



The University of
Nottingham



The role of paracetamol and geohelminth infection on the incidence of wheeze and eczema: a longitudinal birth-cohort study

**Alemayehu Amberbir^{1, 2}, Girmay Medhin², Atalay Alem²,
John Britton¹, Gail Davey², Andrea Venn¹**

¹University of Nottingham, UK

²Addis Ababa University, Ethiopia

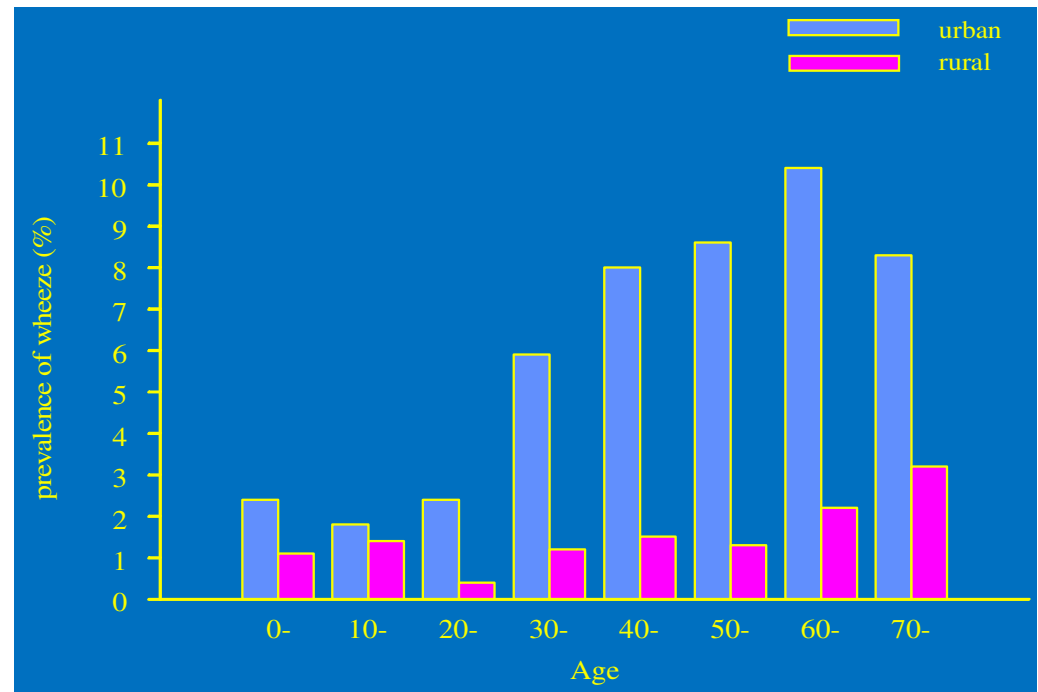
INDEPTH 10th AGM

September 27-30, Accra, Ghana



The hygiene hypothesis

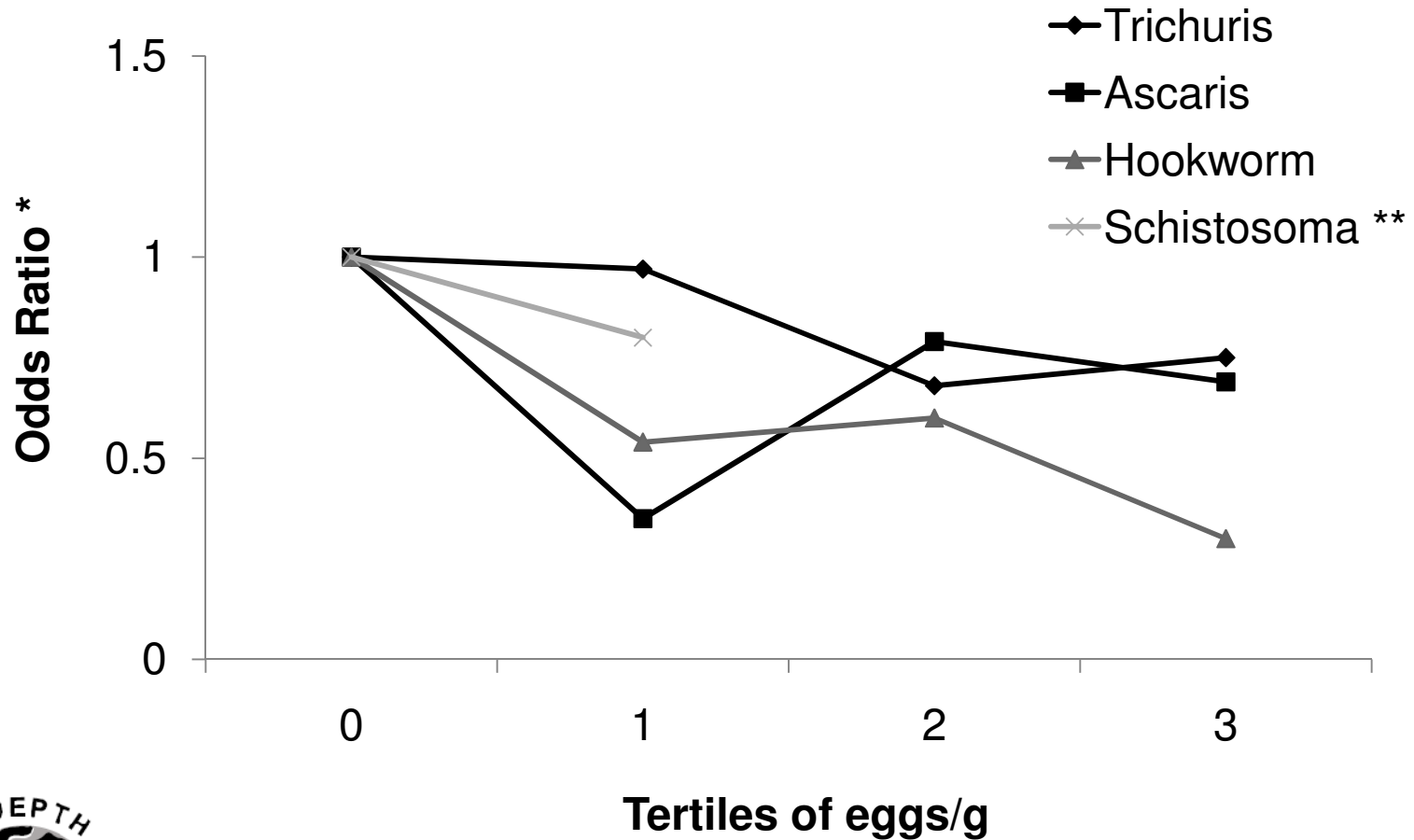
- **Geohelminth exposure:**
 - Asthma and allergic diseases are high in areas where geohelminth exposure is lacking and rare when this exposure exists
 - Urban-rural gradient within developing countries



Yemaneberhan et al, Lancet 1997;350:85-90



Odds of wheeze in relation to intensity of parasite infection in Ethiopia



Scrivener et al, Lancet 2001;358:1493-99

The paracetamol enigma in asthma

- Shift from aspirin to paracetamol over same period as increase in asthma prevalence.
- Positive associations reported between paracetamol and asthma/allergic disease in *utero*, during infancy, childhood and adult life.
- However studies mainly cross-sectional or case-control and based in developed countries.
- Difficult to exclude reverse causation and aspirin avoidance
- No longitudinal cohort studies in children



*Amberbir et al, Am J Resp Crit Care Med 2010 (in press),
Beasley et al, Lancet 2008;372:1039-48 ,
Shaheen et al, Thorax 2002 ; 57:958-963*



Aims of study

- To explore the relation between early infection with geohelminths and use of paracetamol in the first year of life, and the incidence of childhood wheeze and eczema in the Butajira birth cohort, Ethiopia



Butajira town



Rural Butajira

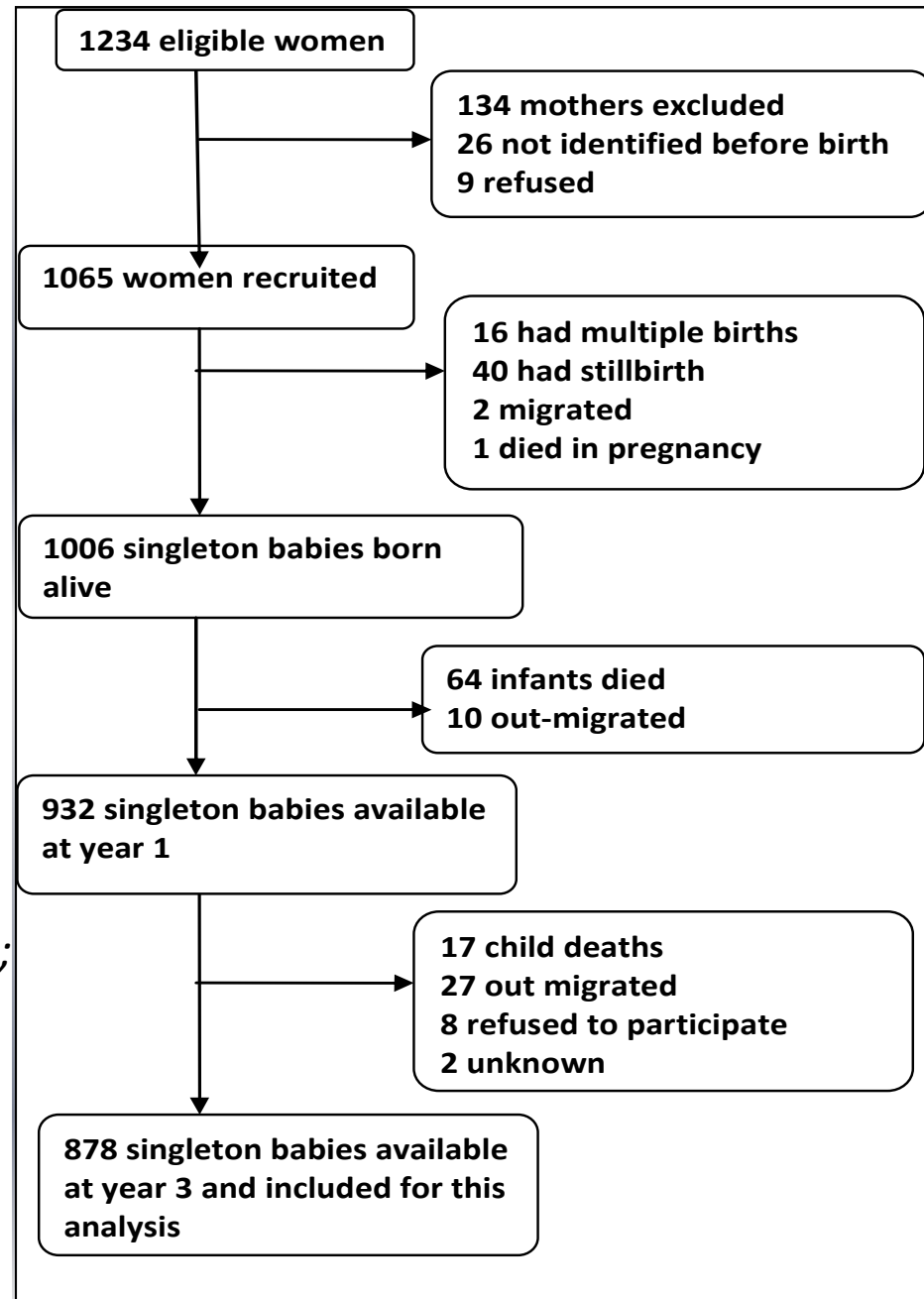


The birth cohort

- Established in 2005
- Women recruited during pregnancy
- Babies followed to age 3

*Belyhun et al, Clin Exp Allergy 2010;
(40): 619-26*

*Hanlon et al, Trop Med Int Health 2009;
14(2): 156-66*

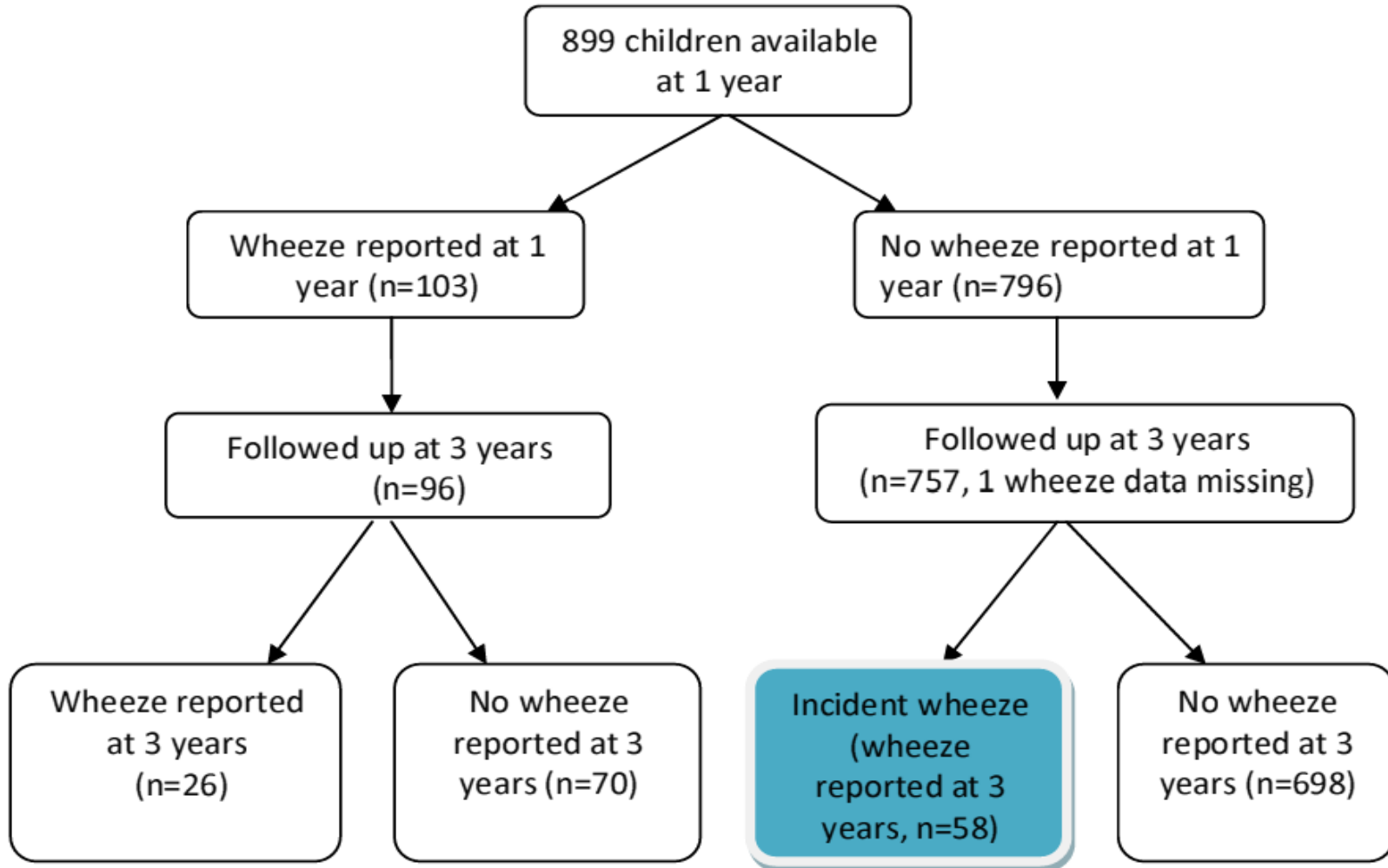


Measures

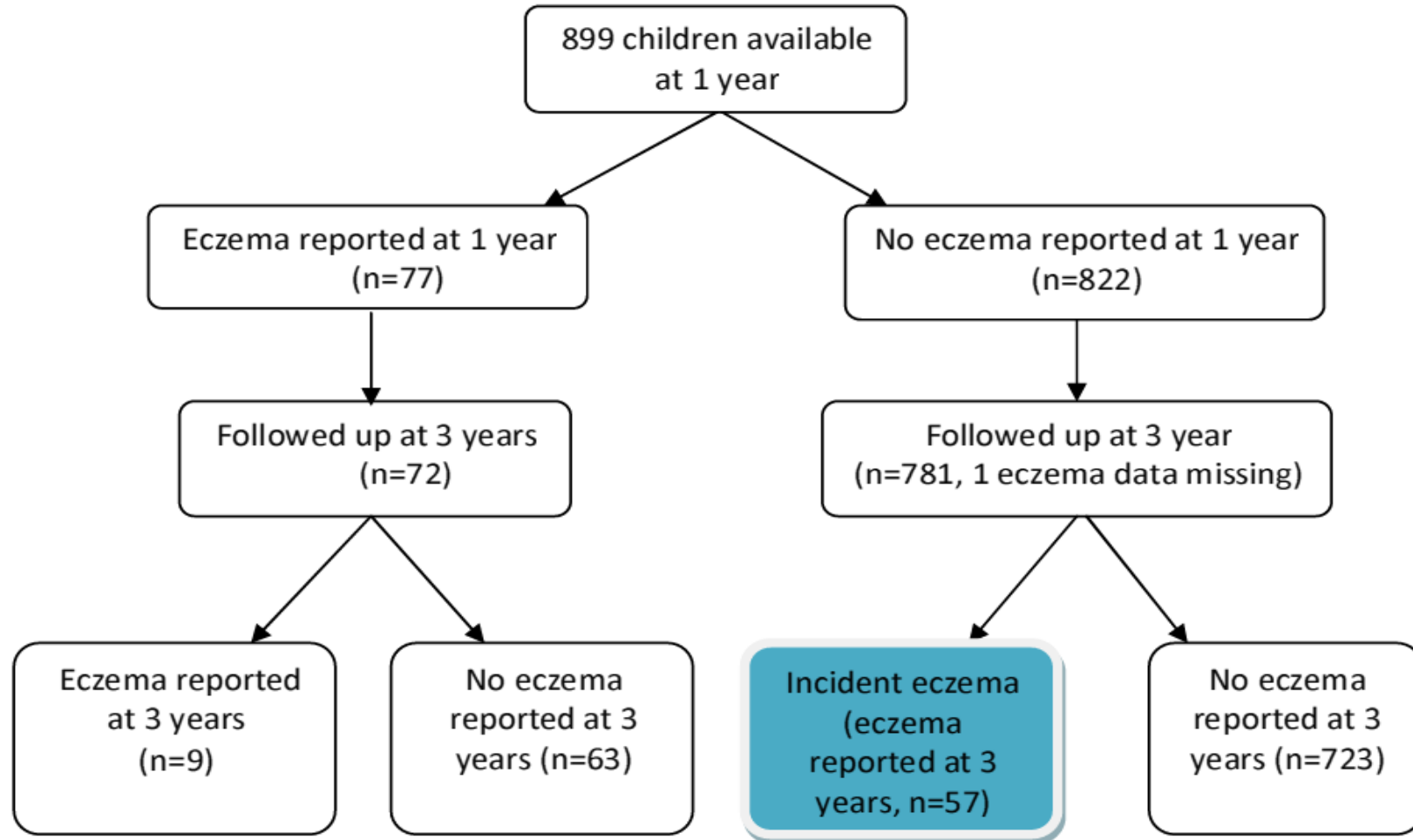
- Outcome measures:
 - ISAAC core allergy questionnaire
 - Wheeze and eczema ever at year 1 and 3
 - Exposure measures:
 - Paracetamol use in the last year (dose quantified in the past month)
 - Stool samples for geohelminth analysis collected at year 1
 - Various potential confounders:
 - Demographic and life style factors
 - Birth weight
 - Symptoms of respiratory tract infection
- (2 months and 1 year)



Wheeze flow chart between one and three years



Eczema flow chart between one and three years



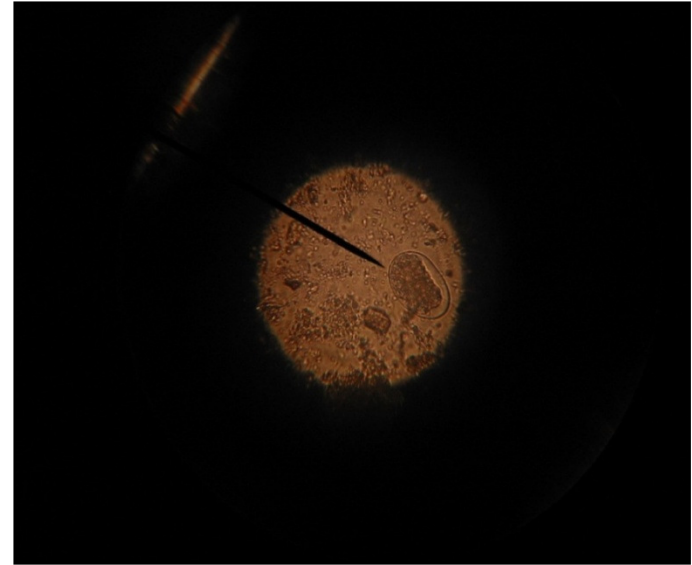
Data analysis

- Paracetamol use in the first year of life categorized as 'never', 'yes but not in the past month', '1-3 tablets in past month' and ' ≥ 4 tablets in the past month'
- Geohelminth infection at age 1 defined as presence of hookworm, *Ascaris lumbricoides* or *Trichuris Trichiura*
- Effects on incident wheeze and eczema determined using multiple logistic regression
- Adjusted for gender, urban/rural location and mothers education as *a priori* confounders
- Additionally explored adjusting for other potential confounders including early life symptoms of respiratory tract infections



Results 1

- Geohelminth infection found in only 4% of children
 - Hookworm (2.4%),
 - *Ascaris lumbricoides* (1.4%)
 - *Trichuris Trichiura* (0.4%)
- Children infected with geohelminths were less likely to develop new wheeze (3.6% vs. 7.8%) (crude OR=0.44 [0.06, 3.27])
- Numbers were too small to compute effects for eczema or carry out multivariate analysis



Results 2

- Paracetamol use in the first year of life was commonly reported (36% in wheeze cohort and 39% in eczema cohort).
- Use was significantly associated with the incidence of wheeze ($p=0.009$), with risks increased in the 1-3 tablets/month group and the ≥ 4 tablets/month group compared with the never users.
- A significant trend across the categories of dose in the past month (0, 1-3, >4 tablets) was also seen (p trend=0.001).
- Further control for other potential confounders collected did not materially alter the associations.



Incident wheeze and eczema in relation to child's use of paracetamol in the first year of life

Outcome	Paracetamol use in the first year of life	Over all N (%)	n(%) new disease	Crude OR (95%CI)	Adjusted OR* (95% CI)	P-value	Further adjusted OR† (95% CI)	P-value
Incident wheeze (N=756)	Never	486 (64.3)	31 (6.4)	1	1	0.009 [‡]	1	0.014 [‡]
	Yes but not in the past month	83 (11.0)	4 (4.8)	0.74 (0.26,2.16)	0.73 (0.25,2.14)	0.001 [¶]	0.70 (0.24,2.04)	0.001 [¶]
	1-3 tablets per month	175 (23.2)	19 (10.7)	1.79 (0.98,3.26)	1.88 (1.03,3.44)		1.77 (0.96,3.26)	
	≥ 4 tablets per month	12 (1.6)	4 (33.3)	7.34 (2.09,25.72)	7.25 (2.02,25.95)		6.78 (1.89,24.39)	
Incident eczema (N=780)	Never	477 (61.3)	30 (6.3)	1	1	0.25 [‡]	1	0.30 [‡]
	Yes but not in the past month	86 (11.1)	6 (7.0)	1.12 (0.45,2.77)	1.17 (0.47,2.91)		1.14 (0.45,2.87)	
	≥ 1 tablet per month	215 (27.6)	21 (9.8)	1.61 (0.90,2.89)	1.66 (0.92,2.98)		1.62 (0.89,2.96)	

* ORs adjusted for gender, urban rural residence and maternal education

† ORs adjusted for child's gender, place of living and maternal education and additionally adjusted for symptoms of respiratory infections in the first year of life.

‡ Likelihood ratio test

¶ P value for trend computed for dose of paracetamol intake in the past month (0, 1-3, and ≥ 4 tablets)



Alternative explanations

1. Exposure reporting bias - previously ascertained mothers can differentiate paracetamol from other analgesics

(Davey et al J Allergy Clin Immunol 2005; 116:863-8)

2. Reverse causation - exposure precedes the outcomes
3. Aspirin avoidance - previously established to be rare (<1%)
4. Confounding by indication - explored symptoms of respiratory tract infections and other potential confounders
5. Over-the-counter prescription - no association with social class
6. Confounding by NSAIDs - not readily available



Putative mechanisms of the adverse role of paracetamol on asthma

- Glutathione depletion in the lung
 - Reactive oxygen species-free radical damage
 - Shift from Th1 to Th2 cytokine production-promotion of atopy
- Impaired antioxidant defence
- Influence in COX-2 activity
- Influence in the production of prostaglandin E2
- Suppression of fever and reduce Th1 cytokine production
- Altered DNA methylation on prenatal exposure



Conclusions

- Findings support a causal role of paracetamol on development of asthma in children
- The effect of geohelminths remains to be seen as the cohort matures
- The cohort is continuing to be followed up



Acknowledgments

- We thank the mothers and children who participated in the birth cohort and the project staff for their stamina during the fieldwork
- The study has been funded by Asthma UK and the Wellcome Trust.
- Support to attend the INDEPTH was provided by INDEPTH Network.

