sample (<i>N</i> = 505) <i>n/N</i> (%)	Total sample (<i>N</i> = 1011) <i>n/N</i> (%)
Male gender	260/505 (51.5)	515/1011 (50.9)
Family history*	424/496 (85.5)	842/996 (84.5)
NZ Deprivation Index (mean, SD)	5.25 (2.71)	4.69 (2.87)
Christchurch location	–	505/1011 (50.0)
Maternal smoking in pregnancy	105/505 (20.8)	206/1011 (20.4)
Household smoking before 15 months	188/505 (37.2)	329/1011 (32.5)
Household smoking at 5–6 years	61/469 [†] (13.0)	118/914 [†] (12.9)
Maternal age at birth (mean, SD)	30.19 (5.30)	30.40 (5.08)
Birth weight (kg) (mean, SD)	3.59 (5.47)	3.55 (0.54)
Parity		
1st born	206/505 (40.8)	462/1011 (45.7)
2nd born	189/505 (37.4)	363/1011 (35.9)
3+ born	110/505 (21.8)	186/1011 (18.4)
Any paracetamol use	454/505 (89.9)	869/914 (95.1)
Paracetamol use		
0–2 times	–	142/914 (15.5)
3–10 times	–	435/914 (47.6)
More than 10 times	–	337/914 (36.9)
Chest infections		
None	313/505 (62.0)	769/912 (84.3)*
1	108/505 (21.4)	82/912 (9.0)*
2+	84/505 (16.6)	61/912 (6.7)*
Systemic antibiotic use	336/499 (67.3)*	373/914 (40.8)
Outcomes at 6 years	Christchurch sub-sample (<i>N</i> = 469) [†]	Total sample (<i>N</i> = 914) [†]
Current asthma	106/469 (22.6)	201/914 (22.0)
Current asthma and atopy [‡]	51/391 (13.0)	104/757 (13.7)
Current asthma without atopy [‡]	36/391 (9.2)	69/757 (9.1)
Atopy without current asthma [‡]	63/391 (16.1)	112/757 (14.8)
No current asthma and no atopy [‡]	241/391 (61.6)	472/757 (62.4)
Wheeze at 6 years	122/469 (26.0)	223/914 (24.4)
Wheeze and atopy [‡]	55/391 (14.1)	112/757 (14.8)
Wheeze without atopy [‡]	47/391 (12.0)	77/757 (10.2)
Atopy without wheeze [‡]	59/391 (15.1)	104/757 (13.7)
No wheeze and no atopy [‡]	230/391 (58.8)	464/757 (61.3)
Transient wheeze [§]	96/445 (21.6)	204/887 (23.0)
Late onset wheeze [§]	48/445 (10.8)	87/887 (9.8)
Persistent wheeze [§]	173/445 (38.9)	300/887 (33.8)
Never wheezed [§]	128/445 (28.8)	296/887 (33.4)
Itchy scaly rash	68/469 (14.5)	148/914 (16.2)
Eczema*	118/459 (25.7)	242/896 (27.0)
Rhinitis symptoms	96/469 (20.5)	196/914 (21.4)
Hayfever*	79/453 (17.4)	149/881 (16.9)
Atopy [‡]	114/391 (29.2)	216/757 (28.5)

n* does not add to total *N* due to missing data.[†]*n* limited to those with 6-year paracetamol data available.[‡]*n* limited to those with skin prick test data available.[§]*n* limited to those with wheeze data available at each time-point from 15 months to 6 years.Table 2.** Associations between exposure to chest infections and antibiotics and paracetamol use before 15 months, and between 5 and 6 years

Exposures before 15 months	Paracetamol use before 15 months [<i>n</i> (%)]			<i>P</i>
	Yes (<i>N</i> = 454)	No (<i>N</i> = 51)		
Chest infections				
None	279 (61.5)	34 (66.7)		0.45
1	98 (21.6)	10 (19.6)		
2+	77 (17.0)	7 (13.7)		
Systemic antibiotic use*				
Yes	307 (68.5)	29 (56.9)		0.09
No	141 (31.5)	22 (43.1)		
Exposures 5–6 years	Paracetamol use between 5 and 6 years [<i>n</i> (%)]			<i>P</i>
	0–2 times (<i>N</i> = 142)	3–10 times (<i>N</i> = 435)	> 10 times (<i>N</i> = 337)	
Chest infections*				
None	130 (91.6)	392 (90.5)	247 (73.3)	<0.0001
1	7 (4.9)	29 (6.7)	46 (13.7)	
2+	5 (3.5)	12 (2.8)	44 (13.1)	
Systemic antibiotic use				
Yes	25 (17.6)	146 (33.6)	202 (59.9)	<0.0001
No	117 (82.4)	289 (66.4)	135 (40.1)	

**n* does not add to total *N* due to missing data. Bold indicates significant results (*P* < 0.0001).

before 15 months and between 5 and 6 years. Neither of these exposures was related to paracetamol use before 15 months but by 6 years, there were highly significant associations of antibiotic use and chest infections with paracetamol use.

Paracetamol use before 15 months and outcomes collected at 6 years in Christchurch

Table 3 shows the associations of paracetamol use before 15 months and outcomes collected at 6 years in Christchurch. Early paracetamol use was significantly associated with atopy, defined by skin prick at 6 years, an association that increased after adjustment for the listed variables [adjusted OR = 3.61, 95% confidence intervals (CI) 1.33–9.77]. This effect was not modified by the presence or absence of atopy at 15 months (*P* = 0.63, for interaction effect). However, the relationship was stronger among those not atopic at 15 months (adjusted OR = 8.48, 95% CI 1.07–67.06). There was no association between paracetamol use at 15 months and log total serum IgE at 6 years [adjusted geometric mean ratio: 1.29 (95% CI 0.70–2.37)]. The ORs were elevated for the effect of early paracetamol use on current asthma and wheeze at 6 years and strengthened in the subgroups with atopic current asthma and atopic wheeze, with both almost reaching significance (Table 3). The numbers with indicators of severe asthma symptoms were too small to analyse. There was no association of early paracetamol use with the presence of eczema,

Table 3. Christchurch – unadjusted and adjusted* associations of paracetamol use before 15 months and outcomes at 6 years

	<i>n</i> (%)	Unadjusted OR (95% CI)	<i>P</i>	<i>n</i> (%)	Adjusted* OR (95% CI)	<i>P</i>
Current asthma (<i>N</i> = 106)	99 (93.4)	1.85 (0.81–4.25)	0.15	98 (93.3)	1.78 (0.75–4.21)	0.19
No current asthma (<i>N</i> = 363)	321 (88.4)	1.00		310 (88.3)	1.00	
Atopy and current asthma (<i>N</i> = 51)	49 (96.1)	3.35 (0.77–14.52)	0.11	48 (96.0)	4.13 (0.93–18.48)	0.06
Current asthma no atopy (<i>N</i> = 36)	33 (91.7)	1.51 (0.43–5.22)	0.52	33 (91.7)	1.53 (0.41–5.68)	0.53
Atopy no current asthma (<i>N</i> = 63)	60 (95.2)	2.74 (0.81–9.29)	0.11	59 (95.2)	3.36 (0.96–11.84)	0.06
No current asthma and no atopy (<i>N</i> = 241)	212 (88.0)	1.00		203 (87.5)	1.00	
Wheeze (<i>N</i> = 122)	115 (94.3)	2.26 (0.99–5.18)	0.053	112 (94.1)	2.15 (0.92–5.03)	0.07
No wheeze (<i>N</i> = 347)	305 (87.9)	1.00		296 (87.8)	1.00	
Atopy and wheeze (<i>N</i> = 55)	53 (96.4)	3.67 (0.85–15.91)	0.08	52 (96.3)	4.36 (0.99–19.20)	0.052
Wheeze no atopy (<i>N</i> = 47)	43 (91.5)	1.49 (0.50–4.47)	0.48	41 (91.1)	1.33 (0.42–4.17)	0.63
Atopy no wheeze (<i>N</i> = 59)	56 (94.9)	2.59 (0.76–8.82)	0.13	55 (94.8)	3.22 (0.91–11.43)	0.07
No wheeze and no atopy (<i>N</i> = 230)	202 (87.8)	1.00		192 (56.5)		
Transient wheeze (<i>N</i> = 96)	83 (86.5)	0.91 (0.42–2.00)	0.82	83 (86.5)	0.83 (0.34–1.99)	0.67
Late onset wheeze (<i>N</i> = 48)	44 (91.7)	1.57 (0.50–4.96)	0.44	44 (91.7)	1.51 (0.43–5.27)	0.52
Persistent wheeze (<i>N</i> = 173)	161 (93.1)	1.92 (0.87–4.21)	0.10	155 (92.8)	1.88 (0.75–4.70)	0.18
Never wheezed (<i>N</i> = 128)	112 (87.5)	1.00		109 (87.2)	1.00	
Atopy present (<i>N</i> = 114)	109 (95.6)	2.85 (1.08–7.50)	0.03	107 (95.5)	3.61 (1.33–9.77)	0.01
No atopy present (<i>N</i> = 277)	245 (88.5)	1.00		236 (88.1)	1.00	

*Adjusted for number of chest infections before 15 months (1, 2+ vs. none), systemic antibiotic use before 15 months, gender, family history, parity, birth weight, maternal age, maternal smoking during pregnancy, any household smoking between birth and 15 months, and NZ Deprivation Index.

Bold indicates significant ($P < 0.05$) results.

Table 4. Unadjusted odds ratios (95% CI) of paracetamol use between 5 and 6 years, and outcomes at 6 years in the total dataset

	0–2 times (<i>n</i> = 142)		3–10 times (<i>n</i> = 435)			> 10 times (<i>n</i> = 337)			
	<i>n</i> (%)	Reference	<i>n</i> (%)	OR (95% CI)	<i>P</i>	<i>n</i> (%)	OR (95% CI)	<i>P</i>	<i>P</i> for trend
Current asthma (<i>N</i> = 201)	18 (9.0)	1.00	85 (42.3)	1.67 (0.97–2.90)	0.07	98 (48.8)	2.83 (1.63–4.88)	0.0002	< 0.0001
No current asthma (<i>N</i> = 713)	124 (17.4)		350 (49.1)			239 (33.5)			
Atopy and current asthma (<i>N</i> = 104)	10 (9.6)	1.00	43 (41.4)	1.48 (0.71–3.09)	0.29	51 (49.0)	2.55 (1.23–5.29)	0.01	0.009
Current asthma no atopy (<i>N</i> = 69)	5 (7.3)	1.00	30 (43.5)	2.07 (0.78–5.51)	0.15	34 (49.3)	3.40 (1.28–9.02)	0.01	0.004
Atopy no current asthma (<i>N</i> = 112)	22 (19.6)	1.00	54 (48.2)	0.85 (0.49–1.48)	0.56	36 (32.1)	0.82 (0.45–1.48)	0.51	0.42
No asthma and no atopy (<i>N</i> = 472)	80 (17.0)		232 (49.2)			160 (33.9)			
Wheeze (<i>N</i> = 223)	18 (8.1)	1.00	97 (43.5)	1.98 (1.15–3.40)	0.01	108 (48.4)	3.25 (1.88–5.60)	< 0.0001	< 0.0001
No wheeze (<i>N</i> = 691)	124 (18.0)		338 (48.9)			229 (33.1)			
Atopy and wheeze (<i>N</i> = 112)	10 (8.9)	1.00	49 (43.8)	1.71 (0.83–3.54)	0.15	53 (47.3)	2.74 (1.32–5.66)	0.007	0.006
Wheeze no atopy (<i>N</i> = 77)	5 (6.5)	1.00	33 (42.9)	2.31 (0.87–6.11)	0.09	39 (50.7)	4.02 (1.53–10.61)	0.005	0.001
Atopy no wheeze (<i>N</i> = 104)	22 (21.2)	1.00	48 (46.2)	0.76 (0.43–1.34)	0.35	34 (32.7)	0.80 (0.44–1.45)	0.46	0.35
No wheeze and no atopy (<i>N</i> = 464)	80 (17.2)		229 (49.4)			155 (33.4)			
Atopy present (<i>N</i> = 216)	32 (14.8)	1.00	97 (44.9)	0.98 (0.62–1.57)	0.94	87 (40.3)	1.19 (0.74–1.92)	0.47	0.57
Atopy absent (<i>N</i> = 541)	85 (15.7)		262 (48.4)			194 (35.9)			

Bold indicates significant ($P < 0.05$) results.

an itchy rash, hayfever or rhinitis symptoms at 6 years before or after adjustment (data not shown).

Paracetamol use between 5 and 6 years and outcomes collected at 6 years in the total dataset

Table 4 shows univariate associations between paracetamol use between 5 and 6 years and outcomes present during the same time period. There were strong and significant dose-dependent associations of paracetamol

use at 5–6 years with current asthma and wheeze at 5–6 years, which persisted after controlling for many potential confounders (Table 5). These associations were stronger for non-atopic than atopic current asthma and wheeze.

Interestingly, there were significant interactions between antibiotic use and paracetamol use 3–10 times ($P = 0.009$) and > 10 times ($P = 0.003$) for current asthma. In the subgroup of children who had used antibiotics, there was a reversal in the effect of paracetamol but the results were not significant. Among those without

Table 5. Adjusted* odds ratios (95% CI) of paracetamol use between 5 and 6 years and outcomes at 6 years in the total dataset

	0–2 times		3–10 times			> 10 times			<i>P</i> for trend
	<i>n</i> (%)	Reference	<i>n</i> (%)	OR (95% CI)	<i>P</i>	<i>n</i> (%)	OR (95% CI)	<i>P</i>	
Current asthma (<i>N</i> = 198)	18 (9.1)	1.00	84 (42.4)	1.63 (0.92–2.89)	0.10	96 (48.5)	2.16 (1.19–3.92)	0.01	0.02
No current asthma (<i>N</i> = 705)	122 (17.3)		348 (49.4)			235 (33.3)			
Atopy and current asthma (<i>N</i> = 102)	10 (9.8)	1.00	42 (41.2)	1.38 (0.64–2.98)	0.42	50 (49.0)	1.90 (0.85–4.24)	0.12	0.17
Current asthma no atopy (<i>N</i> = 68)	5 (7.4)	1.00	30 (44.1)	2.31 (0.84–6.38)	0.11	33 (48.5)	3.25 (1.15–9.21)	0.03	0.02
Atopy no current asthma (<i>N</i> = 111)	22 (19.8)	1.00	54 (48.7)	0.86 (0.48–1.54)	0.61	35 (31.5)	0.81 (0.42–1.55)	0.52	0.40
No current asthma and no atopy (<i>N</i> = 467)	79 (16.9)		230 (49.3)			158 (33.8)			
Wheeze (<i>N</i> = 220)	18 (8.2)	1.00	96 (43.6)	1.83 (1.04–3.23)	0.04	106 (48.2)	2.30 (1.28–4.16)	0.006	0.02
No wheeze (<i>N</i> = 683)	122 (17.9)		336 (49.2)			225 (32.9)			
Atopy and wheeze (<i>N</i> = 110)	10 (9.1)	1.00	48 (43.6)	1.63 (0.75–3.51)	0.22	52 (47.3)	2.08 (0.94–4.59)	0.07	0.14
Wheeze no atopy (<i>N</i> = 76)	5 (6.6)	1.00	33 (43.4)	2.13 (0.78–5.83)	0.14	38 (50.0)	3.24 (1.16–9.03)	0.02	0.03
Atopy no wheeze (<i>N</i> = 103)	22 (21.4)	1.00	48 (46.6)	0.77 (0.43–1.39)	0.39	33 (32.0)	0.82 (0.43–1.59)	0.56	0.42
No wheeze and no atopy (<i>N</i> = 459)	79 (17.2)		227 (49.5)			153 (33.3)			
Atopy present (<i>N</i> = 213)	32 (15.0)	1.00	96 (45.1)	0.96 (0.59–1.56)	0.87	85 (39.9)	1.05 (0.62–1.77)	0.86	0.90
Atopy absent (<i>N</i> = 535)	84 (15.7)		260 (48.6)			191 (35.7)			

*Adjusted for number of chest infections between 5 and 6 years (1, 2+ vs. none), gender, family history, parity, NZ Deprivation Index, household smoking between 5 and 6 years, systemic antibiotic use between 5 and 6 years, paracetamol use before 15 months and study location. Bold indicates significant ($P < 0.05$) results.

antibiotic use, paracetamol use 3–10 times and > 10 times increased the ORs (95% CIs) of current asthma to 2.42 (1.17–5.06) and 3.94 (1.80–8.60), respectively.

A *post hoc* analysis was conducted where the chest infection variable was the only adjustment variable. This showed that among children taking paracetamol > 10 times, the OR (95% CI) for current asthma fell from 2.83 (1.63–4.88) to 2.22 (1.26–3.91) but remained significant ($P = 0.006$); the OR for current wheeze fell from 3.25 (1.88–5.60) to 2.53 (1.44–4.43), also remaining significant ($P = 0.001$).

For severe asthma symptoms, the adjusted ORs for the associations of paracetamol use 3–10 times and > 10 times, compared with 0–2 times, with speech-limiting wheeze were 2.87 (0.64–12.87) and 5.36 (1.19–24.21), respectively, and for sleep disturbance due to wheeze were 2.44 (0.69–8.60) and 4.42 (1.25–15.63), respectively.

There was no association with atopy measured by SPT (Tables 4 and 5) or log total IgE. The adjusted geometric mean ratios for the associations of paracetamol use 3–10 times and > 10 times, compared with use 0–2 times, with log total IgE were 1.11 (95% CI 0.74–1.67) and 1.15 (95% CI 0.74–1.78), respectively.

In a univariate analysis, paracetamol use between 5 and 6 years showed dose-dependent associations with an itchy scaly rash and eczema present during the same time period (P for trend = 0.003, for both). After adjustment, this association remained significant for the presence of an itchy scaly rash only (P for trend = 0.04) (data not shown).

Both environmental tobacco smoke and paracetamol may influence the development or severity of asthma through depleting glutathione levels [22]. In view of this,

we also tested whether environmental smoke exposure at 15 months modified the relationship between paracetamol and wheeze but found no significant interactive effect ($P = 0.53$).

Discussion

This study showed that children in Christchurch who had used paracetamol before 15 months (89.9%) were more than three times as likely to be atopic at 6 years than children not using paracetamol in infancy. The effects of early paracetamol use on current asthma or wheeze at 5–6 years, although elevated, were not statistically significant, possibly due to reduced power when the sample was restricted to one centre and because paracetamol exposure was high. Both these associations strengthened among children whose disease was associated with atopic sensitization. By 6 years, 95% of the children were using paracetamol. At this age, there was no association with atopy but there were increased risks for current asthma and wheeze, which were stronger for non-atopic than atopic current asthma and wheeze. These findings were dose dependent, greater for those with severe asthma symptoms, and consistent with findings from other retrospective or cross-sectional studies of children across the world [4], supportive of a role for paracetamol in asthma aetiology.

There are little published data from epidemiological studies that investigate an effect of paracetamol on atopy. An ecological analysis of paracetamol sales showed some evidence of a positive association with atopy among adults, measured by SPT, but no effect on total IgE serum

levels [23]. The findings of this ecological analysis are consistent with our findings among infants where paracetamol use is positively associated with later atopy measured by SPTs but not with total serum IgE. On the other hand, other reports have shown that exposure *in utero* affected total [8] and allergen-specific [10] serum IgE but not atopy measured by SPT in childhood [8]. Possibly, these discrepant findings are due to the timing of paracetamol exposure, i.e. *in utero* or during infancy or adulthood.

The association between early paracetamol and later atopy may be due to the confounding effects of atopy in infancy as atopy in infancy is a risk factor for atopy at an older age. Atopy in infancy may also reflect impaired Th1 responses, an inability to clear infections and an increased use of paracetamol. However, we have shown a strengthening of the ORs (albeit with wide CI) in the subgroup who were not atopic at 15 months, suggesting that confounding by early atopic status does not explain this association.

Our data suggest that different mechanisms may operate to explain the time-dependent effects of paracetamol exposure. The presence of early fever has been shown to be associated with a reduced risk of developing atopic sensitization [24, 25], which may be due to a surge in Th1 immune cytokines, such as IFN- γ , in the presence of fever, and a corresponding suppression of Th2 cytokines. Theoretically, paracetamol could interfere with this process through limiting the intensity or duration of fever but this seems unlikely given that there is little evidence for the efficacy of paracetamol in treating fever duration [26]. Furthermore, paracetamol use in pregnancy, but not aspirin, has been positively associated with total serum IgE at 7 years [8], which would argue against an antipyretic effect on immune cytokines. An alternative and more widely accepted hypothesis for the association of paracetamol and atopy proposes that there is a reduction of glutathione levels in the lung in the presence of paracetamol. Low glutathione levels may lead to defective antigen processing, thereby promoting the Th2 allergic pathway [27] and this is most likely to occur at a critical time during development of the immune system early in life. On the other hand, later paracetamol use may influence the maintenance of asthma, as glutathione is an important antioxidant and its depletion may result in free radical damage, enhancement of any inflammatory process and bronchospasm [28].

It has been hypothesized that the decline in aspirin use in Western societies has led to the increase in allergic disease due to the loss of the immunological properties of aspirin and its influence on lymphocyte cytokine generation [29]. We cannot test the effects of aspirin avoidance as we did not collect data on any non-steroidal anti-inflammatory at 6 years, and there were no infants in our cohort using aspirin.

In our cross-sectional analysis, reverse causation may have contributed to our positive associations if paracetamol was used to treat wheeze-related illness. Furthermore, viral respiratory infections may have a confounding role as they are independently associated with asthma exacerbations [30] and paracetamol use. We did not collect data on the indication for paracetamol use, although our findings are independent of both lower respiratory tract infection and systemic antibiotic use, potential confounders in the association between paracetamol use and asthma. However, we cannot exclude the possibility that there was residual confounding, reverse causation or selective recall of paracetamol use at 6 years among those with asthma and wheeze. We also did not collect information on paracetamol exposure during pregnancy and thus cannot confirm previous reports of an effect during pregnancy on wheeze in childhood [6, 7, 9, 10].

Nevertheless, our findings raise concern that paracetamol may be contributing to the development of atopic sensitization and to the maintenance of asthma symptoms. Although direct causation has not been established as yet, neither has paracetamol been shown to have a beneficial effect on disease outcomes when used as an antipyretic [31], and guidelines for its use in other settings are unclear [32]. Randomized-controlled trials are urgently required to determine whether these associations are causal and to form the basis of future recommendations for clinical practice in the use of paracetamol in the treatment of children.

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