

# Atopic dermatitis, asthma and allergic rhinitis in general practice and the open population: a systematic review

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## Abstract

**Purpose:** To examine whether significant differences exist between the self-reported prevalence of atopic disorders in the open population compared with physician diagnosed prevalence of atopic disorders in general practice.

**Method:** Medline (OvidSP), PubMed Publisher, EMBASE, Google Scholar and the Cochrane Controlled Clinical Trials Register databases were systematically reviewed for articles providing data on the prevalence of atopic eczema, asthma and allergic rhinitis in a GP setting. Studies were only included when they had a cross-sectional or cohort design and included more than 100 children (aged 0-18 years) in a general practice setting. All ISAAC studies (i.e. the open population) that geographically matched a study selected from the first search, were also included. A quality assessment was conducted. The primary outcome measures were prevalence of atopic eczema, asthma and allergic rhinitis in children aged 0-18 years.

**Results:** The overall quality of the included studies was good. The annual and lifetime prevalences of the atopic disorders varied greatly in both general practice and the open population. On average, the prevalence of atopic disorders was higher in the open population.

**Conclusions:** There are significant differences between the self-reported prevalence of atopic disorders in the open population compared with physician diagnosed prevalence of atopic disorders in general practice. Data obtained in the open population cannot simply be extrapolated to the general practice setting. This should be taken into account when considering a research topic or requirements for policy development. GPs should be aware of the possible misclassification of allergic disorders in their practice.

# Background

The atopic syndrome is a predisposition toward an exaggerated IgE-mediated immune response in reaction to an allergen. A patient with atopy typically presents with one or more of the following disorders: atopic eczema (atopic dermatitis), asthma or allergic rhinitis. In this article atopic disorders refer to allergic manifestations for which atopy is a prerequisite. Epidemiological data on atopic disorders in children can be obtained from various sources, each having its own advantages and limitations. This review examines data obtained from general practice and survey data obtained in the open population. Depending on the research topic or the requirements for policy development, reliable data from either the open population or general practice (or both) might be needed.

The International Study of Asthma and Allergies in Childhood (ISAAC) has yielded many publications related to the open population (1). Albeit such survey data provide useful information on the prevalence of self-reported symptoms of allergic disorders and the derived diagnosis (2), they also imply a risk of overestimation of the prevalence of atopic disorders. For example, a runny nose can be caused by allergic rhinitis or by a viral upper airway infection; distinguishing between these two causes may be difficult for a patient when completing a questionnaire. Although the prevalence based on a clinician-diagnosed disease might solve this problem, it will imply a risk of underestimation of the burden of disease. For example, patients might have a 'threshold' with regard to visiting a physician or might consider their complaints not serious enough to visit one. Because, epidemiological data on atopic conditions in children in a general practice are scarce, we performed a systematic review.

We expected to find a significant difference between the self-reported prevalence in the open population (ISAAC studies) and the clinician-diagnosed prevalence of a disorder in general practice. More insight into these differences may help policy-makers to optimize their policies and help general practitioners (GPs) become more aware about the possible underdiagnosis of allergic conditions in children.

## Method

### Search strategy

Two separate search strategies were used to collect data on the two sources (i.e. general practice and open population). First, a comprehensive search for relevant studies in general practice was performed in Medline (OvidSP), PubMed Publisher,

EMBASE, Google Scholar and the Cochrane Controlled Clinical Trials Register databases. The search strategy (Appendix 1) combined the following items: 'Child' AND 'Epidemiology' AND 'Eczema' AND 'Asthma' AND 'Allergic rhinitis'. All articles in these five databases were considered and reviewed; no language restriction was imposed and the search was completed in January 2015. All references of the included studies were examined in order to be as comprehensive as possible. A second search, performed in the ISAAC database, was also conducted in January 2015. ISAAC provides its users with a database that holds citations on all publications which are part of the ISAAC collaboration (1), representing the open population. However, because of known regional differences (3), we looked for studies that geographically matched (i.e. the same country) the studies finally selected in the first search strategy.

## Study selection

Based on title and abstract, two reviewers (DP and EvA) independently selected articles retrieved in the first search strategy. All studies that provided data on the prevalence of asthma, allergic rhinitis and atopic eczema were considered, so long as they had a cross-sectional or cohort design and included more than 100 children (0-18 years) in a general practice setting. If the abstract was not conclusive regarding these items, the article was included for full-text assessment. Any disagreement was resolved in a consensus meeting. Finally, the full-text of the selected abstracts was independently reviewed by two reviewers (DP and JW). Studies were not included if they did not meet the above-mentioned inclusion criteria or if selection bias was present (e.g. data were retrieved from a specific cohort within a general practice setting).

The second search strategy focused on the ISAAC database (1). Two reviewers (DP and JW) independently checked this database for relevant articles. All studies were included that geographically matched (i.e. the same country) a study selected from the first search.

## Quality assessment

The quality of the included studies was independently assessed by two reviewers (DP and AB). Any disagreement was resolved in a consensus meeting. Assessment of the quality of the finally included studies conducted in general practice, was done by scoring the following items: population size, description of participants (age and percentage males), study year, data sources (paper or digital patient files, structured interviews, etc.), selection bias (e.g. not using all patient files but a selection thereof) and whether or not the methods used are reproducible.

With regard to reproducibility, the emphasis was on the definitions used for atopic eczema, asthma and allergic rhinitis. ISAAC used a standardized method. Ellwood et al. showed that the ISAAC methodology could be replicated to a high standard by the majority of participating centers (4). This indicates that the ISAAC protocol is robust and working in accordance with this protocol implies high quality. Any important violations of this protocol were obtained for the quality assessment of the finally included studies.

## Data extraction

All data extraction was independently performed by two reviewers (DP and AB). Data were collected on the number of children studied, study period, study design, and country. The outcome measures are the prevalences of atopic eczema, asthma, and allergic rhinitis in children aged 0-18 years.

# Results

## Selection and description of the literature

The search strategy regarding general practice yielded 4,274 unique articles. Most of these (n=4,242) did not meet the inclusion criteria, mainly because only 2.2% of these studies (n=95) were conducted in a general practice setting. Of the 34 articles retrieved for full-text evaluation, 28 were excluded because they did not meet the inclusion criteria.

Finally, six studies were included in the present review for further analysis with regard to general practice; one study was performed in the Netherlands (5) and five in the UK (6-10). These six studies were published between 1974 and 2009. In table 1 the results of the quality assessment are presented. There was no evidence of selection bias. Four of the six studies had an adequate description of the methodology, whereas two studies failed to describe the exact definitions used for the disorders examined. Two studies presented data on annual prevalence and four U.K. studies presented data on lifetime prevalence.

The ISAAC database contained 604 articles. Of these, seven eligible studies (11-17) were selected that could be geographically matched to the selected general practice studies. Of these, six were performed in the UK (11-16) and one in the Netherlands (17). All four UK studies were conducted between 1995 and 2002 (11-14). The study on Dutch adolescents was conducted in 2003 (17). Table 2 presents the results of the quality assessment of these studies.

Table 1. Study characteristics and quality items general practice studies

First author/year	Country	No. analyzed	Age (years)	% Males	Study year	Data sources	Bias*	Reproducible
Blair 1974 (6)	UK	1,907	0-10	53.2%	1970-1973	Paper files + interview	No	No
Mortimer 1993 (9)	UK	1,077	3-11	50.5%	<1993	Interviews + survey	No	No
Punekar 2009 (8)	UK	24,112	0-18	51.1%	1990-2008	Digital files	No	Yes
Simpson 2002 (7)	UK	252,538†	0-14	53.6%	1999	Digital files	No	Yes
Simpson 2008 (10)	UK	492,411/486,804	0-14	49.6%/49.8%	2001/2005	Digital files	No	Yes
Wijga 2011 (5, 35)	NL	79,272	0-17	51.3%	2001	Digital files + interviews	No	Yes

\* not using the entire patient files, but some selection thereof.

† Total study population, including adults

Table 2. Study characteristics and quality items of the open population (ISAAC) studies

First author/year	Country	No. analyzed	Age (years)	% Males	Response rate	Study year	English questionnaires	Violations protocol*
Austin 1999 (12)	UK	27,507	12-14	49.2%	85.9%	1995	Yes	3, 6
Jefferies 2000 (16)	UK	3,772	12-14	-	90.7%	1995-1996	Yes	3
Prihantjani 2001 (13)	UK	1,050	13-14	-	79%	1998-2001	Yes	5, 6, 7
Anderson 2004 (11)	UK	15,083/15,755	12-14	-	87%	1995/2002	Yes	3, 6
Austin 2005 (15)	UK	4,298	12-15	49.1%	89%	2002	Yes	3, 6
Shamssain 2007 (14)	UK	6,000	6-7 / 13-14	48.5/50.3%	80-90%	1995-1996	Yes	6
	UK	4,038	6-7 / 13-14	49.8/45.6%	90-92%	2001-2002	Yes	7
Ven 2006 (17)	NL	9,713	12-14	48.8%	91.2%	2003	No	None

\* 1) Recruitment at schools; 2) All schools, or randomly selected; 3) Age groups 6-7 / 13-14 years; 4) Use of validated questionnaires; 5) questionnaires completed by parents (< 12 year olds) or by adolescents themselves (≥ 12 year olds); 6) Participation >90%; 7) N ≥3000

## Atopic eczema

The annual and lifetime prevalences of the atopic disorders varied widely between the studies and the populations involved. The annual prevalence (Table 3) of atopic eczema ranged from 1.8%-9.5% in general practice and from 11.4%-24.2% in the open population, whereas the lifetime prevalences (Table 4) ranged from 7.2%-36.5% in general practice and from 16.5%-27.1% in the open population.

## Asthma

In general practice, the annual prevalence (Table 3) of asthma ranged from 3.0%-6.5%, whereas in the open population it was as high as 12.3%-34.2%. The lifetime prevalence (Table 4) of asthma in general practice was 4.2%-22.9% compared with 19.1%-35.6% in the open population.

## Allergic rhinitis

In general practice the annual prevalence (Table 3) of allergic rhinitis ranged from 0.4%-4.1% compared with 15.1%-37.8% in the open population; the lifetime

Table 3. Studies presenting annual prevalence

Study	Source	Country	No. included	Time period	Age group (years)	Eczema	Asthma	Allergic rhinitis
Wijga et al. 2011	General Practice	NL	79,272	2001	0-9	5.5%	5.3%	0.4%
					10-17	1.8%	3.0%	0.4%
Ven et al. 2006	Open Population	NL	9,713	2003	12-14	13.5%	12.3%	28.3%
Simpson et al. 2002	General Practice	UK	252,538*	1999	0-4	9.5% <sup>†</sup>	4.3% <sup>†</sup>	0.7% <sup>†</sup>
					5-9	4.5% <sup>†</sup>	6.5% <sup>†</sup>	2.3% <sup>†</sup>
					10-14	3.4% <sup>†</sup>	6.2% <sup>†</sup>	4.1% <sup>†</sup>
Austin et al. 1999	Open Population	UK	27,507	1995	12-14	16.4%	33.3%	18.2%
Jeffs 2000	Open Population	UK	3,772	1995-1996	12-14	22.7%	34.2%	37.8%
Anderson et al. 2004	Open Population	UK	15,083	1995	12-14	16.2%	33.9%	18.4%
Anderson et al. 2004	Open Population	UK	15,755	2002	12-14	11.4%	27.5%	15.1%
Austin 2005	Open Population	UK	4,298	2002	12-15	12.0%	27.8%	15.3%
Shamssain et al. 2007	Open Population	UK	3,000	1995-1996	6-7	15.8%	18.1%	20.6%
					13-14	17.0%	19.9%	29.6%
Shamssain et al. 2007	Open Population	UK	1,843	2001-2002	6-7	24.2%	25.4%	15.8%
					13-14	19.0%	22.2%	32.2%

\* Total study population

<sup>†</sup> Prevalences calculated based on the assumption of male/female ratio = 1.04:1.00

Table 4. U.K. studies, lifetime prevalence

Study	Source	No. included	Time period	Age group (years)	Eczema	Asthma	Allergic rhinitis
Blair 1974	General Practice	1,907	1970-1973	0-10	7.2%	6.3%	4.8%
Mortimer 1993	General Practice	1,077	< 1993	3-11	20.2%	19.6%	7.6%
Simpson 2008	General Practice	126,348 366,063	2001	0-4 5-14	13.0%* 13.0%*	6.3% 15.7%	1.0%* 4.5%*
Simpson 2008	General Practice	125,020 361,784	2005	0-4 5-14	18.0%* 19.0%*	4.2% 15.7%	1.4%* 6.7%*
Punekar 2009	General Practice	24,112	2008	0-18	36.5%	22.9%	11.4%
Austin 1999	Open Population	27,507	1995	12-14	22.5%	20.9%	34.9%
Jeffs 2000	Open Population	3,772	1995-1996	12-14	25.6%	19.1%	47.7%
Priftanji 2001	Open Population	1,050	1998-2001	13-14	27.1%	20.2%	19.5%
Anderson 2004	Open Population	15,083	1995	12-14	21.1%	20.6%	34.8%
Anderson 2004	Open Population	15,755	2002	12-14	24.3%	25.9%	37.4%
Austin 2005	Open Population	4,298	2002	12-15	25.0%	24.5%	34.1%
Shamssain 2007	Open Population	3,000 3,000	1995-1996	6-7 13-14	18.3% 17.2%	29.3% 31.6%	22.6% 33.7%
Shamssain 2007	Open Population	1,843 2,195	2001-2002	6-7 13-14	21.8% 16.5%	35.6% 30.5%	18.3% 25.6%

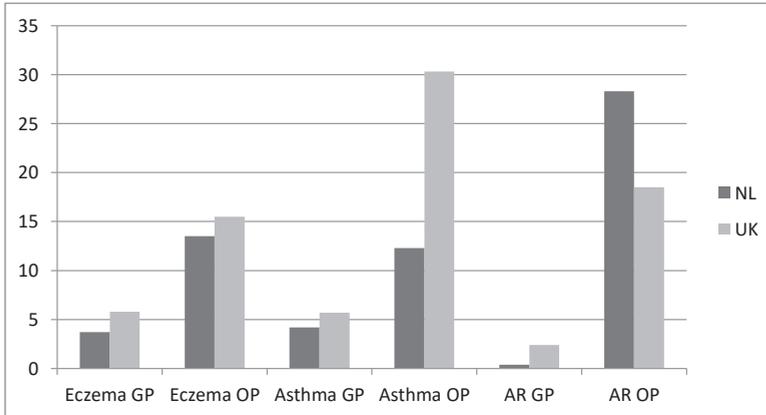
\* Estimation based on graph

prevalence (Table 4) ranged from 1.0%-11.4% in general practice and from 18.3%-47.7% in the open population.

## Differences between the Netherlands and the UK

In both the Netherlands and the UK, similar differences exist between the prevalences of the atopic disorders in the open population and the general practice population (Fig. 1). In general practice the annual prevalence of atopic eczema and asthma are very similar. There is a large difference in the prevalence of diagnosed allergic rhinitis: in the UK this diagnosis is registered more frequently (0.4% vs 2.4%). On the other hand, in the open population there is a higher prevalence of allergic rhinitis in the Netherlands (28.3%) compared to that of the UK (19.3%). Finally, a substantial difference exists between the two countries in the annual prevalence of asthma in the open population (12.3% vs 30.3%). Unfortunately, the data were not sufficient to allow comparisons at the regional level.

Figure 1. Annual prevalence in % (weighted mean): General Practice (GP) vs Open Population (OP) in UK (United Kingdom) and NL (The Netherlands). (AR = allergic rhinitis)



## Discussion

On average, the prevalence of all three atopic disorders was substantially higher in the open population compared to general practice. For example, the annual prevalence of asthma ranged from 3.0%-6.5% in general practice compared to 12.3%-34.2% in the open population. At least a twofold difference. In both the Netherlands and the UK similar differences were found between the open population and the general practice population. Allergic rhinitis was an exception and was diagnosed more frequently in the UK by GPs (0.4% vs 2.4%) whereas a higher prevalence was found in the Netherlands in the open population (28,3% vs 19.3%). Our results implicate that data obtained in the open population cannot simply be extrapolated to the general practice setting. This should be taken into account when considering a research topic or requirements for policy development. General practitioners should be aware of possible underdiagnosis of allergic disorders in their practice. However, overestimation can also occur due to misclassification of the disorder by a GP (18, 19).

No articles were excluded in this review based on language restrictions. All articles were independently examined by two reviewers, all references of the included studies were also checked and all data extraction was done by two independent researchers.

The search strategy for the open population focused exclusively on the ISAAC database, with three related limitations. First, although the ISAAC study has yielded

many international publications, restricting our review to official ISAAC studies carries the risk of missing other relevant studies using different, but also validated, methodologies. A recently published meta-analysis based on both official and non-official ISAAC questionnaires showed annual prevalences for atopic eczema, asthma and allergic rhinitis of 7.9%, 12.0% and 12.7%, respectively (2). These prevalences are lower than the average annual prevalences that were observed in this review. It suggests the possibility of a higher estimation of the prevalence of atopic disorders when only ISAAC studies are included. However, using one methodology allowed us to make safer comparisons, especially because ISAAC's methodology is known to be solid. The second limitation is the ISAAC database itself, which we discovered is not 100% comprehensive. The third limitation is the cross-sectional design of ISAAC and of the studies in general practice. Okkes et al. studied the differences between general practice registration projects and a health survey (20). They considered an observation period of one year to be a source of problems; using data collected over a longer period of time showed more accuracy (20).

Since the definition of atopic disorders has changed over time, one could argue that the conclusions reached in this article do not take these changes into consideration. However, this argument does not hold for ISAAC, since ISAAC uses the same definition to define atopic disorders since its beginning in 1991. For studies conducted in general practice, this might be different, but cannot explain the remarkable difference between the two settings.

Finally, we included only two countries. We focused on general practice and not every country has a GP in its healthcare system. The use of other sources of primary care data is subject to more selection bias and was therefore avoided.

Existing literature provides various explanations for the wide variability found between the two settings. First, the worldwide prevalence of the three disorders have changed over time (3). The studies in this review were conducted between 1970 and 2008 and the reported prevalence might in part, reflect this worldwide time trend. Another explanation for changing prevalences over time are a change in definitions of atopic disorders over time. Van Wonderen et al. found 60 different operational definitions used in the literature on asthma (21). Applied in a single cohort, there was a substantial variation in estimated prevalences depending on the operational definition used. To deal with the remarkable amount of different definitions in atopic disorders worldwide, expert teams were given the task of finding consensus. For example, in 2006 a consensus regarding the diagnosis and treatment of atopic dermatitis was developed for this reason (22). Furthermore, for the lifetime prevalence, the age groups differed between the studies, resulting in different prevalences. Finally, not all GPs may be fully aware of what their patients actually experience regarding allergic symptoms (23) which might lead to misclassification

of allergic and therefore atopic diagnoses. Especially allergic rhinitis might be underestimated, since anti-allergic medication (antihistamines) is freely available over-the-counter thereby limiting the necessity for patients to visit their GP for related symptoms.

Data from both sources have both advantages and disadvantages as proven by existing literature. Data obtained from general practice databases can be considered specific, but not very sensitive. This lack of sensitivity might be the result of underdiagnosis or misclassification (19). This risk is particularly true for asthma. Spirometry under the age of six years is not considered reliable, resulting in a probability or clinical diagnosis. In other cases, spirometry is often underused or the technique is poor (19). Misclassification can also be the result of the differences of 'conceptual vocabulary' between parents and clinicians (24). On the other hand, a prevalence based on self-administered questionnaires will result in more sensitive data, but will be less specific. Questionnaires are often used in population studies mainly for epidemiological purposes. Although ISAAC put considerable effort into the validation of their questionnaires (25-28), external influences cannot be totally ruled out. The accuracy of data obtained from a questionnaire always depends on various influences, including the accuracy and knowledge of the responders and the definitions used. ISAAC uses dichotomous (Yes/No) definitions. There is evidence that suggests that using continuous (graded) definitions would result in better statistical power and will provide relevant additional information (29). Also the terminology used in a questionnaire influences the results. Wheeze for example is the cornerstone of asthma diagnosis. However, conceptual understandings of 'wheeze' differs between physicians, researchers and parents of children with reported wheeze. This difference will influence reported prevalences in the open population (using questionnaires) and clinical practice (using a physician interpretation of wheeze) (24). Dotterud et al. (30) considered questionnaires on atopic conditions a useful epidemiological tool for obtaining rough estimates of the prevalence of atopic disorders. They conclude that atopic eczema was generally underestimated and allergic rhinitis overestimated when using questionnaires in the open population (30); the present study seems to confirm their findings. Furthermore, different prediction scores have been developed based on data from the open population and from general practice. For example, the PIAMA Risk Score, based on the open population, helps to predict which child with suggestive symptoms for asthma could develop asthma at school age (31), whereas the CAPS prediction score was developed in a primary care setting (32). Both models differ substantially with regard to the factors they take into account; this difference might be explained by the different reported prevalences. When using prediction scores, it is important to be aware of the setting in which they were developed and validated.

The prevalences of the three atopic disorders were on average higher in the open population compared with general practice. However, the degree of difference varied depending on the specific disorder. Policymakers should be aware that survey based data, obtained in the open population, cannot simply be extrapolated to the general practice setting.

GPs should consider to critically reevaluate the already diagnosed atopic disorders in a patient's medical record to reduce the risk of misclassification. The present data may also serve to prompt GPs to be more aware of possibly underdiagnosed atopic conditions in children. For example, a relatively large percentage of children in the open population reported symptoms of allergic rhinitis; confirming the results of Dotterud et al. based on survey data (30). The low prevalences found in general practice do not reflect this. Knowing that poorly regulated allergic rhinitis can have an influence on asthma regulation (33), our data emphasizes the importance of actively asking about allergic rhinitis symptoms in children with asthma. GPs should consider different atopic disorders when a child is already diagnosed with one, since the atopic disorders are closely related (2).

Future research could benefit from longitudinal research with standardizing diagnostic definitions and by standardized reporting (e.g. reporting lifetime prevalence's at standardized ages). Diagnosing an atopic disorder in general practice can be difficult, even if a clear definition is used. GPs often work with probability diagnosis and have to label their consultations with a standardized code like the International Classification of Primary Care (ICPC). ICPC is accepted by the WHO for labeling primary care encounters (34). Using ICPC codes in epidemiological studies implies a risk of dealing with misclassification, since some of the diagnosis should be regarded as 'probability diagnosis' and not as 'true diagnosis'. When analyzing electronic medical records from a GP with the use of ICPC codes; duration of follow-up, number of consultations and number of relevant prescriptions for that specific ICPC code should be taken into account. In this way, ICPC codes could be corrected, reducing the risk of misclassification. Regarding allergic rhinitis there is also another problem. GP registrations could show an underestimation of the number of children with allergic rhinitis due to the availability of 'over the counter' (OTC) drugs for this disorder. This may explain the higher observed prevalences for allergic rhinitis in the open population.

## Conclusions

In conclusion, significant differences exist between the self-reported prevalence of atopic disorders in the open population compared with physician diagnosed prevalence of atopic disorders in general practice. Data obtained in the open

population cannot simply be extrapolated to general practice setting. GPs should be aware of possible misclassification of allergic disorders in their practice. Some suggestions how to limit this risk of misclassification in epidemiological research are given.

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# Appendix 1

## Search strategy:

### For Embase

(asthma/exp OR wheezing/de OR (asthma\* OR wheez\* OR hyperresponsiv\* OR hypersensitiv\* OR (hyper NEXT/1 (responsiv\* OR sensitiv\*)):ab,ti) AND (eczema/de OR 'atopic dermatitis'/de OR (eczem\* OR (atopic NEAR/3 dermatit\*)):ab,ti) AND (rhinitis/exp OR conjunctivitis/exp OR (rhinitis\* OR rhinoconjunctivit\* OR conjunctivit\* OR (Pollen NEAR/3 Allerg\*) OR Pollinos\* OR ((hay) NEXT/1 (fever\*)) OR hayfever):ab,ti) AND (Epidemiology/exp OR 'epidemiological data'/exp OR epidemiology:lnk OR (prevalenc\* OR inciden\* OR trend\* OR associat\* OR comorbid\* OR relat\* OR correlat\* OR (case NEAR/3 (control\* OR comparison OR referent)) OR epidemiolog\* OR cohort\* OR risk\* OR caus\* OR (odds NEXT/1 ratio\*) OR etiol\* OR aetiol\* OR (natural NEXT/1 histor\*) OR predict\* OR prognos\* OR outcome\* OR course\*):ab,ti) AND (child/exp OR newborn/exp OR adolescent/exp OR adolescence/exp OR 'child behavior'/de OR 'child parent relation'/de OR (adolescen\* OR infan\* OR newborn\* OR (new NEXT/1 born\*) OR baby OR babies OR neonat\* OR child\* OR kid OR kids OR toddler\* OR teen\* OR boy\* OR girl\* OR minors OR underag\* OR (under NEXT/1 ag\*) OR juvenil\* OR youth\* OR kindergar\* OR puber\* OR pubescen\* OR prepubescen\* OR prepubert\* OR pediatric\* OR paediatric\* OR school\* OR preschool\* OR highschool\*):ab,ti)

### For Medline via OvidSP

(exp asthma/ OR (asthma\* OR wheez\* OR hyperresponsiv\* OR hypersensitiv\* OR (hyper ADJ (responsiv\* OR sensitiv\*))).ab,ti.) AND (exp Dermatitis, Atopic/ OR exp Eczema/ OR Eczem\*.ab,ti. OR (atopic ADJ3 dermatit\*).ab,ti.) AND (exp Rhinitis/ OR exp Conjunctivitis/ OR (rhinit\* OR rhinoconjunctivit\* OR conjunctivit\* OR (Pollen ADJ3 Allerg\*) OR Pollinos\* OR hayfever\* OR hay fever\*).ab,ti.) AND (exp Epidemiologic Studies/ OR exp Epidemiologic Factors/ OR epidemiology.xs. OR (prevalenc\* OR inciden\* OR trend\* OR associat\* OR comorbid\* OR relat\* OR correlat\* OR (case ADJ3 (control\* OR comparison OR referent)) OR epidemiolog\* OR cohort\* OR risk\* OR caus\* OR odds ratio\* OR etiol\* OR aetiol\* OR natural histor\* OR predict\* OR prognos\* OR outcome\* OR course\*).ab,ti.) AND (exp child/ OR exp infant/ OR (infan\* OR newborn\* OR new born\* OR baby OR babies OR neonat\* OR perinat\* OR postnat\* OR child\* OR kid? OR toddler\* OR teen\* OR boy? OR girl? OR minor? OR underag\* OR (under ADJ2 ag?) OR juvenil\* OR youth? OR kindergar\* OR puber\* OR pubescen\* OR prepubescen\* OR prepuberty\* OR pediatric\* OR

pediatric\* OR school\* OR preschool\* OR highschool\* OR suckling\*).ab,ti. OR ((adoles\*.ab,ti. OR adolescent/) NOT exp adult/))

### For Cochrane

((asthma\* OR wheez\* OR hyperresponsiv\* OR hypersensit\* OR (hyper NEXT/1 (responsiv\* OR sensitiv\*)):ab,ti) AND ((eczem\* OR (atopic NEAR/3 dermatit\*)):ab,ti) AND ((rhinitis\* OR rhinoconjunctivit\* OR conjunctivit\* OR (Pollen NEAR/3 Allerg\*) OR Pollinos\* OR ((hay) NEXT/1 (fever\*)) OR hayfever):ab,ti) AND ((prevalenc\* OR inciden\* OR trend\* OR associat\* OR comorbid\* OR relat\* OR correlat\* OR (case NEAR/3 (control\* OR comparison OR referent)) OR epidemiolog\* OR cohort\* OR risk\* OR caus\* OR (odds NEXT/1 ratio\*) OR etiol\* OR aetiol\* OR (natural NEXT/1 histor\*) OR predict\* OR prognos\* OR outcome\* OR course\*):ab,ti) AND ((adolescen\* OR infan\* OR newborn\* OR (new NEXT/1 born\*) OR baby OR babies OR neonat\* OR child\* OR kid OR kids OR toddler\* OR teen\* OR boy\* OR girl\* OR minors OR underag\* OR (under NEXT/1 ag\*) OR juvenil\* OR youth\* OR kindergar\* OR puber\* OR pubescen\* OR prepubescen\* OR prepubert\* OR pediatric\* OR paediatric\* OR school\* OR preschool\* OR highschool\*):ab,ti)

### For PubMed publisher

(asthma[mh] OR (asthma\*[tiab] OR wheez\*[tiab] OR hyperresponsiv\*[tiab] OR hypersensit\*[tiab] OR hyper responsiv\*[tiab] OR hyper sensitiv\*[tiab])) AND (Dermatitis, Atopic[mh] OR Eczema[mh] OR Eczem\*[tiab] OR (atopic AND dermatit\*[tiab])) AND (Rhinitis[mh] OR Conjunctivitis[mh] OR (rhinit\*[tiab] OR rhinoconjunctivit\*[tiab] OR conjunctivit\*[tiab] OR (Pollen AND Allerg\*[tiab]) OR Pollinos\*[tiab] OR hayfever\*[tiab] OR hay fever\*[tiab])) AND (Epidemiologic Studies[mh] OR Epidemiologic Factors[mh] OR epidemiology[sh] OR (prevalenc\*[tiab] OR inciden\*[tiab] OR trend\*[tiab] OR associat\*[tiab] OR comorbid\*[tiab] OR relat\*[tiab] OR correlat\*[tiab] OR (case AND (control\*[tiab] OR comparison OR referent)) OR epidemiolog\*[tiab] OR cohort\*[tiab] OR risk\*[tiab] OR caus\*[tiab] OR odds ratio\*[tiab] OR etiol\*[tiab] OR aetiol\*[tiab] OR natural histor\*[tiab] OR predict\*[tiab] OR prognos\*[tiab] OR outcome\*[tiab] OR course\*[tiab])) AND (child[mh] OR infant[mh] OR (infan\*[tiab] OR newborn\*[tiab] OR new born\*[tiab] OR baby OR babies OR neonat\*[tiab] OR perinat\*[tiab] OR postnat\*[tiab] OR child\*[tiab] OR kid\* OR toddler\*[tiab] OR teen\*[tiab] OR boy\* OR girl\* OR minor\* OR underag\*[tiab] OR under ag\* OR juvenil\*[tiab] OR youth\* OR kindergar\*[tiab] OR puber\*[tiab] OR pubescen\*[tiab] OR prepubescen\*[tiab] OR prepuberty\*[tiab] OR pediatric\*[tiab] OR paediatric\*[tiab] OR school\*[tiab] OR preschool\*[tiab] OR highschool\*[tiab] OR suckling\*[tiab]) OR ((adoles\*[tiab] OR adolescent[mh]) NOT adult[mh])) AND publisher[sb]

**For Google scholar**

asthma eczema rhinitis prevalence | incidence | epidemiology | cohort | risk |  
etiology | prognosis | outcome adolescents | infants | children | newborns "family |  
general|primary physician | practice | doctor | care"