

Environmental tobacco smoke exposure and risk of allergic sensitisation in children: a systematic review and meta-analysis

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ABSTRACT

Background Environmental tobacco smoke (ETS) exposure in children is linked with the development of allergic asthma. However, its influence on allergic sensitisation in children has not been conclusively determined.

Objective To systematically review existing evidence of ETS exposure's impact on markers of allergic sensitisation in children.

Methods CENTRAL, MEDLINE and EMBASE databases were searched. Included studies assessed following markers of atopic sensitisation: total immunoglobulin E (tIgE) concentrations, at least one specific IgE (sIgE+), and positive skin-prick tests (SPTs+) in ETS-exposed and non-exposed children.

Results 8 studies on the influence of ETS on tIgE concentration (2603 patients), 6 studies on ETS and sIgE+ (9230 participants) and 14 papers on ETS and SPT (14 150 patients) met our inclusion criteria. ETS was shown to raise tIgE concentrations by 27.7 IU/mL (95% CI 7.8 to 47.7; $I^2=58\%$; results based on 3 studies) and to increase the risk of atopic sensitisation, as assessed by sIgE+ (OR=1.12, 95% CI 1.00 to 1.25; $I^2=54\%$; results based on 4 studies) and SPT+ (OR=1.15; 95% CI 1.04 to 1.28; $I^2=0\%$; results based on 10 studies). In a subgroup analysis, this effect was most pronounced in children <7 years (preschoolers) by OR=1.20; (95% CI 1.05 to 1.38) and OR=1.30 (95% CI 1.05 to 1.61), (for sIgE+ and SPT+, respectively).

Conclusions Current analysis supports an association between ETS exposure in early childhood and the increased risk of allergic sensitisation. Subgroup meta-analyses demonstrate that younger children suffer the most from detrimental immunomodulating effects of ETS exposure. This study underscores ETS as an important but avoidable risk factor for the development of allergic disease in children.

INTRODUCTION

Environmental tobacco smoke (ETS) in children is believed to be related to impaired lung function and an increased risk to allergy and asthma.¹ According to a recent systematic review by Burke *et al*,² ETS exposure increases the incidence of asthma in children by at least 20%. The development of asthma in those exposed to ETS during pregnancy and early childhood is attributed to increased sensitivity to allergens.³ However, the precise immune pathways driving this phenomenon are still under debate and available data from large cross-sectional and cohort studies are conflicting.⁴⁻⁷ The existing evidence on smoking and allergic sensitisation was summarised by Strachan and Cook in 1998 in a systematic review, however, their results suggest no conclusive association.⁸

What is already known on this topic

Environmental tobacco smoke exposure increases the incidence of asthma in children, however, the mechanisms of this are unclear.

What this study adds

- Data combined from nineteen population-based cohort studies (24,000 children) suggests household smoke exposure influences postnatal immunoregulation.
- Tobacco smoke exposure has been demonstrated to increase sensitivity to allergens in children, measured by serum IgE and skin testing.
- Immunoregulatory mechanisms are suspected to play a role in the increased frequency of allergy, seen in children exposed to household tobacco smoke.

Over the last 15 years, evidence has been surfacing which demonstrates the effect of tobacco smoke on immune function in a variety of in vitro and animal models.⁹ The limited existing data on passive smoking and its direct effects on immune responses and respiratory health in children seem to confirm these observations.¹⁰⁻¹² Therefore, our aim was to systematically review and update data from cross-sectional and cohort studies regarding the effect of ETS on serum total immunoglobulin E (tIgE) and specific IgE (sIgE) and skin-prick tests (SPTs), since they are easily assessable and objective markers of allergic sensitisation in children.¹³

METHODS

The study used standard methods for systematic reviews and was reported in accordance with MOOSE (Meta-analysis of observational studies in epidemiology).

Search and selection

The Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), MEDLINE (1966–2012), and EMBASE (1980–2012) databases were systematically and independently searched by three researchers (WF, MR, BMZ) in April 2013. Disagreements were resolved through discussion (further details online supplementary file).

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Inclusion criteria

The studies were eligible if they met our predefined inclusion criteria: (1) full-text cross-sectional, case-control or prospective cohort studies; (2) study participants aged 0–18 years from non-selected, random populations; (3) studies reporting the effects of postnatal ETS exposure, at longest follow-up for studies with multiple time points. We included only papers reporting: (1) tIgE concentrations, (2) detection of at least one positive result of sIgE antibodies to any common food or inhalant allergen (when IgE ≥ 0.35 kU/L at any point (sIgE+) or (3) presence of any positive SPT to any common food or inhalant allergen (transverse wheal diameter ≥ 3 mm) (SPT+). No further restrictions (eg, regarding the methodological quality of individual studies, language, geographical setting) were imposed.

Exclusion criteria

We excluded studies performed on children in preselected a priori risk factor cohorts (ie, born to parents with history of atopy, diagnosed with any allergic disorder or attending outpatient allergy clinics), studies focusing on prenatal ETS exposure, and studies assessing cord-blood IgE level.

Data extraction

All data were independently extracted by pairs of investigators and underwent triple cross-reference procedure by using a standardised protocol and data extraction form.

Risk of bias assessment

The risk of bias (study quality) was assessed by considering measure exposure and outcomes, methods used to control for confounding factors, and the appropriateness of the statistical analysis, based on elements of the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines,¹⁴ the AHRQ (Agency for Healthcare Research and Quality's) checklist for observational studies,¹⁵ and the Newcastle-Ottawa Scale¹⁶ quality (see online supplementary tables A1 and A2). As recommended by the Center for Reviews and Dissemination,¹⁷ we did not use a scale with a summary score.

Statistical methods

Pooled weighted mean differences between tIgE concentrations in ETS exposed and control (non-exposed) groups were estimated using a random effects meta-analysis.

Positive sIgE and SPT results were pooled using a generic inverse variance fixed-effect (FE) meta-analysis model¹⁸ of OR between the exposed and unexposed groups, as studies were conducted in similar populations regarding the participant's age, health status, time of exposition to ETS, and exposure to other risk factors and no significant between-study heterogeneity was noted.

We also performed a subgroup analysis to evaluate for differences between children under the age of 7 years (hereafter called preschoolers) and school age children (≥ 7 years), as well as between prospective and cross-sectional studies. A vast majority of children in our dichotomy belong to one group (preschoolers) or the other (children of whom the vast majority attends compulsory educational facility) with little overlap, although regional variations mean the terms may not precisely reflect their educational status. Statistical heterogeneity was addressed using the I^2 index ($p < 0.05$ considered statistically significant) as well as through visual inspection of L'Abbé plots. All statistical analyses were done using Review Manager (RevMan) software (V5.1 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011).

RESULTS

Studies included

Our initial search strategy yielded 1655 citations; 181 abstracts were identified for further evaluation. Of these, we retrieved 70 full articles and finally included 24 reports of 19 study cohorts on 24 172 children (figure 1). Altogether there were 11 cross-sectional studies,^{5 7 19–30} 4 prospective cohort studies^{4 6 31–34} and 4 case-control studies.^{10 35–37} The studies were conducted in various regions of the world. The included subjects were aged 0–17 years.

Outcomes reported

Eight studies ($n=2603$) reported tIgE as an outcome (see online supplementary table SI), 6 publications (5 studies) ($n=9230$) assessed sIgE (see online supplementary table SII), and 14 publications/11 studies ($n=14\ 150$) reported positive SPTs (see online supplementary table SIII).

Exposures measured

The definition of smoking varied across the studies and only few reports used cotinine urine measurements to verify tobacco smoke exposure.^{5 30 36} Each study included in this review was investigated for possible confounding factors and the data used in meta-analysis were statistically adjusted for these factors when possible (see online supplementary table SI, SII, SIII and table A3).

Excluded studies and the reasons for exclusion are summarised in online supplementary table IV.

Environmental tobacco smoke and total IgE

Only four studies,^{10 24 26 35} comprising a total of 434 participants (262 ETS-exposed, and 172 non-exposed subjects) were included in this meta-analysis. The summary effect size as assessed by a random-effects model, revealed a strong and significant tendency towards increased tIgE levels in ETS-exposed individuals at the level of 89.9 IU/mL (95% CI 30.9 to 148.9 IU/mL) ($p=0.003$). However, the comparison of included studies revealed considerable heterogeneity among examined populations ($p < 0.0001$, $I^2=95\%$). This effect was mainly attributed to the study conducted by El-Nawawy *et al*¹⁰ on Egyptian children, whose results reported an overall, extremely high concentration of tIgE. Therefore the results should be treated cautiously (figure 2A).

After the exclusion of the questioned study, a statistically significant trend towards increased tIgE concentrations was still present with an acceptable level of homogeneity ($I^2=58\%$, $p=0.07$). All the studies consistently demonstrate the elevated tendency and the mean difference in tIgE level between ETS-exposed and non-exposed children was 27.7 IU/mL (95% CI 7.8 to 47.7; $p=0.006$; figure 2B).

Due to the limited number of studies with high level of heterogeneity, a subgroup analysis was not performed.

ENVIRONMENTAL TOBACCO SMOKE AND SPECIFIC IGE

The four studies eligible for meta-analysis involved 6629 participants (2161 ETS-exposed and 4468 non-exposed) with moderate heterogeneity calculated at $I^2=54\%$ ($p=0.09$).^{5 6 21 33} The FE estimate demonstrated that ETS exposure increased the risk of allergic sensitisation (OR=1.12; 95% CI 1.00 to 1.25), and the effect was on the border of statistical significance ($p=0.06$). Subsequent subgroup analyses performed with the use of the FE model indicated that in children aged <7 years ETS exposure was associated with the increased risk of atopic sensitisation

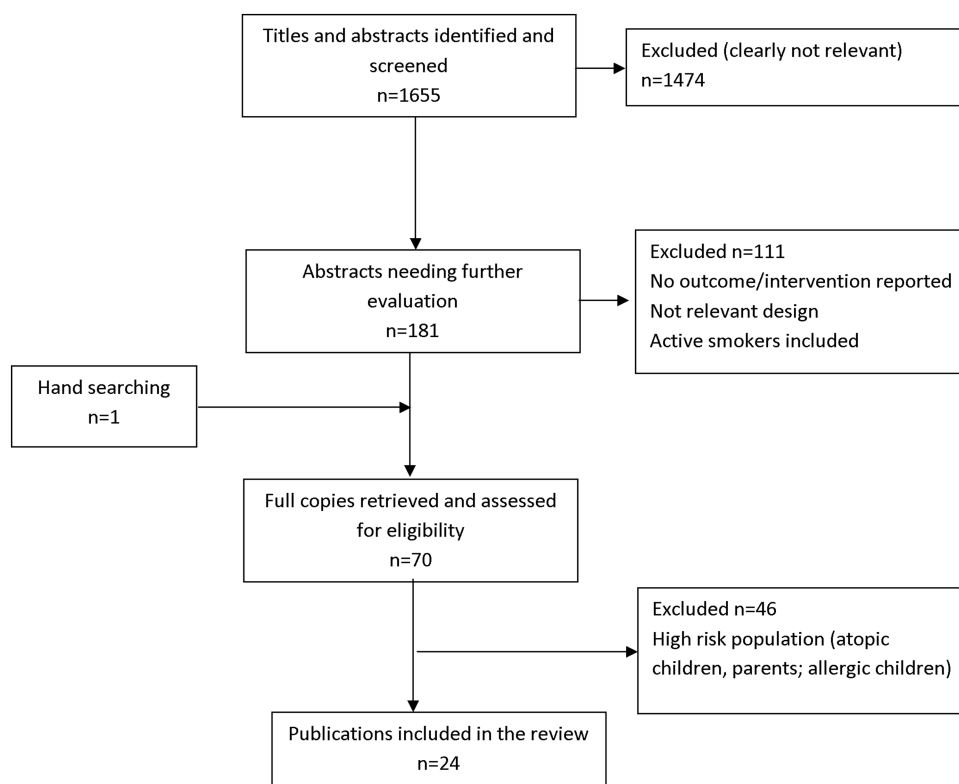


Figure 1 Flow chart of the inclusion and exclusion process for systematic review.

with an OR=1.20 (95% CI 1.05 to 1.38; [figure 3](#)). The observed effect was even stronger in the identified prospective studies with an OR=1.35 (95% CI 1.10 to 1.66; [figure 4](#)).

ENVIRONMENTAL TOBACCO SMOKE ETS AND SKIN-PRICK TESTS

Eight studies (9033 participants)^{4 5 19 22 27 29 33 36} were eligible for dichotomous meta-analysis. In two other reports (4080

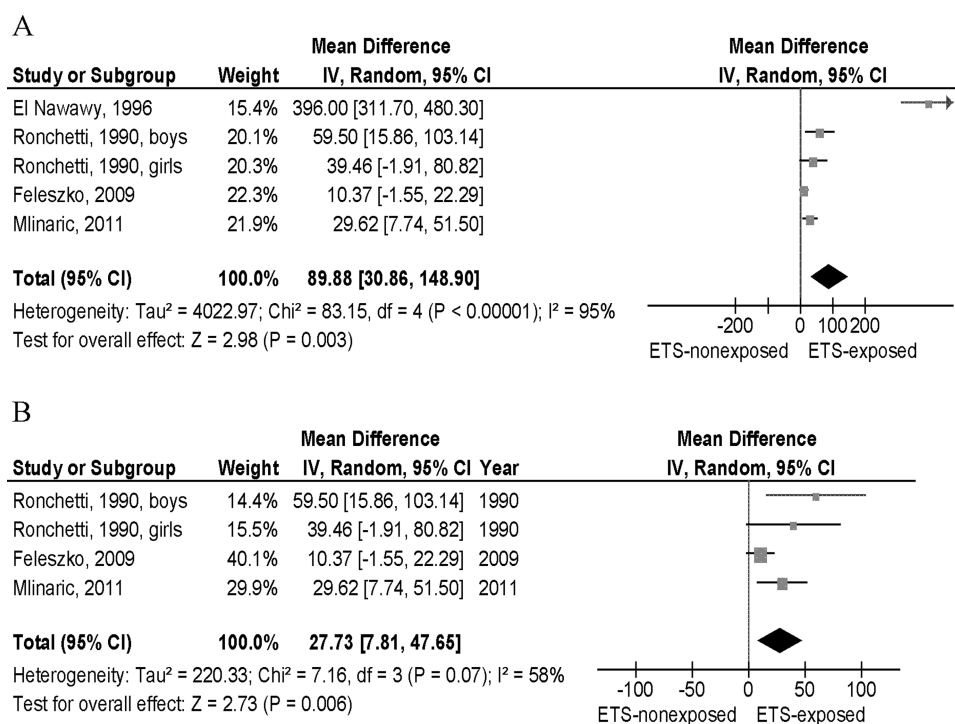


Figure 2 The effect of passive smoking on total IgE concentrations in children. The squares represent individual studies and the error bars represent 95% CIs. The diamond represents the combined result. The solid vertical line extending upwards from 0 is the null value. The arrow (x8E) indicates the upper limit of the CI. CI, confidence interval; ETS, environmental tobacco smoke; I^2 , level of heterogeneity. (A) An overall effect (B) an effect after exclusion of the questioned study.

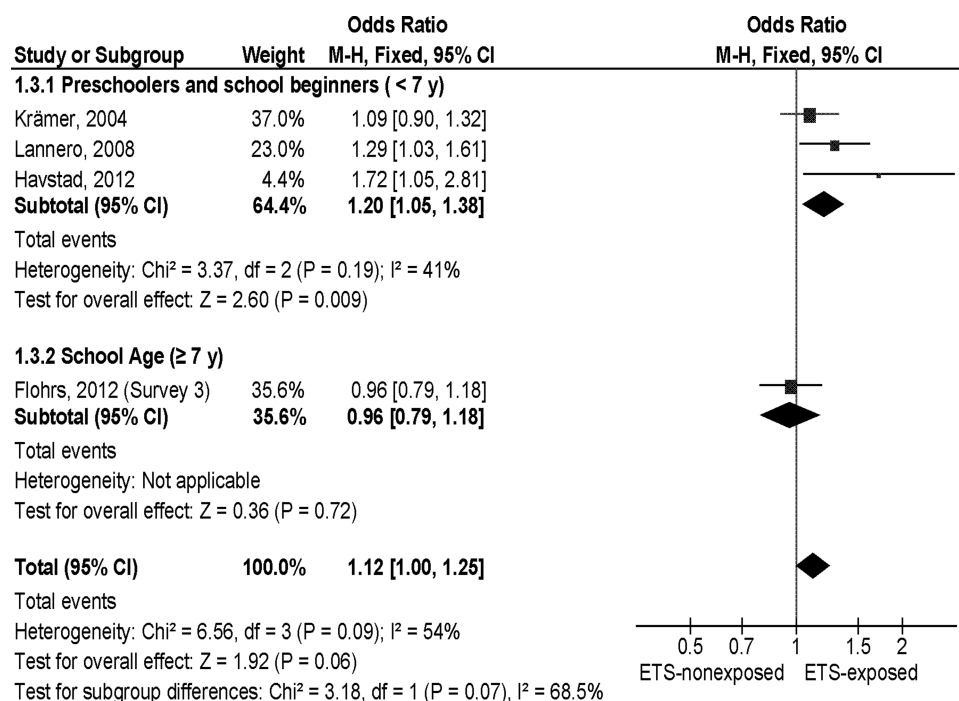


Figure 3 The environmental tobacco smoke (ETS) exposure and specific IgE concentrations in children—effect dichotomised according to the children's age. The squares represent individual studies (weights are from fixed effects analysis) and the error bars represent 95% CIs. The solid vertical line extending upwards from 1 is the null value. The diamond represents the calculated combined result (fixed effects model).

children) analysis was based on OR only, we therefore applied generic inverse variance analysis in order to estimate an overall effect. There was no statistical heterogeneity among the included studies ($I^2=0\%$). ETS exposure increased the risk of a positive SPT result with OR=1.15 (95% CI 1.04 to 1.28,

$p=0.007$). This effect was more pronounced in children under the age of 7 years (preschoolers and those who have just entered primary school) with the subgroup effect size at OR=1.30 (95% CI 1.05 to 1.61, $p=0.02$), but not apparent in the older group (OR=1.11, 95% CI 0.99 to 1.25; [figure 5](#)). Yet

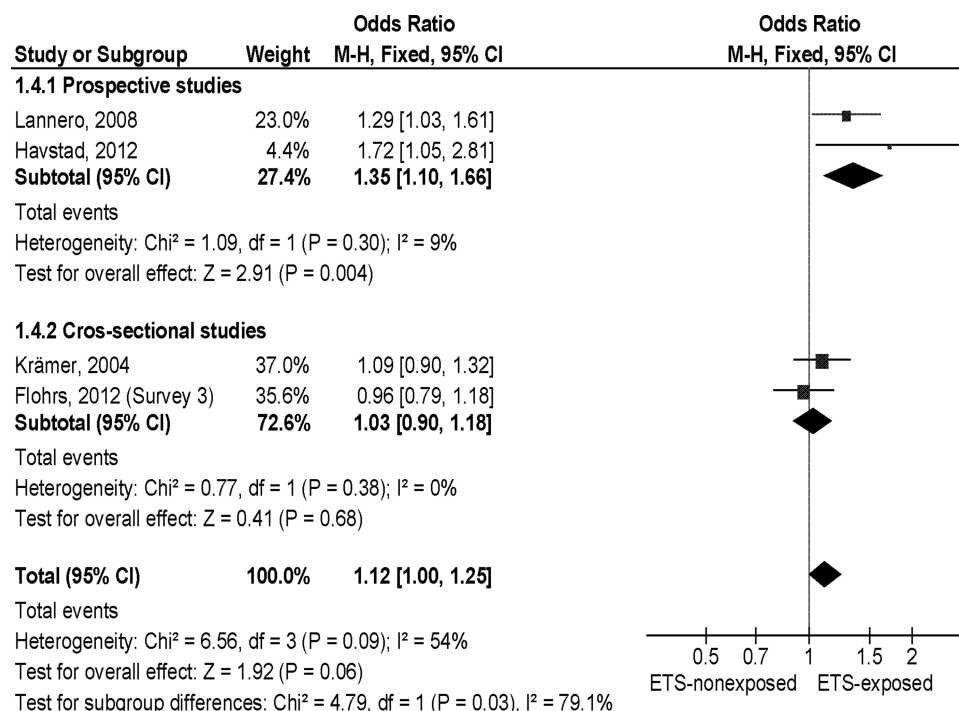


Figure 4 The environmental tobacco smoke (ETS) exposure and specific IgE concentrations in children—effect dichotomised according to the type of the study (prospective vs cross-sectional). The squares represent individual studies (weights are from fixed effects analysis) and the error bars represent 95% CIs. The solid vertical line extending upwards from 1 is the null value. The diamond represents the calculated combined result (fixed effects model).

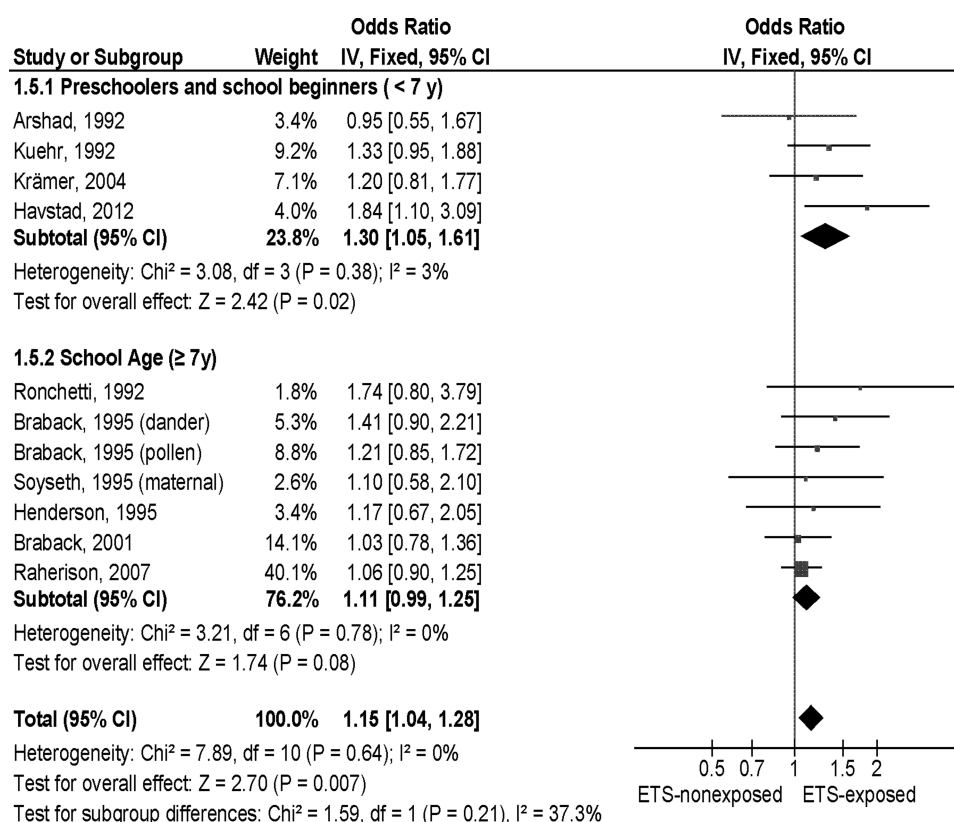


Figure 5 The effect of environmental tobacco smoke (ETS) exposure on skin-prick tests results in children—effect dichotomised according to the children's age. The squares represent individual studies (weights are from generic inverse variance analysis) and the error bars represent 95% CIs. The solid vertical line extending upwards from 1 is the null value. The diamond represents the calculated total result (generic inverse variance analysis).

again, the effect was stronger in prospective as compared with cross-sectional studies, (OR=1.43 and OR=1.13, respectively; [figure 6](#)).

DISCUSSION

Principal findings

In this systematic review and meta-analysis we have demonstrated that ETS exposure in children increases the risk of atopic sensitisation. Parental smoking is associated with: (1) significantly higher tIgE concentrations, (2) the presence of sIgE to any common allergens (>0.35 kU/L); and (3) positive SPT against common allergens in children. The observed effect was moderate and mostly expressed in preschoolers (<7 years).

Methodology

In this systematic review and meta-analysis we included only studies focusing on children from non-selected, random populations. Therefore, all studies conducted in children with an a priori increased risk of allergic sensitisation (eg, positive family history of allergy, atopic children from the outpatient allergy clinics) were excluded. In contrast to the recent meta-analysis by Burke *et al*,² this methodology allowed us to avoid a systematic bias, resulting from baseline differences in the selected populations. However, it can be considered a strength (considerable homogeneity) and a weakness (limited number of studies included) of the presented meta-analysis.

The effect of ETS on tIgE concentrations was analysed in eight studies, but only four studies comprising 434 participants were eligible for meta-analysis ([figure 2A, B](#)). The high level of heterogeneity of the studies was attributed to the higher IgE

concentrations observed in rural Egyptian children (mean tIgE in controls was 189 IU/mL) as compared with Italian and Polish children.¹⁰ The most probable explanation for this discrepancy was a high incidence of parasitic diseases in this group. It is well-known that parasitic infections can produce very intense levels of IgE with the concentrations reaching 3000 kU/L.³⁸ Although our data were too limited to ultimately determine the impact of ETS exposure on serum tIgE, this effect has already been postulated by others and confirmed in adults in the European Community Respiratory Health Survey, a cross sectional analysis of 13 000 participants.³⁹

Strong points and limitations of the study

Since smoking is a well-known factor of morbidity in the course of pre-existing allergic disease, the strong point of this study was an attempt to assess the effects of tobacco smoke exposure on the general population. This enabled us to reliably evaluate the phenomenon of atopy induction by cigarette smoke in children with and without previously known increased risk of allergy and renders these results generalisable. This aspect distinguishes our study from other former analyses.^{2 7 8 40} Studies encompassing only children with allergic disease are at risk of systematic error, since selective avoidance of smoking by parents of atopic children is likely to bias the results. At the same time, the conclusions from our study directly concern healthy children and those who may be predisposed to allergic sensitisation and those already diagnosed with allergic disease.

Another strong point of our work was the assessment of an age-related effect of tobacco smoke exposure. Previous observations suggested that the period of exposure may be important,

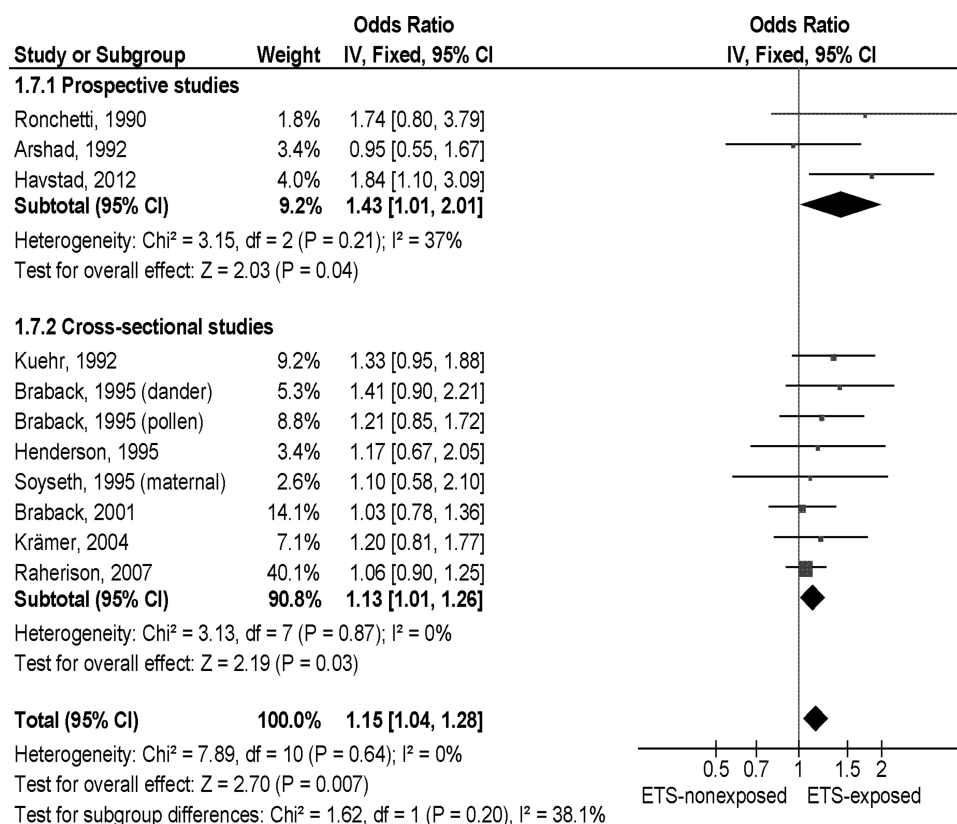


Figure 6 The effect of environmental tobacco smoke (ETS) exposure on skin-prick tests results in children—effect dichotomised according to the type of the study (prospective vs cross-sectional). The squares represent individual studies (weights are from generic inverse variance analysis) and the error bars represent 95% CIs. The solid vertical line extending upwards from 1 is the null value. The diamond represents the calculated total result (generic inverse variance analysis).

especially regarding exposure during pregnancy and infancy.^{8 12} Although the role of prenatal exposure to tobacco smoke is crucial for the development of allergic sensitisation,⁸ we decided to limit our search only to the studies reporting post-natal ETS exposure, since it is extremely difficult to disentangle prenatal from postnatal effects. Studies assessing cord-blood IgE were also excluded, as its level is considered rather a risk factor for the development of atopy and not a reliable marker of current allergic sensitisation.

Our findings indicate however, that the detrimental influence of ETS exposure is significant to children in the preschool era, with an age-related decline in the strength of the effect during the school years.⁴⁰ The observations reflect the time of contact as older children spend less amount of time at home. It has been suggested that critical time in this context is the first 3–4 years of life, since this period is crucial for the development of an individual profile of the respiratory immune response.^{40 41} However, in the view of our results as well as the recent data by Mitchell *et al*⁴² this time window should be extended to 6–7 years.

The presented systematic review with meta-analysis has several limitations. Our rigorous inclusion criteria significantly limited the number of analysed studies (from 1606 identified articles only 16 were included in the meta-analysis) restricting the possibility of a more comprehensive analysis. Even though the search strategy was very comprehensive (several databases, triple checked at each stage, unrestricted language limitations, correspondence contact with the authors of selected studies), some studies may not have been identified, especially if they

have never been published or were published in less indexed languages.⁴³ Moreover, in many of the identified studies the influence of parental smoking on the allergic sensitisation was not the primary outcome. Thus, it is possible that the studies with relevant data were not identified with our search strategy (ETS and allergic markers not mentioned in the title/abstract), and, ‘publication bias’ and ‘selective reporting’ bias cannot be excluded.

Furthermore, the majority of data included in this review were drawn from well-planned cross-sectional studies, and therefore the cause-effect relationship of the observed phenomena may be questioned. The inclusion of randomised control trials would have certainly increased the value of our review,⁴⁴ but such studies were not identified and will probably not be carried out due to the obvious ethical reasons.

Another potential limitation of this systematic review regards a variety of methods used to assess the exposure of children to ETS. These included: cotinine urine measurements, number of cigarettes smoked daily by family members (YES/NO or 1–10 vs 10 or more), smoking by any of the parents (none, smoking mother or father, both smoking). Due to this heterogeneity, the conclusions drawn from the present meta-analysis seem encouraging, but not definite.

Potential confounders

Since confounding factors can influence the strength of the results of observational studies,⁴³ each study included in this review was investigated for possible confounding factors (see online supplementary table A3) and data used in meta-analysis

were statistically adjusted for these factors whenever possible (see online supplementary tables SI, SII, SIII). It is an important argument in the evaluation of the presented study, since analyses that adjust for confounding variables were often proved not to reach statistical significance.^{43 45}

Comparison with other studies

This systematic review with meta-analysis is currently the most recent and reliable review of the topic reported to date. Our results are consistent with earlier observations from several large prospective cohorts and cross-sectional studies demonstrating higher risks of atopic asthma, eczema and rhinitis in children exposed to ETS,^{1 6 19 33 42 46} as well as with the latest reports confirming its detrimental effect on the incidence of asthma in children.^{2 40 42 47} However, in this report we included only studies assessing the influence of ETS exposure on objective markers of allergic sensitisation, and not the studies assessing particular allergic disease (asthma, atopic eczema, hay fever, wheezing) as an outcome. This approach had permitted us to objectively assess the actual influence of tobacco smoke on the immune system, with particular respect to the early mechanisms of allergic immune response. Assessing particular allergic disease as an outcome would not allow for such objectivity, since the majority of diagnostic criteria have changed over time. Moreover, in numerous epidemiological studies, the diagnosis is based only on data from parental questionnaires, which invariably leads to a recall bias. The former studies aiming at similar review are not free from these inaccuracies.^{2 7 8 40}

The most thoroughly conducted previous analysis is a study carried out in 1997 and published by Strachan and Cook in 1998.⁸ Despite the significant number of identified studies (36 articles), it is not free from methodological and formal errors.^{43 48} The major include the lack of information on: language limitations, multiple-referencing and cross-referencing, and verification of identified studies, as well as adopting inappropriate markers of atopic disease (umbilical IgE and SPT results defined positive when ≥ 0 mm), and others.

There are three other reports published recently, demonstrating that ETS exposure in children increases the incidence of asthma and wheezing by at least 20%: two systematic reviews by Burke *et al*² and Tinuoye *et al*,⁴⁷ as well as International Study of Asthma and Allergies in Childhood (Phase 3) report by Mitchell *et al*.⁴² These results correspond to our data, suggesting that ETS exposure increases the risk of atopic disease by 12–15% (and up to 20–30% in preschool children).

CONCLUSIONS AND FUTURE RESEARCH

In summary, the presented systematic review of observational studies with meta-analysis showed that household exposure to tobacco smoke after birth promotes the expression of immunological markers of allergic sensitisation and increases the risk of atopic disease in children. However, the majority of data was drawn from cross-sectional and cohort studies, and therefore the results should be treated with caution.

In future studies, efforts should be made to precisely and uniformly define the exposure to tobacco smoke (the number of cigarettes, hours of exposure, a period of exposure). Clear measures of controlling for important confounders are also required.

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Contributors Conception and design, or analysis and interpretation of data (WF, MR, JJ, AS, BMZ, MK); drafting the article or revising it critically for important intellectual content (WF, MR, AS, BMZ); final approval of the version to be published (WF, MR, JJ, AS, BMZ, MK).

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Cook DG, Strachan DP. Health effects of passive smoking. 3. Parental smoking and prevalence of respiratory symptoms and asthma in school age children. *Thorax* 1997;52:1081–94.
- 2 Burke H, Leonardi-Bee J, Hashim A, *et al*. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. *Pediatrics* 2012;129:735–44.
- 3 Metsios GS, Flouris AD, Koutedakis Y. Passive smoking, asthma and allergy in children. *Inflamm Allergy Drug Targets* 2009;8:348–52.
- 4 Arshad SH, Hide DW. Effect of environmental factors on the development of allergic disorders in infancy. *J Allergy Clin Immunol* 1992;90:235–41.
- 5 Kramer U, Lemmen CH, Behrendt H, *et al*. The effect of environmental tobacco smoke on eczema and allergic sensitization in children. *Br J Dermatol* 2004;150:111–18.
- 6 Lannero E, Wickman M, van HM, *et al*. Exposure to environmental tobacco smoke and sensitisation in children. *Thorax* 2008;63:172–6.
- 7 Raheiser C, Penard-Morand C, Moreau D, *et al*. Smoking exposure and allergic sensitization in children according to maternal allergies. *Ann Allergy Asthma Immunol* 2008;100:351–7.
- 8 Strachan DP, Cook DG. Health effects of passive smoking. 5. Parental smoking and allergic sensitisation in children. *Thorax* 1998;53:117–23.
- 9 Trimble NJ, Botelho FM, Bauer CM, *et al*. Adjuvant and anti-inflammatory properties of cigarette smoke in murine allergic airway inflammation. *Am J Respir Cell Mol Biol* 2009;40:38–46.
- 10 El-Nawawy A, Soliman AT, el-Azzouni O, *et al*. Effect of passive smoking on frequency of respiratory illnesses and serum immunoglobulin-E (IgE) and interleukin-4 (IL-4) concentrations in exposed children. *J Trop Pediatr* 1996;42:166–9.
- 11 Feleszko W, Zawadzka-Krajewska A, Matysiak K, *et al*. Parental tobacco smoking is associated with augmented IL-13 secretion in children with allergic asthma. *J Allergy Clin Immunol* 2006;117:97–102.
- 12 Linnamaa P, Nieminen K, Koulou L, *et al*. Pro-inflammatory and Th2-type cytokine responses in PBMC in infants are associated with parental smoking. *Clin Exp Allergy* 2012;42:1472–8.
- 13 Global Initiative for Asthma (GINA). *Global strategy for asthma management and prevention, 2010*. Bethesda, MD: National Heart, Lung and Blood Institute (NHLBI), 2010.
- 14 von Elm E, Altman DG, Egger M, *et al*. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med* 2007;4:e296.
- 15 West S, King V, Carey TS, *et al*. *Systems to rate the strength of scientific evidence. Evidence Report/Technology Assessment No. 47* (Prepared by the Research Triangle Institute—University of North Carolina Evidence-based Practice Center under Contract No. 290-97-0011). AHRQ Publication No. 02-E016. Rockville, MD: Agency for Healthcare Research and Quality, 2002.
- 16 Wells GA, Shea B, Connell D, *et al*. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2014. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm (accessed 25 May 2014).
- 17 Center for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking reviews in health care*. York, UK: University of York, 2008.
- 18 Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 edn. The Cochrane Collaboration, 2011.
- 19 Braback L, Breborowicz A, Julge K, *et al*. Risk factors for respiratory symptoms and atopic sensitisation in the Baltic area. *Arch Dis Child* 1995;72:487–93.
- 20 Braback L, Kjellman NI, Sandin A, *et al*. Atopy among schoolchildren in northern and southern Sweden in relation to pet ownership and early life events. *Pediatr Allergy Immunol* 2001;12:4–10.
- 21 Flohrs K, Bruske I, Thiering E, *et al*. Temporal changes in total serum immunoglobulin E levels in East German children and the effect of potential predictors. *Int Arch Allergy Immunol* 2012;158:27–34.
- 22 Kuehr J, Frischer T, Karmaus W, *et al*. Early childhood risk factors for sensitization at school age. *J Allergy Clin Immunol* 1992;90:358–63.
- 23 Martinez FD, Antognoni G, Macri F, *et al*. Parental smoking enhances bronchial responsiveness in nine-year-old children. *Am Rev Respir Dis* 1988;138:518–23.
- 24 Mlinaric A, Popovic GS, Nadalín S, *et al*. Passive smoking and respiratory allergies in adolescents. *Eur Rev Med Pharmacol Sci* 2011;15:973–7.

Original article

- 25 Raherison C, Penard-Morand C, Moreau D, *et al.* In utero and childhood exposure to parental tobacco smoke, and allergies in schoolchildren. *Respir Med* 2007;101:107–17.
- 26 Ronchetti R, Macri F, Ciofetta G, *et al.* Increased serum IgE and increased prevalence of eosinophilia in 9-year-old children of smoking parents. *J Allergy Clin Immunol* 1990;86:400–7.
- 27 Ronchetti R, Bonci E, Cutrera R, *et al.* Enhanced allergic sensitisation related to parental smoking. *Arch Dis Child* 1992;67:496–500.
- 28 Ronmark E, Lundback B, Jonsson E, *et al.* Asthma, type-1 allergy and related conditions in 7- and 8-year-old children in northern Sweden: prevalence rates and risk factor pattern. *Respir Med* 1998;92:316–24.
- 29 Soyseth V, Kongerud J, Boe J. Postnatal maternal smoking increases the prevalence of asthma but not of bronchial hyperresponsiveness or atopy in their children. *Chest* 1995;107:389–94.
- 30 Wjst M, Heinrich J, Liu P, *et al.* Indoor factors and IgE levels in children. *Allergy* 1994;49:766–71.
- 31 Arshad SH, Stevens M, Hide DW. The effect of genetic and environmental factors on the prevalence of allergic disorders at the age of two years. *Clin Exp Allergy* 1993;23:504–11.
- 32 Bohme M, Kull I, Bergstrom A, *et al.* Parental smoking increases the risk for eczema with sensitization in 4-year-old children. *J Allergy Clin Immunol* 2010;125:941–3.
- 33 Havstad SL, Johnson CC, Zoratti EM, *et al.* Tobacco smoke exposure and allergic sensitization in children: a propensity score analysis. *Respirology* 2012;17:1068–72.
- 34 Oldak E. The influence of tobacco parental smoking on serum IgE level of their offspring. *Rocz Akad Med Bialymst* 1997;42:191–5.
- 35 Feleszko W, Kielan I, Matysiak K, *et al.* Parental tobacco smoking is associated with increased risk of recurrent wheezing and augmented Th2-biased immune response in infants with first episode of virus-induced wheezing. *Pediatr Allergy Immunol* 2009;20(Suppl 20):56–7.
- 36 Henderson FW, Henry MM, Ivins SS, *et al.* Correlates of recurrent wheezing in school-age children. The Physicians of Raleigh Pediatric Associates. *Am J Respir Crit Care Med* 1995;151:1786–93.
- 37 Ownby DR, McCullough J. Passive exposure to cigarette smoke does not increase allergic sensitization in children. *J Allergy Clin Immunol* 1988;82:634–8.
- 38 Hemida MH, Mahmoud NS, El MM, *et al.* Interleukin (IL)-12, IL-5 and total IgE in hepatosplenic schistosomiasis with or without asthma. *J Egypt Soc Parasitol* 2010;40:367–76.
- 39 Burney PG, Luczynska C, Chinn S, *et al.* The European Community Respiratory Health Survey. *Eur Respir J* 1994;7:954–60.
- 40 U.S. Department of Health and Human Services. *The health consequences of involuntary exposure to tobacco smoke: a report of the surgeon general. Office of the Surgeon General (OSG)*. 2006.
- 41 Carlsen KH, Carlsen KC. Respiratory effects of tobacco smoking on infants and young children. *Paediatr Respir Rev* 2008;9:11–19.
- 42 Mitchell EA, Beasley R, Keil U, *et al.* The association between tobacco and the risk of asthma, rhinoconjunctivitis and eczema in children and adolescents: analyses from Phase Three of the ISAAC programme. *Thorax* 2012;67:941–9.
- 43 Egger M, Smith GD, Schneider M. Systematic reviews of observational studies. In: Egger M, Smith GD, Altman DG, eds. *Systematic reviews in health care. Meta-analysis in context*. London: BMJ Publishing Group, 2001:211–27.
- 44 Smith GD, Egger M. Meta-analyses of observational data should be done with due care. *BMJ* 1999;318:56.
- 45 Pattenden S, Antova T, Neuberger M, *et al.* Parental smoking and children's respiratory health: independent effects of prenatal and postnatal exposure. *Tob Control* 2006;15:294–301.
- 46 Strachan DP, Cook DG. Health effects of passive smoking. 6. Parental smoking and childhood asthma: longitudinal and case-control studies. *Thorax* 1998;53:204–12.
- 47 Tinuoye O, Pell JP, Mackay DF. Meta-analysis of the association between secondhand smoke exposure and physician-diagnosed childhood asthma. *Nicotine Tob Res* 2013;15:1475–83.
- 48 Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ* 2001;323:101–5.



Environmental tobacco smoke exposure and risk of allergic sensitisation in children: a systematic review and meta-analysis

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ONLINE ONLY MATERIAL

Environmental tobacco smoke exposure and risk of allergic sensitization in children: a systematic review and meta-analysis

(Methods, Results, Discussion, Tables)

*Wojciech Feleszko MD, PhD ¹, Marek Ruszczyński MD, PhD ², Joanna Jaworska MD ¹,
Agnieszka Strzelak MD ¹, Bartłomiej Mateusz Zalewski MD ², Marek Kulus MD, PhD ¹.*

METHODS

Search strategy:

The Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), MEDLINE (1966–2012), and EMBASE (1980–2012) databases were systematically and independently searched by 3 researchers (WF, MR, BZ) in April 2013 (described in details in the online supplementary file). All references to ETS exposure were selected by the MESH heading [*tobacco smoke*] and/or word combinations ([*passive, second-hand, second hand, involuntary, parent*, maternal, mother*, paternal, father*, environment* or household*] and [*smok*, tobacco* or cigarette**]). Papers were then restricted to those assessing the markers of atopic disease by relevant words [*atopic disease or atopy or IgE or globulin E or eosinophil* or skin prick test, skin-prick, SPT*]. Subsequently all identified studies were restricted to children as specified in the title or abstract [e.g., *child* or adolescent**] with appropriate truncations and misspellings. The search strategy used both keywords and MeSH terms. No further limitations were made to attain the highest possible sensitivity. The reference lists of all included papers were hand searched for other pertinent publications.

Data extraction:

All data were independently extracted by pairs of investigators and underwent triple cross-reference procedure by using a standardized protocol and data extraction form. The following data were extracted: author, source (journal), year of publication, study design (prospective cohort, cross-sectional or case-control), study population, sample size, location of the study, definition of ETS exposure (e.g. source of exposure, number of cigarettes a day, cotinine measurements), markers of sensitization (e.g. concentrations of tIgE, positive sIgE, positive SPT), adjustment for confounding factors, and study results (crude and/or adjusted estimates with the corresponding 95% Confidence Intervals where possible). If data were not

extractable or insufficient, efforts were made to contact the authors for further details. All discrepancies were discussed and resolved.

1 TABLES: Table I. Characteristics of included trials for total IgE (8 studies)

Study ID	Study design	Study aim	Participants recruited (included)	Definition of smoking	Definition of sensitization	Confounding Factors (CF)	Results	Outcomes (increased risk of sensitization) No / Yes	Included in metaanalysis (reason of exclusion)
Ownby DR et al. (J Allergy Clin Immunol.) 1988 [1]	Observational study – case series	ETS vs tIgE concentrations and allergic sensitization	N=191 2-17 y (USA)	Questionnaire: household smoking	tIgE, sIgE+	ND	Neither tIgE nor allergen-specific IgE concentrations differed significantly between ETS exposed and nonexposed children	No	No (no relevant data provided)
Ronchetti R et al. (J Allergy Clin Immunol) 1990 [2]	Cross-sectional study	ETS and serum tIgE levels or eosinophilia	N=179 (159) 9 y (Italy)	Questionnaire: current parental smoking	tIgE, eosinophilia	ND	Parental smoking was not significantly associated with serum IgE levels. Male children of smoking parents had a significantly higher IgE levels (p = 0.01) compared to nonsmoking counterparts. No difference for female children was found.	Yes (male children)	Yes
Wjst M et al. (Allergy) 1994 [3]	Cross-sectional study	To determine indoor characteristics of households in relation to total serum IgE.	N=1096 (772) 6& 8-12 y (Germany)	Questionnaire: current parental smoking Confirmed with urinary cotinine measurements	tIgE, sIgE+	CF adjusted	Higher urinary cotinine/creatinine ratio was associated with higher total IgE level.	Yes	No (no relevant figures)
el-Nawawy A et al. (J Trop Pediatr.) 1996 [4]	Case-control study	To study correlation between passive smoking and IgE, IL-4 concentrations, eosinophils counts and frequency of respiratory illness	N=120 9-10 y (Egipt)	ND	tIgE, IL-4, eosinophilia	ND	Significant increase in IL-4 and IgE concentrations in children of smoking parents compared to controls.	Yes	Yes
Oldak E. (Rocz Akad Medv Bialymst.) 1997 [5]	Prospective observational birth cohort	To assess correlation between prenatal smoking and IgE level, and atopic diseases	N=82 0-12 m. (Poland)	Questionnaire: early life household ETS	tIgE, incidence of atopic diseases	ND	Elevated tIgE level was seen more frequent in children of smoking mothers (p < 0.05). Paternal smoking did not influence serum IgE levels	Yes (smoking mothers)	No
Krämer U et al. (Br J Dermatol.) 2004 [6]	Cross-sectional study	To determine the impact of ETS on atopic eczema, allergic sensitization and allergic airway diseases in children	N= 1669 (1124) “school beginners” (6-7y) (Germany)	Questionnaire: current parental smoking Confirmed with urinary cotinine measurements	tIgE, SPT+, sIgE+	CF adjusted	serum tIgE >180 IU/L OR=1.34 (0.85–2.12)	No	No (no relevant numbers)
Feleszko W et al. (full paper in preparation) 2009 [7]	Case-control study	To determine the impact of ETS on cytokine concentrations in nasopharyngeal concentrates in infants.	N=105 0-12 y (Poland)	Questionnaire: current parental smoking	tIgE, local cytokine concentrations	CF not adjusted	A non-significant elevated mean serum tIgE level was noted in children of smoking parents.	No	Yes
Mlinaric A et al. (Eur Rev Med Pharmacol Sci.) 2011 [8]	Cross-sectional study	To investigate impact of active and passive smoking on total and specific IgE levels and on incidence of allergic diseases	N=155 (60) (Croatia) 16 y	Questionnaire: Passive smokers-nonsmokers	Serum tIgE, sIgE	CF not adjusted	Total IgE (IU/ml) was significantly higher in passive smokers when compared to non-smokers.	Yes	Yes

2 IgE, immunoglobulin E; tIgE, total IgE concentrations in serum; sIgE+, at least one positive specific IgE (> 0,35 kU/L), SPT, skin prick-test; CI, confidence interval; OR, odds ratio; y, years; cig, cigarettes; CF, confounding factors.

4

5 **Table II. Specific IgE and environmental tobacco smoke exposure. Characteristics of included studies (6 studies)**

Study ID	Study design	Study aim	Participants recruited (included)	Definition of smoking	Definition of sensitization	Confounding Factors	Results	Outcomes (increased risk of sensitization) No / Yes	Included in metaanalysis (reason of exclusion)
Ownby DR et al. (J Allergy Clin Immunol.) 1988 [1]	Observational study – case series	To assess the role of parental cigarette smoking on atopic sensitization and IgE levels.	N=191 2-17 y (USA)	Questionnaire: current household ETS	tIgE, sIgE+	ND	Allergen sIgE concentrations did not differ significantly between ETS exposed and non-exposed children.	No	No (exact number of individuals not provided)
Krämer U et al. (Br J Dermatol.) 2004 [6]	Cross-sectional study (MIRIAM)	To determine the impact of ETS on atopic eczema, allergic sensitization and allergic airway diseases	N= 2444 (1902) “school beginners” (6-7 y) (Germany)	Questionnaire; current household ETS. Confirmed with urinary cotinine measurements.	sIgE+	CF adjusted	ETS and sIgE house dust mite OR=1.07 (95% CI: 0.65–1.76); ETS and sIgE pollen OR=0.88 (95% CI: 0.53–1.45).	No	Yes
Lannerö E et al. 2008 (Thorax) [9]	Prospective observational birth cohort (BAMSE)	Relationship between prenatal and/or postnatal ETS exposure to IgE sensitization	N=2614 (2529) 4 y (Sweden)	Questionnaire: early life household ETS.	sIgE+	CF adjusted	Postnatal exposition to ETS was associated with sensitization ORadj= 1.28 (95%CI 1.01-1.62) for any allergen.	Yes (postnatal ETS exposure)	Yes
Böhme M et al. (J Allergy Clin Immunol). 2010 [10]	Prospective observational birth cohort (BAMSE)	Association between fetal/early ETS exposure and eczema at 4y	N= 2505 1, 2, 4 y (Stockholm, Sweden)	Questionnaire: early life household ETS	sIgE+ (Phadiatop, mix of food allergens - fx5, or both).	CF adjusted	Parental smoking was associated with sensitization OR=1.62; (95% CI, 1.15-2.30)	Yes	No (another report of previously cited study [13])
Flohrs K, et al. (Int Arch Allergy Immunol.) 2012 [11]	Cross-sectional study (three consecutive regional surveys)	To study temporal changes in total serum IgE levels and analyze the impact of potential determinants.	N=4353 5-14 y (Germany)	Questionnaire: current parental smoking	sIgE+ to 1 of 6 aeroallergens	CF adjusted	Household tobacco smoking was inversely associated with sensitization in all surveys OR=0.85; (95% CI, 0.76-0.96). Survey 3 was eligible for metaanalysis OR=0.96 (95% CI, 0.79-1.17)	No	Yes
Havstad S et al. 2012 (Respirology) [12]	Prospective observational birth cohort (Wayne County Health Longitudinal Study)	Assesment of the relationship between ETS and development of allergic disease using propensity score methods.	N=662 2-3 y (USA, Michigan)	Questionnaire: early life household ETS	sIgE+ , SPT(+ve) to 1 out of 10 allergens	CF adjusted	Among children without a maternal history of allergic disease, ETS was positively associated with allergic sensitization in children with ORadj= 2.53 (95% CI, 1.43–4.48). For all children: OR=1.72 (95% CI, 1.05-2.81)	Yes	Yes

6 (+ve): positive; IgE, immunoglobulin E, SPT, skin prick-test; CI, confidence interval; OR, odds ratio; y, years; cig, cigarettes; CF, confounding factors.

8 Table III. Characteristics of included studies for SPT (14 studies)

Study ID	Study design	Study aim	Participants recruited (included)	Definition of smoking	Definition of sensitization	Confounding Factors	Results	Outcomes (increased risk of sensitization) No / Yes	Included in metaanalysis (reason of exclusion)
Martinez FD et al. (Am Rev Respir Dis) 1988 [13]	Cross-sectional study	To study relationship between parental smoking habits and atopy in non-selected schoolchildren.	N=172 9 y (Italy)	Questionnaire: current, early life and pregnancy parental smoking	SPT (+ve)	ND	No significant relationship between ETS and allergy (SPT, p=0.44). but male children of smoking parents had increased reactivity to allergens as assessed by the SPT (correlation between ETS and SPT index r=0.3, p=0.006).	Yes (boys)	No (lack of exact numbers of individuals)
Arshad SH et al. (J Allergy Clin Immunol). 1992 [14]	Prospective observational birth cohort	To study the role of environmental factors in the development of allergic disorders	N= 1215 (1167) 0-1 y (UK, Isle of Wight)	Questionnaire: early life household ETS	Any of SPT(+ve)	CF adjusted	No significant association between ETS and SPT: was found OR= 0.95 (0.55-1.67) However, smoking increase risk of +ve SPT in asthmatic children OR=1.64 (95%CI: 1.1-2.5)	No	Yes
Kuehr J et al. (J Allergy Clin Immunol). 1992 [15]	Cross-sectional data of a longitudinal study	To investigate risk factors in regard to sensitization in SPT.	N=1812 (1470) 6-8 y (Germany)	Questionnaire: early life household ETS	Any of 7 SPT(+ve)	No significant CF	Postnatal ETS exposure and SPT(+ve): OR=1.33 (95%CI: 0.95 - 1.88)	No	Yes
Ronchetti R et Al. (Arch Dis Child.) 1992 [16]	Cross-sectional study	To assess the role of parental smoking in prevalence and severity of the atopic state (cont. of previous study of 1988)	N=166 (142) 13 y (Italy)	Questionnaire: current and previous parental smoking	Any of 10 SPT(+ve)	ND	Any of SPT(+ve): OR: 1.74 (95%CI: 0.80-3.79). Boys had significantly more persistently positive skin tests when exposed to ETS	No	Yes
Arshad SH et al. (Clin Exp Allergy) 1993 [17]	Prospective observational birth cohort	Risk factors in the development of allergic disorders at age of 2 y (cont. of previous study of 1992)	N= 1215 (436) 2y(UK, Isle of Wight)	Questionnaire: early life household ETS	Any of 5 SPT(+ve)	CF adjusted	Any of 5 SPT +ve OR= 0.87 (95%CI 0.45- 1.65) ETS and +ve SPT in asthmatic children OR=2.19 (95% CI: 1.5 - 3.2)	No	No (data from previous report present)
Bråbäck L et al. (Arch Dis Child) 1995 [18]	Cross-sectional study	To investigate risk factors for respiratory symptoms and atopic sensitization in the Baltic area.	N=2594 (2232) 10-12 y (Sweden, Poland, Estonia)	Questionnaire (ISAAC): current household ETS.	Any of 8 SPT(+ve)	CF adjusted	ETS increased risk of positive SPT: pollen, OR=1.21 (0.85-1.72); dander, OR=1.41 (0.90-2.21). Total effect: ORadj=1.41 (1.03-1.93)	Yes	Yes
Henderson FW et al. (Am J Respir Crit Care Med.) 1995 [19]	Case-control study	Correlates of recurrent wheezing and environmental factors	N=401 (343) 7-12 y (USA)	Questionnaire (ATS-NHLBI): current, and pregnancy parental smoking. Confirmed with urinary cotinine measurements.	Any of 14 SPT(+ve)	CF adjusted	Neither maternal nor parental smoking (to the 5 y) was associated with an increased risk of child's positive SPT OR= 1.17 (95%CI 0.67-2.05).	No	Yes (random sample group only)
Søyseth V et al. (Chest) 1995 [20]	Cross-sectional study	To investigate association between ETS and asthma, BHR and atopy	N=620 (556) 7-13y (Norway)	Questionnaire: ETS: different periods and ways of exposure (pregnancy-first year of life; mother-father) and current exposure	SPT(+ve) to 1 out of 8 aeroallergens	CF adjusted	No significant relationship between atopy and postnatal maternal smoking was found. The OR of atopy was 1.1 (95%CI 0.6-2.1) in children who had been exposed to postnatal maternal tobacco smoke.	No	Yes
Rönmark E et al. (Respir Med.) 1998 [21]	Cross-sectional study	To report prevalence rates of allergic conditions and theirs risk factors	N=3525 (2149) 7-8 y (Sweden)	Questionnaire (ISAAC): parental smoking habits.	SPT(+ve) to standard panel of allergens	CF adjusted	Smoking in mothers did not affect SPT (OR=0.8, p=0.1)	No	No (95% CI for OR's not provided)

Bråbäck L et al. (Pediatr Allergy Immunol) 2001 [22]	Cross-sectional study	To evaluate regional differences in atopy among schoolchildren in relation to pet ownership and early life events	N=2505(1848) 10-11 y (Sweden)	Questionnaire (ISAAC): current household ETS.	SPT(+ve)	CF adjusted	Increased risk of positive SPT for heavy ETS exposure: OR=1.6 (95%CI 1.0-2.5) Overall effect calculated: ORadj=1.03 (0.78-1.36)	No	Yes
Krämer U et al. (Br J Dermatol.) 2004 [6]	Cross-sectional study	To determine the impact of ETS on atopic eczema, allergic sensitization and allergic airway diseases in children	N=1669 (1481) 'school beginners' (6-7 y) (Germany)	Questionnaire; current household ETS. Confirmed with urinary cotinine measurements.	SPT(+ve) to 5 aeroallergens	ND	≥1SPT(+ve): OR 1.20 (95%CI 0.87–1.65)	No effect	Yes
Raherison C, et al. (Respir Med) 2007 [23] And Raherison C et al. (Ann Allergy Asthma Immunol) 2008 [24]	Cross-sectional study	To evaluate association between parental smoking and asthma and allergies To evaluate how maternal allergies modulate effect of tobacco exposure on allergic sensitization in children	N=7.798 (1848) 9-11 y (6 cities of France)	Questionnaire: current , early life and pregnancy parental smoking	Any of 10 SPT(+ve)	CF adjusted	Life exposure to parental tobacco smoke and (+ve) SPT to all allergens ORadj= 1.06 (95%CI 0.9-1.24) Sensitization to house dust mites was higher in children exposed to maternal smoking during pregnancy than in the others. P<0,001. Postnatal ETS had no effect on the sensitization rate.	No	Yes
Havstad S et al. 2012 (Respirology) [12]	Prospective observational birth cohort (Wayne County Health Longitudinal Study)	Assessment of the relationship between ETS and development of allergic disease using propensity score methods.	N=662 2-3 y (USA, Michigan)	Questionnaire: early life household ETS	sIgE+ , SPT(+ve) to 1 out of 10 allergens	CF adjusted	ETS was positively associated with allergic sensitization in children with an adjusted odds ratio (aOR) for SPT+ of 2.32 (95% CI: 1.28–4.22). For all children: OR=1.84 (95% CI, 1.10-3.09)	Yes	Yes

9 (+ve): positive; IgE, immunoglobulin E, SPT, skin prick-test; BHR, bronchial hyperresponsiveness; CI, confidence interval; OR, odds ratio; y, years; cig, cigarettes; CF, confounding factors

REFERENCES

References

1. Ownby DR, McCullough J. Passive exposure to cigarette smoke does not increase allergic sensitization in children. *J.Allergy Clin.Immunol.* **1988**;82:634-8.
2. Ronchetti R, Macri F, Ciofetta G, et al. Increased serum IgE and increased prevalence of eosinophilia in 9-year-old children of smoking parents. *J.Allergy Clin.Immunol.* **1990**;86:400-7.
3. Wjst M, Heinrich J, Liu P, et al. Indoor factors and IgE levels in children. *Allergy* **1994**;49:766-71.
4. El-Nawawy A, Soliman AT, el-Azzouni O, et al. Effect of passive smoking on frequency of respiratory illnesses and serum immunoglobulin-E (IgE) and interleukin-4 (IL-4) concentrations in exposed children. *J.Trop.Pediatr.* **1996**;42:166-9.
5. Oldak E. The influence of tobacco parental smoking on serum IgE level of their offspring. *Rocz.Akad.Med.Bialymst.* **1997**;42:191-5.
6. Kramer U, Lemmen CH, Behrendt H, et al. The effect of environmental tobacco smoke on eczema and allergic sensitization in children. *Br.J.Dermatol.* **2004**;150:111-8.
7. Feleszko W, Kielan I, Matysiak,K et al. Parental tobacco smoking is associated with increased Th2-biased immune response in infants with virus-associated wheezing. *Pediatr.Allergy Immunol.* 20[Supl 20], 56-57. 2009.

Ref Type: Abstract

8. Mlinaric A, Popovic GS, Nadalin S, et al. Passive smoking and respiratory allergies in adolescents. *Eur.Rev.Med.Pharmacol.Sci.* **2011**;15:973-7.
9. Lannero E, Wickman M, van HM, et al. Exposure to environmental tobacco smoke and sensitisation in children. *Thorax* **2008**;63:172-6.
10. Bohme M, Kull I, Bergstrom A, et al. Parental smoking increases the risk for eczema with sensitization in 4-year-old children. *J.Allergy Clin.Immunol.* **2010**;125:941-3.
11. Flohrs K, Bruske I, Thiering E, et al. Temporal changes in total serum immunoglobulin E levels in East German children and the effect of potential predictors. *Int.Arch.Allergy Immunol.* **2012**;158:27-34.

12. Havstad SL, Johnson CC, Zoratti EM, et al. Tobacco smoke exposure and allergic sensitization in children: a propensity score analysis. *Respirology*. **2012**;17:1068-72.
13. Martinez FD, Antognoni G, Macri F, et al. Parental smoking enhances bronchial responsiveness in nine-year-old children. *Am.Rev.Respir.Dis*. **1988**;138:518-23.
14. Arshad SH, Hide DW. Effect of environmental factors on the development of allergic disorders in infancy. *J.Allergy Clin.Immunol*. **1992**;90:235-41.
15. Kuehr J, Frischer T, Karmaus W, et al. Early childhood risk factors for sensitization at school age. *J.Allergy Clin.Immunol*. **1992**;90:358-63.
16. Ronchetti R, Bonci E, Cutrera R, et al. Enhanced allergic sensitisation related to parental smoking. *Arch.Dis.Child* **1992**;67:496-500.
17. Arshad SH, Stevens M, Hide DW. The effect of genetic and environmental factors on the prevalence of allergic disorders at the age of two years. *Clin.Exp.Allergy* **1993**;23:504-11.
18. Braback L, Breborowicz A, Julge K, et al. Risk factors for respiratory symptoms and atopic sensitisation in the Baltic area. *Arch.Dis.Child* **1995**;72:487-93.
19. Henderson FW, Henry MM, Ivins SS, et al. Correlates of recurrent wheezing in school-age children. The Physicians of Raleigh Pediatric Associates. *Am.J.Respir.Crit Care Med*. **1995**;151:1786-93.
20. Soyseth V, Kongerud J, Boe J. Postnatal maternal smoking increases the prevalence of asthma but not of bronchial hyperresponsiveness or atopy in their children. *Chest* **1995**;107:389-94.
21. Ronmark E, Lundback B, Jonsson E, et al. Asthma, type-1 allergy and related conditions in 7- and 8-year-old children in northern Sweden: prevalence rates and risk factor pattern. *Respir.Med*. **1998**;92:316-24.
22. Braback L, Kjellman NI, Sandin A, et al. Atopy among schoolchildren in northern and southern Sweden in relation to pet ownership and early life events. *Pediatr.Allergy Immunol*. **2001**;12:4-10.
23. Raheerison C, Penard-Morand C, Moreau D, et al. In utero and childhood exposure to parental tobacco smoke, and allergies in schoolchildren. *Respir.Med*. **2007**;101:107-17.

24. Raheison C, Penard-Morand C, Moreau D, et al. Smoking exposure and allergic sensitization in children according to maternal allergies. *Ann.Allergy Asthma Immunol.* **2008**;100:351-7.

Table A1. Criteria for assessing the quality of studies according to Newcastle-Ottawa Scale
(with own modifications according to STROBE Statement Guidelines).

	Item No	Recommendation for Cohort Studies and Cross-sectional studies	Recommendation for Case Control Studies
SELECTION			
Study Design	A1	Are the key elements of study design presented early in the paper ?	Are the key elements of study design presented early in the paper ?_Are the case definition adequate?
Participant representativeness	A2	Are the patients truly representative of the average, elderly, community-dwelling resident (eligibility criteria, sources and methods of selection of participants, methods of follow-up)	Consecutive or obviously representative series of cases (rationale for the choice of cases and controls in case-control studies)
Selection of non-intervention cohort	A3	Were the subjects drawn from the same community ?	Were the controls similar at the baseline and recruited over the same period?
Setting	A4	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
COMPARABILITY			
	B1	Comparability of cohorts on the basis of study design or analysis	Comparability of cases and controls on the basis of the design or analysis
EXPOSURE			
Ascertainment of intervention/Exposure	C1	Definition of exposure	Structured interview where blind to case/control status. Same method of ascertainment for cases and controls
OUTCOME			
Assessment of outcome (IgE, SPT)	D1	methods of assessment (measurement), comparability of assessment methods if there is more than one group	methods of assessment (measurement), comparability of assessment methods if there is more than one group
Bias	D2	Description potential sources of bias	Description potential sources of bias
Statistical methods	D3	Describe all statistical methods, including those used to control for confounding Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	Describe all statistical methods, including those used to control for confounding
Follow-up	D4	Cohort study — If applicable, explain how loss to follow-up was addressed	

Table A2. Quality assessment of included studies according to Newcastle-Ottawa Scale
(with own modifications according to STROBE Statement Guidelines).

	Study ID	A1	A2	A3	A4	B1	C1	D1	D2	D3
1	Ownby DR et al. (J Allergy Clin Immunol.) 1988 [34]	+/-	+	+	-	-	+/-	+	-	+/-
2	Ronchetti R et al. (J Allergy Clin Immunol) 1990 [23]	+	+	+	+	+	+/-	+	-	+/-
3	Wjst M et al. (Allergy) 1994 [27]	+/-	+	+	+	-	+	+	+	+
4	el-Nawawy A et al. (J Trop Pediatr.) 1996 [10]	+	-	+	+/-	+	+	+	+	+/-
5	Oldak E. (Rocz Akad Medv Białymst.) 1997 [31]	+	+	+	+	+	+	+	+	+
6	Krämer U et al. (Br J Dermatol.) 2004 [7]	+	+	+	+	+	+	+	+	+
7	Feleszko W et al. (full paper in preparation) 2009 [32]	+/-	+	+	-	+	-	+	-	-
8	Mlinaric A et al. (Eur Rev Med Pharmacol Sci.) 2011 [21]	+	-	+	-	+	+	+	-	-
9	Lannerö E et al. 2008 (Thorax) [6]	+	+	+	+	+	+	+	+	+
10	Böhme M et al. (J Allergy Clin Immunol). 2010 [29]	+	+	+	+	+	+	+	+	+
11	Flohrs K, et al. (Int Arch Allergy Immunol.) 2012 [18]	+	+	+	+	+	+	+	+	+/-
12	Havstad S et al. 2012 (Respirology) [30]	+	+	+	+	+	+	+	+	+
13	Martinez FD et al. (Am Rev Respir Dis) 1988 [20]	-	+/-	+	+/-	+	+	+	-	+
14	Arshad SH et al. (J Allergy Clin Immunol). 1992 [4]	+	+	+	+	+	+	+	+	+
15	Kuehr J et al. (J Allergy Clin Immunol). 1992 [19]	+	+	+	+	+	-	+	+	+
16	Ronchetti R et al. (Arch Dis Child.) 1992 [24]	+	+	+	+	+	+	+	-	+
17	Arshad SH et al. (Clin Exp Allergy) 1993 [28]	+	+	+	+	+	+	+	+	+
18	Bråbäck L et al. (Arch Dis Child) 1995 [14]	+	+	+	+	+	+	+	+	+
19	Henderson FW et al. (Am J Respir Crit Care Med.) 1995 [33]	+	+	+	+	+	+	+	-	+
20	Søyseth V et al. (Chest) 1995 [26]	+	+	+	+	+	+	+	+	+
21	Rönmark E et al. (Respir Med.) 1998 [25]	+	+	+	+	+	-	+	-	+
22	Bråbäck L et al. (Pediatr Allergy Immunol) 2001 [17]	+	+	+	+	+	+	+	-	+
23	Raherison C, et al. (Respir Med) 2007 [15]	+	+	+	+	+	+	+	+	+
24	Raherison C et al. (Ann Allergy Asthma Immunol) 2008 [22]	+	+	+	+	+	+/-	+	+	+

Table A3. Confounding factors (and its method of control)

Study ID	CF considered by the authors	Method of CF control applied by the author	Baseline characteristics data regarding CF
Ownby DR et al. (J Allergy Clin Immunol.) 1988 [34]	Unclear	None	+
Ronchetti R et al. (J Allergy Clin Immunol) 1990 [23]	Possible quitting of smoking in families of atopic children	Repeated analysis after excluding CF	+
Wjst M et al. (Allergy) 1994 [27]	Sex, age, study site, season of examination, atopic heredity	Multivariate linear regression analysis	+
el-Nawawy A et al. (J Trop Pediatr.) 1996 [10]	Age, sex, number of siblings, housing conditions	Multiple regression logistic analysis	Selected population
Oldak E. (Rocz Akad Medv Bialymst.) 1997 [31]	Atopic heredity	Logistic regression analysis	+
Krämer U et al. (Br J Dermatol.) 2004 [7]	nationality, gender, atopic heredity, education, bedroom sharing, playing predominantly outdoors, month of investigation, housing characteristics (age of the house, type of furniture, carpet, and dampness of flat)	Logistic regression analysis	+
Feleszko W et al. (full paper in preparation) 2009 [32]	Unclear	Unclear	Unclear
Mlinaric A et al. (Eur Rev Med Pharmacol Sci.) 2011 [21]	Unclear	Unclear	+
Lannerö E et al. 2008 (Thorax) [6]	sex, atopic heredity, SE status, maternal age, parental education, cat and dog ownership, older siblings, duration of breastfeeding, ambient NOx (from traffic), signs of indoor dampness	Logistic regression	+
Böhme M et al. (J Allergy Clin Immunol). 2010 [29]	Parental atopic heredity, breast-feeding, furred pets at home, sex, parental education. Recall bias concerning eczema,	Logistic regression models	+
Flohrs K, et al. (Int Arch Allergy Immunol.) 2012 [18]	Age group, sex, study region	Unclear	-
Havstad S et al. 2012 (Respirology) [30]	African American race, high school degree, urban address, furred pets at home, first pregnancy, SE status (unemployed, household income, rental or mortgage payment), atopic heredity, mother's age	Nonparametric regression tree technique, was used to estimate the propensity score	+
Martinez FD et al. (Am Rev Respir Dis) 1988 [20]	Sex, asthma	Log-linear multivariate model	-
Arshad SH et al. (J Allergy	SE status, sex, birth weight,	Logistic regression	+

Clin Immunol). 1992 [4]	method of feeding, smoking, season of birth, pets		
Kuehr J et al. (J Allergy Clin Immunol). 1992 [19]	atopic heredity, low gestational age, maternal smoking in pregnancy, prior exposure to cat dander, gender	Multiple logistic regression	+
Ronchetti R et al. (Arch Dis Child.) 1992 [24]	Sex, eosinophilia levels	Least square regression analysis	+
Arshad SH et al. (Clin Exp Allergy) 1993 [28]	SE status, sex, birth weight, method of feeding, smoking, season of birth, pets	Logistic regression	+
Bråbäck L et al. (Arch Dis Child) 1995 [14]	Breathing problems, nasal/ocular symptoms, atopic heredity, gender, passive smoking, sings of dampness at home, siblings, number of persons in the household, cat presence	Logistic regression	+
Henderson FW et al. (Am J Respir Crit Care Med.) 1995 [33]	Unclear	Multivariate analysis	+
Søyseth V et al. (Chest) 1995 [26]	Gender, bronchitis before 2 years of age, familial history of asthma, age	Multivariate analysis	+
Rönmark E et al. (Respir Med.) 1998 [25]	Sex, history of allergic disease, house dampness, mother smoker, pets at home, area of domicile	Multiple logistic regression analysis	+
Bråbäck L et al. (Pediatr Allergy Immunol) 2001 [17]	SE status, gestational age	Logistic model	+
Raherison C, et al. (Respir Med) 2007 [15]	Gender, parental atopy, siblings, length of breast feeding, day care outside the home, pet`s ownership	Logistic regression	+
Raherison C et al. (Ann Allergy Asthma Immunol) 2008 [22]	See above	Logistic regression	+

ND – Not described; SE – socioeconomic,

Table IV. Characteristics of excluded trials (45)

	Study ID	Year	Reason for exclusion
1	Atici A, et al. (Acta Paediatr Jpn.)	1994	Selection bias (allergic children)
2	Becker A, et al (J Allergy Clin Immunol.)	2004	Inclusion bias (atopic parents)
3	Chan-Yeung M et al. (J Allergy Clin Immunol.)	2005	No results of interest provided/Inclusion bias
4	Chan-Yeung M, et al. (Pediatr Allergy Immunol.)	2008	High-risk children
5	Cogswell JJ et al. (Archives of Disease in Childhood)	1987	Inclusion bias (atopic parents)
6	De Longueville M. et al. (Pediatr Allergy Immunol)	1997	Population bias (selected children)
7	Flores D'Arcais (Minerva Pediatr)	1993	Wrong outcome (cord-blood IgE)
8	Geller-Bernstein G (Allergy)	1987	Inclusion bias (atopic parents)
9	Genuneit J, et al. (Thorax)	2006	No results of interest provided
10	Goksör E, et al. (Acta Paediatr.)	2006	Selection bias (children with wheezing)
11	Janson C, et al. (Respir Med.)	2005	No results of interest provided
12	Keil T,2009 (Allergy)	2009	Population bias (high-risk parents)
13	Kjellman NI et al. (Lancet)	1981	No results of interest provided
14	Lau S et al. (Paediatr Respir Rev)	2002	Review –no original data
15	Lau S et al. (European Respiratory Journal)	2003	Population bias (high-risk parents)
16	Lewis SA, et al. (Am. J. Epidemiol.)	2005	Data not relevant to study outcomes
17	Lindfors A et al. (J Allergy Clin Immunol)	1999	Population bias (selected children)
18	Liu X et al (J Allergy Clin Immunol.)	2004	No results of interest provided
19	López N, et al. (J Investig Allergol Clin Immunol)	1999	Wrong outcome (cord-blood IgE)
20	Magnusson CG. (J Allergy Clin Immunol)	1986	Outcome not relevant (cord-blood IgE)
21	Melén E et al. (Allergy)	2001	Inclusion bias (atopic children)
22	Michel FB et al. (J Allergy Clin Immunol.)	1980	Inappropriate outcome (cord-blood IgE)
23	Michel FB, 1980 _ J Allergy Clin Immunol.	1980	Wrong outcome (cord-blood IgE)
24	Murray CS et al. (Pediatr Pulmonol).	2004	Population bias (selected children)
25	Oryszczyn et Al. (Allergy)	1999	Wrong outcome (cord-blood IgE)
26	Ownby DR et al. (J Allergy Clin Immunol).	1991	Wrong outcome (cord-blood IgE)
27	Palmieri M et al. (Eur J Pediatr.)	1990	Population bias (selected children)
28	Piippo-Savolainen E, et al. (Allergy Asthma Proc.)	2006	Selection bias (children with bronchiolitis)
29	Ruskamp J, et al. (Arch Dis Child)	2010	Inclusion bias (atopic neonates)
30	Stazi MA, et al. (Pediatr Allergy Immunol.)	2002	No results of interest provided
31	Stern DA, et al. (Lancet)	2008	Study population out of age-range
32	Von Mutius E et al (BMJ)	1994	Data not relevant to study outcomes
33	Weiss ST, et al. (Am Rev Respir Dis)	1985	Sample contamination
34	Wickman M et al (Pediatr Allergy Immunol)	1992	Inclusion bias (atopic children)
35	Wright AL et al. (Pediatrics)	1994	No results of interest provided
36	Zeiger RS, Heller S (JACI)	1995	Inclusion bias (atopic parents)
37	Civelek (Pediatr Pulmonol.)	2011	Outcome not relevant
38	Vlaski (Allergol Immunopathol_Madr)	2011	Outcome not relevant
39	Wahn (PAI)	2011	No data – review paper
40	Semple MG (PLOS One)	2011	Inclusion bias, no relevant outcome
41	Stankiewicz-Choroszuca BL (Ann Agric Environ Med.)	2011	Adult population
42	Wood ((J Allergy Clin Immunol.)	2011	Population bias (high-risk population/parents)
42	Virkula (Acta Paediatr.)	2011	Population bias (snoring children)
43	Agache (Phys Sportsmed.)	2010	Population bias (allergic rhinitis children)
44	Neogi (Fam Pract.)	2012	No data – review paper
45	Boneberger A, (J Asthma.)	2011	Population bias (asthmatic children)