American Journal of Respiratory and Critical Care Medicine/AJRCCM

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

Journal:	*American Journal of Respiratory and Critical Care Medicine*
Manuscript ID:	Blue-201006-0989OC
Manuscript Type:	OC - Original Contribution
Date Submitted by the Author:	29-Jun-2010
Complete List of Authors:	Amberbir, Alemayehu; University of Nottingham, Division of Epidemiology and Public Health; Addis Ababa University, School of Public Health Medhin, Girmay; Addis Ababa University, Aklilu Lemma Institute of Pathobiology Alem, Atalay; Addis Ababa University, Department of Psychiatry Britton, John; University of Nottingham, Division of Epidemiology and Public Health Davey, Gail; Addis Ababa University, School of Public Health Venn, Andrea; University of Nottingham, Division of Epidemiology and Public Health
Key Words:	acetaminophen, parasite, asthma, wheeze, eczema

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

Alemayehu Amberbir[1, 2*], Girmay Medhin[3], Atalay Alem[4], John Britton[2], Gail Davey[1], Andrea Venn[2]

Running Title: Acetaminophen, geohelminths and allergic disease

1. School of Public Health, Addis Ababa University, Addis Ababa, Ethiopia.
2. Division of Epidemiology and Public health, University of Nottingham, Nottingham, UK.
3. Aklilu Lemma Institute of Pathobiology, Addis Ababa University, Addis Ababa, Ethiopia.
4. Department of Psychiatry, Addis Ababa University, Addis Ababa, Ethiopia.

*Corresponding author, Email[1]: alamwo1@yahoo.com, Email[2]: mcxaa10@nottingham.ac.uk

School of Public Health, Addis Ababa University, PO Box 80596, Addis Ababa, Ethiopia

Tel: 00251-115-531567, Fax: 00251-114-672494

Descriptor number: 1.17 - Epidemiology (Pediatric): Risk Factors

Funding: This study was funded by Asthma UK (grant 07/036) and the Wellcome Trust (WT081504/Z/06/Z).

At a Glance Commentary:

Acetaminophen has been consistently linked with an increased risk of asthma and allergy but evidence of causality is limited by a lack of longitudinal studies. This study looks for the first time at the longitudinal effect of acetaminophen use in early life on the incidence of allergic disease in children and shows a positive dose-response association with the risk of new onset wheeze, providing further support for a causal role of acetaminophen in the etiology of asthma.

Word count 2,823 (excluding abstracts, references, and online repository)

Abstract

Rationale: Acetaminophen has been hypothesized to increase the risk of asthma and allergic disease, and geohelminth infection to reduce the risk, but evidence from longitudinal cohort studies is lacking.

Objectives: To investigate the independent effects of these exposures on the incidence of wheeze and eczema in a birth cohort.

Methods: In 2005/6 a population based cohort of 1065 pregnant women from Butajira, Ethiopia was established, to whom 1006 live singleton babies were born. At age one and three, questionnaire data were collected on wheeze, eczema, child's use of acetaminophen and various potential confounders, along with a stool sample for geohelminth analysis. Those without wheeze (n=756) or eczema (n=780) at age one were analysed to determine the independent effects of geohelminth infection and acetaminophen use in the first year of life on the incidence of wheeze and eczema by age three.

Results: Wheeze and eczema incidence between the ages of one and three were reported in 7.7% (58/756) and 7.3% (57/780) of children respectively. Acetaminophen use was significantly associated with a dose-dependent increased risk of incident wheeze (adjusted ORs 1.88 [1.03 to 3.44] for 1-3 tablets and 7.25 [2.02, 25.95] for ≥ 4 tablets in past month at age 1 versus never), but not eczema. Geohelminth infection was insufficiently prevalent (<4%) to compute estimates of effect.

Conclusions: These findings suggest frequent acetaminophen use early in life increases the risk of new onset wheeze, whilst the role of geohelminth infection on allergic disease incidence remains to be seen as the cohort matures.

Key words: acetaminophen, parasite, asthma, wheeze, eczema; **Word count:** 250

Introduction

Asthma has become one of the most common disorders among children and adults.[1] Epidemiological studies have demonstrated a higher prevalence of asthma and related allergic conditions in more developed countries, and increases in prevalence over recent decades in both developed and developing countries, observations that are likely be due largely to environmental factors.[1-3] One such environmental factor that has attracted interest, and that fits with the 'hygiene hypothesis',[4] is geohelminth infection. An increasing body of evidence points to geohelminth infection, particularly hookworm infection protecting against asthma and allergic conditions.[5;6]

Also attracting recent interest but lacking longitudinal support, is the hypothesis that acetaminophen use might increase the risk of asthma and allergic disease, and that the shift from aspirin to acetaminophen use may have contributed to the rise in these conditions over recent decades.[7] The evidence to date implicating acetaminophen in the etiology of asthma and other allergic diseases has been remarkably consistent,[7-20] with adverse effects reported in relation to acetaminophen exposure *in utero*,[8-11] during infancy,[11;12] in childhood[13;14] and during adult life.[15-18] The relation also extends to objective markers of allergy.[14-16] However, support from prospective data is limited to one study in women which reported an increased risk of adult-onset asthma in relation to frequent use of acetaminophen.[18] Studies have also tended to rely on recall of acetaminophen use in the past, or not adequately eliminated the possibility of confounding by early respiratory infections, a problem highlighted by Beasley et al.[13] Moreover, in studies based in developed countries, the possibility that acetaminophen and asthma are associated through aspirin avoidance is difficult to exclude.

The aim of this study was therefore to establish the temporal relation between early infection with geohelminths and use of acetaminophen in the first year of life, and the incidence of childhood wheeze and eczema in an Ethiopian birth cohort.

Methods

Study setting and design

The study was sited in and around Butajira town, which is located 130 km south of the Ethiopian capital, Addis Ababa. The Butajira Rural Health Program (BRHP), a Demographic Surveillance Site (DSS) covering nine rural and one urban (Butajira town) administrative areas was set up in 1987.[21] In 2005 a birth cohort nested in the BRHP was established, a detailed description of which has been published previously.[22;23] In brief, all women in the BRHP aged 15-49 and in their third trimester of pregnancy, were identified by the BRHP fieldworkers between July 2005 and February 2006 and invited to participate in the study. Of the 1234 eligible women, 1065 were recruited (86% of eligible) and all live, singleton babies born to these women (n=1006) were followed up as a birth cohort.

Data collection and measurements

Data were collected on the cohort at intervals from pregnancy to age 3, primarily using interview led questionnaires administered to mothers. Information on demographic factors was collected during pregnancy and numerous additional potential confounders at birth, two months, first birthday and third birthday (see online repository). Symptoms of respiratory tract infection (cough, fast breathing and fever) were collected at two months and one year.

At age one and three, wheeze ever and eczema ever were ascertained using questions from the International Study for Asthma and Allergies in Children (ISAAC), and mothers were also asked if the child had taken any acetaminophen in last year and if so, how much in the last month (see online repository).

In addition to the questionnaire, stool samples were collected at age one and three and qualitatively examined for geohelminth infections using the formol-ether concentration method.[24]

Statistical data analysis

Statistical analysis was carried out using Stata 11 (Statacorp, College Station, Texas, USA). Exposure to any geohelminth infection was defined as infection with any of hookworm, *Ascaris lumbricoides* or *Trichuris trichiura*. To assess associations with incidence of new onset wheeze between age one and three, those children without reported wheeze ever at age one were selected for analysis, and the outcome defined as reported wheeze ever at age three. Similarly, children without eczema ever at age one were selected for analysis of incident eczema, defined as a positive response at age three. Multiple logistic regression was performed to compute adjusted odds ratios and 95% confidence intervals for incident wheeze and eczema in relation to acetaminophen group and geohelminth infection, controlling for *a priori* confounders place of residence, child's gender and maternal education (as a marker of socioeconomic status). The impact of further controlling for any other potential confounders collected including early life respiratory tract infections (cough, fever and fast breathing) was also explored.

Ethics

Ethical approval was granted by the National Ethics Review Committee of the Ethiopian Science and Technology Ministry and the University of Nottingham ethics committee, United Kingdom. Written consent was obtained from the mothers and in keeping with the requirements of the Ethiopian ethics committee all women and their children were reimbursed for health care costs.

Role of the funding source

The study sponsors had no role in study design, data collection, analysis of the data, interpretation and writing of the report, or the decision to submit the paper for publication.

Results

Description of cohort participants

Of the 1006 babies in the cohort, 64 (6.4%) had died and 10 (0.9%) migrated from the study area before their first birthday, and a further 33 had missing data on core variables at age 1, leaving 899 (89%) available for analyses at one year. A detailed description of the cohort at year one is reported elsewhere.[23] Of these, 95% (853) were followed up and outcome data collected at age 3; 17 died, 27 migrated and 2 lost with unidentified reason between age 1 and 3.

Natural history of wheeze and eczema between age one and three

Of the 96 children with reported wheeze ever at age one who were successfully followed-up, 26 (27.1%) still had reported wheeze ever at age three and 70 (72.9%) did not (Fig 1a). Of the 756 non wheezers at age one, 58 (7.7%) had reported wheeze ever at age 3 and were defined as incident wheezers (Fig 1a). Similarly of the 72 children with reported eczema ever at age one, 9 (12.5%) still had reported eczema at age three, with the other 63 (87.5%) not (Fig 1b). Incident eczema was reported in 7.3% (57/780) of children without reported eczema at age 1 followed to age 3 (Fig 1b).

Determinants of incident wheeze and eczema

Table 1 shows the distribution of demographic and potential confounding variables amongst the wheeze and eczema free children at age one on whom subsequent analyses were performed. The majority of children lived in rural areas (87%) and had mothers without formal education (80%). The risk of incident wheeze was non-significantly greater in urban children and boys, and significantly greater in those of low birth weight (Table 1). There was a borderline significant

increased risk of new onset eczema in girls and those in large households, and a significant increased risk with increasing number of older siblings (Table 1).

Table 2 shows that infantile symptoms of respiratory infections (cough, fast breathing and fever) were commonly reported at age 2 months but not related to wheeze or eczema incidence. All three symptoms in the first year of life however were significantly positively associated with the incidence of wheeze between age 1 and 3, but not eczema (Table 2).

Geohelminth infection at age one was found in only 4% of children, with hookworm being the most common infection (2.3%), followed by *A. lumbricoides* (1.4%) and *T. trichiura* (0.4%). The risk of new onset wheeze was lower in those infected (3.6%) than uninfected (7.8%), but the 95% CI was wide and significance not reached (crude OR [95% CI] 0.44, [0.06 to 3.27] for any infection and 0.80 [0.10 to 6.16] for hookworm infection). As only one infected child had incident wheeze, no further adjusted analysis could be carried out. No children with geohelminth infection reported incident eczema, and therefore ORs could not be computed or further analysis performed.

Acetaminophen use in the first year of life was commonly reported (36% in wheeze cohort and 39% in eczema cohort), with around a quarter reporting use in the past month (Table 3). Use was significantly associated with the incidence of wheeze (p=0.009), with risks increased in the 1-3 tablets/month group (adjusted OR [95% CI] 1.88 [1.03 to 3.44]) and the >=4 tablets/month group (adjusted OR 7.25 [2.02, 25.95]) 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; adjustment for symptoms of respiratory infections in the first year of life slightly reduced the strength of the wheeze association but overall significance remained (Table 3; overall p=0.014; p trend=0.001). For eczema, the odds ratio for use of acetaminophen in the past month was increased (adjusted OR [95% CI] 1.66 [0.92, 2.98]) compared to never use, but no overall significant association was seen (Table 3).

Discussion

In this longitudinal birth cohort in Ethiopia, we have been able to look for the first time at the effect of acetaminophen use in infancy (first year of life) on the incidence of childhood allergic disease symptoms and found a positive dose-response association with incident wheeze but not eczema. We have also explored effects of geohelminth infection in the first year of life, but small numbers resulted in insufficient power to determine independent effects on incident wheeze and eczema at this age, and any effect remains to be seen as the cohort matures and more children become infected.

Strengths of this study are the longitudinal design, ensuring that exposures precede the outcomes, as well as the high response rate and good retention of participants between birth and three years. Additionally, the large number of demographic and lifestyle variables collected allowed us to control for potential confounders. Of particular concern was confounding by socioeconomic status, as this may influence access to acetaminophen. However we found that none of our markers of social advantage and affluence (urban/rural residence, maternal education, maternal occupation and income) were related to acetaminophen use and therefore the effects seen are unlikely to be due to residual confounding by social advantage. We also explored the possibility of confounding by indication since acetaminophen may be taken by children for respiratory tract infections in early life, who are also more susceptible to the subsequent development of allergic diseases.[25] When we adjusted for the main symptoms of respiratory infections in the first year of life, the wheeze association reduced in magnitude slightly but remained highly statistically significant.

The possibility of reporting bias, introduced by the use of interview-led questionnaires, needs to be considered when interpreting our findings. In particular, poor recall may have led to a degree of error in our wheeze and eczema variables since mothers were asked about symptoms since birth. Our observation of a large proportion of children with reported wheeze ever at age 1 having a negative response to ever wheeze at age 3 is likely to be explained by mothers not remembering wheeze symptoms experienced by their child as a baby but which then resolved. This transient wheeze phenotype is thought to be infection-related and more common in those born with small airways,[26] and in our previous risk factor analysis of the cohort at age 1, evidence of such a phenotype was found.[23] The implications of poor recall on our current findings are that some incident cases may have been missed if symptoms only occurred early in the 1 to 3 year follow-up period, although such non-persistent cases are likely to those with mild disease. For eczema, whilst we have previously shown that the symptoms being reported appear to be linked to an allergic etiology,[23] some degree of misclassification with scabies or other skin conditions cannot be ruled out. To ascertain child's use of acetaminophen, mothers were asked about use in the first year of life at the one year follow-up, and additionally about consumption in the past month to minimize recall bias and quantify use. Since our previous qualitative and quantitative work in the same setting has shown that our study participants were able to distinguish different analgesics, and that the majority of the general population in the study area know acetaminophen to be different from aspirin, [15;27] reporting error is likely to be low.

An issue in previous studies has been the possibility that observed associations between acetaminophen and wheeze have arisen through aspirin avoidance in those with asthma. Whilst this is unlikely to confound our findings due to the fact that acetaminophen consumption

preceded the outcome in our study, there is the possibility that parents with asthma may avoid giving their child aspirin and hence an association arises because children with genetic susceptibility are more likely to be given acetaminophen. However, we have previously established that only 1% of the population in the study area reported avoidance of aspirin due to asthma risk,[27] making this an unlikely explanation for the observed association. Information on use of non steroidal anti inflammatory drugs (NSAIDs) that may be linked to asthma and allergic diseases[12] were not collected as they are not readily available or affordable in this rural community.

The acetaminophen and asthma hypothesis has attracted interest for more than a decade[19] and many studies, though primarily cross-sectional, have independently demonstrated an increased prevalence of asthma, and other allergic conditions amongst acetaminophen users.[8;9;11-19] Our current findings fit with our previous research in children and adults in the same Butajira study area which reported a similar level of acetaminophen use (42% vs. 39% in the current study), and a significant dose-dependent association with wheeze.[15] Findings from the large ISAAC multi-country study of 205,487 6-7 year old children of a significant association between current and first year use of acetaminophen and the risk of asthma,[13] also fit with our findings. However both these cross-sectional studies reported significant associations with eczema, not seen in our current study, as well as effects on other allergic outcomes.[13;15] Prospective evidence has been limited to a handful of studies showing a positive relation between acetaminophen exposure in the intrauterine environment, particularly in late pregnancy, and the risk of wheeze but not eczema during childhood,[8-11] and a single study looking at personal consumption, which was in adults not children, and reported a positive relation between acetaminophen use and adult-onset

asthma in women.[18] The reason why no prospective study, including ours, has found independent associations between acetaminophen use and eczema may be attributed to low statistical power or misclassification of eczema symptoms, or there may be no true effect and underlying mechanisms relate specifically to the lung.

Possible suggested mechanisms whereby acetaminophen intake might increase the risk of asthma and allergic diseases include the depletion of pulmonary glutathione concentration,[28;29] and the inhibition of basal INF-α and IL-6 secretion, predisposing the lung to epithelial damage, mast cell activation, excess mucus secretion and bronchoconstriction.[28;29] The animal model used demonstrated that the lung was the first organ in which this depletion action persisted further potentiating other toxic products.[30] Peterson *et al*, using two immunologic animal models, suggest that depletion of glutathione decreased levels of Th1 cytokine responses thereby favoring allergenic patterns of Th2.[31]

The hypothesis that geohelminth infections, which are highly prevalent in areas where allergy remains rare, may protect against asthma and allergic diseases has gained support from a range of independent studies, meta analysis and systematic reviews.[5;6] Whilst we found no significant associations in our study, the observed effects were in the expected direction, and our analyses were limited by insufficient statistical power as a result of the low prevalence of geohelminth infection in the first year of life and small numbers with the outcomes amongst the infected children. The low prevalence of geohelminths in children in this population is probably linked to a mass de-worming strategy that started in 2006 in under-five year olds in this area.[32] We

anticipate that as the cohort ages, more children will become infected and we will be better able to assess these associations.

In conclusion, this longitudinal study from a developing country birth cohort provides further support for an association between infantile use of acetaminophen and increased risk of incident wheeze, which is unlikely to be explained by aspirin avoidance, reverse causation or confounding by indication. As the use of acetaminophen preceded the outcomes, a causal explanation is increasingly likely. Further research is therefore needed, particularly randomized controlled trials and longitudinal birth cohort studies. We found no significant association between geohelminth exposure in the first year of life and risk of incident wheeze and eczema but were limited by low geohelminth prevalence. We intend to continue following up these children, to further explore the temporal relationships between acetaminophen, geohelminth exposure and allergic outcomes.

Acknowledgments

We thank the mothers and children who participated in the birth cohort; the data collectors for their stamina during the field work; and the technicians of Aklilu Lemma Institute of Pathobiology for examining the stool samples.

References

1. Eder, W., M. J. Ege, E. von Mutius. The Asthma Epidemic. *N Engl J Med* 2006;355:2226-2235.

2. Patel, S., M. R. Jarvelin, M. Little. Systematic review of worldwide variations of the prevalence of wheezing symptoms in children. *Environ Health* 2008; 7:57.

3. Asher, M. I., S. Montefort, B. Bjorksten, C. K. Lai, D. P. Strachan, S. K. Weiland, H. Williams. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *The Lancet* 2006; 368:733-743.

4. Strachan, D. P. Family size, infection and atopy: the first decade of the 'hygiene hypothesis'. *Thorax* 2000; 55:S2-10.

5. Leonardi-Bee, J., D. Pritchard, J. Britton, and the Parasites in Asthma Collaboration. Asthma and Current Intestinal Parasite Infection: Systematic Review and Meta-Analysis. *Am.J.Respir.Crit.Care Med* 2006; 174:514-523.

6. Flohr, C., R. J. Quinnell, J. Britton. Do helminth parasites protect against atopy and allergic disease? *Clin Exp Allergy* 2009;39:20-32.

7. Varner, A. E., W. W. Busse, R. F. Lemanske. Hypothesis: decreased use of pediatric aspirin has contributed to the increasing prevalence of childhood asthma. *Ann Allergy Asthma Immunol* 1998;81:347-351.

8. Shaheen, S. O., R. B. Newson, A. Sherriff, A. J. Henderson, J. E. Heron, P. G. J. Burney, J. Golding, and the Alspac Study Team. Paracetamol use in pregnancy and wheezing in early childhood. *Thorax* 2002;57:958-963.

9. Shaheen, S. O., R. B. Newson, A. J. Henderson, J. E. Headley, F. D. Stratton, R. W. Jones, D. P. Strachan. Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. *Clin Exp Allergy* 2005; 35:18-25.

10. Rebordosa, C., M. Kogevinas, H. T. Sorensen, J. Olsen. Pre-natal exposure to paracetamol and risk of wheezing and asthma in children: A birth cohort study. *Int.J.Epidemio* 2008; 37:583-590.

11. Persky, V., J. Piorkowski, E. Hernandez, N. Chavez, C. Wagner-Cassanova, C. Vergara, D. Pelzel, R. Enriquez, S. Gutierrez, A. Busso. Prenatal exposure to acetaminophen and respiratory symptoms in the first year of life. *Annals of Allergy, Asthma and Immunol* 2008; 101:271-278.

12. Lesko, S. M., C. Louik, R. M. Vezina, A. A. Mitchell. Asthma Morbidity After the Short-Term Use of Ibuprofen in Children. *Pediatrics* 2002;109:e20.

13. Beasley, R., T. Clayton, J. Crane, E. von Mutius, C. K. Lai, S. Montefort, A. Stewart. 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. *The Lancet* 2008; 372:1039-1048.

14. Newson, R. B., S. O. Shaheen, S. Chinn, and P. G. Burney. Paracetamol sales and atopic disease in children and adults: an ecological analysis. *Eur Respir J* 2000; 16:817-823.

15. Davey, G., Y. Berhane, P. Duncan, G. ref-Adib, J. Britton, A. Venn, G. Davey, Y. Berhane, P. Duncan, G. ref-Adib, J. Britton, and A. Venn. 2005. Use of acetaminophen and the risk of self-reported allergic symptoms and skin sensitization in Butajira, Ethiopia. *J of Allergy Clin Immunol* 2005; 116:863-868.

16. McKeever, T. M., S. A. Lewis, H. A. Smit, P. Burney, J. R. Britton, P. A. Cassano. The Association of Acetaminophen, Aspirin, and Ibuprofen with Respiratory Disease and Lung Function. *Am.J.Respir.Crit.Care Med* 2005; 171:966-971.

17. Shaheen, S. O., J. A. C. Sterne, C. E. Songhurst, P. G. J. Burney.Frequent paracetamol use and asthma in adults. *Thorax* 2000; 55:266-270.

18. Barr, R. G., C. C. Wentowski, G. C. Curhan, S. C. Somers, M. J. Stampfer, J. Schwartz, F. E. Speizer, C. A. Camargo. Prospective Study of Acetaminophen Use and Newly Diagnosed Asthma among Women. *Am.J.Respir.Crit.Care Med* 2004; 169:836-841.

19. Farquhar, H., A. Stewart, E. Mitchell, J. Crane, S. Eyers, M. Weatherall, R. Beasley. The role of paracetamol in the pathogenesis of asthma. *Clin Exp Allergy* 2010; 40:32-41.

20. Eneli, I., K. Sadri, C. Camargo, and R. G. Barr. Acetaminophen and the risk of asthma. *Chest* 2005; 127:604-612.

21. Berhane, Y., Wall S, Kebede D. Establishing an epidemiological field laboratory in rural areas-potential for public health research and interventions. *Ethiop J Health Dev* 1999; S13.

22. Hanlon, C., G. Medhin, A. Alem, F. Tesfaye, Z. Lakew, B. Worku, M. Dewey, M. Araya, A. Abdulahi, M. Hughes, M. Tomlinson, V. Patel, M. Prince. Impact of antenatal common mental disorders upon perinatal outcomes in Ethiopia: the P-MaMiE population-based cohort study. *Trop Med Int Health* 2009; 14:156-166.

23. Belyhun, Y., A. Amberbir, G. Medhin, B. Erko, C. Hanlon, A. Venn, J. Britton, G. Davey. Prevalence and risk factors of wheeze and eczema in one year old children: the Butajira birth cohort, Ethiopia. *Clin Exp Allergy* 2010; 619-626.

24. WHO. Basic laboratory methods in medical parasitology. *World Health Organization, Geneva* 1991.

25. Illi, S., E. von Mutius, S. Lau, R. Bergmann, B. Niggemann, C. Sommerfeld, U. Wahn, and the MAS Group. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *BMJ* 2001;322:390-395.

26. Martinez, F. D., A. L. Wright, L. M. Taussig, C. J. Holberg, M. Halonen, W. J. Morgan, and The Group. Asthma and Wheezing in the First Six Years of Life. *N Engl J Med* 1995; 332:133-138.

27. Duncan, P., G. Aref-Adib, A. Venn, J. Britton, G. Davey. Use and misuse of Aspirin in Rural Ethiopia. *East Afr Med J* 2006; 83:31-36.

28. Nuttall, S. L., J. Williams, and M. J. Kendall. Does paracetamol cause asthma? *J Clin Pharm Ther* 2003;28:251-257.

29. Dimova, S., P. H. M. Hoet, D. Dinsdale, B. Nemery. Acetaminophen decreases intracellular glutathione levels and modulates cytokine production in human alveolar macrophages and type II pneumocytes in vitro. *Int J Biochem & Cell Biol* 2005; 37:1727-1737.

30. Micheli, L., D. Cerretani, A. Fiaschi, G. Gioorgi, R. Romeo, and R. F.Runci. Effect of Acetaminophen on Glutathione Levels in Rat Testis and Lung. *Environ Health Perspect* 1994; 102:63-64.

31. Peterson, J. D., L. A. Herzenberg, K. Vasquez, and C. Waltenbaugh. Glutathione levels in antigen-presenting cells modulate Th1 versus Th2 response patterns. *Proceedings of the National Academy of Sciences of the United States of America* 1998; 95:3071-3076.

32. Federal Ministry of Health. Guidelines for the Enhanced Outreach Strategy (EOS) for child survival interventions. Addis Ababa, Ethiopia, 2004.

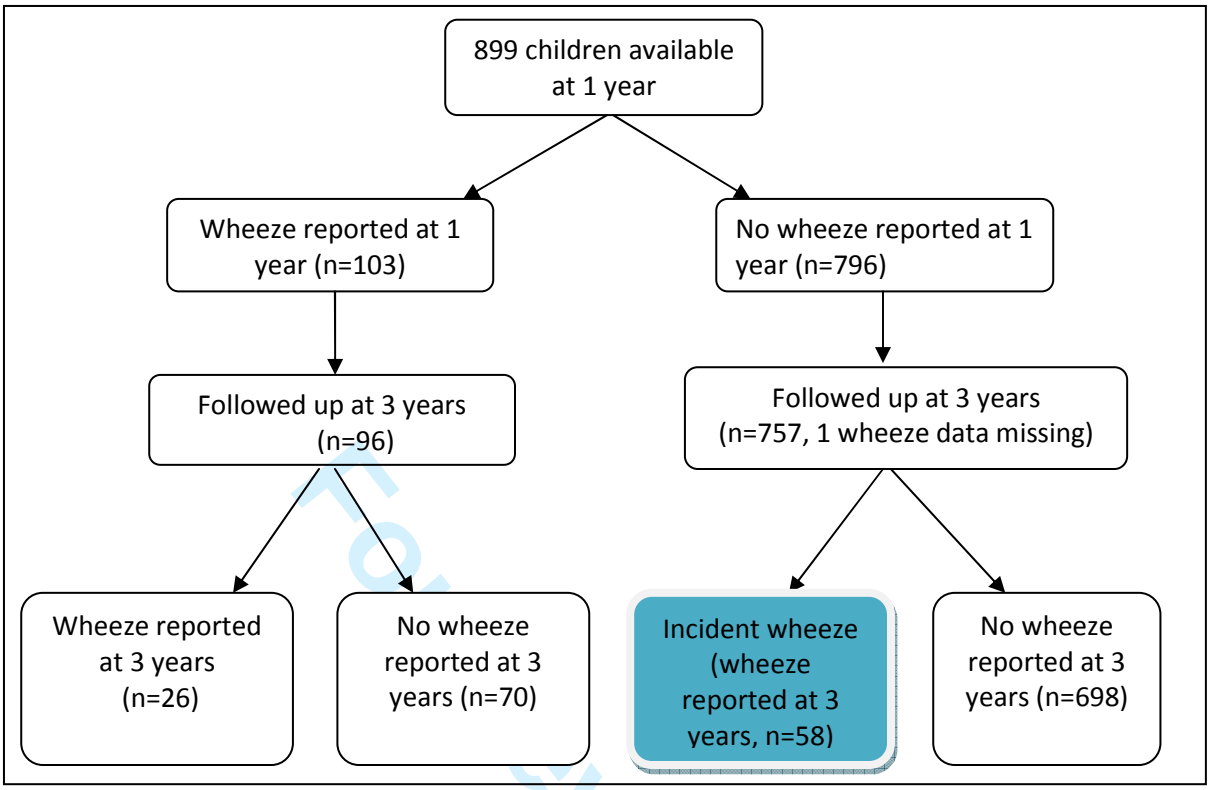

Fig. 1a Flow chart showing reporting of wheeze between one and three years

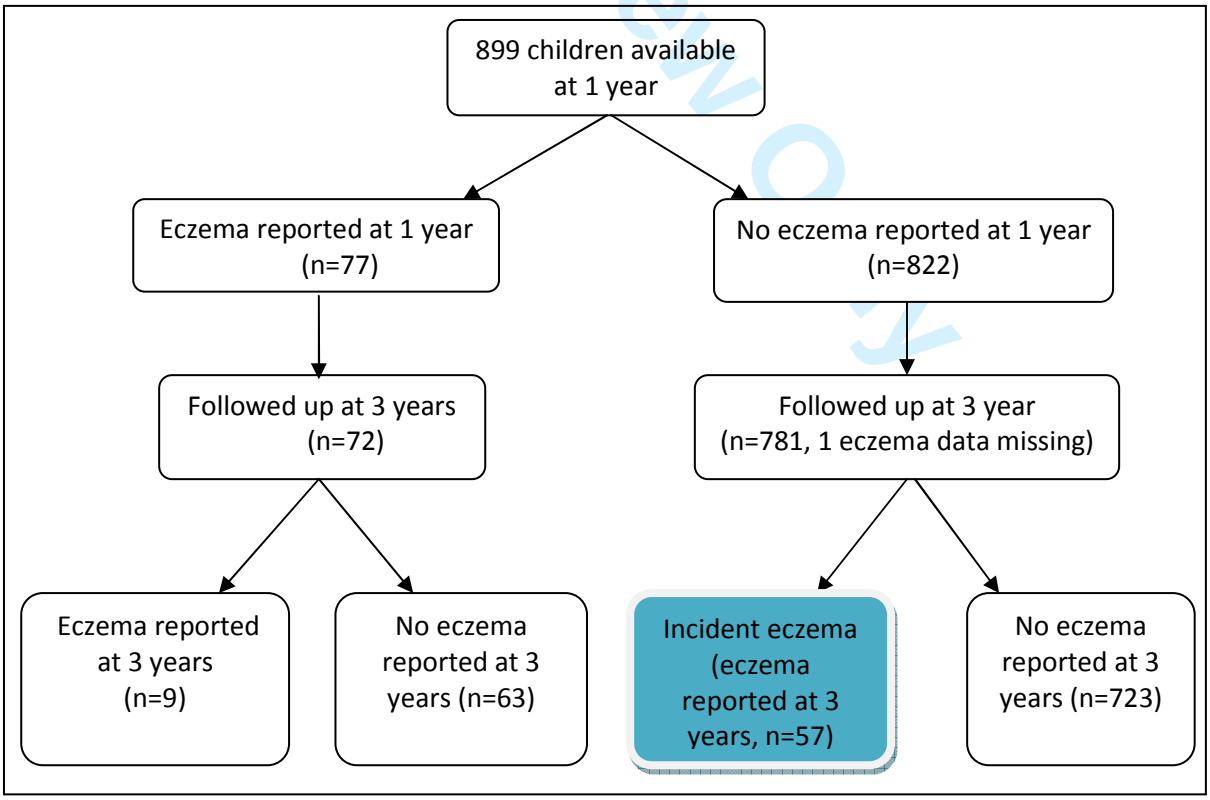

Fig. 1b Flow chart showing reporting of eczema between one and three years

Table 1 Distribution of potential confounders and association with incidence of wheeze and eczema

Variables	Wheeze never at age 1 (N=756)				Eczema never at age 1(N=780)			
	Overall N (%)	n (%)new wheeze*	Crude OR (95% CI)	P-value	Overall N (%)	n (%)new eczema*	Crude OR (95% CI)	P-value
Place of living								
Urban	95 (12.6)	10 (10.5)	1.50(0.73,3.08)	0.27	98 (12.6)	8 (8.2)	1.15 (0.53,2.50)	0.73
Rural	661 (87.4)	48 (7.3)	1		682 (87.4)	49 (7.2)	1	
Maternal age				0.92†				0.32†
15-24	293 (38.8)	21 (7.2)	0.88 (0.39,1.99)	0.71‡	297 (38.1)	19 (6.4)	1.25 (0.49,3.22)	0.96‡
25-34	351 (46.4)	28 (8.0)	0.99 (0.45,2.17)		367 (47.1)	32 (8.7)	1.75 (0.71,4.30)	
35-44	112 (14.8)	9 (8.0)	1		116 (14.9)	6 (5.2)		
Gender								
Male	378 (50)	33 (8.7)	1.35 (0.79,2.32)	0.28	394 (50.5)	22 (5.6)	0.59 (0.34,1.03)	0.06
Female	378 (50)	25 (6.6)	1		386 (49.5)	35 (9.1)	1	
Maternal education								
Formal	148 (19.6)	16(10.8)	1.63 (0.89,2.99)	0.11	155 (19.9)	12 (7.7)	1.08 (0.56,2.10)	0.82
No formal	608 (80.4)	42 (6.9)	1		625 (80.1)	45 (7.2)	1	
Exclusively breastfed¥								
Yes	633 (84.1)	51 (8.1)	1.41 (0.63,3.20)	0.40	659 (84.7)	49 (7.4)	1.11 (0.51,2.42)	0.78
No	120 (15.9)	7 (5.8)	1		119 (15.3)	8 (6.7)	1	
Vaccination at 2 months¶								
Yes	443 (58.8)	35 (7.9)	1.07 (0.62,1.85)	0.81	463 (59.5)	34 (7.3)	1.01 (0.58,1.74)	0.98
No	310 (41.2)	23 (7.4)	1		315 (40.5)	23 (7.3)	1	
Birth weight								
Low (< 2.5kg)	35 (7.0)	6 (17.1)	2.73 (1.06,7.04)	0.04	39 (7.4)	1 (2.6)	0.32 (0.04,2.40)	0.27
Normal	468 (93.0)	33 (7.1)	1		487 (92.6)	37 (7.6)	1	
Parental allergic history								
Yes	39 (5.2)	4(10.3)	1.40 (0.48,4.08)	0.54	42 (5.4)	3(7.1)	0.97 (0.29,3.25)	0.96
No	714 (94.8)	54 (7.6)	1		736 (94.6)	54 (7.3)	1	
Insecticide use in home								
Yes	623 (82.4)	46 (7.4)	0.81 (0.42,1.57)	0.53	648 (83.3)	50 (7.7)	1.47 (0.65,3.32)	0.36
No	133 (17.6)	12 (9.0)	1		130 (16.7)	7 (5.4)	1	
Household size				0.58†				0.11†
1-3	98 (13.0)	7 (7.1)	1	0.58‡	89 (11.4)	5 (5.6)	1	0.06‡
4-6	422 (55.8)	36 (8.5)	1.21 (0.52,2.81)		446 (57.3)	27 (6.1)	1.08 (0.41,2.89)	
7+	236 (31.2)	15 (6.4)	0.88 (0.35,2.24)		243 (31.2)	25(10.3)	1.93 (0.71,5.20)	
No. of older siblings				0.52†				0.01†
0	111 (14.7)	7 (6.3)	1	0.81‡	104 (13.4)	3 (2.9)	1	0.002‡
1-3	415 (54.9)	36 (8.7)	1.41 (0.61,3.26)		437 (56.2)	27 (6.2)	2.22 (0.66,7.45)	
4-10	230 (30.4)	15 (6.5)	1.04 (0.41,2.62)		237 (30.5)	27(11.4)	4.33(1.28,14.61)	

Table 1 (continued)

Variables	Wheeze never at age 1 (N=756)				Eczema never at age 1(N=780)			
	Overall N (%)	n (%)new wheeze*	Crude OR (95% CI)	P-value	Overall N (%)	n (%)new eczema*	Crude OR (95% CI)	P-value
Child's sleeping place				0.87†				0.89†
Bed/platform	59 (7.8)	5 (8.5)	1		59 (7.6)	5 (8.5)	1	
Floor	324 (42.9)	23 (7.1)	0.83 (0.30,2.26)		344 (44.3)	26 (7.6)	0.88 (0.32,2.40)	
Grass matting	372 (49.3)	30 (8.1)	0.95 (0.35,2.55)		374 (48.1)	26 (7.0)	0.81 (0.30,2.19)	
Indoor cooking								
Yes	609 (80.9)	46 (7.6)	0.90 (0.46,1.74)	0.75	628 (80.7)	46 (7.3)	1.00 (0.50,1.98)	0.99
No	144 (19.1)	12 (8.3)	1		150 (19.3)	11 (7.30	1	
Indoor kerosene use								
Yes	88 (11.7)	6 (6.8)	0.86 (0.36,2.07)	0.74	87 (11.2)	6 (6.9)	0.93 (0.39,2.23)	0.87
No	665 (88.3)	52 (7.8)	1		691 (88.8)	51 (7.4)	1	
Types of roof								
Thatched	578 (76.8)	41 (7.1)	0.71 (0.39,1.28)	0.26	595 (76.5)	42 (7.1)	0.85 (0.46,1.57)	0.61
Corrugated iron	175 (23.2)	17 (9.7)	1		183 (23.5)	15 (8.2)	1	

‡Likelihood ratio test, † p for trend

¥ Exclusive breast feeding status at 2 months

¶ Any vaccination history at 2 months

*Reported wheeze and eczema ever at year 3 follow-up.

Table 2 Prevalence of symptoms of respiratory infections in early life in those with and without incident wheeze and eczema between age 1 and 3

Symptoms of respiratory infections n (%)	Wheeze never at age 1 (N=756)				Eczema never at age 1 (N=780)			
	All children	With incident wheeze	Without incident wheeze	p-value	All children	With incident eczema	Without incident eczema	p-value
Respiratory infection symptoms at 2 months								
Cough	298 (39.6)	22 (37.9)	276 (39.7)	0.79	318 (40.9)	23 (40.4)	295 (40.9)	0.93
Fast breathing	180 (23.9)	15 (25.9)	165 (23.7)	0.72	192 (24.7)	13 (22.8)	197 (24.8)	0.73
Fever	248 (32.9)	21 (36.2)	227 (32.7)	0.58	275 (35.4)	17 (29.8)	258 (35.8)	0.37
Respiratory infection symptoms at 1 year								
Cough	443 (58.6)	41 (70.7)	402 (57.6)	0.05	487 (62.4)	37 (64.9)	450 (62.2)	0.67
Fast breathing	251 (33.2)	27 (46.6)	224 (32.1)	0.03	297 (38.1)	24 (42.1)	273 (37.8)	0.52
Fever	581 (76.9)	51 (87.9)	530 (75.9)	0.04	618 (79.2)	48 (84.2)	570 (78.8)	0.34

Missing data on symptoms of respiratory infection at age 2 months on 3 in wheeze free cohort and 2 in eczema free cohort.

Table 3 Univariate and multivariate associations between child's use of acetaminophen in the first year of life and incident wheeze and eczema between age one and three.

Outcome	Acetaminophen 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)						0.009‡		0.014‡
	Never	486 (64.3)	31 (6.4)	1	1	0.001¶	1	0.001¶
	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)		0.70 (0.24,2.04)	
	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)						0.25‡		0.30‡
	Never	477 (61.3)	30 (6.3)	1	1		1	
	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 acetaminophen intake in the past month (0, 1-3, and ≥ 4 tablets)

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

Alemayehu Amberbir, Girmay Medhin, Atalay Alem, John Britton, Gail Davey, Andrea Venn

Online Repository

Methods

Demographic factors collected by questionnaire during pregnancy included mother's age, place of residence, ethnicity, religion, maternal occupation and education, household income. Potential confounders collected by questionnaire at the follow-up visits included parental history of allergic diseases, household amenities, sanitation, birth order, household size, immunization history, breastfeeding, infant's bed and mattress materials, insecticide use, roof type and indoor fuels. Weight of the child was measured immediately after birth on over 60% of the cohort babies.

At age one and three, symptoms on wheeze and eczema were ascertained using questions from the International Study for Asthma and Allergies in Children (ISAAC): *'Has your child ever had wheezing or whistling in their chest?*' (wheeze ever) and *'Has your child ever had an itchy skin rash which has affected the skin creases, e.g., the folds of the elbow or behind the knees*? (eczema ever). Mothers were also asked about the child's use of acetaminophen in the first year of life: *"Has your child taken any acetaminophen in the last year?"*, and if a positive response given, further asked "*How many tablets of acetaminophen has the child taken in the last month?"* Child's use of acetaminophen in the first year of life was categorized into 4 groups for analysis: 'never', 'yes but not in the past month', '1-3 tablets in last month' and '≥4 tablets in last month.' Due to small numbers, it was necessary to merge the two highest acetaminophen

categories in the analysis of eczema. Evidence of a dose-response trend across acetaminophen categories could therefore only be assessed in relation to wheeze; for this analysis a baseline category of 0 tablets in the past month was created by merging the first two acetaminophen groups and p for trend computed.