
Exposure to Paracetamol and Antibiotics in Early Life and Elevated Risk of Asthma in Childhood

53

M. Muc, C. Padez, and A. Mota Pinto

Abstract

Prospective studies on increased risk of childhood asthma due to exposure to paracetamol and antibiotics in early life have yielded contradictory results. Therefore, the aim of the present study was to investigate the association between administration of paracetamol and antibiotics in the first 12 months of life and delayed asthma symptoms later in childhood. This is a cross-sectional study that included 1,063 children from the primary schools in Coimbra, Portugal. ISAAC-based environmental and core asthma and rhinitis questionnaires were used to obtain information about children's respiratory health and administration of paracetamol and antibiotics. We found that early paracetamol use significantly increased the risk of asthma ever (at least one episode in life) (OR = 2.9; 95 % CI:1.8–4.5), current asthma (OR = 2.4; 95 % CI:1.5–3.6), wheezing ever (OR = 2.5; 95 % CI:1.8–3.4), rhinitis ever (OR = 2.4; 95 % CI:1.7–3.3), and current rhinitis (OR = 2.8; 95 % CI:2.0–3.9). Antibiotic exposure showed a similar effect with the risk for current asthma (OR = 1.6; 95 % CI:1.0–2.5), asthma ever (OR = 2.0; 95 % CI:1.3–3.1), wheeze ever (OR = 2.3; 95 % CI:1.7–3.2), and rhinitis symptoms (OR = 1.8; 95 % CI:1.3–2.6, OR = 1.8; 95 % CI:1.3–2.6, OR = 1.9; 95 % CI:1.2–3.0 for rhinitis ever, current rhinitis, and tearing, respectively). We further found that increased frequency of paracetamol use during the last 12 months preceding the study facilitated the appearance of allergic symptoms, suggesting a dose-dependent associations. In conclusion, the study shows a significant association between exposure to paracetamol

M. Muc (✉) • C. Padez
Department of Life Sciences, University of Coimbra,
Apartado 3046, 3001-401 Coimbra, Portugal

CIAS – Research Center for Anthropology and Health,
University of Coimbra, Coimbra, Portugal
e-mail: magdalenamuc@gmail.com

A.M. Pinto
General Pathology Laboratory, Faculty of Medicine,
University of Coimbra, Coimbra, Portugal

and antibiotics in the first 12 months of life and both prevalence and severity of asthma and rhinitis symptoms in children 5–9 years old.

Keywords

Antibiotics • Asthma • Children • Paracetamol • Rhinitis • Wheeze

1 Introduction

A rapidly increasing prevalence of atopic diseases world-wide has led to a research interest in the possible underlying reasons (Eder et al. 2006), although a consensus regarding the asthmatic and allergic states has not yet been reached. On the list of putative factors increasing the prevalence of asthma is the early use of paracetamol and antibiotics (Rusconi et al. 2011).

Paracetamol was indicated as a candidate asthma facilitating factor in 1998, suggesting that the switch in the use pattern from aspirin to paracetamol in early childhood could increase susceptibility to allergic diseases by enhancing the Th2 response (Varner et al. 1998). Indeed, paracetamol is currently the most commonly used analgesic and antipyretic prescribed to pediatric patients as an alternative to aspirin that may be associated with the Reye syndrome (Newson et al. 2000; Rahwan and Rahwan 1986).

A large amount of epidemiological data demonstrating the role of paracetamol and antibiotic use in infancy for the development of asthma comes from the International Study of Asthma and Allergies in Childhood (ISAAC) (Foliaki et al. 2009; Beasley et al. 2008) or, like this work, from studies using the ISAAC tools (Barragan-Meijueiro et al. 2006).

A frequently described phenomenon justifying the rising prevalence of allergic diseases, including asthma, is the ‘hygiene hypothesis’, underlining the importance of microflora, especially gastrointestinal, in the development of a healthy immune system (Strachan 1989). Prescription of antibiotics applied in early life can alter microflora, prevent the boosting of immune system activity, and lead to increased allergic sensitization (Schaub et al. 2006). The perinatal period is

characterized by the development of a Th1/Th2 balance, which could be distorted if exposed to antibiotic action (Prescott et al. 1999). Nevertheless, the results of studies are contentious. The ISAAC study resulted in many publications supporting the role of antibiotics in the development of atopic diseases. Data obtained from 193,412 children representing 29 countries show a significantly increased risk of allergic disorders in children who get antibiotics in the first year of life (Foliaki et al. 2009). There is increased risk for current asthma, asthma ever (at least one episode in life), severe asthma, or current rhinoconjunctivitis. Similar results were revealed for the cohort of 1,401 children from the US. This longitudinal study, initiated during pregnancy, show significantly higher risks for asthma and allergy, even stronger if the diagnosis takes place before the age of 3 (Risnes et al. 2011). On the other hand, no association between antibiotic and atopic diseases has been reported in 5 introspective studies in England (Celedon et al. 2002).

The objective of our study was to examine the association between antibiotics and paracetamol intake in the first year of life and the development of asthmatic symptoms in childhood.

2 Methods

The questionnaire was approved by the DGIDC (Direção-Geral da Educação) and the study had the approval of a local Ethics Committee.

This cross-sectional study evaluated 1,063 children from the first and second grade of primary school in the district of Coimbra, Portugal and was performed from September 2011 to June 2012. To assess data on respiratory conditions, the core ISAAC based asthma and rhinitis

questionnaires were used. For the analyses of the environmental and family factors, an ISAAC-based environmental questionnaire was applied. The questionnaires, translated to Portuguese, were used with the authorization of the national coordinator of the ISAAC initiative in Portugal. Parents filled out a questionnaire regarding the paracetamol and antibiotic exposure of children: In the first 12 months of your child's life, did you usually give paracetamol for fever? In the past 12 months, how often, on average, have you given your child paracetamol? In the first 12 months of life, did your child have any antibiotics?

Asthma ever was determined as a positive response to a question of a child ever having an asthma attack, and current asthma as at least one wheezing episode in the last 12 months of life or at least one night of cough attack not related to infection. Severity of the disease was estimated based on the responses to three questions about the number of wheeze attacks in the last 12 months, number of wake-up episodes caused by wheeze and problems in speaking caused by wheezing. Rhinitis ever was defined as ever having a problem of sneezing, running or blocked nose not caused by infections and current rhinitis as the same symptoms occurring in the last 12 months. Prematurity was defined as gestational age under 37 weeks.

Demographic data were presented in the percentage terms. Chi² test was run to calculate the prevalence differences between children exposed or not to antibiotics and paracetamol. Binary and Multinomial Logistic Regression were run to estimate the risk of atopic disease symptoms, depending on drug exposure, adjusted for children's age and sex, family history of asthma and rhinitis, and prematurity. Statistical software SPSS v 19 was used for data analysis.

3 Results

A total number of 1,063 questionnaires were returned by the parents of children. The children with severe chronic diseases not related to asthma or allergies were excluded from the

study giving the final number of 1,037 children studied. The mean age of the children was 7.2 years (range 6–9 years) and 51 % of the children were girls, 49 % boys. Boys had a general tendency to have a higher prevalence of respiratory symptoms, although only current asthma prevailed significantly ($p < 0.05$). An attack of wheeze at least once in children's lives was reported by 35.2 % of parents and an attack during the last 12 months by 11.8 %. An asthma episode at least once in the child's lifetime was experienced by 10.4 %. A night cough attack was experienced by 24.3 % and exercise-induced asthma by 6.4 % children. Symptoms of rhinitis, at least once, were experienced by 22.8 % children during the last 12 months. Tearing and itchy eyes occurred in 9.6 %. Administration of paracetamol in the first year of life was reported in 21.3 % and antibiotics in 23.1 % children. In the last 12 months, 72.7 % of children were given paracetamol at least once and 12.7 % at least once per month. The full demographic characteristics can be found in Table 53.1.

Administration of paracetamol in early life significantly increased the prevalence of asthma ever (OR = 2.9; 95 %CI:1.8–4.5), current asthma (OR = 2.4; 95 %CI:1.5–3.6), wheezing ever (OR = 2.5; 95 %CI:1.8–3.4), rhinitis ever (OR = 2.4; 95 %CI:1.7–3.3) and current rhinitis (OR = 2.8; 95 %CI:2.0–3.9), episodes of itchy and tearing eyes (OR = 2.9; 95 %CI:1.8–4.5), and night cough attacks (OR = 3.1; 95 %CI:2.2–4.4) (Table 53.2). Among children who were given paracetamol in the first year of life, 53.6 % reported wheezing symptoms at least once later in life, compared with 30.8 % who did not receive the drug ($p < 0.01$). Not only the prevalence but also severity of symptoms appeared strongly associated with paracetamol administration in the first 12 months of life, such as the number of wheeze attacks in the last year (OR = 2.3; 95 %CI:1.4–3.8 for 1–3 attacks, OR = 2.7; 95 %CI:1.3–5.7 for 4 or more attacks), the number of wake-up episodes caused by the attacks (OR = 2.7; 95 %CI:1.5–4.9 for less than one per week and OR = 2.9; 95 %CI:1.2–7.0 for one or more per week).

Table 53.1 Demographic and prevalence data of the studied population

Variable	Yes (n)	Yes (%)
Sex F/M	529/508	51/49
Prematurity	191	19
Family history of asthma	427	41.5
Family history of rhinitis	445	43.5
Wheeze ever	357	35.2
Wheeze in the past 12 months	120	11.8
4 or more attacks of wheeze in the past 12 months	33	3.3
Sleep disturbance from wheeze, 1 or more nights a week in the past 12 months	23	2.3
Speech limited by wheeze in the past 12 months	18	1.8
Asthma ever	106	10.4
Wheeze during or after exercise in the past 12 months	65	6.4
Night cough in the past 12 months	248	24.3
Nose symptoms ever	233	22.8
Nose symptoms in the past 12 months	198	19.4
Nose and eye symptoms in the past 12 months	98	9.6
Nose symptoms affecting activities a lot in the past 12 months	4	2.0
Hay fever ever	13	1.3
Paracetamol intake in the first 12 months	218	21.3
Paracetamol intake at least once per month in the past 12 months	130	12.7
Paracetamol intake at least once the past 12 months	744	72.7
Antibiotic intake in the first 12 months	237	23.1
Number of participants	n = 1,037	

Prevalence of the factors included in this study was presented as the number and percentage of individuals declaring the existence of a factor

Table 53.2 Odds ratios (OR) for symptoms depending on paracetamol exposure in the first 12 months of life, with the level of significance (p) and confidence intervals (CI), both unadjusted and adjusted for sex, age, prematurity, and positive history of asthma and rhinitis

	Paracetamol exposure in the first 12 months of life						
	Unadjusted			Adjusted			
	OR	p	95 %CI	OR	p	95 %CI	
Asthma ever	3.168	<0.001	2.074–4.838	2.851	<0.001	1.825–4.454	
Current asthma (wheeze in the past 12 months)	2.615	<0.001	1.740–3.931	2.362	<0.001	1.532–3.642	
Exercise induced asthma in the past 12 months	2.692	<0.001	1.598–4.534	2.392	0.002	1.381–4.143	
Wheeze ever	2.598	<0.001	1.909–3.537	2.478	<0.001	1.794–3.422	
Rhinitis ever	2.738	<0.001	1.974–3.799	2.372	<0.001	1.682–3.344	
Current rhinitis	3.247	<0.001	2.311–4.562	2.754	<0.001	1.962–3.937	
Night cough attacks in the past 12 months	3.427	<0.001	2.482–4.733	3.104	<0.001	2.205–4.370	
Four or more wheeze attacks in the past 12 months	2.757	<0.001	1.345–5.652	2.711	0.008	1.286–5.717	
One or more wake up episodes with wheeze/week in the past 12 months	2.642	<0.001	1.126–6.201	3.094	0.021	1.294–7.399	
Nose and eye symptoms in the past 12 months	3.313	<0.001	2.143–5.124	2.876	<0.001	1.824–4.534	

A similar association was found for antibiotics. The use of antibiotics resulted in increased risk of current asthma (OR = 1.6; 95 %CI:1.0–2.5), asthma ever (OR = 2.0; 95 %CI:1.3–3.1), wheeze ever (OR = 2.3; 95 %CI:1.7–3.2), night cough attacks (OR = 1.9; 95 %CI:1.3–2.6), and all rhinitis symptoms (OR = 1.8; 95 %CI:1.3–2.6, OR = 1.8; 95 %

Table 53.3 Odds ratios (OR) for each symptom depending on the antibiotic exposure in the first 12 months of life, with the levels of significance (p) and confidence

	Antibiotic exposure by 12 months					
	Unadjusted			Adjusted		
	OR	p	95 %CI	OR	p	95 %CI
Asthma ever	2.094	0.001	1.364–3.216	1.963	0.003	1.251–3.081
Current asthma (wheeze in the past 12 months)	1.676	0.015	1.104–2.543	1.596	0.038	1.026–2.483
Exercise induced asthma in the past 12 months	1.537	0.125	0.888–2.659	2.465	0.266	0.780–2.465
Wheeze ever	2.292	<0.001	1.699–3.092	2.326	<0.001	1.702–3.180
Rhinitis ever	1.882	<0.001	1.357–2.611	1.836	0.001	1.302–2.589
Current rhinitis	1.884	<0.001	1.336–2.657	1.808	0.001	1.258–2.599
Night cough attacks in the past 12 months	1.909	<0.001	1.385–2.632	1.852	<0.001	1.315–2.608
Four or more wheeze attacks in the past 12 months	1.554	0.255	0.727–3.320	1.482	0.275	0.679–3.233
One or more wake up episodes with wheeze/week in the past 12 months	1.539	0.349	0.625–3.791	1.119	0.662	0.427–2.932
Nose and eye symptoms in the past 12 months	1.869	0.006	1.193–2.927	1.856	0.018	1.162–2.966

CI:1.3–2.6, and OR = 1.9; 95 %CI:1.2–3.0 for rhinitis ever, current rhinitis, and tearing and itching eyes, respectively). Although antibiotic intake was associated with the prevalence of asthma, it did not seem to influence its severity. We found no association between antibiotic intake and the number of wake-up episodes or speech problems, nor with the disturbance of daily activities caused by symptoms. A list of selected odds ratios was presented in Table 53.3.

We further found that increased frequency of paracetamol use during the last 12 months preceding the study facilitated the appearance of allergic symptoms, suggesting a dose-dependent associations. Here, risk of current asthma was OR = 3.3; 95 %CI:1.5–7.6, exercise-induced asthma (OR = 3.9; 95 %CI:1.2–12.1), night cough attacks (OR = 5.4; 95 %CI:2.9–9.9), current rhinitis (OR = 5.3; 95 %CI:2.7–10.5), and tearing and itchy eyes (OR = 6.7; 95 %CI:2.5–18.3). Finally, we found a strong association between the intake of paracetamol early in life and that during the last 12 months preceding the study; 30.6 % of the children who were given paracetamol in the first year of life also received paracetamol at least once per month during the last 12 months compared with just 7.8 % of those not having paracetamol exposure early in life ($p < 0.01$).

intervals (CI) both unadjusted and adjusted for sex, age, prematurity, and positive history of asthma and rhinitis

4 Discussion

The major finding of our study was that children exposed in early life to paracetamol or antibiotics appeared to have highly increased risk of developing asthma and rhinitis by the age of 5–9 and they also had more severe symptoms than those unexposed. We found positive associations between the use of paracetamol and antibiotics and the appearance of asthma ever or current asthma and rhinitis ever or current rhinitis. We also found an association between the dose-dependent current use of paracetamol and both prevalence and severity of current respiratory symptoms. Our results demonstrate that parents who gave paracetamol to their children early in life continue its administration later in life, and do so at higher doses. These associations remained strong after adjustments for sex, age, family history of asthma and rhinitis, and prematurity.

The present results are consistent with other epidemiological data, demonstrating an important role of antibiotics and paracetamol in the development of allergic diseases. A multicenter study on a sample of 205,487 children aged 6–7 from 31 countries, originating from the phase three of the ISAAC program, found that the intake of paracetamol in the first year of life increases the risk of

asthma, rhinoconjunctivitis, and eczema (Beasley et al. 2008). That study also verified the role of antibiotic intake in the prevalence of atopic diseases. Exposure to antibiotics in the first 12 months of life had a strong impact on future respiratory health. The reported use of antibiotics was strongly associated with increased risk of current asthma symptoms, severe asthma, and asthma ever and less, but still significantly, with current symptoms of rhinitis (Foliaki et al. 2009). These results were corroborated in other studies as well (Gonzalez-Barcala et al. 2012; Kozyrskyj et al. 2007).

The mechanisms behind these associations are unclear. Yet some plausible explanations could be proposed. Evidence exists that frequent increases of body temperature above 38 °C reduce the risk of asthma later in life (Williams et al. 2004). Therefore, antipyretic effects of paracetamol and antibiotics could reduce the protective role of fever, increasing the risk of asthma and allergies. Another theory suggests that the substitution of the anti-inflammatory ibuprofen for paracetamol has been a real cause of a higher allergic susceptibility. That claim is based on the fact that ibuprofen could have a protective effect against atopic diseases (Varner et al. 1998). Finally, paracetamol can lead to asthmatic inflammation by lowering glutathione level, which impairs the antioxidant defences (Rahman and MacNee 2000) and triggers inflammation through disruption of Th1-Th2 cytokine responses (Dimova et al. 2005).

'Hygiene hypothesis' (Strachan 1989) combined with 'antioxidant hypothesis' (Soutar et al. 1997) propose that decreased exposure to microbes and diet changes in the last decades (lower intake of antioxidants) could be responsible for a rapid increase in asthma prevalence in industrialized countries. Others also believe that administration of antibiotics early in life has a destructive effect on microflora, preventing the immunological system from correct maturation (Verhulst et al. 2008).

Despite the evidence from epidemiological studies, prospective research on the subject is less consistent. A birth cohort study including 16,933 6–7-year-olds from Italy analyzed the association between antibiotic and paracetamol

use and asthma symptoms, using the ISAAC questionnaire. The focus was on two different phenotypes of asthma: early (first 2 years of life) and late onset of wheezing (during the last 12 months). A positive association has been confirmed only with the former (Rusconi et al. 2011), which is explained by the fact that early wheeze caused by viral infection is often misdiagnosed as asthma or allergy, and treated with paracetamol and antibiotics. Another cohort study of 198 children at high atopic risk also questions the true association between paracetamol and antibiotic use and asthma symptoms (Kusel et al. 2008). The authors reported that children who are given antibiotics in the first year of life have over twice the odds for asthma diagnosis, but this association became insignificant after adjustments for antibiotic predictor score, sex, first year pets, childcare, and general practitioner visits.

The above-mentioned inconsistencies are most frequently explained by 'reverse causation'. According to this assumption, children with respiratory disorders, including asthma, are more likely to be prescribed antibiotics and paracetamol (Kummeling and Thijs 2008). Following this reasoning, intake of drugs is a consequence rather than cause of atopic diseases. Conflicting results may be due also to another confounder – 'indication'. In infancy it is difficult to distinguish the allergic from viral or bacterial infection symptoms, which all are treated by paracetamol and antibiotics, and those infections could be a real underlying trigger for further development of asthma and allergies (Kummeling and Thijs 2008). However, studies on *in utero* exposure to paracetamol demonstrate increased risk of wheezing in children whose mothers received the drug, and such results are devoid of the 'indication' confounder (Bakkeheim et al. 2011).

5 Conclusions

Although the cross-sectional studies are prone to bias due to the lack of chronological information about the dosage and onset of symptoms, a strong association between early administration of antibiotics and paracetamol should not be

ignored. Further investigation should be focused on different phenotypes and epigenetic character of these associations. Unnecessary exposure to paracetamol and antibiotics, especially in infancy, should be avoided.

Acknowledgments Supported by a grant of the Fundação para a Ciência e a Tecnologia number SFRH/BD/66877/2009.

Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

References

- Bakkeheim, E., Mowinkel, P., Carlsen, K. H., Haland, G., & Carlsen, K. C. (2011). Paracetamol in early infancy: The risk of childhood allergy and asthma. *Acta Paediatrica*, 100(1), 90–96.
- Barragan-Mejueiro, M. M., Morfin-Maciél, B., & Nava-Ocampo, A. A. (2006). A Mexican population-based study on exposure to paracetamol and the risk of wheezing, rhinitis, and eczema in childhood. *Journal of Investigational Allergology and Clinical Immunology*, 16(4), 247–252.
- Beasley, R., Clayton, T., Crane, J., von Mutius, E., Lai, C. K., Montefort, S., Stewart, A., & IPTS Group. (2008). 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. *Lancet*, 372(9643), 1039–1048.
- Celedon, J. C., Litonjua, A. A., Ryan, L., Weiss, S. T., & Gold, D. R. (2002). Lack of association between antibiotic use in the first year of life and asthma, allergic rhinitis, or eczema at age 5 years. *American Journal of Respiratory and Critical Care Medicine*, 166(1), 72–75.
- Dimova, S., Hoet, P. H., Dinsdale, D., & Nemery, B. (2005). Acetaminophen decreases intracellular glutathione levels and modulates cytokine production in human alveolar macrophages and type II pneumocytes in vitro. *The International Journal of Biochemistry & Cell Biology*, 37(8), 1727–1737.
- Eder, W., Ege, M. J., & von Mutius, E. (2006). The asthma epidemic. *The New England Journal of Medicine*, 355(21), 2226–2235.
- Foliaki, S., Pearce, N., Björkstén, B., Mallol, J., Montefort, S., von Mutius, E., & International Study of Asthma and Allergies in Childhood Phase III Study Group. (2009). Antibiotic use in infancy and symptoms of asthma, rhinoconjunctivitis, and eczema in children 6 and 7 years old: International Study of Asthma and Allergies in Childhood Phase III. *The Journal of Allergy and Clinical Immunology*, 124(5), 982–989.
- Gonzalez-Barcala, F. J., Pertega, S., Castro, T. P., Sampedro, M., Lastres, J. S., Gonzalez, M. A., Bamonde, L., Garnelo, L., Valdes, L., Carreira, J. M., Moure, J., & Silvarrey, A. L. (2012). Exposure to paracetamol and asthma symptoms. *European Journal of Public Health*. doi:10.1093/eurpub/cks061.
- Kozyrskyj, A. L., Ernst, P., & Becker, A. B. (2007). Increased risk of childhood asthma from antibiotic use in early life. *Chest*, 131(6), 1753–1759.
- Kummeling, I., & Thijs, C. (2008). Reverse causation and confounding-by-indication: Do they or do they not explain the association between childhood antibiotic treatment and subsequent development of respiratory illness? *Clinical and Experimental Allergy*, 38(8), 1249–1251.
- Kusel, M. M., de Klerk, N., Holt, P. G., & Sly, P. D. (2008). Antibiotic use in the first year of life and risk of atopic disease in early childhood. *Clinical and Experimental Allergy*, 38(12), 1921–1928.
- Newson, R. B., Shaheen, S. O., Chinn, S., & Burney, P. G. (2000). Paracetamol sales and atopic disease in children and adults: An ecological analysis. *The European Respiratory Journal*, 16(5), 817–823.
- Prescott, S. L., Macaubas, C., Smallacombe, T., Holt, B. J., Sly, P. D., & Holt, P. G. (1999). Development of allergen-specific T-cell memory in atopic and normal children. *Lancet*, 353(9148), 196–200.
- Rahman, I., & MacNee, W. (2000). Oxidative stress and regulation of glutathione in lung inflammation. *The European Respiratory Journal*, 16(3), 534–554.
- Rahwan, G. L., & Rahwan, R. G. (1986). Aspirin and Reye's syndrome: The change in prescribing habits of health professionals. *Drug Intelligence & Clinical Pharmacy*, 20(2), 143–145.
- Risnes, K. R., Belanger, K., Murk, W., & Bracken, M. B. (2011). Antibiotic exposure by 6 months and asthma and allergy at 6 years: Findings in a cohort of 1,401 US children. *American Journal of Epidemiology*, 173(3), 310–318.
- Rusconi, F., Gagliardi, L., Galassi, C., Forastiere, F., Brunetti, L., La Grutta, S., Piffer, S., Talassi, F., & S-C. Group. (2011). Paracetamol and antibiotics in childhood and subsequent development of wheezing/asthma: Association or causation? *International Journal of Epidemiology*, 40(3), 662–667.
- Schaub, B., Lauener, R., & von Mutius, E. (2006). The many faces of the hygiene hypothesis. *The Journal of Allergy and Clinical Immunology*, 117(5), 969–977.
- Soutar, A., Seaton, A., & Brown, K. (1997). Bronchial reactivity and dietary antioxidants. *Thorax*, 52(2), 166–170.
- Strachan, D. P. (1989). Hay fever, hygiene, and household size. *BMJ*, 299(6710), 1259–1260.
- Varner, A. E., Busse, W. W., & Lemanske, R. F., Jr. (1998). Hypothesis: Decreased use of pediatric aspirin has contributed to the increasing prevalence of childhood asthma. *Annals of Allergy, Asthma & Immunology*, 81(4), 347–351.

- Verhulst, S. L., Vael, C., Beunckens, C., Nelen, V., Goossens, H., & Desager, K. (2008). A longitudinal analysis on the association between antibiotic use, intestinal microflora, and wheezing during the first year of life. *The Journal of Asthma*, 45(9), 828–832.
- Williams, L. K., Peterson, E. L., Ownby, D. R., & Johnson, C. C. (2004). The relationship between early fever and allergic sensitization at age 6 to 7 years. *The Journal of Allergy and Clinical Immunology*, 113(2), 291–296.