

REVIEW

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Risk factors for non-atopic asthma/wheeze in children and adolescents: a systematic review

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Abstract

Background: The study of non-atopic asthma/wheeze in children separately from atopic asthma is relatively recent. Studies have focused on single risk factors and had inconsistent findings.

Objective: To review evidence on factors associated with non-atopic asthma/wheeze in children and adolescents.

Methods: A review of studies of risk factors for non-atopic asthma/wheeze which had a non-asthmatic comparison group, and assessed atopy by skin-prick test or allergen-specific IgE.

Results: Studies of non-atopic asthma/wheeze used a wide diversity of definitions of asthma/wheeze, comparison groups and methods to assess atopy. Among 30 risk factors evaluated in the 43 studies only 3 (family history of asthma/rhinitis/eczema, dampness/mold in the household, and lower respiratory tract infections in childhood) showed consistent associations with non-atopic asthma/wheeze. No or limited period of breastfeeding was less consistently associated with non-atopic asthma/wheeze. The few studies examining the effects of overweight/obesity and psychological/social factors showed consistent associations. We used a novel graphical presentation of different risk factors for non-atopic asthma/wheeze, allowing a more complete perception of the complex pattern of effects.

Conclusions: More research using standardized methodology is needed on the causes of non-atopic asthma.

Keywords: Non-atopic asthma, Non-atopic wheeze, Risk factors, Mould, Respiratory infections

Introduction

Asthma is the most common chronic noninfectious disease of childhood and is estimated to affect 300 million people worldwide, causing a quarter of a million deaths and 15 million disability-adjusted life years (DALYs) lost annually [1]. The prevalence of asthma may have reached a plateau in many industrialized countries, but appears to be increasing in many low- and middle-income countries [2]. Asthma is a complex group of conditions, and efforts have been made to define phenotypes/endotypes based on age of onset, duration, severity, presence of allergy and other factors [3-8]. There is no agreed definition of asthma for research purposes and different research projects use different definitions, based on clinical symptoms, questionnaire data and pulmonary function tests. Asthma has traditionally been considered an allergic disease, but although allergic children are more likely to have asthma,

a large proportion of children with asthma do not appear to be allergic. The proportion of asthma that can be attributable to atopy varies geographically [9,10], and clinical features are similar between atopic and non-atopic asthma [11]. Causation of asthma remains poorly understood with little consensus about the relative importance of different putative causal factors. Most studies have ignored the distinction between atopic and non-atopic disease even though these phenotypes are likely to have distinct causal mechanisms.

Recently, studies have started to investigate separately risk factors for non-atopic asthma and atopic asthma, and in so doing have raised at least two additional methodological challenges: the definition of atopy and the use of an appropriate comparison group. With respect to atopy, there is a high level of concordance between the results of skin prick test (SPT) reactivity and specific IgE (sIgE) to aeroallergens in studies done in Europe and the USA – many studies have used SPT for reasons of cost and convenience. However, in low- and middle-income countries there is often a marked

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dissociation between the results of SPT and allergen-specific IgE, particularly in underprivileged populations. Such an effect may relate to the immune modulatory effects of chronic infections [12,13] that target allergic effector responses rather than allergic sensitization. There is the risk, therefore, that the use of SPT to measure atopy in such populations may misclassify atopic individuals (i.e. sIgE+) as non-atopic.

The other important methodological challenge is the choice of the appropriate comparison group. Studies of risk factors for non-atopic asthma have used different comparison groups: some used all non-asthmatic children, some atopic asthmatics, and others non-atopic non-asthmatics. There are substantive consequences to this choice; this has been discussed elsewhere [14,15].

This is the first systematic review of the evidence for association between a wide range of risk factors and non-atopic asthma or wheeze in children and adolescents. Given the variations in definitions of atopy and in the comparison groups used, we present the evidence for consistent associations but do not provide a statistical summary of these associations.

Methods

Following the reporting guidelines recommended in PRISMA [16] (Additional file 1), we conducted a systematic review of the scientific literature to identify studies that have investigated factors associated with asthma or wheeze in children and adolescents, including studies that investigated non-atopic asthma exclusively, and those presenting results separately for non-atopic asthma.

Search: The electronic database Medline was searched by AS. The search covered the period 1972 to February 25th, 2014. The search algorithm applied in free text was: *((intrinsic asthma) OR (neutrophilic asthma) OR (nonatopic asthma) OR (non-atopic asthma) OR ("non atopic" asthma) OR (nonallergic asthma) OR (non-allergic asthma) OR ("non allergic" asthma) OR (nonatopic wheez*) OR (non-atopic wheez*) OR ("non atopic" wheez*)) AND (risk OR ratio)*. Reference lists of past reviews or meta-analyses and of publications retained for review were evaluated also. Articles in English, French, Italian, Portuguese and Spanish were read in the original language. We were inclusive in accepting studies with a wide range of definitions of asthma/wheeze based on clinical symptoms or questionnaire.

Eligibility criteria: Titles and abstract of the articles identified with the initial search were screened, and articles were excluded from further analysis based on title (not relevant) or abstract (unequivocal presence of excluding features). Excluding features were: article languages other than those specified, adult asthma/wheeze, occupational asthma/wheeze, study designs other than

cohort, case-control or cross-sectional designs, genetic studies, definition of atopy other than measurement of sIgE, skin-prick test (SPT) or both, and studies without a non-asthmatic comparison group (i.e., those that did not compare asthmatics with non-asthmatics or explored risk factors for exacerbations, severity or mortality in asthmatic populations). Review and meta-analysis articles were used as sources of references only. No contact was made with study investigators.

Articles not excluded in the first screen were read by one author (AS), and either were excluded based on the criteria listed above, or had information saved in a working table including: author(s) name, year of publication, geographic region, size and age of the study population, study design, way of ascertainment and definition of the endpoint (asthma/wheeze), definition of atopy, definition of comparison group, adjustment for confounding, and effect measures (see Additional file 2). Any doubts and uncertainties were discussed with another author (LR). Results of studies in which only univariate analysis was performed were included. We considered that no statistically significant association with outcome was found for those factors for which data were presented in descriptive or univariate tables but were not retained in multivariate analysis.

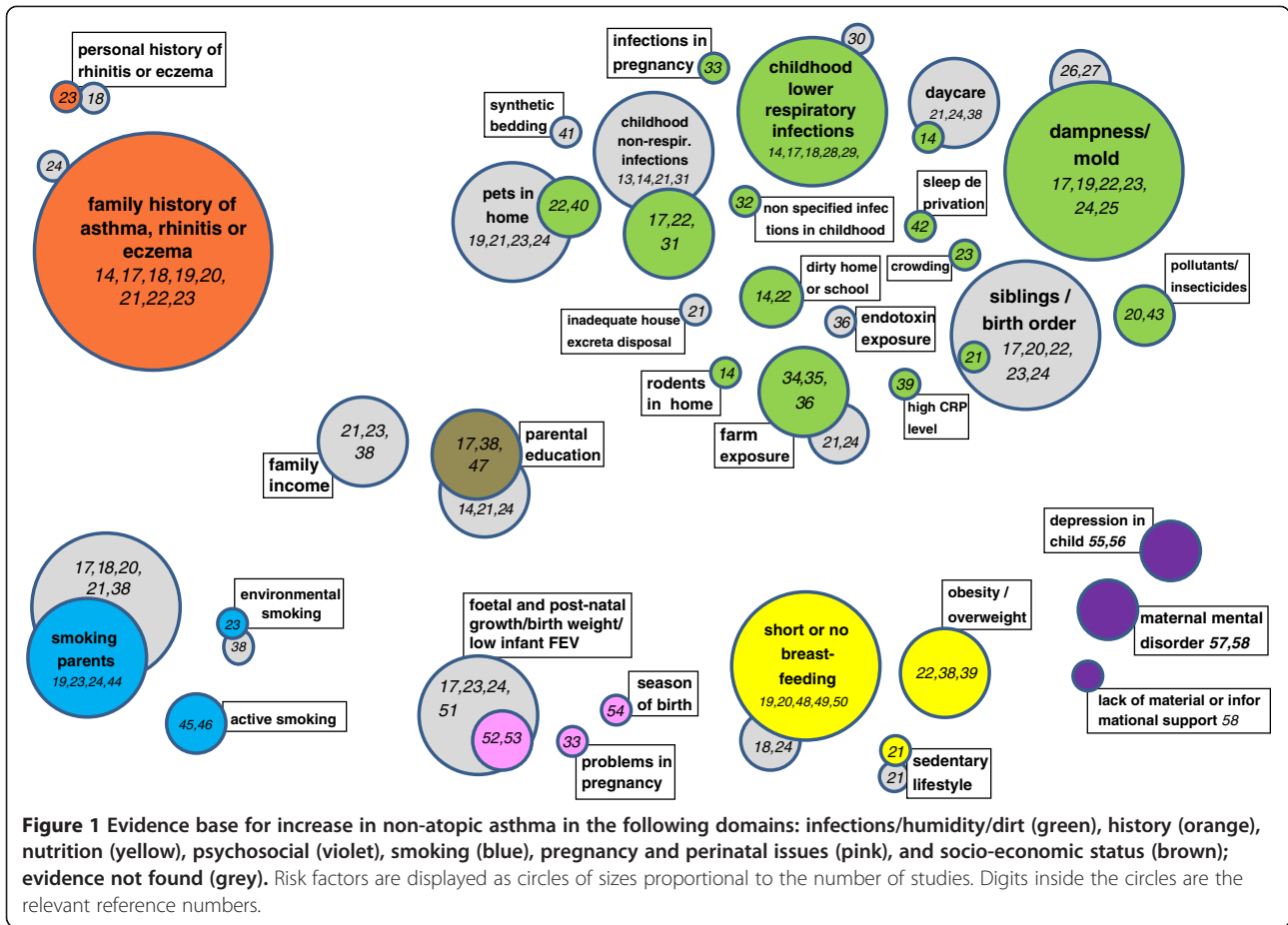
Risk factors were grouped in domains: family history, smoking, socioeconomic factors, pregnancy and perinatal factors, nutritional factors, psychosocial factors and dirt/infection factors. Because many different exposures were studied, we present an overview of the results in a summary figure (Figure 1) using a novel graphic presentation (Frequency of Risk factors Circles or FRiskC). FRiskCs displays risk factors as circles of sizes proportional to the number of studies. For each factor, a colour circle represents the number of studies that found a statistically significant association and the grey circle the number of studies that did not. Domains were colour-coded. Digits inside the circles are the relevant reference numbers.

Summary measures were not estimated for each factor because of the diversity of methods used between studies.

Results

The initial search of the literature identified 875 articles, to which 244 more were added from reference lists of reviews/meta-analyses and articles retained for review. After eliminating duplicates and performing the first screening, based on title or abstract, 95 articles were retained for full-text reading, after which 52 were excluded for different reasons and 43 articles were retained for review (Figure 2).

Figure 1 displays risk factors by domain and whether the studies showed a statistically significant association; ORs and 95% CI are shown in Table 1 and Additional file 2. Of the 30 individual or grouped factors, only three



were investigated in a large number of studies and showed very consistent associations with non-atopic asthma/wheeze: family history of asthma, living in a home with damp or humidity, and history of respiratory infections in childhood. Another two factors that were investigated in numerous papers, were consistently not associated with

non-atopic asthma/wheeze: family income and birth order. For all other factors, either the studies were less numerous or showed conflicting results.

Family history of asthma, rhinitis or eczema showed a consistently high and significantly positive association with asthma or wheeze in eight studies, with magnitudes

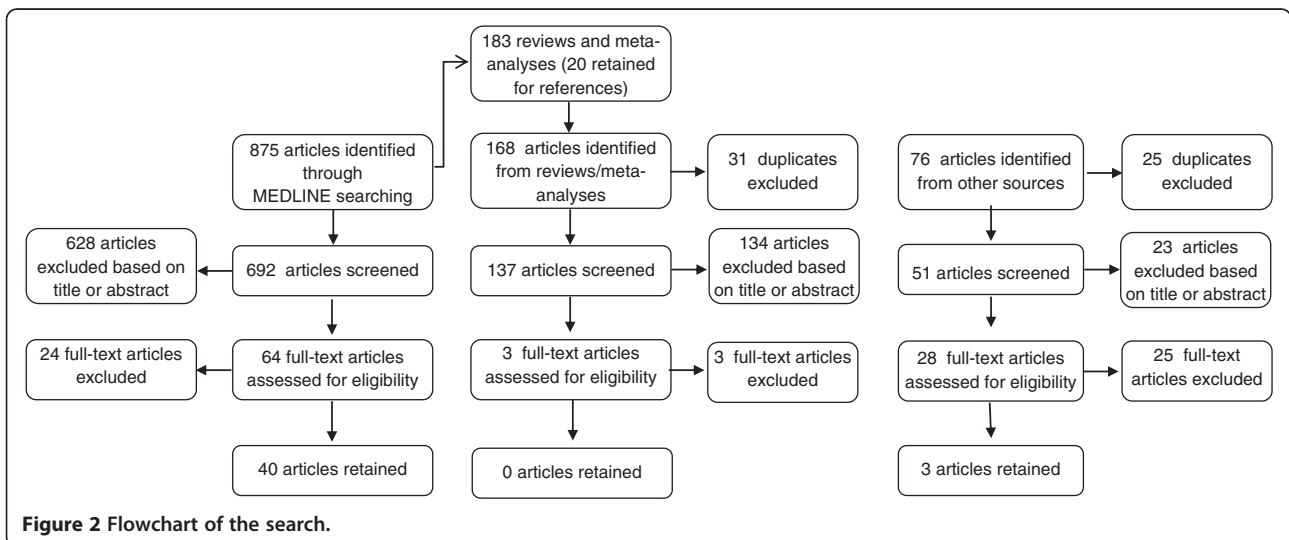


Table 1 Factors associated with non-atopic asthma/wheeze by domain, OR and 95% CI

Reference	Domain		OR	(95% CI)
	Grouped risk factors	Individual risk factors		
	History of asthma, rhinitis or eczema			
	Family history			
[14]		Family history of asthma, rhinitis or eczema	1.91	(1.25–2.92)
[17]		Family history of asthma, rhinitis or eczema	5.4	(2.5–11.7)
[18]		Family history of asthma, rhinitis or eczema	4.08	(1.85–9.00)
[19]		Family history of asthma, rhinitis or eczema	3.63	(2.33–5.66)
[20]		Family history of asthma, rhinitis or eczema	3.45	(1.18–10.10)
[21]		Family history of asthma, rhinitis or eczema	3.24	(2.42–4.32)
[22]		Family history of asthma, rhinitis or eczema	2.35	(1.23–4.52)
[23]		Family history of asthma, rhinitis or eczema	1.74	(1.30–2.32)
	Personal history			
[23]		Personal history of rhinitis	2.49	(2.10–2.95)
[23]		Personal history of eczema	2.16	(1.63–2.88)
	Infection/humidity/dirt			
	Dampness/mold			
[17]		Current damp in the household	2.7	(1.4–5.2)
[19]		Current or past damp	1.78	(1.10–2.89)
[22]		Current damp in the household	2.45	(1.11–5.40)
[23]		Current damp in the household	1.48	(1.06–2.08)
[23]		Past damp in household	2.44	(1.73–3.44)
[24]		Current damp in the household	2.70	(1.16–6.30)
[25]		Current damp in the household	1.54	(1.33–1.77)
	Childhood lower respiratory infections			
[14]		Respiratory symptoms < 8 days	1.54	(1.01–2.36)
[14]		Respiratory symptoms ≥ 8 days	4.87	(2.26–9.76)
[17]		Bronchiolitis	14.5	(7.0–30.0)
[18]		Recurrent chest infections	3.99	(1.78–8.92)
[28]		Wheezing LRI	4.10	(2.48–6.77)
[29]		Seropositivity to <i>Chlamidia pneumonia</i> (in girls)	2.39	(1.25–4.57)
	Childhood infections other than LRI			
[22]		Croup	2.80	(1.44–5.43)
[22]		Otitis	1.99	(1.02–3.88)
[31]		Anti- <i>A.lumbricoides</i> IgE	3.07	(1.13–8.35)
[17]		Ascaris infection	3.1	(1.1–6.6)
	Non-specified infections in childhood			
[32]		5+ episodes of fever	11.48	(5.95–22.12)
[32]		6+ antibiotic courses	24.29	(11.86–49.76)
	Infections in pregnancy			
[33]		'Flu' during pregnancy	2.28	(1.15–4.52)
[33]		Fever during pregnancy	2.18	(0.98–4.86)
	Farming exposure			
[34]		Living in a farm	0.45	(0.32–0.63)
[35]		Use of silage	0.55	(0.31–0.98)

Table 1 Factors associated with non-atopic asthma/wheeze by domain, OR and 95% CI (Continued)

[36]		Exposure to farming	0.43	(0.19–0.97)
[14]		Daycare	1.52	(1.01–2.29)
	Dirty home or school			
[14]		Infrequent household cleaning	2.49	(1.27–4.90)
[22]		Dirty school	2.50	(1.28–4.89)
[23]		One-room house	2.24	(1.48–3.39)
[21]		Older siblings	0.39	(0.25–0.62)
[39]		High CPR	1.45	(1.61–1.81)
	Pets in home			
[22]		Cat or dog when infant	2.17	(1.16–4.04)
[40]		Cat and dog in early childhood	3.66	(1.50–8.93)
[14]		Rodents in home	1.68	(1.21–2.34)
[42]		Sleep deprivation (and asthma at age 6 years)	1.87	(1.08–3.25)
[42]		Sleep deprivation (and asthma at age 14 years)	2.18	(1.15–4.13)
	Pollutants/insecticides			
[20]		Insecticide (dichlorodiphenyldichloroethylene)	2.49	(1.00–6.19)
[43]		NO _x from road traffic	2.4	(1.0–5.6)
	Smoking			
	Smoking parents			
[23]		Mother smoking during pregnancy	1.43	(1.08–1.89)
[24]		Mother smoking during the 1 st year of life	1.74	(1.17–2.58)
[19]		Mother smoking in general	1.67	(1.04–2.68)
	Active smoking			
[45]		Active smoking by the adolescent	17.1	(4.9–60.1)
[46]		Active smoking by the adolescent	3.92	(2.01–7.65)
[23]		Environmental smoking	1.63	(1.28–2.09)
	Socioeconomic factors			
	Parental education			
[17]		High parental education	0.3	(0.1–0.9)
[47]		High parental education	0.65	(0.43–0.99)
	Nutrition			
	Obesity/overweight			
[22]		per 5 units increase of BMI	1.55	(1.02–2.36)
[39]		Obesity	2.46	(1.21–5.02)
[21]		Sedentary life	1.51	(1.06–2.16)
	Breastfeeding			
[20]		Any breastfeeding	0.34	(0.17–0.69)
[48]		Any breastfeeding	0.52	(0.27–0.98)
[49]		Any breastfeeding in non-affluent countries	0.69	(0.53–0.90)
[19]		Short period of breastfeeding	1.80	(1.11–2.92)
[50]		Short period of breastfeeding	2.95	(1.31–6.66)
	Pregnancy and perinatal issues			
[52]*		Lower early fetal growth trajectory	0.90	(0.81–1.00)
[54]		Born in autumn	2.35	(1.14–4.83)

Table 1 Factors associated with non-atopic asthma/wheeze by domain, OR and 95% CI (Continued)

	Pregnancy			
[33]		Threatened abortion/premature labour	1.66	(0.96–2.86)
[33]		Exposure to isoxsuprine	1.87	(1.12–3.12)
	Psychosocial			
	Depression in child			
[55]		Depression in child	2.47	(1.12–5.44)
[56]		Depression in child	2.90	(1.46–5.73)
	Maternal mental disorder			
[57]		Maternal anxiety	1.78	(1.24–2.57)
[58]		Maternal mental disorder	1.73	(1.17–2.55)
	Social support			
[58]		Informational support	0.60	(0.40–0.90)
[58]		Material support	0.63	(0.42–0.95)

*RR (95% CI).

of association ranging from OR = 5.4 to OR = 1.74 [14,17-23]. One study also detected risks associated with a personal history of rhinoconjunctivitis and of eczema [23].

After family history of asthma, the second most frequently studied risk factor for which a consistent and positive association with the outcome was found was presence of damp in the household, either observed currently [17,22-24], in the past [23], or in either periods [19,25]. One study detected a non-significant risk [26], and another showed no effect [27].

Many studies investigated the effect of infections and related factors. Five studies reported a positive association with lower respiratory symptoms or infections (LRI) in early childhood, including bronchiolitis at age 2 years [17], wheezing LRI at age 1 year [28], recurrent chest infections at 2 years [18], respiratory symptoms by 4 years of age lasting less than 8 days, or 8 days or more [14], and, in girls, but not in boys, seropositivity to *Chlamidia pneumoniae* at 4 years of age [29]. One study found no association of non-atopic wheeze at 5 years of age with wheezy or febrile viral LRI in the first year of age [30].

The effect of infections in childhood other than lower respiratory infections was less consistent. A study found a positive effect of croup and of otitis [22]. The presence of anti-*Ascaris lumbricoides* IgE was a risk for non-atopic asthma in one study [31], while in the same study active infections (i.e., stool positive) with *A.lumbricoides* or *Trichuris trichiura* were not, whereas *Ascaris* infection was a risk factor for non-atopic wheeze in another study [17]. Three studies failed to detect significant risks associated with diarrhea episodes in infancy [14], heavy parasite burdens with *T.trichiura* presently [21], or burden of past or present infections of different etiologies [13].

Unspecified infections, expressed as number of episodes of fever or number of antibiotic courses in childhood, represented large and significant risks in one study [32]. 'Flu' and fever during pregnancy were also positively associated with non-atopic asthma [33].

Studies of the effect of farming exposures showed contradictory results: of five studies identified, three from Central and Northern Europe reported a significant and similar protective effect [34-36]. A similar effect as in the latter study was found in a different analysis in the same population [37]. Two studies failed to find any effect of farming exposures [21,24]. The only study that considered endotoxin exposure found a non-significant risk [36].

Four studies considered the effect of daycare [14,21,24,38], but only one showed a significant associated risk [14]. Among other conditions related to or associated with infections in childhood, presence of visible dirt at home or school was reported as a risk factor in two studies with similar results [14,22], but inappropriate household excreta disposal was not [21]. Crowding was found also to be significantly associated with asthma [23], whereas, of the six studies evaluating the effect of sibship size and birth order [17,20-24], only one found a significant protective effect of having older siblings [21]. Increased levels of C-reactive protein (CRP), a marker of systemic inflammation, yielded a significant risk [39]. Other conditions potentially associated with infections are keeping household pets [19,21-24,40], the use of synthetic bedding [41], and the presence of rodents in the household [14]. Among studies that examined these conditions, only three detected significant risks, in two, associated with cats and/or dogs during early life [22,40], and in one, with rodents [14]. Frequent waking at night during the first 3 years of life, possibly related to respiratory

infections, was associated with non-atopic asthma at ages 6 and 14 years [42].

Two studies examined the effects of environmental pollutants and found significant positive associations: prenatal exposure to the insecticide dichlorodiphenyldichloroethylene [20], and exposure in first year of life to NO_x from road traffic [43].

Parental smoking was extensively studied but showed contradictory findings: statistically significant risks were detected in 4 of 9 studies [17-21,23,24,38,44]. These included maternal smoking during pregnancy [23] or during the 1st year of life [24], mother smoking in general [19], and heavily smoking parents (67% among non-atopic asthmatics vs 40% among non-asthmatics) [44]. Active smoking by the adolescent was identified as a significant risk in two studies [45,46]. Inconsistent results were reported for second-hand smoking: one study estimated a risk [23], whereas another one reported no effect [38].

Among factors representing socioeconomic circumstances of the child's family, parental education was evaluated in six studies showing conflicting effects: three studies found no association [14,21,24], two found a protective effect [17,47], and one found a risk (parental education level was statistically significantly higher among non-atopic asthmatic than non-asthmatic children, 12.2 years vs 12.0 years, $P < 0.05$) [38]. The three studies evaluating income showed no significant effects [21,23,38].

All three studies addressing the effect of obesity/overweight observed increased risks: with 5 units increase of BMI [22], obesity [39], and mean BMI percentile (68.5 in non-atopic asthmatic children vs 57.7 in non-asthmatic children, $P < 0.05$ [38]). Sedentary lifestyle was identified as a risk factor [21].

Breastfeeding was investigated in seven studies. Three observed a significant protective effect of any breastfeeding [20,48] (one study found an association in non-affluent countries only [49]), and two others found a risk associated with short period of breastfeeding [19,50]. A further two studies did not detect a significant effect of breastfeeding [18,24]. One study did not find an association in affluent countries [49].

There was no effect of prematurity [17,23], low birth weight [24] nor birth weight ≥ 4510 g [51]. However, a lower early fetal growth trajectory (lower head circumference growth velocity between 11 and 18 weeks) [52] and a lower lung function in early infancy (mean (95% CI) FEV_{0.4} 123.7 (114.6-133.5) ml in non-atopic wheezers vs 139.0 (132.2-146.2) ml in non-atopic non-wheezers) [53] were associated with non-atopic wheeze. In a study done in Northern Europe, being born in the autumn was associated with an increased risk [54]. Threatened abortions and exposure to isoxsuprine, a tocolytic drug, were both independently associated [33].

Two studies reported associations with depression in the child and in both the risk was higher in girls, and lower and not significant in boys [55,56]. A study reported the impact of maternal anxiety [57], and another one of maternal mental disorder [58]. The same study found also a protective effect of social support, which was highest for informational support and material support.

Discussion

In summary, 43 studies were identified that investigated 30 grouped or individual risk factors for non-atopic asthma. Consistent and strong associations with the risk of non-atopic asthma were observed only for 3 factors: family history of asthma, rhinitis or eczema [14,17-23], dampness or mold in the household [17,19,22-25], and lower respiratory infections in childhood [14,17,18,28,29]. A brief period or no breastfeeding also showed a strong, albeit less consistent, association. Fewer studies investigated the effects of overweight/obesity and of psychological or social factors, but those that did showed consistent findings.

Family history of asthma was consistently associated with non-atopic asthma, as it has been reported for atopic asthma [14,19,22,23]. This is in agreement with genetic studies that have identified SNPs predicting both atopic and non-atopic asthma, but may also indicate the effects of a shared environment by families [59].

Equally consistent is the reported association between non-atopic asthma and indoor dampness or mold in the household [17,19,22-25], and is consistent with evidence from studies and meta-analyses showing a wide variety of respiratory effects of such exposures including the development of asthma/wheeze and exacerbations in both atopic and non-atopic individuals including infants [60]. Several plausible biological mechanisms have been proposed to mediate these effects including the induction of inflammatory, cytotoxic and immunosuppressive responses to components of microbes or fungi [60].

Wheezing related to respiratory viral infections in early life has been linked to the development of asthma at school age [61-63], although it is still matter of controversy whether lower respiratory tract infections (LRI) and asthma share a common (genetic) predisposition [64], or whether LRIs have a causal role in asthma development through impaired epithelial barrier or anti-viral immune responses or other underlying mechanisms that cause damage to, and remodeling of, the airways in susceptible children [65]. It has been suggested that exposure to an 'aggressive' environment, with widespread viral respiratory infections and high levels of environmental pollution, such as observed among urban poor populations in Latin America, may lead to enhanced inflammatory responses and respiratory symptoms that appear to be dissociated from atopy [66].

The effects of exposures to helminth parasites on asthma/wheeze is unclear and may vary according to type of helminth, age of first infection and infection intensity [67,68]. A consistent observation is the strong inverse association between active helminth infections and prevalence of SPT [69,70]. The modulatory effects of chronic childhood infections such as those caused by helminths on SPT prevalence [13] may add to the measurement error for atopy, because definitions of atopy based on SPT in endemic populations may lead to significant misclassification of atopy, particularly if sIgE has better explanatory value for the allergic mechanisms that mediate atopic asthma.

Farming exposures were protective in some studies [34-36], although not all studies demonstrated an association [21,24].

All but one of the studies that evaluated the number of siblings failed to find an effect, despite the protective association frequently detected when asthma (irrespective of atopy) is considered [71]. The apparent inverse association with asthma overall might be explained by the inverse association between a greater number of siblings and prevalence of atopy in populations where most asthma is atopic. The presence of household pets had no effect on non-atopic asthma except in two studies [22,40].

Almost all studies evaluating breastfeeding found a consistent, protective effect on non-atopic asthma [19,20,48-50] (one study observed an effect only in univariate analysis [18]). Interestingly, all but one studies found that the effect was on non-atopic but not on atopic asthma, and one study observed an effect only on non-atopic asthma in less affluent countries [49]. The role of breastfeeding in causation of asthma remains controversial [72-74], and may differ by atopic phenotype [49,74].

Surprisingly few studies explored the effects on non-atopic asthma of obesity/overweight [75]. Studies done, principally in adults, show that risk is increased particularly among non-atopics [76], as was observed among children in two of three studies included in the present review [38,39]. It has been suggested that these effects may be mediated through factors other than the induction of eosinophilic airway inflammation [76], and that a state of systemic inflammation may be a key factor in mediating the effects of overweight/obesity [75].

The results of parental smoking were contradictory, reflecting a complex picture of the association of parental smoking with asthma [77]. Some studies reported a risk, whereas others did not, which could be a true finding, or could be explained by parents of asthmatic children stopping smoking.

Level of parental education showed mixed effects in some studies [17,38,47], and no effect in others [14,21,24]. No effect of family income was observed [21,23,38].

Few studies have examined the associations between non-atopic asthma and child depression, maternal psychological disorders or social support, but all show an apparent effect in diverse settings. Two cross-sectional studies reported an association of depression or abnormal emotional symptoms with non-atopic asthma, but not with atopic asthma [55,56]. In both studies, the effect was found in girls, but not in boys, and in one study it persisted after controlling for abdominal adiposity [55]. It has been suggested that higher levels of leptin may link non-atopic asthma with psychological disorders: levels of leptin are elevated in girls with asthma, in non-atopic-asthmatics, and also in children with symptoms of depression [55]. A study found an association between prenatal maternal anxiety and asthma in childhood, an effect that was stronger in non-atopics than atopics and that was greater the more severe the symptoms [57]. Maternal mental disorders, including depression and anxiety, were associated, independent of maternal history of asthma and the child's age, with both non-atopic and atopic asthma [58]. An independent protective effect of social support was found in the same study, but only for non-atopic wheezing.

This review exposed the wide heterogeneity between studies with respect to methodology: studies used different comparison groups (non-atopic non-asthmatic children, all non-asthmatic children, atopic asthmatic children), different definitions of atopy (skin test positivity to allergens, presence or levels of allergen specific IgE using different cut-off points for positivity and different panels of allergens), different definitions of asthma/wheeze (doctor's diagnosis of asthma used in some studies may select more severe cases, whereas use of asthma-related symptoms such as wheeze adopted in other studies may lead to inclusion of milder cases), and different study designs with different ability to establish causality. Some studies were underpowered.

Despite the number of studies found, their heterogeneity with respect to the above did not allow separate analyses by specific characteristics (e.g. comparison group used), nor to explore how much of the variation is due to the methodological diversity. And yet, a few, remarkably consistent risk factors (respiratory infections in childhood, family history of asthma, eczema or rhinitis, and presence of mold or damp in the household) were identified.

Strengths and Limitations. We developed a novel graphic presentation of data, which we believe enhances the perception of the complex pattern of effects. Given the highly heterogeneous methodologies used in the studies, a meta-analysis was not performed even for the risk factors investigated in a sufficient number of studies. Maybe the most important finding of this review is the very marked heterogeneity of methods used in the

existing studies, which in our view has delayed scientific progress in this field.

Conclusion

Research in asthma and the ability to compare between studies clearly requires a consistent and standardized methodological approach. Allergen-specific IgE levels seem to provide a more reliable and stable characterization of atopy than SPT positivity, particularly in populations living in low- and middle-income countries where the two measures are dissociated [12,13], and should, therefore, be preferably used to define atopic status in studies of asthma epidemiology. The debate is ongoing on which is the best comparison group (and on the implications for the interpretation of findings) [14,15].

Recommendations

Research using agreed, rigorous methodology is needed to elucidate the pattern of association and causal mechanisms underpinning non-atopic asthma.

Additional files

Additional file 1: PRISMA 2009 checklist.

Additional file 2: Articles retained for the review.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AS and LCR designed the study, AS conducted the search and read the abstracts and the papers, AS and LCR classified the papers, AS conducted the analysis, AS, MLB, PJC and LCR interpreted the results, AS wrote up the manuscript, and MLB, PJC and LCR contributed to writing. All authors read and approved the final manuscript.

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References

- GINA: Global initiative for asthma. Global strategy for asthma and prevention - update 2012. URL: http://www.ginasthma.org/local/uploads/files/GINA_Report_March13_1.pdf.
- Cooper PJ, Rodrigues LC, Barreto ML: Influence of poverty and infection on asthma in Latin America. *Curr Opin Allergy Clin Immunol* 2012, **12**:171-178.
- Stein RT, Martinez FD: Asthma phenotypes in childhood: lessons from an epidemiological approach. *Paediatr Respir Rev* 2004, **5**:155-161.
- Handoyo S, Rosenwasser LJ: Asthma phenotypes. *Curr Allergy Asthma Rep* 2009, **9**:439-445.
- Lotvall J, Akdis CA, Bacharier LB, Bjerner L, Casale TB, Custovic A, Lemanske RF Jr, Wardlaw AJ, Wenzel SE, Greenberger PA: Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011, **127**:355-360.
- Herr M, Just J, Nikasinovic L, Foucault C, Le Marec AM, Giordanella JP, Momas I: Risk factors and characteristics of respiratory and allergic phenotypes in early childhood. *J Allergy Clin Immunol* 2012, **130**:389-396. e384.
- Corren J: Asthma phenotypes and endotypes: an evolving paradigm for classification. *Discov Med* 2013, **15**:243-249.
- Martinez FD, Vercelli D: Asthma. *Lancet* 2013, **382**:1360-1372.
- Sunyer J, Jarvis D, Pekkanen J, Chinn S, Janson C, Leynaert B, Luczynska C, Garcia-Esteban R, Burney P, Anto JM: Geographic variations in the effect of atopy on asthma in the European Community Respiratory Health Study. *J Allergy Clin Immunol* 2004, **114**:1033-1039.
- Weinmayr G, Weiland SK, Bjorksten B, Brunekreef B, Buchele G, Cookson WO, Garcia-Marcos L, Gotua M, Gratziou C, van Hage M, von Mutius E, Riiikjrv M-A, Rzehak P, Stein RT, Strachan DP, Tsanakas J, Wickens K, Wong GW, the ISAAC Phase Two Study Group: Atopic sensitization and the international variation of asthma symptom prevalence in children. *Am J Respir Crit Care Med* 2007, **176**:565-574.
- Sinisgalli S, Collins MS, Schramm CM: Clinical features cannot distinguish allergic from non-allergic asthma in children. *J Asthma* 2012, **49**:51-56.
- van den Biggelaar AH, van Ree R, Rodrigues LC, Lell B, Deelder AM, Kremsner PG, Yazdanbakhsh M: Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite-induced interleukin-10. *Lancet* 2000, **356**:1723-1727.
- Alcantara-Neves NM, Veiga RV, Dattoli VC, Fiaccone RL, Esquivel R, Cruz AA, Cooper PJ, Rodrigues LC, Barreto ML: The effect of single and multiple infections on atopy and wheezing in children. *J Allergy Clin Immunol* 2012, **129**:359-367. 367 e351-353.
- Barreto ML, Cunha SS, Fiaccone R, Esquivel R, Amorim LD, Alvim S, Prado M, Cruz AA, Cooper PJ, Santos DN, Strina A, Alcantara-Neves N, Rodrigues LC: Poverty, dirt, infections and non-atopic wheezing in children from a Brazilian urban center. *Respir Res* 2010, **11**:167.
- Pekkanen J, Lampi J, Genuneit J, Hartikainen AL, Jarvelin MR: Analyzing atopic and non-atopic asthma. *Eur J Epidemiol* 2012, **27**:281-286.
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D: The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009, **6**:e1000100.
- Pereira MU, Sly PD, Pitrez PM, Jones MH, Escouto D, Dias AC, Weiland SK, Stein RT: Nonatopic asthma is associated with helminth infections and bronchiolitis in poor children. *Eur Respir J* 2007, **29**:1154-1160.
- Kurukulaaratchy RJ, Fenn M, Matthews S, Arshad SH: Characterisation of atopic and non-atopic wheeze in 10 year old children. *Thorax* 2004, **59**:563-568.
- Ronmark E, Jonsson E, Platts-Mills T, Lundback B: Different pattern of risk factors for atopic and nonatopic asthma among children-report from the obstructive lung disease in Northern Sweden study. *Allergy* 1999, **54**:926-935.
- Sunyer J, Torrent M, Munoz-Ortiz L, Ribas-Fito N, Carrizo D, Grimalt J, Anto JM, Cullinan P: Prenatal dichlorodiphenyldichloroethylene (DDE) and asthma in children. *Environ Health Perspect* 2005, **113**:1787-1790.
- Moncayo AL, Vaca M, Oviedo G, Erazo S, Quinzo I, Fiaccone RL, Chico ME, Barreto ML, Cooper PJ: Risk factors for atopic and non-atopic asthma in a rural area of Ecuador. *Thorax* 2010, **65**:409-416.
- Janson C, Kalm-Stephens P, Foucard T, Alving K, Nordvall SL: Risk factors associated with allergic and non-allergic asthma in adolescents. *Clin Respir J* 2007, **1**:16-22.
- Civelek E, Cakir B, Orhan F, Yuksel H, Boz AB, Uner A, Sekerel BE: Risk factors for current wheezing and its phenotypes among elementary school children. *Pediatr Pulmonol* 2011, **46**:166-174.
- Garcia-Marcos L, Castro-Rodriguez JA, Suarez-Varela MM, Garrido JB, Hernandez GG, Gimeno AM, Gonzalez AL, Ruiz TR, Torres AM: A different pattern of risk factors for atopic and non-atopic wheezing in 9-12-year-old children. *Pediatr Allergy Immunol* 2005, **16**:471-477.
- Weinmayr G, Gehring U, Genuneit J, Buchele G, Kleiner A, Siebers R, Wickens K, Crane J, Brunekreef B, Strachan DP: Dampness and moulds in relation to

- respiratory and allergic symptoms in children: results from phase two of the International Study of Asthma and Allergies in Childhood (ISAAC Phase Two). *Clin Exp Allergy* 2013, **43**:762–774.
26. Pekkanen J, Hyvärinen A, Haverinen-Shaughnessy U, Korppi M, Putus T, Nevalainen A: **Moisture damage and childhood asthma: a population-based incident case-control study.** *Eur Respir J* 2007, **29**:509–515.
27. Venn AJ, Cooper M, Antoniak M, Laughlin C, Britton J, Lewis SA: **Effects of volatile organic compounds, damp, and other environmental exposures in the home on wheezing illness in children.** *Thorax* 2003, **58**:955–960.
28. Oddy WH, de Klerk NH, Sly PD, Holt PG: **The effects of respiratory infections, atopy, and breastfeeding on childhood asthma.** *Eur Respir J* 2002, **19**:899–905.
29. Normann E, Gnärpe J, Wettergren B, Janson C, Wickman M, Nordvall L: **Association between Chlamydia pneumoniae antibodies and wheezing in young children and the influence of sex.** *Thorax* 2006, **61**:1054–1058.
30. Kusel MM, de Klerk NH, Kebabdzic T, Vohma V, Holt PG, Johnston SL, Sly PD: **Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma.** *J Allergy Clin Immunol* 2007, **119**:1105–1110.
31. Alcantara-Neves NM, Badaro SJ, dos Santos MC, Pontes-de-Carvalho L, Barreto ML: **The presence of serum anti-Ascaris lumbricoides IgE antibodies and of Trichuris trichiura infection are risk factors for wheezing and/or atopy in preschool-aged Brazilian children.** *Respir Res* 2010, **11**:114.
32. von Mutius E, Illi S, Hirsch T, Leupold W, Keil U, Weiland SK: **Frequency of infections and risk of asthma, atopy and airway hyperresponsiveness in children.** *Eur Respir J* 1999, **14**:4–11.
33. Calvani M, Alessandri C, Sopo SM, Panetta V, Tripodi S, Torre A, Pingitore G, Frediani T, Volterrani A: **Infectious and uterus related complications during pregnancy and development of atopic and nonatopic asthma in children.** *Allergy* 2004, **59**:99–106.
34. Fuchs O, Genuneit J, Latzin P, Buchele G, Horak E, Loss G, Sozanska B, Weber J, Boznanski A, Heederik D, Braun-Fahrlander C, Frey U, von Mutius E, GABRIELA Study Group: **Farming environments and childhood atopy, wheeze, lung function, and exhaled nitric oxide.** *J Allergy Clin Immunol* 2012, **130**:382–388. e386.
35. Ege MJ, Frei R, Bieli C, Schram-Bijkerk D, Waser M, Benz MR, Weiss G, Nyberg F, van Hage M, Pershagen G, Brunekreef B, Riedler J, Lauener R, Braun-Fahrlander C, von Mutius E, PARISFAL Study team: **Not all farming environments protect against the development of asthma and wheeze in children.** *J Allergy Clin Immunol* 2007, **119**:1140–1147.
36. Braun-Fahrlander C, Riedler J, Herz U, Eder W, Waser M, Grize L, Maisch S, Carr D, Gerlach F, Bufe A, Lauener RP, Schierl R, Renz H, Nowak D, von Mutius E, and Endotoxin Study Team: **Environmental exposure to endotoxin and its relation to asthma in school-age children.** *N Engl J Med* 2002, **347**:869–877.
37. Riedler J, Braun-Fahrlander C, Eder W, Schreuer M, Waser M, Maisch S, Carr D, Schierl R, Nowak D, von Mutius E: **Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey.** *Lancet* 2001, **358**:1129–1133.
38. Kelley CF, Mannino DM, Homa DM, Savage-Brown A, Holguin F: **Asthma phenotypes, risk factors, and measures of severity in a national sample of US children.** *Pediatrics* 2005, **115**:726–731.
39. Visnes CM, London SJ, Daniels JL, Kaufman JS, Yeatts KB, Siega-Riz AM, Calatroni A, Zeldin DC: **Association of childhood obesity with atopic and nonatopic asthma: results from the National Health and Nutrition Examination Survey 1999–2006.** *J Asthma* 2010, **47**:822–829.
40. Lodrup Carlsen KC, Roll S, Carlsen KH, Mowinckel P, Wijga AH, Brunekreef B, Torrent M, Roberts G, Arshad SH, Kull I, Krämer U, von Berg A, Eller E, Høst A, Kuehni C, Spycher B, Sunyer J, Chen CM, Reich A, Asarnoj A, Puig C, Herbarth O, Mahachie JM, Van Steen K, Willich SN, Wahn U, Lau S, Keil T, GALEN WP 1.5 'Birth Cohorts' working group: **Does pet ownership in infancy lead to asthma or allergy at school age? Pooled analysis of individual participant data from 11 European birth cohorts.** *PLoS One* 2012, **7**:e43214.
41. Ponsoy AL, Gatenby P, Glasgow N, Mullins R, Hurwitz M, McDonald T: **The association between synthetic bedding and adverse respiratory outcomes among skin-prick test positive and skin-prick test negative children.** *Allergy* 2002, **57**:247–253.
42. Kozyrskyj AL, Kendall GE, Zubrick SR, Newnham JP, Sly PD: **Frequent nocturnal awakening in early life is associated with nonatopic asthma in children.** *Eur Respir J* 2009, **34**:1288–1295.
43. Gruzjeva O, Bergstrom A, Hulchiy O, Kull I, Lind T, Melen E, Moskalenko V, Pershagen G, Bellander T: **Exposure to air pollution from traffic and childhood asthma until 12 years of age.** *Epidemiology* 2013, **24**:54–61.
44. Palmieri M, Longobardi G, Napolitano G, Simonetti DM: **Parental smoking and asthma in childhood.** *Eur J Pediatr* 1990, **149**:738–740.
45. Yoo S, Kim HB, Lee SY, Kim BS, Kim JH, Yu J, Kim BJ, Lee DH, Seong MW, Hong SJ: **Effect of active smoking on asthma symptoms, pulmonary function, and BHR in adolescents.** *Pediatr Pulmonol* 2009, **44**:954–961.
46. Genuneit J, Weinmayr G, Radon K, Dressel H, Windstetter D, Rzehak P, Vogelberg C, Leupold W, Nowak D, von Mutius E, Weiland SK: **Smoking and the incidence of asthma during adolescence: results of a large cohort study in Germany.** *Thorax* 2006, **61**:572–578.
47. de Meer G, Reijneveld SA, Brunekreef B: **Wheeze in children: the impact of parental education on atopic and non-atopic symptoms.** *Pediatr Allergy Immunol* 2010, **21**:823–830.
48. Burr ML, Limb ES, Maguire MJ, Amarah L, Eldridge BA, Layzell JC, Merrett TG: **Infant feeding, wheezing, and allergy: a prospective study.** *Arch Dis Child* 1993, **68**:724–728.
49. Nagel G, Buchele G, Weinmayr G, Bjorksten B, Chen YZ, Wang H, Nystad W, Saraclar Y, Braback L, Battles-Garrido J, Garcia-Hernandez G, Weiland SK, ISAAC Phase II Study Group: **Effect of breastfeeding on asthma, lung function and bronchial hyperreactivity in ISAAC Phase II.** *Eur Respir J* 2009, **33**:993–1002.
50. Nwaru BI, Takkinen HM, Niemela O, Kaila M, Erkkola M, Ahonen S, Haapala AM, Kenward MG, Pekkanen J, Laheesmaa R, Kere J, Simell O, Veijola R, Ilonen J, Hyöty H, Knip M, Virtanen SM: **Timing of infant feeding in relation to childhood asthma and allergic diseases.** *J Allergy Clin Immunol* 2013, **131**:78–86.
51. Remes ST, Patel SP, Hartikainen AL, Jarvelin MR, Pekkanen J: **High birth weight, asthma and atopy at the age of 16 yr.** *Pediatr Allergy Immunol* 2008, **19**:541–543.
52. Pike KC, Crozier SR, Lucas JS, Inskip HM, Robinson S, Roberts G, Godfrey KM: **Patterns of fetal and infant growth are related to atopy and wheezing disorders at age 3 years.** *Thorax* 2010, **65**:1099–1106.
53. Pike KC, Rose-Zerilli MJ, Osvald EC, Inskip HM, Godfrey KM, Crozier SR, Roberts G, Clough JB, Holloway JW, Lucas JS: **The relationship between infant lung function and the risk of wheeze in the preschool years.** *Pediatr Pulmonol* 2011, **46**:75–82.
54. Knudsen TB, Thomsen SF, Ulrik CS, Fenger M, Nepper-Christensen S, Backer V: **Season of birth and risk of atopic disease among children and adolescents.** *J Asthma* 2007, **44**:257–260.
55. Bahreinian S, Ball GD, Colman I, Becker AB, Kozyrskyj AL: **Depression is more common in girls with nonatopic asthma.** *Chest* 2011, **140**:1138–1145.
56. Kohlboeck G, Koletzko S, Bauer CP, von Berg A, Berdel D, Kramer U, Schaaf B, Lehmann I, Herbarth O, Heinrich J: **Association of atopic and non-atopic asthma with emotional symptoms in school children.** *Pediatr Allergy Immunol* 2013, **24**:230–236.
57. Cookson H, Granell R, Joinson C, Ben-Shlomo Y, Henderson AJ: **Mothers' anxiety during pregnancy is associated with asthma in their children.** *J Allergy Clin Immunol* 2009, **123**:847–853. e811.
58. Dos Santos LM, Dos Santos DN, Rodrigues LC, Barreto ML: **Maternal mental health and social support: effect on childhood atopic and non-atopic asthma symptoms.** *J Epidemiol Community Health* 2012, **66**:1011–1016.
59. Sibbald B, Horn ME, Brain EA, Gregg I: **Genetic factors in childhood asthma.** *Thorax* 1980, **35**:671–674.
60. Mendell MJ, Mirer AG, Cheung K, Tong M, Douwes J: **Respiratory and allergic health effects of dampness, mold, and dampness-related agents: a review of the epidemiologic evidence.** *Environ Health Perspect* 2011, **119**:748–756.
61. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, Wright AL, Martinez FD: **Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years.** *Lancet* 1999, **354**:541–545.
62. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B: **Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7.** *Am J Respir Crit Care Med* 2000, **161**:1501–1507.
63. Sigurs N, Gustafsson PM, Bjarnason R, Lundberg F, Schmidt S, Sigurbergsson F, Kjellman B: **Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13.** *Am J Respir Crit Care Med* 2005, **171**:137–141.
64. Thomsen SF, van der Sluis S, Stensballe LG, Posthuma D, Skytthe A, Kyvik KO, Duffy DL, Backer V, Bisgaard H: **Exploring the association between**

- severe respiratory syncytial virus infection and asthma: a registry-based twin study. *Am J Respir Crit Care Med* 2009, **179**:1091–1097.
65. Jackson DJ, Lemanske RF Jr: **The role of respiratory virus infections in childhood asthma inception.** *Immunol Allergy Clin North Am* 2010, **30**:513–522. vi.
 66. Mallol J, Castro-Rodriguez JA, Cortez E, Aguirre V, Aguilar P, Barrueto L: **Heightened bronchial hyperresponsiveness in the absence of heightened atopy in children with current wheezing and low income status.** *Thorax* 2008, **63**:167–171.
 67. Leonardi-Bee J, Pritchard D, Britton J: **Asthma and current intestinal parasite infection: systematic review and meta-analysis.** *Am J Respir Crit Care Med* 2006, **174**:514–523.
 68. Cooper PJ, Rodrigues LC, Cruz AA, Barreto ML: **Asthma in Latin America: a public health challenge and research opportunity.** *Allergy* 2009, **64**:5–17.
 69. Feary J, Britton J, Leonardi-Bee J: **Atopy and current intestinal parasite infection: a systematic review and meta-analysis.** *Allergy* 2011, **66**:569–578.
 70. Cooper PJ: **Interactions between helminth parasites and allergy.** *Curr Opin Allergy Clin Immunol* 2009, **9**:29–37.
 71. Karmaus W, Botezan C: **Does a higher number of siblings protect against the development of allergy and asthma? A review.** *J Epidemiol Community Health* 2002, **56**:209–217.
 72. Duncan JM, Sears MR: **Breastfeeding and allergies: time for a change in paradigm?** *Curr Opin Allergy Clin Immunol* 2008, **8**:398–405.
 73. van Odijk J, Kull I, Borres MP, Brandtzaeg P, Edberg U, Hanson LA, Host A, Kuitunen M, Olsen SF, Skerfving S, Sundell J, Wille S: **Breastfeeding and allergic disease: a multidisciplinary review of the literature (1966–2001) on the mode of early feeding in infancy and its impact on later atopic manifestations.** *Allergy* 2003, **58**:833–843.
 74. Brew BK, Allen CW, Toelle BG, Marks GB: **Systematic review and meta-analysis investigating breast feeding and childhood wheezing illness.** *Paediatr Perinat Epidemiol* 2011, **25**:507–518.
 75. Papoutsakis C, Priftis KN, Drakouli M, Prifti S, Konstantaki E, Chondronikola M, Antonogeorgos G, Matziou V: **Childhood overweight/obesity and asthma: is there a link? A systematic review of recent epidemiologic evidence.** *J Acad Nutr Diet* 2013, **113**:77–105.
 76. Sideleva O, Black K, Dixon AE: **Effects of obesity and weight loss on airway physiology and inflammation in asthma.** *Pulm Pharmacol Ther* 2013, **26**:455–458.
 77. Strachan DP, Cook DG: **Health effects of passive smoking. 6. Parental smoking and childhood asthma: longitudinal and case-control studies.** *Thorax* 1998, **53**:204–212.

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